# The genetics of exercise behavior and psychological well-being

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# THE GENETICS OF EXERCISE BEHAVIOR AND PSYCHOLOGICAL WELL-BEING

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# Chapter 1

## General introduction

## Introduction

A sedentary lifestyle has been cited as one of the main causes of the explosive rise in obesity that starts at an increasingly younger age (Martinez-Gonzalez *et al.*, 1999). Furthermore, regular exercisers have lower risks for cardiovascular disease (CVD) and type 2 diabetes than non-exercisers (Albright *et al.*, 2000; Kaplan *et al.*, 1996; Kesaniemi *et al.*, 2001) and the percentage of people at risk because of inactivity is higher than for hypertension, smoking, and cholesterol (Stephens and Craig, 1990). Despite these well-documented benefits of exercise, a large proportion of adults in the Western world does not exercise on a regular basis (Crespo *et al.*, 1996; Haase *et al.*, 2004; Stephens and Craig, 1990). As a consequence, a sedentary lifestyle remains a major threat to health in today's society. This is reflected in public health recommendations which unanimously include an encouragement to a more active lifestyle (World Health Organization, 1995; US Department of Health and Human Services, 2005).

Besides the effects of a lack of exercise on physical health there is also a large body of literature that suggests that non-exercisers are characterized by chronically higher levels of anxiety and depression (Gauvin and Spence, 1996; Salmon, 2001; Scully *et al.*, 1998; Yeung, 1996). The causality of the association between a sedentary lifestyle and low mental health is much less clear, however, than that of the association between a lack of exercise and low physical health. Moreover, most studies have focused on the "bad" end of the distribution, i.e. psychopathology in non-exercisers rather than on increased levels of psychological well-being in the normal range in regular exercisers.

In this thesis, data on exercise participation of twins and their siblings of the Netherlands Twin Registry (NTR) are analyzed to unravel the etiology of individual differences in exercise participation. Furthermore, the association between exercise behavior and psychological well-being is explored and it is tested whether such an association reflects a causal effect of exercise or the effect of a third "underlying" factor.

## Definition of exercise behavior

Operational definitions of regular exercise in leisure time have differed strongly across studies. Only two very specific phenotypes can be defined in a highly comparable way. Sedentary subjects simply do not engage in any type of leisure time

physical activity, whereas vigorous exercisers perform activities above the intensity and frequency thresholds required to maintain a continued increase in aerobic fitness above their sedentary level. To achieve such an increase, subjects need to engage in large muscle dynamic exercise activities requiring more than 50% of their maximal oxygen consumption at least three times a week for 20 minutes or more per occasion (Blair *et al.*, 1996; Pate *et al.*, 1995).

Measures of light or moderate exercise, i.e. all activity levels in between sedentary and vigorous exercise, are much harder to define. First, a distinction can be made between "pure" exercise activities (jogging, gymnasia, and all solitary or team sports) versus all physical activities which may improve cardiorespiratory health but are not primarily intended that way (gardening, walking the dog, or bicycling to school/work) (Caspersen *et al.*, 1985). Second, there is no agreement about the minimum frequency or the minimum intensity that is required to classify participants as "regular exercisers". Criteria for frequency have varied from once per two weeks (Haase *et al.*, 2004; Steptoe *et al.*, 1997; Steptoe *et al.*, 2002) to five or more times a week (Caspersen *et al.*, 2000). Furthermore, the reported specific exercise activities are in some studies coded for intensity and have to meet a certain minimal intensity (de Geus *et al.*, 2003; Perusse *et al.*, 1989; Stubbe *et al.*, 2005a), whereas in others no specific exercise activities are reported or no minimum intensity is specified (Haase *et al.*, 2004; Steptoe *et al.*, 1997).

The differences in operational definition of regular exercise data are compounded by the varying methods of assessment of regular exercise. Some studies use surveys with only a single yes/no question (Boomsma *et al.*, 1989; Koopmans *et al.*, 1994) whereas others query the type, duration, frequency and intensity in great detail (Martinez-Gonzalez *et al.*, 2001). Other studies use an interview strategy (Caspersen *et al.*, 2000) or direct measurements of energy expenditure with accelerometers, or physiological recordings (Pate *et al.*, 2002; Sirard and Pate, 2001). This makes it difficult to either pool or compare the prevalence of exercise behavior across studies. Therefore, it is important to clearly specify the phenotype that is investigated.

In this thesis, the phenotype exercise participation is a dichotomous variable primarily based on the question: "Do you participate in exercise regularly?", which could be answered with "yes" or "no". To further qualify exercise participation, those answering "yes" were asked what kind of exercise (name of the exercise) they were involved in, and how much time (minutes a week) they spent on these activities

(Appendix I). Ainsworth's Compendium of physical activity was used to recode each exercise activity into METs, representing one MET as the rate of energy expenditure of an individual at rest which is approximately one kcal/kg/h (Ainsworth *et al.*, 1993; Ainsworth *et al.*, 2000).

Participants were classified as exercisers if they answered yes to the question "Do you participate in sports regularly?", if the minimum intensity of the exercise was at least four METs (which excludes bowling, fishing, chess etc.), and if the frequency was at least 60 minutes a week. They were classified as non-exercisers otherwise.

**Exercise data collection in the Netherlands Twin Registry**

Individual differences in exercise participation are investigated using existing and newly collected data from the Netherlands Twin Registry (NTR). Since 1991 every two to three years twins and their families have received a survey sent by mail containing a large number of personality inventories, and items about health, exercise behavior, alcohol consumption and smoking behavior.

**Table 1.1.** *Overview of the collected exercise data.*

| | 1991 | 1993 | 1995 | 1997 | 2000 | 2002 |
|---|---|---|---|---|---|---|
| Participate in exercise regularly | √ | √ | √ | √ | √ | √ |
| Which types of exercise | √ | √ | √ | √ | | √ |
| Competitive versus non-competitive | √ | √ | √ | | √ | |
| Years participated in exercise | √ | √ | √ | | | √ |
| Duration in minutes | √ | √ | √ | | √ | √ |
| Frequency in times per month | √ | √ | √ | | √ | √ |
| At least 20 minutes physically active | √ | √ | √ | √ | √ | √ |
| Sweat index | | √ | √ | √ | √ | √ |
| Cycle regularly | | √ | √ | | √ | √ |
| Minutes per week spent on cycling | | √ | √ | | √ | √ |
| Frequency walking (days per week) | | | | | | √ |
| Duration walking (minutes per day) | | | | | | √ |
| Physical activities in the household | | | | | | √ |
| Occupational or school activities | | | | | | √ |

Primary exercise data were collected in six surveys mailed in 1991, 1993, 1995, 1997, 2000, and 2002. In 1991, 1993 and 1995 twins and their parents were invited to

complete the surveys. Siblings and spouses of twins were additionally recruited into the study in 1995 and 2000, respectively. Table 1.1 gives an overview of the exercise variables that were assessed in the six waves (1991, 1993, 1995, 1997, 2000, and 2002).

**Reliability of the measurement of exercise participation**

To get more insight in the test-retest reliability of our measurement instrument, we used data from a seventh survey. This survey was sent to twins and their family members in November 2004. In June 2005, a shortened version of the seventh survey, which included all exercise items, was sent to a random sample of 240 participants. This sample consisted of twins and siblings in the ages between 30 and 40 years. At this moment, data of the original and shortened version of the seventh survey are available of 186 twins and siblings.

**Table 1.2.** *Overview of the agreement between exercise participation measured in November 2004 (original) and exercise participation measured in June 2005 (shortened).*

| | No (shortened) | Yes (shortened) | Total |
|---|---|---|---|
| No (original) | 50 | 13 | 63 |
| Yes (original) | 10 | 113 | 123 |
| Total | 60 | 126 | 186 |

Table 1.2 shows that there is a large amount of agreement between exercise participation in November 2004 and exercise participation in June 2005. In total, 163 persons did not change their exercise participation; 50 persons did not exercise on both time points, and 113 subjects exercised at both times. To test if this agreement is significant, we used the McNemar test, which uses an adaptation of the chi-square formula to test the direction of change in two dichotomous measures on the same subjects (Munro, 2001). The McNemar test yielded a non-significant p-value of 0.68 indicating that there is no significance change in the percentage of people exercising. We calculated the tetrachoric correlation to investigate whether there is an association between the first and second measurement of exercise participation. The correlations was 0.91 (95% CI = 0.82 – 0.96), indicating high association between measurement one and two.

After selecting the 113 subjects who exercised in November 2004 and June 2005, we investigated whether they still participated in the same exercise activity. A

chi-square test was used to test whether there was a significant association between the two nominal variables (name of the exercise activity). The test yielded a p-value of 0.00 indicating that there is a strong association between the first and second measurement.

We used a Pearson correlation to investigate whether there is an association between the frequencies (i.e. times per week) and whether there is an association between the durations (i.e. minutes per exercise occasion) in the original and retest data set. The Pearson's correlations were 0.78 and 0.69, respectively, again indicating high stability.

In conclusion, the test-retest reliabilities of our exercise questions are high. Even though the time between the two measurements is more than six months, there is a large association between the two exercise variables of the original and shortened version of the seventh survey, indicating that exercise is a stable trait and that the test-retest reliability of the items is high.

**Definition and measurement of psychological well-being**

Subjective well-being (SWB) is defined as the evaluative reaction of a person to his or her life and can be partitioned into the components life satisfaction (cognitive evaluation) and affect (emotional aspects of the construct, such as happiness) (Diener, 1984). Life satisfaction refers to the cognitive component of SWB and can be defined as a global assessment of a person's quality of life according to a person's own subjective judgment (Shin and Johnson, 1978). This means that the degree of life satisfaction is based on a unique set of criteria which each individual sets for himself (Diener *et al.*, 1985). The Satisfaction With Life Scale (SWLS) was used to assess global life satisfaction (Diener, 2005). The five SWLS items are presented in Table 1.3. Participants respond on a scale ranging from one (strongly disagree) to seven (strongly agree).

The scale was translated into Dutch by Arrindell and colleagues (1991). In designing the Dutch version of the SWLS, guidelines proposed in the literature on cross-cultural methodology were followed (e.g. independent blind back-translation and small-scale pretests). Both the original and the Dutch version of the SWLS have demonstrated good psychometric properties, including high internal consistency and reliability, and the scale is suitable for use with different age groups (Arrindell *et al.*, 1991; Diener *et al.*, 1985; Pavot and Diener, 1993). A total score was calculated by

summing the scores of each individual item resulting in a possible range of scores from 5 (low satisfaction) to 35 (high satisfaction). In our sample, Cronbach's alpha was 0.85.

**Table 1.3**. *Overview of the five items of the Satisfaction With Life Scale (SWLS).*

| Satisfaction with life scale |
|---|
| 1. In most ways my life is close to my ideal. |
| 2. The conditions of my life are excellent. |
| 3. I am satisfied with my life. |
| 4. So far I have gotten the important things I want in life. |
| 5. If I could live my life over, I would change almost nothing. |

Happiness was assessed with a Dutch adjusted version of the subjective happiness scale (Lyubomirsky and Lepper, 1999), containing four items on happiness. The four items of this scale are presented in Table 1.4. Participants responded to these question by stating to which extent they disagree or agree, with scores ranging from one (strongly disagree) to seven (strongly agree). A total score for global subjective happiness was computed by summing the responses to the four items (the second and the fourth items were reverse-coded). The possible scores on the subjective happiness scale range from 4 to 28, with higher scores reflecting greater happiness. Reliability in our sample was high (Cronbach's alpha = 0.83).

**Table 1.4.** *Overview of the four items of the happiness scale.*

| Happiness scale |
|---|
| 1. In general, I consider myself a happy person. |
| 2. Compared to most of my peers, I consider myself less happy. |
| 3. In general, I am very happy. I enjoy life regardless of what is going on, getting the most out of everything. |
| 4. In general, I am not very happy. Although I am not depressed, I never seem as happy as I might be. |

**Outline of the thesis**

In this thesis, data on exercise participation and well-being of twins and their siblings of the Netherlands Twin Registry (NTR) are analyzed to unravel the etiology

of individual differences in exercise participation and in well-being and to get more insight in the association between them.

Chapter two reviews evidence from twin and family studies on exercise behavior. We will focus on leisure time exercise behavior, but end by briefly looking at studies targeting physical activity in general.

Chapter three presents an overview of the data collection of the sixth assessment in a longitudinal study on health and life style in twin families registered with the NTR. To get a better understanding of response patterns, four studies were conducted and these studies will be described.

In chapter four, a twin design was used to assess the relative contribution of genetic and environmental influences on the variation in exercise participation of Dutch male and female twins between the ages of 13 and 20 years. Data from survey one to five was used to create a cross-sectional data set. Survey data from 2,628 complete twin pairs were available and the sample was divided into five cohorts: 13 – 14 year old twins, 15 – 16 year old twins, 17 – 18 year old twins, and 19 – 20 year old twins.

Chapter five extends the previous study by assessing the relative contribution of genetic and environmental influences on variation in exercise participation across adult twin samples (aged 19 – 40 years) from seven countries participating in the GenomEUtwin project. Self-reported data on frequency, duration, and intensity of exercise behavior from Australia, Denmark, Finland, Norway, The Netherlands, Sweden and United Kingdom were used to create an index of exercise participation in each country. The total sample consisted of 85,198 subjects.

Chapter six examines the relative contribution of genes and environment to individual differences in life satisfaction in a sample of Dutch twins and their singleton siblings. An extended twin design was used to obtain correlations in life satisfaction scores for monozygotic twins, dizygotic twins and sibling pairs.

Chapter seven investigates the underlying mechanisms of association between exercise participation and life satisfaction as well as happiness. The co-twin control method was used to evaluate whether the association between exercise participation and well-being was causal or non-causal.

In a closing chapter, the main results are summarized and a number of outstanding issues are discussed.

# Chapter 2

# Genetics of exercise behavior

This chapter is based on:
Stubbe JH, and De Geus EJC (accepted). Genetics of exercise behavior. Handbook of Behavior Genetics.

## Introduction

Despite the well-documented benefits of exercise, a large proportion of adults in the Western world does not exercise on a regular basis (Crespo *et al.*, 1996; Haase *et al.*, 2004; Stephens and Craig, 1990). As a consequence, a sedentary lifestyle remains a major threat to health in today's society. To increase the success of intervention on this important health behavior, much research has been devoted to the determinants of exercise behavior. The bulk of these studies has attempted to explain low exercise prevalence in terms of social and environmental barriers. These include, amongst others, poor access to facilities (Matson-Koffman *et al.*, 2005; Varo *et al.*, 2003), low socio-economic status (Haase *et al.*, 2004; Varo *et al.*, 2003), non-Caucasian race (Kaplan *et al.*, 1991), high job strain (Payne *et al.*, 2005; Van Loon *et al.*, 2000), subjective "lack of time" (Shephard, 1985; Sherwood and Jeffery, 2000), inadequate health beliefs (Haase *et al.*, 2004), and low social support by family, peers or colleagues (King *et al.*, 1992; Orleans *et al.*, 2003; Sherwood and Jeffery, 2000). Despite their face validity, none of these factors has emerged as a strong causal determinant of exercise behavior (Dishman *et al.*, 1985; Seefeldt *et al.*, 2002). Increasingly, therefore, biological factors have been invoked to explain why exercisers exercise and why non-exercisers do not (Rowland, 1998; Thorburn and Proietto, 2000; Tou and Wade, 2002). As will become evident in this chapter, these factors should prominently include a genetic disposition to exercise.

Before examining in detail the existing work by behavior genetics in this area, we will briefly review the prevalence of exercise behavior in industrialized societies. Because our angle is a behavioral one we will mainly focus on voluntary exercise behavior, i.e. self-chosen exercise activities performed in leisure time.

## Prevalence of exercise behavior

Due to differences in operational definition of regular exercise data, it is generally difficult to either pool or compare the prevalence of exercise behavior across studies. Fortunately, five very large survey studies on exercise behavior have been performed that used a single instrument across 1) a wide age range in a single country, or 2) across multiple countries. Together these studies provide reasonable insight into the prevalence of exercise in industrialized societies.

The European Health and Behavior Study (EHBS) (Steptoe *et al.*, 1997) and the International Health and Behavior Study (IHBS1/IHBS2) (Haase *et al.*, 2004; Steptoe

*et al.*, 2002) assessed the prevalence of leisure time physical activity in 18 to 30 year old university students. The EHBS survey was carried out in 16,483 students from 21 European countries in 1990 (Steptoe *et al.*, 1997). The IHBS1 and IHBS2 studies of 2000 used the same measures as the EHBS study and partly the same sample. The IHBS1 study (Steptoe *et al.*, 2002) included 10,336 participants from 13 of the 21 European countries included by the EHBS. The IHBS2 study (Haase *et al.*, 2004) extended the sample by using more countries world wide resulting in a final sample of 19,298 university students from 23 countries.

In all three studies, leisure time exercise participation was assessed by responses to three items. The first item asked whether an individual had participated in any exercise (e.g. sports activities, physically active pastime) over the past two weeks. Those who responded positively were asked what kind of activity they carried out. The most reported forms of activity were jogging/running, swimming, football (soccer), and aerobics. Furthermore, participants were asked how many times they had exercised in the past two weeks. Data were analyzed by dividing the sample into three groups. Inactive subjects (i.e. sedentary subjects) did not engage in any exercise at all; subjects who engaged one to four times per two weeks in exercise were considered regular exercisers at "low frequent activity"; subjects who exercised more than five times per two weeks were considered "frequent" exercisers (corresponding to vigorous exercise as defined in the previous paragraph).

In the 1990 study, 73% of men and 68% of women exercised at least once over the past two weeks, suggesting that 27% of male and 32% of female students are sedentary. A total of 36% of men and 30% of women were frequent exercisers, i.e. had exercised on five or more occasions during the previous two weeks (Steptoe *et al.*, 1997). In the EHBS study (Steptoe *et al.*, 2002), the survey was repeated 10 years later for 13 of the 21 countries (IHBS1). Figure 2.1 shows that the prevalence of regular exercise remained fairly stable over a 10 year time period. Extending the sample with students from countries world wide (IHBS2) again resulted in comparable prevalences (Haase *et al.*, 2004).

All three studies showed that men were more likely than women to have exercised in the previous two weeks. In the third and largest study, for instance, more women than men reported to be sedentary (38% versus 27%), whereas the proportion engaged in high frequent activity was larger in men (28%) than in women (19%).

There was no overall difference in the proportion of men (45%) and women (43%) active at a low frequency (active one to four times per two weeks).

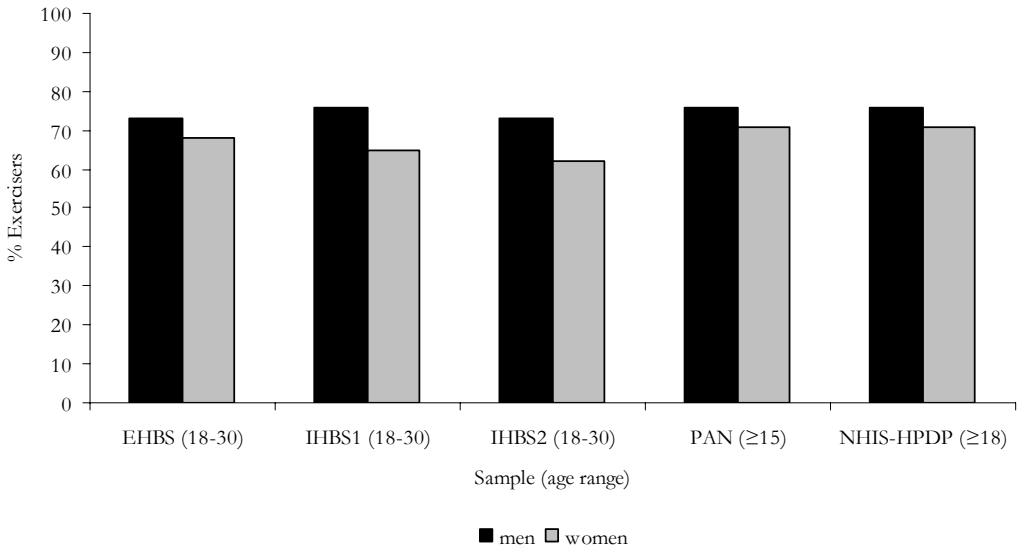


**Figure 2.1.** *Prevalence of regular exercise in five different studies, the Health and Behavior Study (EHBS, IHBS1, and IHBS2), the pan-European study of adults from 15 member states of the European Union (PAN), and the National Health Interview Survey-Health Promotion/Disease Prevention (NHIS-HPDP).*

The samples used in the EHBS and IHBS studies may not be representative for the whole population, because it was conducted in students 18 – 30 years old. A pan-European study of adult exercise participation by Martinez-Gonzalez and colleagues (2001) used a population-based sample of more than 15,000 adults from 15 member states of the European Union, aged 15 and upward. To assess activity levels, subjects were asked to select the activities in which they participated from a list of 17 activities (i.e. athletics, cycling, dancing, equestrian sports, fishing, football, gardening, golf, hill-walking, climbing, keep fit, aerobic, jogging, martial arts, racquet sports, rowing, canoeing, skiing, skating, swimming, team sports, walking, and water sports). Participants expressed the number of hours a week they participated in each activity. On average, 76% of male and 71% of female EU population participated in some kind of exercise activity, although a wide variability in the prevalence of activity among European countries was found. Northern European countries showed higher exercise prevalences than southern ones. Figure 2.1 shows that, across all countries, the overall

percentage of exercisers is in close agreement with the estimates of prevalence by the EHBS and IHBS studies (Haase *et al*., 2004; Steptoe *et al*., 1997; Steptoe *et al*., 2002). As in the EHBS and IHBS studies, a higher percentage of men engaged in any leisure time exercise activities, and the average intensity of their activities (in METs) was higher than in women.

In the 1991 National Health Interview Survey-Health Promotion/Disease Prevention (NHIS-HPDP) study, physical activity levels were assessed in 43,732 men and women aged 18 year and older from the USA (Caspersen *et al*., 2000). Frequency and duration was assessed of gardening and exercise activities (i.e. walking for exercise, stretching exercises, weightlifting, jogging, aerobics, bicycling, stair climbing for exercise, swimming for exercise, play tennis, golf, baseball, basketball, volleyball, handball, soccer, football, racquetball or squash, bowling, and skiing (downhill, cross-country, and water). To get information about the intensity level, questions were asked about increases in breathing or heart rate. According to the Healthy people 2000 objectives (US Department of Health and Human Services, 2005) exercise behavior among participants was categorized into three activity patterns: physically inactive (i.e. no participation in any leisure time physical activity), engaging in regular, sustained light to moderate activities (five or more times a week and 30 minutes or more per occasion of any activity), and engaging in regular, vigorous activities (three or more times per week and 20 minutes or more per occasion of any activity performed at ≥ 50% of maximal oxygen consumption. Adult women (27%) had a significant higher prevalence of inactivity than men (21%). Men reported more often regular, sustained activities than did women (27% versus 21%). The prevalence of regular, vigorous activity was marked by an almost U-shaped relationship with age.

A clear picture arises from these five studies. Despite the well-documented benefits of exercise, a large group of people does not engage in exercise on a regular basis. World wide the prevalence for sedentary people varies between 21% and 27% for males and between 27% and 38% for females. Prevalence for low frequent activities ranges between 27% and 45% for males and between 38% and 43% for females. Finally, between 28% and 36% of males are engaged in high frequent activities and this percentage varies between 19% and 30% for females.

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 behavioral genetic studies for a substantial genetic contribution to voluntary exercise behavior.

**Familial studies on exercise behavior**

Familial resemblance in exercise behavior is explained by a combination of shared genetic variation by family members and their shared environmental influences (i.e. family, neighborhood, culture). Its presence can be tested in parent-child, sister-sister, brother-brother, and sister-brother correlations, but the extent to which the correlations reflect shared genes or shared environment cannot be resolved in family studies. The resemblance between spouses can derive from shared environments and/or phenotypic assortment. Significant familial resemblance in exercise behavior between parents and their offspring has been reported in various studies. Parent-offspring correlations have ranged from low ($r$ = 0.09 – 0.13) for participation defined as activities requiring at least five times the resting metabolic rate (Perusse *et al.*, 1989) or weekly time spent on the main exercise activity during the previous year (Simonen *et al.*, 2002) to moderate ($r$ = 0.29 – 0.37) for exercise participation defined as a dichotomous variable using the single question "Do you participate in sports?"(Koopmans *et al.*, 1994).

In the Canadian Fitness Survey (Perusse *et al.*, 1988a), the degree of familial resemblance for leisure time energy expenditure, total time spent on leisure time activities and the activity level (derived from total time spent on leisure time activities and total number of months for the reported activities) was assessed in 16,477 subjects, aged 10 years and older. Spouses, siblings and parent-offspring pairs were formed to compute familial correlations in energy expenditure, time spent on activities and activity level. These correlations ranged between 0.12 and 0.62 for the three variables, suggesting evidence for familial resemblance. However, familial correlations were higher within generations (spouses and siblings) than across generations (parent-offspring) and the correlations within generations were similar for spouses and for siblings. This suggests that familial resemblance resulted primarily from environmental factors common to members of the same generation.

In conclusion, there is evidence for familial resemblance in exercise behavior, but the estimates of the magnitude of this resemblance show large fluctuation across studies.

**Twin studies on exercise behavior**

Twin studies can, as opposed to nuclear family designs, discriminate between genetic and environmental influences within and between families by comparing the resemblance in exercise behavior between monozygotic (MZ) and dizygotic (DZ) twins. MZ twins are genetically identical, whereas DZ twins share on average only half of their segregating genes. Therefore, greater resemblance among MZ twins makes a strong case for the contribution of genetic factors to individual differences in exercise behavior. In the basic genetic model, the total variance ($V_{tot}$) in exercise behavior is partitioned into genetic ($V_g$), shared environmental ($V_c$) and unique environmental ($V_e$) variation components ($V_{tot} = V_g + V_c + V_e$). Heritability refers to the proportion of the total variation that can be attributed to genetic effects ($V_g/V_{tot}$).

A variety of twin studies have shown that genetic factors contribute to individual differences in exercise participation and quantity (i.e. frequency, duration and/or intensity (Beunen and Thomis, 1999; Boomsma *et al.*, 1989; De Geus *et al.*, 2003; Frederiksen and Christensen, 2003; Heller *et al.*, 1988; Koopmans *et al.*, 1994; Lauderdale *et al.*, 1997; Maia *et al.*, 2002; Perusse *et al.*, 1989). The main results of these studies are summarized in Table 2.1. Studies were included only if estimates of additive ($a^2$) or non-additive ($d^2$) genetic contribution or shared environmental ($c^2$) contribution to total variance were given in the paper or if the correlations of MZ and DZ twins were supplied. The latter makes it possible to calculate the contribution of additive ($a^2 = 2(r_{MZ} - r_{DZ})$ or non-additive ($d^2 = 4r_{DZ} - r_{MZ}$) genetic factors or of shared environmental ($c^2 = 2r_{DZ} - r_{MZ}$) factors (Plomin *et al.*, 2000). Table 2.1 shows these various estimates to range widely across studies. The large range in these estimates may be caused in part by the use of various definitions of exercise and the different age ranges studied.

Two twin studies have focused on heritability estimates in young adolescents. In a large family cohort based on the Quebec family study, a three-day activity record was used to determine the activity level of young adolescent twins (mean age 14.6) (Perusse *et al.*, 1989). Each day was divided into 96 periods of 15 minutes, and for each 15-minute period subjects were asked to note, on a scale from one to nine, the energy expenditure of the dominant physical activity of that period. Regular exercise behavior was assessed from the number of periods in which exercise activities or moderate to intense manual work (i.e. tree cutting, snow shoveling etc.) were reported that were rated six or higher on the nine-point scale (i.e. activities requiring 4.8 times

the resting oxygen consumption). The average value of the ratings across these periods was used as the measure of regular exercise. Monozygotic and dizygotic twin correlations did not differ significantly from each other, indicating that genetic factors did not explain any variation in regular exercise behavior. Individual differences in regular exercise were attributed to common environmental (74%) and unique environmental factors (26%).

In the Leuven Longitudinal Twin Study (Beunen and Thomis, 1999), 92 Flemish male twin pairs and 91 female twin pairs aged 15 years reported the number of hours they exercised each week. For girls, 44% of the variation in exercise participation was explained by genetic factors and 54% by common environmental factors. For boys, genetic factors already explained about 83% of the total variance at age 15.

Studies collapsing twin data across the entire period of adolescence found heritability estimates between the low estimates of the Quebec family study and the high estimates of the Leuven Longitudinal Twin Study. In agreement with Beunen and Thomis (1999), a study based on 411 Portuguese twins aged 12 to 25 years (mean age was approximately 17 years) found larger heritability estimates for males (68%) compared to females (40%). The phenotype was based on an exercise participation index, which is a composite score of items that take into account the expected energy expenditure for a given exercise activity, number of hours practiced per week, and number of months per year (Maia *et al.*, 2002).

A Dutch twin study estimated the genetic and environmental influences on individual differences in exercise participation coded as a dichotomous variable (Koopmans *et al.*, 1994). Exercise participation was defined by the response to the single question "Have you been involved in exercise activities during the last three months?". Based upon a sample of 13 to 22 year old Dutch twins (mean age of 18 years), Koopmans and colleagues (1994) estimated heritability and common environmental influences to be 48% and 38%, respectively.

**Table 2.1.** *Twin studies on exercise participation.*

| Study | Sample | Phenotype | Results |
|---|---|---|---|
| Stubbe *et al.* (submitted a)[1] | 13,676 MZ and 23,375 DZ pairs from seven different countries participating in the GenomEUtwin project (aged 19 – 40) | Engage in leisure time exercise activities with a minimal intensity of four METs for at least 60 minutes per week (yes/no) | $a^2$ = 27% – 67%; $c^2$ = 0% – 37% for males<br>$a^2$ = 48% – 71%; $c^2$ = 0% for females |
| Stubbe *et al.* (2005a)[1] | 2,628 complete Dutch twin pairs (aged 13 – 20) | Engage in leisure time exercise activities with a minimal intensity of four METs for at least 60 minutes per week (yes/no) | $a^2$ = 0%; $c^2$ = 84% for 13 – 14 year old twins<br>$a^2$ = 0%; $c^2$ = 78% for 15 – 16 year old twins<br>$a^2$ = 36%; $c^2$ = 47% for 17 – 18 year old twins<br>$a^2$ = 85%; $c^2$ = 0% for 19 – 20 year old twins |
| Beunen *et al.* (2003)[1] | 92 male and 91 female Belgium twin pairs (aged 15) | Number of hours spent on sports each week | $a^2$ = 83%; $c^2$ = 0% for males<br>$a^2$ = 44%; $c^2$ = 54% for females |
| De Geus *et al.* (2003)[1] | 157 adolescent (aged 13 – 22) and 208 middle-aged Dutch twin pairs (aged 35 – 62) | Average weekly METs spent on sports or other vigorous activities in leisure time in the last three months (≥ four METS) | $a^2$ = 79%; $c^2$ = 0% for adolescent twins<br>$a^2$ = 41%; $c^2$ = 0% for middle-aged twins |
| Frederiksen *et al.* (2003)[1] | 616 MZ and 642 same-sex DZ twin pairs (aged 45 – 68) | Engage in leisure time in any of 11 different exercise activities (yes/no) | $a^2$ = 49%; $c^2$ = 0% for males and females |
| Maia *et al.* (2002)[1] | 411 Portuguese twin pairs (aged 12 – 25) | A composite sports participation index (SPI) that takes into account the energy expenditure for a given sport, number of hours practiced per week and number of months per year | $a^2$ = 68%; $c^2$ = 20% for males<br>$a^2$ = 40%; $c^2$ = 26% for females |

[1]*Heritability was estimated using variance component methods*
[2]*Heritability was estimated using formulas to calculated the percentage by hand*

**Table 2.1.** *Twin studies on exercise participation (continued).*

| Study | Sample | Phenotype | Results |
|---|---|---|---|
| Lauderdale *et al.* (1996)[2] | 3,344 male twin pairs of the Vietnam Era Twin Registry (aged 33 – 51) | Five questions assessed regular participation in specific, intense athletic activities (running, bicycling, swimming, racquet, and other sports) (yes/no) | $a^2$ = 0%; $d^2$ = 53% for jogging<br>$a^2$ = 48%; $c^2$ = 4% for racquet sports<br>$a^2$ = 30%; $c^2$ = 17% for strenuous sports<br>$a^2$ = 0%; $d^2$ = 58% for bicycling<br>$a^2$ = 8%; $c^2$ = 31% for swimming |
| Koopmans *et al.* (1994)[1] | 1,587 adolescent Dutch twin pairs (aged 13 – 22) | Do you participate in leisure time exercise? (yes/no) | $a^2$ = 48%; $c^2$ = 38% for males and females |
| Boomsma *et al.* (1989)[1] | 44 MZ and 46 DZ Dutch adolescent twin pairs (aged 14 – 20) | Do you participate in leisure time exercise? (yes/no) | $a^2$ = 64% |
| Heller *et al.* (1988)[2] | 200 twin pairs (aged 17 – 66) | Engaged in vigorous exercise in the past two weeks (yes/no) | $a^2$ = 39% |
| Perusse *et al.* (1989)[2] | 55 monozygotic and 56 dizygotic Canadian twin pairs (aged 15) | A three day activity record was used to determine the activity level of the subjects. The number of periods corresponding to activities with an intensity of ≥ 4.8 METs was counted each day and the average value was used as an indicator of exercise participation | $a^2$ = 0%; $c^2$ = 78% for males and females |

[1]*Heritability was estimated using variance component methods*
[2]*Heritability was estimated using formulas to calculated the percentage by hand*

To our knowledge, three studies have investigated the influences of genes and environment on exercise behavior in adults (Frederiksen and Christensen, 2003; Heller *et al.*, 1988; Lauderdale *et al.*, 1997). An Australian study of 200 twin pairs assessed genetic influences on several lifestyle risk factors, including a single exercise question, "vigorous exercise in the past two weeks" (Heller *et al.*, 1988). Ages ranged from 17 to 66 years with the mean ages of MZ and DZ twins being 36.9 (SD = 13.2) and 35.6 (SD = 11.5) years, respectively. Heritability was estimated at 39% for this question. In 3,344 male twin pairs aged 33 – 51 years from the Vietnam Era Twin Registry (Lauderdale *et al.*, 1997), regular exercise was assessed with five questions about vigorous forms of exercise (> 4.5 METs) performed in the last three months: 1) jog or run at least 10 miles per week, 2) play strenuous racquet sports at least five hours per week, 3) play other strenuous sports (basketball, soccer etc.), 4) ride a bicycle at least 50 miles per week, 5) swim at least two miles per week. For all of the measures, MZ correlations were higher than DZ correlations, which suggests that genes play a role in explaining individual differences in regular exercise. For running or jogging, racquet sports, and bicycling, broad sense heritability was estimated between 48% and 58%.
For bicycling and jogging, MZ correlations exceeded the DZ correlations by more than a factor of two, making this the only study to report significant non-additive effects.

Frederiksen and Christensen (2003) were the only ones to report the influence of genetic factors on exercise participation in a group of middle-aged to elderly twins. Information on leisure time exercise participation of people aged 45 – 68 years was assessed through the questions: "Do you in your leisure time participate in any of the following sports: jogging, gymnastics, swimming, tennis, badminton, football, handball, aerobics, rowing, table tennis, or volleyball?". The exercisers were defined as those indicating participation in any of these activities, whereas the sedentary participants did not report any participation. Genes explained 49% of the variance in exercise participation.

In conclusion, in support of a genetic influence on adult exercise participation, twin studies have unanimously shown larger within pair resemblance in identical than in dizygotic twins (Beunen and Thomis, 1999; Boomsma *et al.*, 1989; De Geus *et al.*, 2003; Frederiksen and Christensen, 2003; Heller *et al.*, 1988; Koopmans *et al.*, 1994; Lauderdale *et al.*, 1997; Maia *et al.*, 2002; Perusse *et al.*, 1989). At young adulthood,

heritability of exercise behavior peaks at 85% and then drops to about 50% in middle adulthood at which level it remains into old age.

**Twin studies on physical activity**

Since the innate drive to exercise will be most obvious in leisure time we have focused above on voluntary leisure time exercise behavior. A number of twin studies have quantified regular total physical activity rather than leisure time exercise behavior. Since a large part of regular physical activity can effectively be attributed to voluntary exercise activities in leisure time we briefly review these studies here.

More caution is needed in the interpretation of these studies, because the heterogeneity in the definition of regular physical activity is even larger than that in the definition of regular exercise. Table 2.2 summarizes the relevant twin studies, again including only those where heritability and 'environmentability' estimates or correlations of MZ and DZ twins were given in the paper. Common environmental influences were again almost completely restricted to children and young adolescents. In adults, reported heritability estimates vary between 46% and 56%. In spite of the larger heterogeneity in the phenotype, Table 2.2 confirms the overall finding that genetic factors contribute significantly to individual differences in physical activity of adults.

**Conclusion**

Twin studies on exercise participation and physical activity have shown that these traits are moderately heritable. However, fairly large fluctuations in heritability estimates between twin studies exist. These may be due to the small sample size of some of the studies or the vastly different definitions of exercise participation. They may alternatively reflect a change in genetic architecture with age, or true differences in the heritability of exercise. These topics are addressed in the next three chapters.

Data from the Netherlands Twin Registry (NTR) were used to test the effects of age, particularly in the range from adolescence to young adulthood where the largest discrepancies in heritability estimates were found. Furthermore, exercise data from Dutch twins is merged to the exercise data in twin samples from six different countries participating in the GenomEUtwin project to test for true differences in the genetic architecture of exercise participation.

**Table 2.2.** *Twin studies on physical activity level (PA).*

| Study | Sample | Phenotype | Results |
|---|---|---|---|
| Franks *et al.* (2005)[1] | 100 same-sex dizygotic (n = 38) and monozygotic (n = 62) twin pairs (aged 4 – 10) | 1) Physical activity energy expenditure (PAEE) | $a^2$ = 0%; $c^2$ = 69% for PAEE |
| | | 2) Total energy expenditure (TEE) labeled water | $a^2$ = 19%; $c^2$ = 59% for TEE |
| Kujala *et al.* (2002)[2] | Data on both members of 1,772 MZ and 3,551 dizygotic same-sex twin pairs (aged 24 – 60) | Participation in vigorous physical activity based on the question: "is your physical activity during leisure time about as strenuous, on average, as: 1) walking, 2) alternatively walking and jogging, 3) jogging (light running), or 4) running?". Those who chose alternative 2, 3, or 4 were classified as participating in vigorous activity. | $a^2$ = 56%; $c^2$ = 4% for vigorous activity |
| | | Assessment of leisure activity volume was based on a series of structured questions on leisure PA (frequency, duration, and intensity of PA sessions) and PA during journey to and from work. The activity MET index was expressed as the summary score of leisure MET-hours per day. Subjects whose volume of activity was ≥ 2 MET-hours per day were classified as physically activate at leisure. | $a^2$= 46%; $c^2$ = 0% for leisure activity |

[1]*Heritability was estimated using variance component methods*
[2]*Heritability was estimated using formulas to calculated the percentage by hand*

**Table 2.2.** *Twin studies on physical activity level (PA) (continued).*

| Study | Sample | Phenotype | Results |
|---|---|---|---|
| Maia *et al.* (2002)[1] | 411 Portuguese twin pairs (aged 12 – 25) | Leisure time PA is a composite score based on the following four items:<br>- hours watching tv<br>- frequency of walking in leisure time<br>- minutes spent walking per day<br>- frequency of cycling | $a^2$ = 63%; $c^2$ = 0% for males<br>$a^2$ = 32%; $c^2$ = 38% for females |
| Aarnio *et al.* (1997)[2] | 3,254 twins at age 16, their parents and grandparents | Five activity physical activity classes were made ranging from very active to hardly active based on two questions about the:<br>- frequency of leisure time PA<br>- intensity of leisure time PA | $a^2$ = 54%; $c^2$ = 18% for males<br>$a^2$ = 46%; $c^2$ = 18% for females |
| Perusse *et al.* (1989)[1] | 55 monozygotic and 56 dizygotic Canadian twin pairs (aged 15) | A three day activity record was used to determine the activity level of the subjects. The mean sum of the three days was used as an indicator of the level of habitual PA | $a^2$ = 20%; $c^2$ = 52% |
| Kaprio *et al.* (1981)[2] | 1,537 MZ and 3507 DZ male twin pairs (aged ≥18 years) | Leisure time PA was based on the<br>- PA on work journey<br>- subjective opinion of own PA<br>- intensity, duration and activity score<br>- years of physical training in adulthood<br>A factor analysis was carried out to yield a condensed score | $a^2$ = 46%; $d^2$ = 11% (age adjusted) |

[1]*Heritability was estimated using variance component methods*
[2]*Heritability was estimated using formulas to calculated the percentage by hand*

# Chapter 3

## Data collection and participants

## Introduction

In this chapter, we will present an overview of the data collection of the sixth survey in a longitudinal study on health and life style in twin families registered with the Netherlands Twin Registry (NTR). We will first describe the existing data of the previous surveys in 1991, 1993, 1995, 1997, and 2000. Next the sixth survey is described as well as specific data collected by telephone interviews in 2002 and 2003 for the purpose of a non-response study. Finally, we will estimate the true response rate of the 2002-survey based on the results of the non-response studies.

## Longitudinal data on health and lifestyle

Since 1991 every two to three years (young) adult twins and their families have received a survey sent by mail containing a number of personality inventories, and items about health, regular exercise, smoking behavior and alcohol consumption. Adolescent twins and their families were recruited in 1991 by contacting City Councils in The Netherlands for addresses of twins aged 13 – 22 years old. Later, additional twins were contacted via City Councils, as well as by advertisements in the media and in the information bulletin of the Netherlands Twin Registry (NTR) and through the Dutch Twin Club (Boomsma *et al.*, 2002b). Data were collected in 1991, 1993, 1995, 1997, and 2000. In 1991, 1993 and 1995 twins and their parents were invited to complete surveys. Siblings and spouses of twins were recruited into the study in 1995 and 2000, respectively.

New data collection for the sixth survey started in 2002 and continued until 2003. For the first time spouses, siblings, and parents were included in addition to the twins. In October 2002, twins and their family members received the sixth survey together with extensive information by letter and an introductory brochure informing them of the study outline, its purpose and the procedures. Table 3.1 lists the total number of twins, siblings, parents and spouses participating in the six waves of the survey.

Most individuals participated more than once, which is shown in Table 3.2. Not all individuals are registered since the beginning of the study, and therefore have not had the opportunity to reach the maximum number of participations (six times for twins, four times for parents and siblings and two times for spouses).

**Table 3.1.** *Cross-sectional participation.*

| | 1991 | 1993 | 1995 | 1997 | 2000 | 2002 |
|---|---|---|---|---|---|---|
| Father | 1,439 | 1,774 | 1,572 | - | - | 1,266 |
| Mother | 1,607 | 1,920 | 1,688 | - | - | 1,529 |
| Male twin | 1,543 | 1,882 | 1,509 | 1,247 | 1,522 | 1,446 |
| Female twin | 1,843 | 2,343 | 1,904 | 1,984 | 3,088 | 3,077 |
| Brother | - | - | 734 | 673 | 592 | 579 |
| Sister | - | - | 747 | 847 | 881 | 875 |
| Male spouse | - | - | - | - | 442 | 1,000 |
| Female spouse | - | - | - | - | 265 | 520 |
| Sex missing | - | - | - | 1 | 2 | 7 |
| Total | 6,432 | 7,919 | 8,154 | 4,752 | 6,792 | 10,299 |

In March 2003, non-respondents received a letter to remind them that they yet did not complete the sixth survey. The letter was accompanied by the survey booklet and a reply card. On the reply card participants could mark if they needed extra information or help with completing the survey, or if they were not willing to participate. Twins and family members who registered after March 2003 received an invitation to complete the survey immediately after registration. A copy of the two letters (October 2002 and March 2003), the brochure, and the reply card is included in the appendices (see appendix II to VI).

**Table 3.2.** *Longitudinal participation.*

| | Twin ♂ | Twin ♀ | Father | Mother | Brother | Sister | Spouse ♂ | Spouse ♀ | Total |
|---|---|---|---|---|---|---|---|---|---|
| 1x | 1,193 | 1,607 | 927 | 1,070 | 507 | 507 | 1,004 | 563 | 7,425 |
| 2x | 833 | 1,363 | 654 | 683 | 380 | 462 | 219 | 111 | 4,705 |
| 3x | 637 | 839 | 737 | 808 | 252 | 365 | - | - | 3,638 |
| 4x | 448 | 683 | 402 | 471 | 127 | 205 | - | - | 2,336 |
| 5x | 317 | 581 | - | - | - | - | - | - | 898 |
| 6x | 167 | 292 | - | - | - | - | - | - | 459 |
| Total | 3,595 | 5,365 | 2,720 | 3,032 | 1,313 | 1,539 | 1,223 | 674 | 19,461 |

The sixth survey was sent to 14,162 twins/triplets, 3,606 siblings, and 11,449 parents from 7,363 families. There were 3,432 families in which at least one family member returned the survey. A total of 4,523 twins (response rate = 32%), 1,454

siblings (response rate = 40%), and 2,795 parents (response rate = 24%) returned and completed a survey. In conclusion, of the 29,217 surveys sent to twins, siblings and parents, 8,772 surveys were completed and returned. All twins received a survey for their spouse. Of the 4,523 twins who returned and completed a survey, 3,163 reported to have a spouse and 1,527 spouses completed and returned a survey (spousal response rate = 48%).

**Non-response survey data collected in 2002 and 2003**

Although the response rate of survey six corresponds with the response rates of some of the earlier surveys (Boomsma *et al.*, 2000; Vink *et al.*, 2004), the number of people not returning a survey is rather high. Four separate studies were conducted to determine the reasons why a survey was not returned (e.g. did we send the survey to the correct address; is the subject still alive etc.). Table 3.3 gives an overview of the four non-response studies.

**Table 3.3.** *Overview of the four non-response studies.*

| Date | Non-response survey |
|---|---|
| March 2002 | non-response I: selection of 200 persons who never participated in a longitudinal survey (wave 1 to 5) |
| May 2003 | non-response II: based on reply cards, telephone calls, and e-mails (N = 4,371) |
| June 2003 | non-response III: selection of 400 persons not responding to survey 6 |
| September 2003 | non-response IV: selection of 1,513 non-responding twins whose family member(s) did complete the sixth survey |

First, before sending the sixth survey, 200 persons who never participated in one of the previous surveys (1991, 1993, 1995, 1997, or 2000) were selected at random and contacted by telephone. They were asked if they still wanted to participate in the study, and if not what their main reason was for their refusal.

The results are presented in Table 3.4 and provide insight in the traceability and the number of surveys returned by correctly traced persons. With regard to the traceability, of the 200 persons who never participated in the longitudinal survey study, addresses were correct for 85 persons (43%), incorrect for 64 persons (32%), and for 51 persons it was unclear if the address was correct (26%).

Fifty-one persons with correct addresses were not willing to participate anymore. Twenty-five participants with a correct address agreed to complete the sixth survey. Of these 25 persons, however, only two participants actually completed and returned the survey. After tracing the correct addresses, 23 subjects responded that they were willing to participate. Of these 23 persons, four participants completed and returned the sixth survey.

In March 2003, subjects not returning survey six, received a reminder accompanied by the booklet and a reply card. Twins and family members who registered after March 2003 received the survey, the reply card, and an invitation to complete the survey immediately after registration.

**Table 3.4.** *Results non-response study I. Selection of 200 persons who never participated in the longitudinal survey (wave 1 to 5).*

| Results | N | |
|---|---|---|
| address is correct | 85 | |
| 1. not willing to participate | | 51 |
| 2. person deceased | | 1 |
| 3. unable to participate (does not speak Dutch) | | 1 |
| 4. willing to participate | | 25 |
| 5. unclear if person wants to participate | | 7 |
| | | |
| address is incorrect: | 64 | |
| 1. new address not traced | | 23 |
| 2. new address traced | | |
| - person willing to participate | | 23 |
| - unclear if person is willing to participate | | 6 |
| - person not willing to participate | | 12 |
| | | |
| unclear if address is correct (no/incorrect phone number) | 51 | |
| Total | 200 | |

4,371 persons gave a reason for not participating by sending back the reply card, by calling or by writing an e-mail, and if the address was incorrect, we received the mail "returned to sender". Table 3.5 gives an overview of the reasons for non-

participation. Not willing to participate in this survey and an incorrect address were the two main reasons for not completing and returning the survey.

**Table 3.5.** *Results non-response study II (N = 4,371).*

| Results | N |
|---|---|
| Address not correct ('returned to sender') | 1,011 |
| Not willing to participate in survey six | 3,075 |
| Deceased | 107 |
| Not able to participate (illness/handicap) | 25 |
| Lives temporary in a foreign country | 14 |
| To young to participate | 12 |
| Double registration | 127 |
| Total | 4,371 |

**Table 3.6.** *Results non-response study III (N = 400).*

| Results | N | |
|---|---|---|
| 1. willing to participate | 161 | |
| 2. answered exercise questions by telephone | 45 | |
| 3. not willing to participate | 57 | |
| - not interested/motivated | | 47 |
| - not able to participate | | 10 |
| 4. unclear if person is willing to participate | 132 | |
| - no telephone number | | 65 |
| - address is incorrect | | 67 |
| 5. deceased | 5 | |
| Total | 400 | |

A total of 16,947 persons did not respond at all to the first and/or second sending of the survey. Of this group of non-respondents, a sample of 400 persons (200 twins, 38 siblings, and 162 parents) taken at random was selected to be contacted by telephone to get insight in the traceability and the number of surveys yielded after tracing persons. Table 3.5 gives an overview of the results. In total, of the 400 addresses and phone numbers selected, 118 were correct (30%), 217 were incorrect

(54%), and of 65 persons it was unclear if the address was correct (16%). After tracing the correct address, 161 persons said they were willing to participate, of whom 52 (32.3%) filled in the questionnaire. In 33% of the cases, we did not succeed in contacting the person.

The fourth non-response undertaking aimed at getting a larger sample of monozygotic and dizygotic male and female twins. Twins were selected whose co-twin, father or mother already completed and returned the survey. The parental addresses and the addresses of the co-twin were used as a proxy. A total of 1,513 participants were selected to be contacted by phone to gain, again, more insight into the traceability and the number of surveys yielded after tracing people.

**Table 3.7.** *Results non-response study IV (N = 1,513).*

| Result | N | |
|---|---|---|
| Address correct | 795 | |
| Address incorrect: | 623 | |
| - address traced | | 595 |
| - new address not (yet) traced | | 28 |
| Unknown if address is correct | 95 | |
| Total | 1,513 | |

Table 3.7 shows the results and is in agreement with the previous non-response surveys, indicating that a large percentage of addresses were incorrect (41.3%). Of the 795 persons with correct addresses, 109 completed a questionnaire (13.7%). Of the 595 persons with incorrect addresses, but whose addresses were traced, 214 completed a questionnaire (36.0%).

**Conclusion**

Of the 29,217 twins, siblings and parents to whom survey six was sent, 8,772 participants (excluding spouses) completed and returned a survey and 20,445 persons did not participate. Taking a closer look at the outcome of our non-response studies, we try to estimate the true response. Based on study I, III and IV, the traceability can be calculated as an estimation of the percentages of correct, incorrect and unknown addresses. Table 3.8 gives an overview of the percentages per study.

Taking the mean percentages of correct (42%), incorrect (42%) and unknown (16%) addresses based on the three non-response surveys, the number of people actually receiving survey six can be estimated. Of the 29,217 addresses to which survey six was sent, 12,271 (42%) addresses were correct and 12,271 addresses were incorrect (42%). It is unknown if the remaining 4,675 addresses (16%) are correct or incorrect.

**Table 3.8.** *Overview of the number correct, incorrect and unknown addresses based on the non-response studies I, III, and IV.*

| | N | N correct (%) addresses | N incorrect (%) addresses | N unknown (%) addresses |
|---|---|---|---|---|
| Study I | 200 | 85 (43%) | 64 (32%) | 51 (26%) |
| Study III | 400 | 118 (30%) | 217 (54%) | 65 (16%) |
| Study IV | 1,513 | 795 (53%) | 623 (41%) | 95 ( 6%) |

In 2004, an additional method was used to get insight into the percentage incorrect addresses in our current database. Our database was merged to an up-to-date national address database. A total of 20,251 addresses of the NTR were checked. Valid results were obtained on 19,056 addresses. Comparison to these addresses indicated that around 38% of the addresses in our database were incorrect. This is in agreement with the 42% estimated by our non-response studies.

There are two ways of calculating the estimated response rate. If we take the 12,271 correct addresses, and divide it by the 8,772 persons returning the survey, the overall response rate of the sixth survey is 71%. However, it might be that the 4,675 "unknown" addresses are correct, resulting in a total number of 16,946, indicating that the overall response rate of the sixth questionnaire is 52%. In conclusion, when taking into account the percentage incorrect address, the actual response rate probably ranges from 52% to 71%.

**Increasing the response rate by tracing the correct address**

We examined the gain from our non-response studies by looking at the extra number of surveys completed and returned after tracing the correct address. Of the 41 addresses traced in non-response study I, 23 persons were willing to participate of whom four really completed and returned the survey. Hence, the gain in response to this survey was 10%. In non-response study III, 161 participants were willing to complete and return the survey, but at the end of the data collection 52 (32%) really

filled in the questionnaire. In non-response study IV, 595 addresses were incorrect. After tracing the correct addresses and sending the survey to this new address, 36% (N = 214) completed and returned the booklet.

In conclusion, the gain of tracing addresses, which is very time-consuming, ranges between 10% and 36%.

**Are exercisers and persons with high well-being more difficult to trace?**

A question specific to this thesis was whether exercisers more often have an incorrect address than non-exercisers (or the reverse). This would lead to bias in the estimation of exercise prevalence and heritability estimation. Of the 270 persons who filled in the questionnaire after tracing the correct address, 51% engaged in regular exercise. This is highly comparable to the percentage exercisers calculated in the early respondents whose addresses were correct in our database (46%). These results indicate that there is no bias, i.e. incorrect addresses do not occur more often among exercisers than among non-exercisers.

Furthermore, incorrect addresses do not occur more often among persons with high well-being than among persons with low well-being. The 270 persons who filled in the questionnaire after tracing the correct address, had an average score on life satisfaction and happiness of 26.87 and 22.65, respectively. This is highly comparable to the average score of the early respondents whose addresses were correct in our database (mean life satisfaction = 26.60; mean happiness = 22.42), suggesting that there is no bias.

# Chapter 4

# Exercise participation during adolescence: A shift from environmental to genetic factors

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**Abstract**

A twin design was used to assess the relative contribution of genetic and environmental influences on the variation in exercise participation of Dutch male and female twins between the ages of 13 and 20 years. Survey data from 2,628 complete twin pairs were available (443 male and 652 female monozygotic twin pairs, 377 male and 434 female dizygotic twin pairs, and 722 opposite-sex twin pairs). Subjects were classified as exercisers if they engaged in competitive or non-competitive leisure time exercise activities with a minimal intensity of four METs for at least 60 minutes per week. An overall main effect of age and sex was found on the exercise participation dichotomy. Younger twins participated more in exercise than older twins, and for each age group males participated more often than females. Genetic analyses of twin resemblance showed a shift in the factors contributing to exercise participation from adolescence to adulthood. Between the ages of 13 and 16 years environmental factors shared by children from the same family largely account for individual differences in exercise participation (78 – 84%), whereas genes are of no importance. At the age of 17 – 18 years, genetic influences start to appear (36%) and the role of common environment decreases (47%). After the age of 18 years, genes largely explain individual differences in exercise participation (85%), and common environmental factors no longer contribute. Environmental factors shared by family members determine exercise participation in young adolescence, but cease to be of importance in adulthood when individual differences in exercise participation are largely due to genetic variation.

**Introduction**

Research has clearly established that regular exercise is a key contributor to health (Berlin and Colditz, 1990). Despite these well-documented benefits, the majority of people do not engage in exercise on a regular basis (Crespo *et al.*, 1996). To ensure more successful intervention on this important health behavior, much research has been devoted to the determinants of exercise behavior. These studies have mainly focused on personality and on social and environmental characteristics (King *et al.*, 1992; Sallis and Hovell, 1990), but innate biological mechanisms are increasingly being considered as additional factors influencing exercise behavior (Rowland, 1998). The innate drive to exercise will be most obvious in leisure time (i.e. self-chosen) exercise behavior that can be operationalized as regular exercise.

Studies of genetically related subjects have confirmed a familial component affecting exercise participation, although there are inconsistencies in the estimates of its magnitude, which may be caused by the use of various definitions of exercise participation with different restrictions in terms of minimal intensity, duration, and frequency of activities used to classify subjects as exercisers or non-exercisers. Parent-offspring correlations, for instance, have ranged from low (0.09) for participation defined as activities requiring at least five times the resting oxygen consumption (Perusse *et al.*, 1989) to moderate (0.29 – 0.37) for exercise participation defined as a dichotomous variable using the single question "Do you participate in sports?" (Koopmans *et al.*, 1994).

Twin studies can, as opposed to parent-offspring family designs, discriminate between genetic and environmental influences within a family by comparing the resemblance in exercise participation in monozygotic (MZ) twins and dizygotic (DZ) twins. MZ twins are genetically identical, whereas DZ twins share on average only half of their segregating genes. Therefore, a greater resemblance of MZ twins makes a strong case for the contribution of genetic factors to individual differences in exercise participation. Beunen and Thomis (1999) have reviewed the existing twin studies on exercise participation, and confirmed that heritability estimated for exercise participation range widely. Besides the problem of defining exercise participation differently, most twin studies so far have been based on samples with different age ranges, and different sample sizes, which may also explain the fact that heritability estimates of exercise participation are widely divergent, ranging from moderate genetic effects (Boomsma *et al.*, 1989) to a high heritability (Beunen and Thomis, 1999).

In this paper we focus on the relative contribution of genes and common environment to individual differences in exercise participation in a large Dutch twin sample. Exercise participation was assessed by the question: "Do you participate in sports regularly?" and could be answered with "yes" or "no", resulting in a dichotomous variable. Using the standard twin design, genetic and common environmental contributions to the liability to exercise participation were computed separately within age groups 13 – 14 years, 15 – 16 years, 17 – 18 years, and 19 – 20 years. This period of time is of particular interest, because several studies have shown that exercise participation in both sexes significantly decline with increasing age, and that this decline is particularly steep in the adolescent period, although changes in participation with age depend on the characteristics and types of the exercise behavior investigated (Telama *et al.*, 1994; Telama and Yang, 2000; Van Mechelen *et al.*, 2000). The use of two-year periods was deemed optimal in terms of temporal resolution and statistical power in model comparison. In view of the known sex difference in the prevalence of exercise participation (Kemper *et al.*, 2001), we tested whether the relative contribution of genetic and environmental factors to exercise participation is different in males and females, and whether different genetic and environmental factors influence exercise participation in males and females.

## Methods

*Subjects*

This study is part of an ongoing study on health and lifestyle in twin families registered with the Netherlands Twin Registry (NTR). Adolescent twins and their families were recruited by contacting City Councils in The Netherlands for addresses of twins in 1991. Later, additional twins were contacted via city councils, as well as by advertisements in the media and in the information bulletin of the NTR and through the Dutch Twin Club (Boomsma *et al.*, 2002b).

Since 1991, every two to three years twins and their families have received a survey sent by mail containing a large number of personality inventories, and items about health, exercise behavior, alcohol consumption and smoking behavior. Data were collected in 1991, 1993, 1995, 1997, and 2000. In 1991 and 1993, twins and their parents were asked to fill in surveys. Siblings and spouses of twins were recruited into the study in 1995 and 2000, respectively. The exact procedures have been described in detail elsewhere (Boomsma *et al.*, 2002b). Written informed consent was obtained

from the subjects, and approval of the study was obtained from the Medical Ethics Committee of the Vrije Universiteit.

In this paper, we focus on exercise participation of MZ and DZ twins between the ages of 13 and 20 years. Data from the five surveys were used to create a maximal cross-sectional dataset that had adequate numbers of twins in each of the age categories. First, data of complete twin pairs in 1991 were used to define exercise participation. If no data on exercise participation were available in 1991, then data on exercise participation of complete twin pairs in 1993 were used. This was done until all five surveys had been used as a possible source of information, resulting in a sample of 2,628 complete twin pairs.

Zygosity of 352 same-sex twin pairs was determined on the basis of DNA typing. For the remaining 1,554 same-sex twin pairs, zygosity was based on questions on physical similarity and confusion in identifying the twins by family members, friends, and strangers. In our sample, agreement between zygosity based on questionnaire data and zygosity based on DNA results was 98%. Grouped according to zygosity and sex, the sample consisted of 443 monozygotic male twin pairs (MZM), 377 dizygotic male twin pairs (DZM), 652 monozygotic female twin pairs (MZF), 434 dizygotic female twin pairs (DZF), and 722 dizygotic opposite-sex twin pairs (DOS). We subdivided participants into the age groups 13 – 14 years, 15 – 16 years, 17 – 18 years, and 19 – 20 years.

Exercise participation was a dichotomous variable primarily based on the question: "Do you participate in sports regularly?", which could be answered with "yes" or "no". Although different cultural meaning is attached to the term "sports" in other countries, in The Netherlands it is unambiguously taken to mean any form of leisure time exercise, including solitary jogging, dancing, or a workout at a fitness center. To further qualify exercise participation, those answering "yes" were asked what kind of exercise activities (name of the exercise activities) they were involved in, whether they did it competitively or non-competitively, and how much time (minutes a week) they spent on these exercise activities. Ainsworth's Compendium of physical activity was used to recode each sport into METs, representing one MET as the rate of energy expenditure of an individual at rest which is approximately one kcal/kg/h (Ainsworth *et al.*, 2000). The Compendium is organized by "activity types" and includes sections on daily living or self-care, leisure and recreation, occupation,

bicycling, running, sports and rest activities. We only used METs scores listed under the major headings: sports, conditioning exercises, dancing, bicycling, and running.

Twins were classified as exercisers if 1) they answered "yes" to the question "Do you participate in sports regularly?", 2) the minimum intensity of at least one of the exercise activities was four METs, and 3) the time spent on the exercise activities that exceeded the four METs criterion totaled at least 60 minutes a week. They were classified as non-exercisers otherwise. Dutch adolescents are obliged to participate in one to three hours of physical education at school per week. Note that in our classification we discarded all exercise activities engaged in only during such compulsory physical education. Furthermore, physical activity, even vigorous activity, related to manual labor, household activities or transportation did not classify as exercise participation.

*Analytic approach*

We used a standard liability threshold model to estimate genetic and environmental contributions to exercise participation (Falconer and Mackay, 1996). A categorical characteristic such as exercise participation is assumed to have an underlying liability, which is continuous and normally distributed in the population. The underlying normal distribution can be separated by one or more thresholds into different categories. In the current study, the liability to exercise participation is divided into two categories, exercisers and non-exercisers, separated by a single threshold. The threshold is obtained from the observed proportions in the two categories and can be interpreted as a z-value. Individuals falling below the threshold do not exercise; those exceeding the threshold do exercise regularly.

Information about twin resemblance in liability is given by tetrachoric correlations. Comparing the MZ correlations with the DZ correlations provides a first estimate of the sources of variation in individual differences in liability. While MZ pairs are genetically identical, DZ pairs share on average only half of their segregating genes. Additive genetic effects on exercise participation are suggested if the intrapair correlation in MZ twins is larger than in DZ twins. Common environmental effects, in contrast to genetic effects, are assumed to be unrelated to zygosity. Hence, resemblance due to common environment is similar in MZ and DZ twins, leading to significant but comparable intrapair correlation in MZ and DZ twins (Plomin *et al.*, 2000). Finally, because MZ twins have identical common environment and identical

genes, an intrapair correlation different from unity indicates unique environmental effects on exercise participation. Specific information on sex differences derives from the correlation in DOS twins. If the phenotypic correlation in DOS twins is lower than in same-sex dizygotic twins (DZM and DZF), this might be due to shared environmental effects that influence one sex but not the other, or genetic effects that are expressed in one sex but not in the other.

*Model fitting procedure*

Structural equation model fitting was used to partition the variance in the latent liability into three sources: genes, common environment (factors shared by members of a twin pair), and unique environment (factors not shared by members of a twin pair plus measurement error). Using the software package Mx (Neale *et al.*, 2003), we fitted different models on raw ordinal data.

First, we fitted a saturated model to describe the correlation structure between twin pairs in each zygosity group. We tested whether the thresholds for males in the MZ and DZ pairs could be constrained to be equal and whether the thresholds for females in these zygosity groups were the same. In Mx, twice the negative log-likelihood (-2LL) of the raw data of each twin pair is calculated and summed over all pairs. When two models are nested, subtracting the two -2LLs from each other yields a statistic that is asymptotically distributed as $\chi^2$ with degrees of freedom (df) equal to the difference in the number of parameters in the two models. According to the principle of parsimony, models with fewer parameters are preferred if they do not give a significant deterioration of the fit ($p > 0.05$). Akaike's information criterion (AIC = $\chi^2 - 2df$) was also used to guide model selection. The model with the lowest AIC (i.e. largest negative) reflects the best balance between goodness of fit and parsimony.

In all models, the threshold in each age group was allowed to differ in magnitude between males and females and thresholds across age groups could also differ. We tested whether the tetrachoric correlation of DOS twins differed significantly from the correlations of the DZ same-sex twins. Therefore, the saturated model was compared to a model in which the correlations of the DOS and same-sex DZ twin pairs were constrained to be equal. A much lower DOS correlation in comparison with the correlation of DZ same-sex twins indicates that different environmental factors and/or different genes are expressed in males and females. Because we only had one observed statistic to model these qualitative sex differences

(i.e. DOS correlation), we had to make an a priori decision to evaluate whether different genes or different environmental factors were expressed. We based this decision on the best fitting genetic model that was obtained from a genetic analysis in the four groups of same-sex twins (i.e. MZM, DZM, MZF, and DZF).

To obtain estimates for the proportions of variance explained by genes (A), common environment shared by family members (C), and unique environment (E), analyses without DOS data were carried out. The first step was to analyze these four zygosity groups; a model in which A, C and E were allowed to differ between males and females was compared with a model in which these parameters were constrained to be equal. This approach tested whether the magnitude of the contribution of genes and environment to individual differences in exercise participation was the same in males and females. The last step in the analyses without DOS twins was to test whether genes and/or environmental factors play a crucial role in exercise participation by successively constraining the A and C to zero. Both parameters were also dropped at the same time.

After selecting the most parsimonious model in the analyses without the DOS twins, we added this group to the analyses and tested if genetic or shared environmental correlation between DOS twins could be fixed at 0.5 or at 1, respectively. In the first test, the genes that contribute to the liability to exercise participation in males and females were allowed to differ. In the other test, the environmental factors operating in both sexes may differ.

**Results**

Prevalence of exercise participation for the four age groups is shown in Figure 4.1. A Pearson chi-square test yielded an overall sex difference in exercise participation ($\chi^2 = 28.63$, df = 1, p = 0.00). Post-hoc testing within each age group showed that the sex difference was present in all age groups, except for the 17 – 18 year old twins ($\chi^2 = 3.43$, df = 1, p = 0.06).

Figure 4.1 shows that there is a large decrease in exercise participation when subjects grow older. The Kruskal-Wallis test indicated that the four groups differ significantly on exercise participation ($\chi^2 = 94.59$, df = 3, p = 0.00). For pair wise comparisons, we used the Mann-Whitney test. The difference in exercise participation between the ages of 13 – 14 years and 15 – 16 years was not significant (Z = -0.32; p

= 0.75); however, a significant decrease in participation was found from the ages of 15 – 16 years to 17 – 18 years (Z = -5.23; p = 0.00) and from the ages of 17 – 18 years to 19 – 20 years (Z = -2.78; p = 0.01). The pattern of age-related changes was similar in males and females.

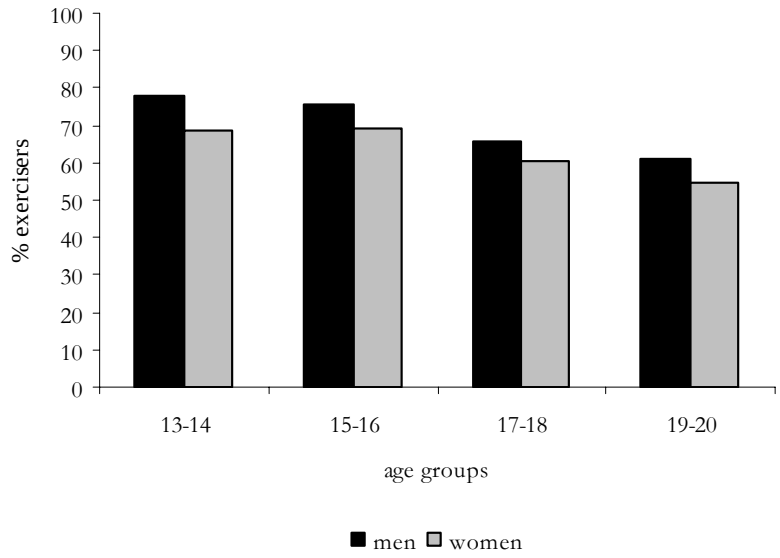


**Figure 4.1.** *Prevalence of exercise participation for the different age groups.*

Table 4.1 displays the tetrachoric correlations for all zygosity groups in the different age cohorts. In the two youngest age groups the correlations for MZ and DZ twins were almost the same, indicating that common environmental factors play an important role in explaining individual differences in exercise participation. In the two oldest age groups the resemblance in exercise participation between MZ twins was higher than in DZ twins, indicating genetic influences on exercise participation. Furthermore, the differences between the correlations became more substantial with increasing age, suggesting that the influence of genes on individual differences in exercise participation gain importance during late adolescence. DOS correlations generally were smaller than DZ same-sex correlations.

**Table 4.1.** *Number of complete twin pairs in each age group with the tetrachoric twin correlations for exercise participation (95% confidence intervals added in parentheses).*

| | 13 – 14 | 15 – 16 | 17 – 18 | 19 – 20 |
|---|---|---|---|---|
| MZM | N = 115 | N = 136 | N = 100 | N = 92 |
| | 0.88 (0.71 – 0.96) | 0.80 (0.62 – 0.91) | 0.88 (0.73 – 0.96) | 0.86 (0.68 – 0.95) |
| DZM | N = 87 | N = 112 | N = 96 | N = 82 |
| | 0.82 (0.56 – 0.94) | 0.68 (0.41 – 0.85) | 0.65 (0.38 – 0.83) | 0.35 (-0.01 – 0.63) |
| MZF | N = 161 | N = 185 | N = 148 | N = 158 |
| | 0.87 (0.74 – 0.94) | 0.83 (0.70 – 0.92) | 0.80 (0.64 – 0.90) | 0.83 (0.70 – 0.92) |
| DZF | N = 109 | N = 115 | N = 113 | N = 97 |
| | 0.84 (0.67 – 0.94) | 0.81 (0.62 – 0.92) | 0.68 (0.45 – 0.84) | 0.53 (0.24 – 0.74) |
| DOS | N = 174 | N = 215 | N = 186 | N = 147 |
| | 0.47 (0.23 – 0.67) | 0.46 (0.25 – 0.63) | 0.18 (-0.05 – 0.39) | 0.48 (0.25 – 0.67) |

*MZM, monozygotic males; DZM, dizygotic males; MZF, monozygotic females; DZF, dizygotic females; DOS, dizygotic opposite-sex twins.*

Model fitting results for all age groups are shown in Table 4.2. In all models, thresholds for MZ and DZ pairs within one sex could be set to be equal. Thresholds had to be allowed to differ for males and females and across age groups to accommodate the age and sex differences in the prevalence of exercise participation. The first six models in Table 4.2, under the heading "Model: 4 groups" are based on analyses using the four groups of same-sex twins. These analyses without DOS twins first tested for sex differences in the relative contribution of genetic and common and unique environmental influences. For every age group the AIC of the model without sex differences (model 3) was lower than the AIC of the model with sex differences (model 2), indicating that the model without sex differences was the most parsimonious model. The p-value for model 3 in every age group was higher than 0.05, which shows that constraining the variance components to be equal across sexes did not lead to a significant worsening of the fit.

**Table 4.2.** *Univariate model fitting results for twins in the four different age groups; comparisons of models are shown. The first six models are based on analyses using the four groups of same-sex twins (i.e. MZM, DZM, MZF and DZF) and are listed under the heading "model: 4 groups". After selecting the most parsimonious model in the analyses without the DOS twins, this fifth group was added to the analyses. Results of these five group analyses are listed under the heading "model: 5 groups".*

| | | 13 – 14 years | | | | 15 – 16 years | | | | 17 – 18 years | | | | 19 – 20 years | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | vs | -2LL | df | p | AIC | -2LL | df | p | AIC | -2LL | df | p | AIC | -2LL | df | p | AIC |
| Model: 4 groups | | | | | | | | | | | | | | | | | |
| 1) Saturated model | | 913.32 | 932 | - | - | 1094.16 | 1084 | - | - | 1043.22 | 902 | - | - | 1017.41 | 834 | - | - |
| 2) ACE: sex diff. | 1 | 922.38 | 938 | 0.17 | -2.94 | 1107.86 | 1090 | 0.03 | 1.70 | 1051.03 | 908 | 0.25 | -4.18 | 1021.08 | 840 | 0.72 | -8.32 |
| 3) ACE: no sex diff. | 2 | 922.61 | 940 | 0.89 | -6.71 | 1108.68 | 1092 | 0.67 | -0.14 | **1052.07** | **910** | **0.60** | **-7.15** | 1021.51 | 842 | 0.81 | -11.90 |
| 4) AE: no sex diff. | 3 | 940.39 | 941 | 0.00 | 9.07 | 1120.19 | 1093 | 0.00 | 8.03 | 1058.55 | 911 | 0.01 | -2.67 | **1021.54** | **843** | **0.87** | **-13.87** |
| 5) CE: no sex diff. | 3 | **923.58** | **941** | **0.32** | **-7.74** | **1110.52** | **1093** | **0.18** | **-1.64** | 1056.51 | 911 | 0.04 | -4.71 | 1037.00 | 843 | 0.00 | 1.60 |
| 6) E: no sex diff | 5 | 1095.00 | 942 | 0.00 | 162.68 | 1264.39 | 1094 | 0.00 | 150.22 | 1189.96 | 912 | 0.00 | 126.74 | 1140.79 | 844 | 0.00 | 103.38 |
| Model: 5 groups | | | | | | | | | | | | | | | | | |
| 1) Saturated model | | 1301.20 | 1277 | - | - | 1605.40 | 1511 | - | - | 1540.03 | 1271 | - | - | 1400.67 | 119 | - | - |
| 2) ACE (rc estimated) | 1 | 1313.27 | 1287 | 0.28 | -7.93 | 1622.02 | 1521 | 0.08 | -3.39 | 1551.03 | 1281 | 0.36 | -9.00 | 1408.61 | 1129 | 0.63 | -12.06 |
| 3) ACE (rc fixed at o) | 2 | - | - | - | - | - | - | - | - | **1551.03** | **1282** | **1.00** | **-11.00** | - | - | - | - |
| 4) ACE (rc fixed at 1) | 2 | - | - | - | - | - | - | - | - | 1562.61 | 1282 | 0.00 | 0.58 | - | - | - | - |
| 5) CE (rc estimated) | 2 | **1314.23** | **1288** | **0.33** | **-8.97** | **1623.89** | **1522** | **0.17** | **-3.51** | - | - | - | - | - | - | - | - |
| 6) CE (fixed at 0) | 5 | 1327.61 | 1289 | 0.00 | 2.41 | 1641.20 | 1523 | 0.00 | 11.80 | - | - | - | - | - | - | - | - |
| 7) CE rc fixed at 1) | 5 | 1329.83 | 1289 | 0.00 | 4.63 | 1636.24 | 1523 | 0.00 | 6.84 | - | - | - | - | - | - | - | - |
| 8) AE rg estimated) | 2 | - | - | - | - | - | - | - | - | - | - | - | - | 1408.84 | 1130 | 0.63 | -13.82 |
| 9) AE (rg fixed at 0) | 8 | - | - | - | - | - | - | - | - | - | - | - | - | 1423.58 | 1131 | 0.00 | -1.08 |
| 10)AE (rg fixed at 0.5) | 8 | - | - | - | - | - | - | - | - | - | - | - | - | **1408.84** | **1131** | **1.00** | **-15.82** |

*Note: rg, genetic correlation between DOS twins; rc, common environmental correlation between DOS twins; vs, versus and indicates with which model the submodel is compared to; –2LL, –2 loglikelihood; df, degrees of freedom; p, p-value. Most parsimonious solutions are printed in boldface type*

In models without sex differences, we next tested whether genes and/or environmental factors play a crucial role in exercise participation (model 4 to 6). According to the principle of parsimony, a model in which the genetic component was set to be zero was preferred for the two youngest age groups. Again, AIC was lowest for the CE model (model 5) and dropping the genetic component did not give a deterioration of the fit (AIC = -7.74; p = 0.32).

In the 17 – 18 year old twins no parameters could be dropped, leading to an ACE model as the most parsimonious model. Finally, in the oldest age groups the common environment parameter could be constrained to zero, resulting in an AE model.

Adding DOS twins allowed us to test whether different genetic or environmental influences operated in males and females, even though their relative contribution was shown to be the same. Under the heading "model: 5 groups" Table 4.2 shows that for the two youngest age groups, the environmental correlation could not be set at 1.0 but was estimated at approximately half of it, indicating that partly different environmental influences act in males and females. In the age group 17 – 18 years, the environmental correlation was even lower, and was estimated at its boundary of 0.00, suggesting that common environmental factors influencing exercise participation in males do not play a role in influencing exercise participation in females and vice versa. In the oldest age group, the genetic correlation between the DOS twins was estimated and could be fixed at 0.5. Because DOS twins share on average half of their genes, this means that the same genes act in males and females.

**Table 4.3.** *Parameter estimates and 95% confidence intervals of the best-fitting models of the five groups analyses for the different age groups.*

| | $h^2$ (95% CI) | $c^2$ (95% CI) | $e^2$ (95% CI) | $r_c$ |
|---|---|---|---|---|
| 13 – 14 | - | 0.84 (0.77-0.90) | 0.16 (0.10-0.23) | 0.55 |
| 15 – 16 | - | 0.78 (0.70-0.85) | 0.22 (0.15-0.30) | 0.58 |
| 17 – 18 | 0.36 (0.09-0.64) | 0.47 (0.21-0.71) | 0.17 (0.10-0.27) | 0.00 |
| 19 – 20 | 0.85 (0.76-0.91) | - | 0.15 (0.09-0.24) | - |

*$h^2$, heritability; 95% CI, 95% confidence interval; $c^2$, common environmental variance component; $e^2$, unique environmental variance component; $r_c$, environmental correlation between DOS twins.*

Table 4.3 shows parameter estimates and 95% confidence intervals of the best-fitting models of the five group analyses for the different age groups. The heritability

estimates for exercise participation in the two youngest age groups could be set to zero, whereas common environment explained about 80% of the variance in exercise participation. In the 17 – 18 year old twins both genetic and common environment accounted for individual differences in exercise participation, 36% and 47%, respectively. In the oldest age group common environmental factors did not play a role in explaining individual differences in exercise participation, whereas genetic factors explained 85% of the variance in exercise participation.

**Discussion**

An overall main effect of age and sex on exercise participation was found. Younger twins participated more in exercise activities than older twins and within each age group males were more physically active than females. There was a decline in exercise participation from adolescence to adulthood that was particularly steep in the period between the ages of 15 and 19 years, which was observed in both males and females. These findings correspond to results obtained in a large Finnish population sample (Telama *et al.*, 1994; Telama and Yang, 2000). In that study, self-reported physical activity was measured from 1980 to 1989, resulting in data covering ages from 9 to 27. Frequency of physical activity as measured by the question "How often do you engage in physical activity during leisure time for at least half an hour each time?" and frequency of exercising in organized activities both show a marked decline from the age of 12. Our results are also in keeping with the results from a cross-national comparison between two large longitudinal studies of adolescents in Glasgow, Scotland and Dunedin, New Zealand (West *et al.*, 2002). In interviews at age 15 and 18, subjects were asked what kind of physical activities they were involved in. These activities included activities undertaken as part of school programs, competitive exercise, and leisure time activities undertaken for exercise or recreation. In both locations participation in physical activity declined. Finally, Dovey and colleagues (1998) found in a longitudinal cohort study of 775 adolescents that there was a 37% reduction in total time spent in exercise and leisure time physical activity at age 18 compared with age 15. However, other studies measuring physical activity in a broader sense than exercise participation alone suggest that changes over age may vary across different aspects of physical activity (Telama *et al.*, 1994; Telama and Yang, 2000; Van Mechelen *et al.*, 2000). In a Dutch study over a 15-year period covering adolescence and young adulthood, a gradual decline was observed in the total weekly time spent on

physical activities exceeding four METs and in the weekly time spent on non-organized exercise activities, but not for the time spent on organized exercise activities (Van Mechelen *et al.*, 2000).

The main aim of our study was to assess the relative contribution of genetic and environmental influences in the period from adolescent to adulthood. To our knowledge, no other study has used fine-grained age groups, as were used here. Genetic analysis strongly confirmed the expected age-dependency of the factors influencing variation in exercise participation. A shift was observed from environmental to genetic factors from adolescence to adulthood in both males and females. Between the ages of 13 and 16 years, environmental factors shared by children in the same family accounted for the differences in exercise participation. In these age groups, such influence may still include peer support and peer physical activity, which have been a source of influence on exercise participation in children (Anderssen and Wold, 1992). A review of 108 studies on factors influencing physical activity levels of children and adolescents (aged 13 to 18 year old), however, suggests parental support and direct help from parents as the environmental factors most consistently associated with the physical activity levels of adolescents (Sallis *et al.*, 2000). At the age of 17 – 18 years, the role of common environment starts to decrease in favor of genetic influences. In The Netherlands, the majority of children finish high school when they are 16 or 17. As long as they attend high school, children are obliged to participate in compulsory physical education classes. The ending of those classes may cause part of the decline in exercise participation in this age period, and could also contribute to the shift from common environmental to genetic factors.

After the age of 18, common environmental factors cease to contribute to individual differences in exercise participation, and genes entirely account for the remaining familial resemblance. Thus, our study confirms a major role of genetic influences on adult exercise participation (De Geus *et al.*, 2003) and suggests that the influence of these genes start to appear in late adolescence. Two major pathways for genetic influences to affect exercise behavior may be through personality characteristics (e.g. sensation seeking or extraversion) or physical fitness parameters (e.g. muscle strength, muscle endurance, and aerobic power) both of which are highly heritable (Boomsma *et al.*, 2002a; Perusse *et al.*, 1988b).

Several previous studies have examined genetic and environmental determinants of exercise participation. In a partly overlapping Dutch sample,

Koopmans and colleagues (1994) looked at exercise participation in 13 to 22 year old twins, but did not divide the sample into different age cohorts. As in our study, exercise participation was based on the question "Do you participate in sports regularly?", which resulted in a dichotomous variable. Models fitted on the total sample, which had a mean age of 17.7 years, resulted in a heritability and common environment estimate of 48% and 38%, respectively. This corresponds closely to our findings in the age group of 17 to 18 year old twins. Boomsma and colleagues (1989) also investigated heritability of exercise participation in a sample of the Dutch Twin Registry by analyzing responses from 90 adolescent Dutch twin pairs aged 14 to 20 years (average age = 17 years old), using the single question "Have you been involved in sports activities during the last three months?". For females, the heritability estimate was 35%, and for males 77%. For a single model in which the variance components across sexes were constrained to be equal an estimated heritability of 64% was found.

In a small sample of 92 Flemish male twin pairs and 91 female twin pairs aged 15 years, Beunen and Thomis (1999) found a slightly different pattern than that seen in Dutch 15 year olds. For girls, 44% of the variation in exercise participation was explained by genetic factors and 54% by common environmental factors. For boys, genetic factors already explained about 83% of the total variance at age 15. However, these results were not based on exercise participation as a dichotomous variable, but on the number of hours spent on exercise activities each week. It might be that higher heritability estimates for exercise participation are obtained if it is defined by a continuous variable.

No sex differences were found in the relative contributions of genetic and environmental factors to exercise participation. This extends previous findings in a comparable sample from the Netherlands Twin Registry, where sex differences in variance components were also absent for exercise participation (Koopmans *et al.*, 1994). However, a study of 411 Portuguese twins aged 12 to 25 years and a study on 183 Flemish 15 year old twins showed larger heritability estimates in males than in females (Beunen and Thomis, 1999; Maia *et al.*, 2002). In these studies, exercise participation was based on continuous data rather than on a dichotomy which may explain the different finding. It is also possible that familial resemblance in social learning and parental role modeling is different for males and females in Portugal and Belgium, but less so in The Netherlands. Alternatively, because of the modest sample

size of the groups of same-sex twins, these studies may simply have been more vulnerable to accidental results due to sampling variation.

Although the relative contribution of the variance components was of similar magnitude in males and females, a key finding of our study was that shared environmental influences do appear to differ across sexes. Except for the 19 – 20 year old male twins, DOS correlations were significantly smaller than dizygotic same-sex correlations. This pattern of correlations signals that different environmental factors contribute to variation in exercise participation in boys and girls aged 13 to 16 years. A study by Whitehead and colleagues (1997) helps qualify these findings by showing that exercise activities were more important to boys than to girls. Furthermore, there is some suggestive evidence that parental exercise involvement in exercise participation influence boys and girls differently. Results showed that the effect of parents on exercise participation is larger for girls than for boys (Sallis *et al.*, 1999). Boomsma and colleagues (1989) also found a difference in the socialization of males and females into exercise. The environment of spouses and female twins were highly correlated, but for male twins this correlation was absent.

A correlation between the phenotypes of spouses may be a problem influencing genetic and environmental factors contributing to individual differences in exercise participation in twin studies. Assortative mating refers to non-random selection of spouses (Falconer and Mackay, 1996). In the example of exercise participation, non-random mating can occur when exercisers become member of a sports club, thereby enlarging the change of selecting an exercising spouse. Boomsma and colleagues (1989) indeed found positive correlations between exercise participation of spouses. Assortment results in a larger genetic resemblance of offspring than the average 50% predicted under the standard biometric model. In twin studies this will result in a greater similarity of DZ twins relative to MZ twins, resulting in an underestimation of heritability in favor of overestimated common environmental influences. It is very difficult to envision how assortment could have resulted in the pattern of findings reported in this paper, because overestimation of common environment should not show any age dependency. Nonetheless, in future research, parents and spouses of twins could be added to the twin design to help resolve this issue.

Future studies could also address two further limitations of this study: the use of a dichotomy rather than a continuous variable, and the cross-sectional design. In our study, exercise participation was assessed as a yes/no dichotomy, using exercise

activities with a minimal intensity of four METs for at least 60 minutes per week as the arbitrary cut-off. Within those who satisfied our criterion of exercise participation, huge individual differences may still exist in the total duration and intensity of exercise behavior. By modeling a liability response pattern and not a continuous variable expressing type, duration, intensity, and frequency, we defined a narrow phenotype that is probably more reliably extracted from self-report data, but need not generalize to a quantitative measure of the total weekly energy expenditure attained in exercise activities. Such individual differences in weekly energy expenditure may, but need not, be influenced by the same genetic and environmental influences that determine who regularly exercises. A combined model has been proposed to explicitly address this question in twin samples (Heath *et al.*, 1991). This approach, however, requires a more detailed survey of the frequency, duration and intensity of exercise behavior than was available here.

A second limitation of the study is that we used a cross-sectional twin design to assess the relative contribution of genes and environmental influences on variation in exercise participation of Dutch male and female twins between the ages of 13 and 20 years. Although little cohort effects are likely to have occurred in such a brief time span, the shift in genetic architecture is most properly addressed in a longitudinal design. However, due to sample size we were unable to provide a longitudinal design. Unfortunately, even in our large sample a longitudinal genetic analysis would still be underpowered, because the number of twin pairs in each of the five zygosity groups that filled out the survey on all time points was too small.

In summary, this twin study showed that common environmental factors determine exercise participation in young adolescence, but cease to be of importance in adulthood when individual differences in exercise participation are largely genetic. These results may have implications for the promotion of physical activity in children and adolescents. Future physical activity interventions in children between the ages of 13 and 16 years should do well to target the common environment. This prominently included the parents whose support and direct help can play an important role in the physical activity levels of children. Furthermore, school exercise programs or community-based programs could take advantage of the influence that peers have on exercise participation. Because shared environmental influences do appear to differ across sexes in the ages of 13 to 16 years, it may be important to develop different exercise programs for males and females. From adolescence onward, genetic

influences seem to determine exercise participation. This is often mistakenly interpreted as a life sentence for those who are sedentary. Future understanding of the pathways from gene to exercise behavior may well yield novel strategies for promoting physical activity in (young) adults, for instance by tailoring exercise programs to fit a wider range of abilities and personalities.

# Chapter 5

# Genetic influences on adult exercise participation: A comparative study in twin samples from seven countries

This chapter is based on:

Stubbe JH, Boomsma DI, Cornes BK, Martin NG, Skytthe A, Kyvik KO, Rose RJ, Kujala UM, Kaprio J, Harris JR, Pedersen NL, and De Geus EJC (submitted). Genetic influences on exercise participation: A comparative study in adult twin samples from seven countries. International Journal of Epidemiology.

**Abstract**

The purpose of this study was to assess the relative contribution of genetic and environmental influences on variation in exercise participation across twin samples from seven countries participating in the GenomEUtwin project. Self-reported data on frequency, duration, and intensity of exercise behavior from Australia, Denmark, Finland, Norway, The Netherlands, Sweden and United Kingdom were used to create a comparable index of exercise participation in each country (60 minutes weekly at a minimum intensity of four metabolic equivalents). Results obtained from 85,198 subjects, aged 19 – 40 years, revealed modest geographical variation in exercise participation. Modeling of monozygotic and dizygotic twin resemblance showed that genetic effects play an important role in explaining individual differences in exercise participation in each country. Shared environmental effects played no role except for Norwegian males. Heritability of exercise participation in males and females was similar and ranged from 48% to 71% (excluding Norwegian males). Genetic variation is important in individual exercise behavior and may involve genes influencing the acute mood effects of exercise, high exercise ability, high weight loss ability, and personality. This collaborative study shows that finding genes influencing exercise participation is very feasible.

**Introduction**

Regular exercisers have reduced cardiovascular morbidity and mortality (Berlin and Colditz, 1990; Kaplan *et al.*, 1991; Kesaniemi *et al.*, 2001). In addition, exercisers are characterized by enhanced psychological well-being and sharper minds. They have a lower incidence of depression and anxiety disorders (Camacho *et al.*, 1991; Farmer *et al.*, 1988; Gauvin and Spence, 1996; Steptoe and Butler, 1996) and show cognitive advantages, specifically in frontal executive functions (Colcombe and Kramer, 2003; Etnier *et al.*, 1997; Hillman *et al.*, 2004; Richards *et al.*, 2003). These advantages for mental and physical health are well-known. Even so, a large part of the population remains nearly completely sedentary (Caspersen *et al.*, 2000; Haase *et al.*, 2004; Martinez-Gonzalez *et al.*, 2001) and this percentage appears to be resistant to more than 50 years of population campaigning. As a consequence, a sedentary lifestyle remains a major threat to health in contemporary societies.

Studies on the determinants of exercise behavior have mainly focused on social and environmental characteristics like access to facilities (Matson-Koffman *et al.*, 2005; Varo *et al.*, 2003), socio-economic status (Haase *et al.*, 2004; Varo *et al.*, 2003), race (Kaplan *et al.*, 1991), job strain (Payne *et al.*, 2005; Van Loon *et al.*, 2000), marital status (Kaplan *et al.*, 1991), subjective "lack of time" (Shephard, 1985; Sherwood and Jeffery, 2000), health beliefs (Haase *et al.*, 2004), and social support by family, peers or colleagues (King *et al.*, 1992; Orleans *et al.*, 2003; Sherwood and Jeffery, 2000). Despite their face validity, none of these factors has emerged as a strong causal determinant of exercise behavior (Dishman *et al.*, 1985; Seefeldt *et al.*, 2002). Increasingly, therefore, the influence of biological factors has been considered (Rowland, 1998; Thorburn and Proietto, 2000; Tou and Wade, 2002).

Dispositional differences in the drive to exercise will be most obvious in leisure time, i.e. self-chosen, exercise behavior. Parent-offspring studies have confirmed a significant familial influence on leisure time exercise participation (Aarnio *et al.*, 1997; Perusse *et al.*, 1989; Sallis *et al.*, 1988; Simonen *et al.*, 2002) and twin studies have further shown this influence to reflect the shared genetic make-up of family members (Beunen and Thomis, 1999; Boomsma *et al.*, 1989; Kaprio *et al.*, 1981; Koopmans *et al.*, 1994; Kujala *et al.*, 2002; Lauderdale *et al.*, 1997; Maia *et al.*, 2002; Simonen *et al.*, 2004; Stubbe *et al.*, 2005a). The estimates of genetic contribution are very inconsistent, ranging from no genetic effects (Perusse *et al.*, 1989) to a high heritability (Beunen and Thomis, 1999). These inconsistencies may reflect relatively small samples sizes and

different definitions of exercise participation. They may also reflect a change in genetic architecture with age, or true differences in the relative contribution of the environment related to country-specific traditions, attitudes about exercise, and opportunities to engage in exercise (Haase *et al.*, 2004).

In this paper, we estimated the heritability of exercise participation using very large twin samples from seven countries participating in the GenomEUtwin project, a multinational collaboration of twin registries aiming to uncover the genetic variation that influences, amongst others, risk factors for cardiovascular disease. We restricted our analyses to adults aged 19 to 40 years. Age 19 was used as a lower limit, because a previous study suggested that environmental factors shared by children in the same family accounted for much of the differences in adolescent exercise participation, but cease to be of importance by age 19, when genes account for most of the individual differences in exercise participation (Stubbe *et al.*, 2005a). Age 40 was chosen as an upper limit, because most countries had twin data up to this age and after age 40 the increasing prevalence of disease and disability affects the ability and motivation to exercise.

## Methods

*Study population*

This study is based on (repeated) surveys in twin samples from seven countries participating in the GenomEUtwin project: Australia, Denmark, Finland, The Netherlands, Norway, Sweden, and United Kingdom. The exact descriptions of the twin registries of these countries have been described in detail elsewhere (Mulder *et al.*, 2003; Schousboe *et al.*, 2003; Silventoinen *et al.*, 2003).

When exercise data were available from more than one survey in a country, we used the most recent survey. If only one twin had completed the most recent survey, we searched for the most recent survey that was completed by both members of the pair. If the other member never filled out a survey, the single twin was nonetheless retained in the analysis to improve on the estimation of exercise prevalence and its variance. Only complete twin pairs, however, are informative for the analyses of twin resemblance. Below, the surveys from which the data are drawn are briefly described by country. The final sample sizes are summarized in Table 5.1.

**Table 5.1.** *Number of twins in the countries participating in the GenomEUtwin project.*

| | Australia | Denmark | Finland | Netherlands | Norway | Sweden | UK |
|---|---|---|---|---|---|---|---|
| Total N | 5,856 | 23,807 | 19,633 | 6,222 | 9,066 | 19,516 | 1,098 |
| | | | | | | | |
| Complete pairs | 2,728 | 9,456 | 8,842 | 2,681 | 3,995 | 8,927 | 422 |
| MZM | 411 | 1,319 | 1,243 | 423 | 639 | 1,633 | - |
| DZM | 269 | 1,642 | 2,672 | 295 | 544 | 2,523 | - |
| MZF | 849 | 1,727 | 1,598 | 843 | 863 | 1,965 | 163 |
| DZF | 529 | 1,860 | 2,737 | 463 | 741 | 2,806 | 259 |
| DOS | 670 | 2,908 | 592 | 657 | 1,208 | - | - |

*MZM, monozygotic male twin pairs; DZM, dizygotic male twin pairs; MZF, monozygotic female twin pairs; DZF, dizygotic female twin pairs; DOS, dizygotic opposite-sex twin pairs (male-female pairs). No data on opposite-sex twins were available in Sweden and no data on male or opposite-sex twins were available in the UK.*

*Australia.* Data were obtained from two different mail surveys conducted in 1980 and 1990. Combining the data from the two surveys and selecting twin pairs between the ages of 19 and 40 years, gave a total of 5,856 participants and 2,728 complete twin pairs.

*Denmark.* Data were derived from three different mail surveys conducted in 1995, 1997 up to 2000, and 2002. The final sample consisted of 23,807 participants and 9,456 complete twin pairs between ages 19 and 40 years.

*Finland.* The Finnish data were obtained from two different mail surveys. The first survey, of the older Finnish Twin Cohort, was conducted in 1975 and consists of same-sex twins born before 1958 (Kaprio *et al.*, 1981). The second survey is from participants in *FinnTwin16*, which consists of twins born in 1975 – 1979. Data were collected at four time points from an age 16 baseline (ages 16, 17, 18½, and 22 – 25). For these analyses, we used survey data from the fourth wave assessment when twins were between the ages of 23 to 27 years (Kaprio *et al.*, 2002). Combining the two cohorts and selecting the 19 to 40 year old twins resulted in a total of 19,633 participants and 8,842 complete twin pairs.

*The Netherlands.* The Dutch data were obtained from a longitudinal study on health and lifestyle in twin families registered with the Netherlands Twin Registry (NTR). Since 1991, every two to three years, twins and their families have received a mail survey (Boomsma *et al.*, 2002b). Combining the six surveys (1991, 1993, 1995, 1997, 2000, and 2002) and excluding the twins younger than 19 and older than 40, resulted in a total sample of 6,222 participants and 2,681 complete twin pairs.

*Norway.* The Norwegian exercise data were derived from two mail surveys, the first in 1992, and the second in 1998 (Harris *et al.*, 2002). Combining the two surveys and excluding the twin pairs younger than 19 years, resulted in a total sample of 9,066 participants and 3,995 complete twin pairs.

*Sweden.* The Swedish data were obtained from a mail survey sent in 1972 to all same-sex twin pairs born 1926 – 1958 (Lichtenstein *et al.*, 2002). The final sample includes a total of 19,516 participants older than 18 years and younger than 41 years of which 8,927 complete twin pairs could be formed.

*United Kingdom.* Exercise data from two studies in the St. Thomas' UK Adult Twin Registry (TwinsUK) were used for the analyses. The first study assessed self-reported exercise behavior with a detailed mail survey on health and lifestyle sent out in 2000. The second study comprises data from clinical interviews on lifestyle that were held between 1992 and 2001. Some twins participated in one interview, while others have been interviewed twice. Exercise data from the two studies were combined and the pairs older than 40 and younger than 19 years were removed from the data set. As numbers of male pairs in the age range were small, only female data were retained, resulting in a total sample of 1,098 female participants, from which 422 complete twin pairs could be formed.

*Exercise participation*

Different exercise questions were asked in each of the countries. All recorded exercise activities were first recoded into metabolic equivalents (METs) using Ainsworth's Compendium of physical activity (Ainsworth *et al.*, 2000). One MET is the rate of energy expenditure of an individual sitting quietly, which is approximately one kcal/kg/h. We then established the frequency and duration of such activities in the data from each of the countries. As a general strategy, subjects were classified as an exerciser if they met a predefined criterion of at least 60 minutes per week with a minimum intensity of four METs.

In Australia, to meet the criteria, subjects had to exercise in their leisure time once a week with a minimal intensity comparable to moderate activities like gardening; in Denmark, they had to engage in hard physical activity (contrasted with light physical activity) outside their working hours for at least one hour a week; in Finland, they had to engage in leisure time exercise at least once a week with a minimum intensity comparable to light jogging for a duration of at least one hour; in The

Netherlands they had to engage in one or more leisure time exercise activities with a minimum intensity of four METs, and the total time spent on all such activities was at least 60 minutes a week; in Norway, they exercised during leisure time between one and two times a week at sufficient intensity to build up a sweat and with each session between 30 – 60 minutes in duration; in Sweden, they had to exercise "rather a lot", "a lot" or "really a lot" (in contrast to "not very much", "rather little", "very little", and "almost none"); in the UK, they had to be regularly engaged in exercise activities with a minimum intensity of four METs.

*Analysis of twin similarity*

*Correlations.* Comparing the correlations of MZ and DZ twins provides information about the nature of the influences contributing to the twin resemblance. MZ twins are genetically identical, while DZ twins share on average half of their segregating genes. If MZ twins resemble each other more than DZ twins, this is an indication that genetic factors (A) play an important role in explaining individual differences in exercise participation. Similar MZ and DZ twin correlations suggest that common environmental factors (C), i.e. factors shared by members of a twin pair, influence variance in exercise participation, because the common environment is similar in MZ and DZ twins (Plomin *et al.*, 2000). Finally, an MZ intrapair correlation different from unity suggests unique environmental effects (E), i.e. factors not shared by members of a twin pair plus measurement error, because MZ twins have identical common environments and identical genes. Adding dizygotic opposite-sex twins (DOS) to the twin design enables us to investigate sex differences. If the DOS correlation is lower than the same-sex dizygotic correlations, this indicates that different common environmental or genetic effects influence exercise participation in males and females.

*Threshold model.* We estimated tetrachoric correlations from a standard liability threshold model (Falconer and Mackay, 1996). The model assumes that there is an underlying liability for exercise behavior, which is continuous and normally distributed in the population. This underlying normal distribution is divided by a threshold, which is obtained from the observed proportions of exercisers and non-exercisers. Individuals whose scores fall below the threshold, which can be interpreted as a z-value, do not meet the exercise criteria and are classified as non-exercisers; those with

scores exceeding the threshold are classified as regular exercisers. The thresholds may, or may not be equivalent for males and females, which will be tested.

*Model fitting procedure.* We used structural equation model (SEM) fitting to partition the variance in latent liability into three components, i.e. genetic, common environmental, and unique environmental factors. Different models were fitted to raw ordinal data using the software package Mx (Neale *et al.*, 2003). First, we fitted a saturated model to estimate the tetrachoric correlations between twins. The saturated model is fully parameterized (i.e. it has no constraints) and is used to evaluate the fit of nested, more restricted models. If the fit of a nested model is significantly worsened ($p < 0.01$), the predicted contributions of genetic and environmental factors are inconsistent with the data, and the nested model should be rejected. Alpha levels were set to .01 in all samples.

We tested whether the prevalence of exercise was the same for males and females, whether there was an effect of age on the prevalence of exercise, and whether this effect was the same for both sexes. Next, we tested whether different genes in males and females contribute to the liability to exercise participation, and whether the magnitude of the contribution of genes and environment was the same in males and females. Finally, we analyzed whether both genetic and common environmental factors play a role in familial resemblance by consecutively constraining their contribution to exercise participation to zero. In each country, the most parsimonious model was retained to estimate the relative contribution of genes, common environment shared by family members, and unique environment to individual differences in exercise participation.

**Results**

Prevalence of exercise participation for the seven countries is given in Figure 5.1, which shows that the percentage of male exercisers is generally higher than the percentage of female exercisers ($p < 0.01$), except for the Dutch sample ($p = 0.05$). The average percentage of male and female exercisers was 44% and 35% respectively.

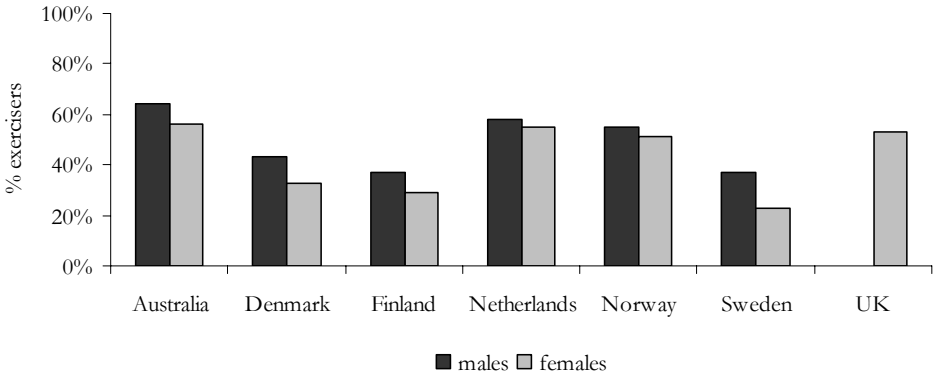


**Figure 5.1.** *Prevalence of exercise participation by country and sex*

Lowest participation was found in Sweden (37% for males and 23% for females) and highest participation in Australia (64% for males and 56% for females). The prevalence of exercise gradually decreased from age 19 to age 40 in most countries ($p < 0.01$) and the decrease with age in prevalence was the same for males and females ($p > 0.01$). Exercise prevalence remained stable across this age range only for males and females in The Netherlands and for females in the UK and Sweden.

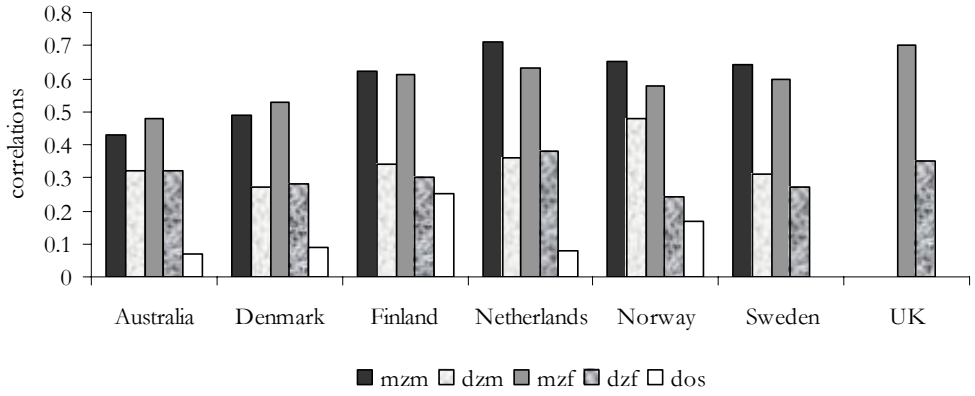


**Figure 5.2.** *Twin correlations for exercise participation by country and zygosity group*

Figure 5.2 displays the tetrachoric correlations for all zygosity groups in the different countries. The resemblance in exercise participation of MZ twin pairs was nearly twice as high as for DZ twins, indicating clear genetic influences on exercise

participation in all groups except Norwegian males. Non-genetic factors shared by members of a twin pair were not of significance except for Norwegian males. With the exception of Finland, the DOS correlations were significantly lower than the dizygotic same-sex correlations. This indicates that the genetic factors influencing exercise participation in males do not completely overlap with those in females.

Sequential model fitting suggested that the variance in exercise participation was due to additive genetic and unique environmental factors in all samples; in the Norwegian males additional common environmental factors were also found.

Heritability estimates and confidence intervals under the best fitting models in each country are shown in Table 5.2. Heritability of exercise participation in males ranged from 27% in Norway to 67% in The Netherlands and in females from 48% in Australia to 71% in the UK. The median figure for all groups was 62%.

**Table 5.2.** *Heritability estimates and confidence intervals by country.*

| | A (95% CI) | C (95% CI) | E (95% CI) |
|---|---|---|---|
| Australia | 48.2 (41.0 – 54.9) | - | 51.9 (45.2 – 60.0) |
| Denmark | 51.8 (47.0 – 56.0) | - | 48.2 (48.2 – 52.5) |
| Finland | 61.7 (57.8 – 65.5) | - | 38.3 (34.5 – 42.2) |
| The Netherlands | 66.7 (60.9 – 71.9) | - | 33.3 (28.1 – 39.1) |
| Norway (males) | 26.5 (10.1 – 46.8) | 36.8 (18.9 – 51.5) | 36.7 (29.4 – 44.7) |
| Norway (females) | 56.4 (48.5 – 63.6) | - | 43.6 (36.4 – 51.5) |
| Sweden | 61.8 (58.1 – 65.3) | - | 38.2 (34.7 – 42.0) |
| UK | 70.5 (55.2 – 82.3) | - | 29.5 (17.7 – 44.8) |

*A, additive genetic factors; C, common environmental factors; E, unique environmental factors; 95% CI, 95% confidence interval*

## Discussion

This study compared the intrapair resemblance in exercise behavior in 13,676 MZ twin pairs to that in 23,375 DZ twin pairs from seven different countries. In all countries, a significant contribution of genetic factors to exercise participation in leisure time was found. The median heritability of exercise participation was 62% across the seven countries and ranged from 27% in Norwegian males to 70% in female twins from the UK. These findings underscore the robustness of the genetic contribution to this lifestyle behavior. Different birth cohorts and survey periods were studied across the countries and different questions were used to assess regular

exercise in each of the countries. Moreover some countries used clinical interviews as well as mail questionnaires. Despite this variation in the assessment instruments and the inclusion of different age cohorts, highly comparable results were found in all countries, as evidenced by the substantial overlap in the heritability estimates. Common (shared) environmental factors such as home environment, education and culture appear to play little or no role in adult exercise behavior (with the exception of the Norwegian males).

What is the nature of the genetic factors causing individual differences in voluntary exercise behavior? Extensive interviews with persistent exercisers, recent adopters, fitness program dropouts, and persistently sedentary individuals by Gauvin (1990) suggested that exercisers differed from individuals with less active lifestyles mainly in that they enjoyed the exercise itself and felt that something was missing in their lives when they did not regularly exercise. A number of genetic mechanisms may explain why the act of exercising itself is rewarding to some and aversive to others. The immediate aversive effects caused by exercise-related fatigue related to monoamine depletion (Davis and Bailey, 1997) may depend on genetic differences in monoaminergic systems. The extent of immediate rewarding effects may well depend on genetic variation in the opioid and dopamine systems (Simonen *et al.*, 2003a). Genetic differences in aversive/rewarding effects may also be found in the period after exercise. For instance, strong cardiac vagal control enabling faster heart rate recovery, a genetically influenced trait (Kupper *et al.*, 2005a), may tip the balance between rewarding and aversive effects of acute exercise in favor of reward, by reducing some of the aversive effects of exercise (e.g. prolonged palpitations). Likewise, the temporary reduction in sympathetic stress reactivity after exercise (Halliwill, 2001) and the positive mood states paired to it (Yeung, 1996) may depend on the exact genotype of the subjects. Thirdly, individual genotypes may differ strongly in the longer lasting rewarding effects on happiness, satisfaction with life and quality of life, visceral awareness to emotional appraisals and perhaps cognitive function.

There is also a powerful social-psychological mechanism that may make some people more attracted to exercise than others. People generally like doing what they are good at, and will pursue those activities in leisure time as much as possible. Given the strong positive cultural attitudes towards exercise ability, people who notice that they gain more in performance than others who follow the same exercise regime will

experience strong feelings of competence and mastery. Studies of the ACE I/D polymorphism (Williams *et al.*, 2000; Woods *et al.*, 2000) and the HERITAGE family study (An *et al.*, 2003; Bouchard *et al.*, 1999; Boule *et al.*, 2005; Lakka *et al.*, 2005; Perusse *et al.*, 1988a; Rice *et al.*, 2002; Teran-Garcia *et al.*, 2005) have shown that such differences in the gains in exercise performance during training are strongly heritable. Favorable "trainability genes" may well become genes that predispose to exercise behavior. In support of this "competence hypothesis", a multicenter study in Italian borderline hypertensive subjects (Winnicki *et al.*, 2004) showed that the ACE polymorphism accounted for 21% of the variance in exercise participation. The regular exercisers had a clear excess of the same genotype (I/I) that was associated with the largest training-induced increase in muscle efficiency in British recruits (Williams *et al.*, 2000; Woods *et al.*, 2000). Here, at least, higher exercise ability indeed seems to coincide with higher exercise motivation.

A mechanism related to genetic differences in exercise ability may be the genetic differences in the ability to lose weight. In the HERITAGE family study, large differences in weight loss in response to exercise were observed in response to a highly controlled exercise-training stimulus over a period of 20 weeks in a previously sedentary population (Wilmore *et al.*, 1999). In a follow-up genome scan based on that study, evidence of significant linkage was observed for changes in fat-free mass with the S100A and the insulin-like growth factor I genes, confirming a role for genetic factors in weight-loss in response to exercise. This is rather meaningful, because the desire to lose weight is a frequently cited reason for participation in exercise across many different countries (Haase *et al.*, 2004). Hence, a genetic advantage in the ability to lose weight through exercise may facilitate adherence to regular exercise.

Lastly, the genetic contribution to exercise behavior may act through personality factors, which have been shown to be heritable almost without exception (Boomsma *et al.*, 2002a). Conscientiousness, self-motivation, and self-discipline are essential to adhere to a chosen long term goal even if it violates immediate needs and such factors have long been implied as important determinants of exercise behavior (Dishman *et al.*, 1985). Neuroticism, anxiety, and depression are all associated with lower exercise prevalence (Camacho *et al.*, 1991; Weyerer, 1992). This association has been explained as reflecting a causal effect of exercise, but reversed causality cannot be ruled out. Low self-esteem and depressed mood may well act against participation in exercise, particularly when this needs to be done in an evaluative context.

These various pathways (acute mood effects, high exercise/weight loss ability, and personality) are not mutually exclusive and may operate simultaneously to cause genetic variation in voluntary exercise behavior. Different mixtures of these pathways may apply across countries, depending on the cultural value attached to exercise or the awareness of its health effects. Also, the finding that different genes may influence exercise participation in males and females (significantly so in the Australian, Danish and Dutch samples) may reflect a sex difference in the relative importance of acute mood effects, exercise ability or exercise-induced weight loss. Among adolescents, for instance, the most commonly reported benefit of exercising for females is "to stay in shape", whereas the most commonly reported benefit of exercising among males is "to become strong" (Tergerson and King, 2002).

Our threshold models detected modest geographical variation in exercise participation. The lowest proportion of exercisers was found in Sweden (37% for males and 23% for females) and highest in Australia (64% for males and 56% for females). We hesitate to interpret these prevalence differences as meaningful, because different instruments were used to query exercise in the seven countries. This is an important limitation of this study impairing the comparison of prevalences. A second limitation is the difference in the birth cohorts. Data in Finland and Sweden were collected in the late 70's, and since that time more people are engaging in regular exercise in these countries. In spite of these limitations, Figure 5.1 does not seem to paint an encouraging picture of the exercise habits in the seven participating countries. To maintain improved aerobic fitness, subjects must engage in prolonged (> 20 minutes) exercise activities that require six METs or more for at least three times a week (Blair *et al.*, 1996; Pate *et al.*, 1995). Even at our much milder criterion of 60 minutes at four METs weekly, only about 50% of the subjects were classified as being regularly active in leisure time across all seven countries.

This low prevalence of regular leisure time exercise has been a cause for concern in many countries, and encouragement of a more active lifestyle is an important component of international public health recommendations (World Health Organization, 1995). Combining the strong evidence for its heritability to the importance of exercise for health suggests that identification of the actual genetic variation underlying this crucial health behavior is badly needed. For exercise *ability,* coordinated efforts are ongoing worldwide and a number of genes for endurance and strength have been identified and replicated (Rankinen *et al.*, 2004; Wolfarth *et al.*,

2005). For exercise behavior, no such coordinated effort exists. Apart from the link between the ACE polymorphism and exercise behavior (Winnicki *et al.*, 2004), four associations have been reported. In women but not in men, physical activity levels were associated with polymorphisms in the dopamine D2 receptor gene, which is proposed to play a role in rewarding mechanisms (Simonen *et al.*, 2003a). In 331 early postmenopausal women, physical activity was associated with the aromatase genes (CYP19 polymorphism) (Salmen *et al.*, 2003). In the Quebec Family study, the Melanocortin-4 receptor gene (MC4R-C-2745T variant) showed significant associations with moderate-to-strenuous activity scores and with inactivity scores (Loos *et al.*, 2005). Finally, in 97 healthy girls physical activity was associated with polymorphisms in a calcium-sensing receptor gene (Lorentzon *et al.*, 2001). To our knowledge, only one whole genome scan based on linkage analysis exists for physical exercise (Simonen *et al.*, 2003b). A few putative genomic regions were identified that might harbor genes influencing participation in regular exercise, but the evidence was suggestive only, as the power for linkage in this relatively small and unselected sample was low.

In summary, we find strong evidence for a role of genetic factors in voluntary exercise behavior in population-based samples from seven countries with a predominant North European background. Randomized controlled training trials have clearly shown that regular exercise has a beneficial effect on mental (Babyak *et al.*, 2000; Moore and Blumenthal, 1998; Steptoe *et al.*, 1989) and physical health (Berlin and Colditz, 1990). It is possible, therefore, that the well-known heritability of many health parameters like depression (Kendler and Aggen, 2001), obesity (Schousboe *et al.*, 2003), thrombosis (Dunn *et al.*, 2004), hypertension (Kupper *et al.*, 2005b), diabetes (De Lange *et al.*, 2003) and even cardiovascular mortality (Zdravkovic *et al.*, 2004) may partly reflect the genetic factors for exercise. Detection of these underlying genetic factors will improve our understanding of why some persons fail to engage in regular exercise and potentially improve our ability to intervene. The ability to pool databases of genotype and exercise information across multiple countries would greatly enhance detection of genomic regions implied in exercise behavior. Data from this study suggest that this can be successfully done.

# Chapter 6

# Heritability of life satisfaction in adults: A twin-family study

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Stubbe JH, Posthuma D, Boomsma DI, and de Geus EJC (2005). Heritability of life satisfaction in adults: A twin-family study. Psychological Medicine 35, 1581-1588.

**Abstract**

Subjective well-being (SWB) can be partitioned into the components life satisfaction and affect. Research on factors influencing these components of well-being has mainly focused on environmental characteristics. The aim of this study was to investigate the relative contribution of genes and environment to individual differences in life satisfaction in a large sample of Dutch twins and their singleton siblings. Life satisfaction of 5,668 subjects registered with the Netherlands Twin Registry (NTR) was measured with a Dutch version of the self-reported Satisfaction With Life Scale. An extended twin design was used to obtain correlations in life satisfaction scores for monozygotic twins, dizygotic twins and sibling pairs and to estimate the contribution of genes and environment to the variation in life satisfaction. No differences between males and females were found in the mean level of life satisfaction. Broad-sense heritability was 38%. Non-additive genetic factors explained all or most of the genetic influences. The remaining 62% of the variance in life satisfaction could be attributed to unique environmental factors, both persistent and transitory, plus measurement error. Individual differences in life satisfaction are determined in part by genetic factors that are largely or entirely non-additive in nature.

**Introduction**

Psychiatry and clinical psychology, almost by definition, have focused largely on negative affective states like anxiety, anger, and depression rather than on positive affective states like joy, vigor, happiness, or life satisfaction. This has led to a widespread definition of mental well-being as the absence of negative affect instead of the presence of positive affect (Korten and Henderson, 2000). The latter, however, is arguably more deserving of the predicate well-being. Although this focus on negative affect has given us powerful techniques for the reduction of human suffering, it may also have limited and biased our theories on mental health (Gillham and Seligman, 1999). According to Seligman and Csikszentmihalyi (2000) science and clinical practice that incorporate positive mood states will more optimally serve to increase the quality of life of many patients. They convincingly plea that we should not stop at attenuating the negative mood state of patients but aim further to build positive beliefs such as optimism, self-esteem, subjective well-being, courage, the capacity of pleasure and humor. These qualities will serve as a protective buffer to ensure future mental (Atienza *et al.*, 2002) as well as somatic health (Giltay *et al.*, 2004; Kubzansky *et al.*, 2001).

To further expand our understanding of sources of variation in positive affective states, this paper focuses on subjective well-being (SWB). SWB is defined as the evaluative reaction of a person to his or her life and can be partitioned into the components *life satisfaction* (cognitive evaluation) and *affect* (emotional aspects of the construct, such as happiness) (Diener, 1984). Several studies have focused on the correlates of SWB, such as income (Veenhoven, 1991), and friendship and social activity (Harlow and Cantor, 1996). These factors correlate with well-being, but Lykken and Tellegen (1996) showed in an American twin sample that factors like socio-economic status, educational level, income, marital status, and religious commitment only explain about 3% of the variance in SWB. Costa and colleagues (1987) found similar results and concluded that stable characteristics (i.e. enduring dispositions in an individual) are more useful in predicting SWB than life circumstances, such as changes in work and residence. This finding is in agreement with results from a study by Brickman and colleagues (1978). They confirmed that SWB is strongly influenced by enduring characteristics of the individual by stating that even paralyzed accident victims and lottery winners differ little in happiness level. A recent study in an American sample of 909 employed women also showed that

positive affect and enjoyment are strongly influenced by aspects of temperament and character (Kahneman *et al.*, 2004).

Currently, there are four studies addressing the question to what extent genetic factors contribute to variation in SWB. Lykken and Tellegen (1996) used the Well-Being (WB) scale of the Multidimensional Personality Questionnaire to assess happiness in 2,310 adult twins (age span from 20 to 30 years), resulting in a heritability estimate of around 50%. The correlation for MZ twins was substantial, whereas the correlation for DZ twins was negligible, suggesting that the genetic effects are non-additive (i.e. comprise interactions between genes). Similar results were found in an earlier study using the same measurement instrument (Tellegen *et al.*, 1988). The heritability in this study was estimated at 48% and results showed that non-additive effects played an important role in explaining individual differences in well-being. In both studies the unique environment explained the remaining variance. In a sample of 5,140 young Norwegian adult twins (aged 18 – 25 years) genetic factors also explained about 50% of the variance in SWB and unique environmental factors explained the remaining part (Røysamb *et al.*, 2002). Contrary to Lykken and Tellegen (1996) and Tellegen et al. (1988), Røysamb found slightly different estimates for men (46%) and women (54%). All genetic effects were explained by additive genetic effects and non-additive genetic effects could be omitted from the model. This is in keeping with results from a study using a larger sample of 6,576 Norwegian twins aged 18 – 31 years (Røysamb *et al.*, 2003). Interestingly, an observation study using 128 zoo chimpanzees found similar results for SWB (Weiss *et al.*, 2002), resulting in substantial additive genetic effects.

To our knowledge, not much attention has been paid to the heritability estimates of affect and life satisfaction separately, although research has suggested that these two components of SWB show some degree of independence and, therefore, should be measured and studied individually (Lucas *et al.*, 1996). Therefore, in this paper we investigate the relative contribution of genes and environment to variation in life satisfaction in a large sample of Dutch twins and their non-twin siblings. Adding siblings to the classical twin design increases the statistical power to detect sources of variance due to additive and non-additive genetic influences, and common environment (Posthuma and Boomsma, 2000). Furthermore, this approach provides an optimal design to address the question whether levels of life satisfaction differ

between twins and non-twins and, therefore, whether the results from twin studies on the genetics of life satisfaction may be generalized to the general population.

## Methods

*Subjects*

This study is part of an ongoing study on health and lifestyle in twin families registered with the Netherlands Twin Registry (NTR). Since 1991 every two to three years twins and their families have received a survey sent by mail containing a number of personality inventories, and items about health, regular exercise, alcohol consumption and smoking behavior (Boomsma *et al.*, 2002b). In October 2002, questionnaires were sent to twins, their spouses, parents, and siblings. In March 2003, non-respondents received the questionnaire for the second time. Twins and family members who registered after March 2003 received the questionnaire once.

**Table 6.1.** *Number of families with a specific family constitution.*

| Number of siblings | 0 | 1 | | 2 | | | 3 | | 4 |
|---|---|---|---|---|---|---|---|---|---|
| Sex of siblings | | ♂ | ♀ | ♂♂ | ♀♀ | ♂♀ | ♂♂♀ | ♂♀♀ | ♂♂♀♀ |
| MZM families | | | | | | | | | |
| 2 twins | 139 | 39 | 32 | 5 | 7 | 7 | 3 | 2 | 1 |
| 1 twin | 143 | 10 | 17 | 2 | 1 | 2 | 2 | - | - |
| DZM families | | | | | | | | | |
| 2 twins | 59 | 12 | 21 | 1 | - | - | 2 | 3 | - |
| 1 twin | 115 | 12 | 12 | 1 | 5 | 2 | 2 | - | - |
| MZF families | | | | | | | | | |
| 2 twins | 409 | 53 | 99 | 11 | 14 | 15 | 2 | 4 | 4 |
| 1 twin | 272 | 30 | 44 | - | 3 | 1 | - | - | - |
| DZM families | | | | | | | | | |
| 2 twins | 182 | 31 | 41 | 7 | 9 | 10 | - | 2 | - |
| 1 twin | 206 | 16 | 3 | 24 | 5 | 4 | - | - | - |
| DOS families | | | | | | | | | |
| 2 twins | 167 | 36 | 49 | 3 | 10 | 6 | - | 4 | 1 |
| 1 twin | 294 | 30 | 51 | 1 | 6 | 8 | - | 1 | - |
| No twins | - | 64 | 149 | 2 | 11 | 12 | 2 | 3 | 2 |

*MZM, monozygotic males; DZM, dizygotic males; MZF, monozygotic females; DZF, dizygotic females; DOS, dizygotic opposite-sex twins.*

In this paper we analyze the twin and sibling data from this survey. Questionnaires were sent to 14,162 twins/triplets and 3,606 siblings from 7,261 families. At the end of the data collection, a total of 4,521 twins (response rate = 32%) and 1,455 siblings (response rate = 40%) from 3,153 families had returned a questionnaire. Data from non-biological siblings (n = 30) were discarded. If information on sex (n = 2), age (n = 5), zygosity (n = 73) or life satisfaction (n = 170) was missing, we did not include the participants in the analyses. Finally, we used a maximum number of two additional male sibs and two additional female sibs per twin family, thereby excluding 28 siblings. After removing these participants, the final dataset consisted of 4,329 twins and 1,339 siblings (N = 5,668 participants) with an average age of 33.2 years (sd = 11.3, range 14.1 – 88.3 years). About 75% of the subjects were between 20 and 40 years of age. Table 6.1 gives the twin/sibling composition of the participating families.

Zygosity of 919 same-sex twins was determined on the basis of DNA typing. For the remaining 2,467 same-sex twins, zygosity was based on questions about physical similarity and confusion in identifying the twins by family members, friends, and strangers. For the opposite-sex twin pairs, zygosity is known (DZ) based on their sex. In our sample, agreement between zygosity based on questionnaire data and zygosity based on DNA results was 98%. Grouped according to zygosity and sex, the twin sample consists of 647 monozygotic male twins (MZM), 345 dizygotic male twins (DZM), 1,572 monozygotic female twins (MZF), 822 dizygotic female twins (DZF), and 943 dizygotic opposite-sex twins (DOS). The sibling sample is composed of 535 males and 804 females.

*Measurement*

Life satisfaction refers to the cognitive component of SWB and can be defined as a global assessment of a person's quality of life according to a person's own subjective judgment (Shin and Johnson, 1978). This means that the degree of life satisfaction is based on a unique set of criteria which each individual sets for himself (Diener *et al.*, 1985). The Satisfaction With Life Scale (SWLS) was used to assess global life satisfaction (Diener, 2005) The SWLS contains five items on life satisfaction, such as "In most ways my life is close to my ideal". Participants respond on a scale ranging from one (strongly disagree) to seven (strongly agree).

The scale was translated into Dutch by Arrindell *et al.* (1991). Both the original and the Dutch version of the SWLS have demonstrated good psychometric properties, including high internal consistency and reliability, and the scale is suitable for use with different age groups (Arrindell *et al.*, 1991; Diener *et al.*, 1985; Pavot and Diener, 1993). A total score was calculated by summing the scores of each individual item resulting in a possible range of scores from 5 (low satisfaction) to 35 (high satisfaction). In our sample, Cronbach's alpha was 0.86.

*Analytic procedure*

Quantitative analyses of life satisfaction were carried out in several steps. First, to determine the extent to which MZ twin pairs are more similar than DZ pairs or sibling pairs, correlation coefficients were calculated using the software package Mx (Neale *et al.*, 2003). Comparing the MZ twin-pair correlations with the DZ twin-pair and sibling-pair correlations provides a first estimate of the sources of variation in individual differences in life satisfaction. MZ pairs are genetically identical, whereas DZ and sibling pairs on average share 50% of their segregating genes. Therefore, additive genetic effects (A) on life satisfaction are suggested if the intra-pair correlation in MZ twins is substantially larger than the correlation in DZ twins/singleton sibling pairs. These effects reflect the additive effects of alleles of multiple genes. If the DZ correlation is higher than half the MZ correlation, this indicates that common environmental effects (C) contribute to individual differences in life satisfaction and these effects refer to all environmental factors that contribute to twin similarity. If the opposite is true (i.e. the DZ correlation is lower than half the MZ correlation), this suggests that non-additive genetic effects explain individual variation in life satisfaction (Neale and Cardon, 1992; Plomin *et al.*, 2000). Non-additive genetic effects comprise interactions between two alleles at a locus (dominance) or interactions between genes at different loci (epistasis). Common environmental and non-additive genetic sources of variance are confounded in the classical twin study (i.e. including only MZ twin pairs and DZ twin pairs/sib pairs) as in most non-experimental genetic studies. Therefore, they cannot be estimated at the same time. Finally, because MZ twins have identical common environment and identical genes, an intra-pair correlation different from unity indicates unique environmental effects on life satisfaction (including measurement error).

Structural equation modeling was used to fit different models to the data. First, we fitted a saturated model to estimate the correlations between twin pairs, twin-sibling pairs, and sibling-sibling pairs. In model-fitting procedures, the saturated model is used as a starting-point for the comparison of different, nested models. The fit and parsimony of the various nested models are judged using likelihood ratio tests in which the negative log-likelihood (–2LL) of the nested model is compared with –2LL of the saturated model. Subtracting the two –2LLs from each other yields a statistic that is asymptotically distributed as $\chi^2$ with degrees of freedom (df) equal to the difference in the number of parameters in the two models. According to the principle of parsimony, models with fewer parameters are preferred if they do not give a significant deterioration of the fit ($p > 0.05$).

After estimating the correlations for the different groups, we tested the assumptions of homogeneity of means and variances for MZ twins, DZ twins, and singletons by constraining parameters to be equal or fixing parameters to be zero in the saturated model. We tested whether age and sex influenced individual differences in life satisfaction by retaining these two variables as covariates in model-fitting procedure.

Finally, we tested for heterogeneity of correlations between men and women and between DZ twin and sibling pairs. The latter comparison tests whether there is a specific twin environment. A lower correlation in sibling pairs compared to the correlation in DZ pairs indicates that there may be a specific twin environment influencing individual differences in life satisfaction.

The most parsimonious model was retained to estimate the relative contribution of genetic and environmental influences to individual differences in life satisfaction. The pattern of twin and sibling correlations indicated an ADE model (and not ACE), therefore, the first model decomposes the variances into additive genetic influences (A), non-additive genetic influences (D), and unique environmental influences (E) and tested the significance of D.

**Results**

Mean score for life satisfaction was 27.83 and did not differ between males and females. A small decrease in life satisfaction was found with increasing age (ß = -0.03). This is in keeping with findings from earlier research indicating that there are few age effects and only very small or no differences between men and women in life

satisfaction (Arrindell *et al.*, 1991; Pavot *et al.*, 1991). Means and variances of MZ and DZ twins and singleton siblings did not differ significantly from each other, indicating that there are no twin-singleton differences in life satisfaction. In the saturated model, we tested whether there were male-female differences in total variance. The variance in males ($\sigma^2 = 26.83$) was smaller than in females ($\sigma^2 = 29.70$).

Table 6.2 displays the correlations for all zygosity groups and for the sibling pairs. For both males and females, MZ correlations are larger than DZ correlations, indicating that genetic factors play an important role in explaining individual differences in life satisfaction. The MZ correlations for both men and women are more than twice as large as the correlations for the DZ twins and sibling pairs, suggesting that non-additive genetic effects contribute to individual differences in life satisfaction. The twin correlations for MZM and MZF were the same. All correlations in dizygotic twins were also equal (i.e., *r*DZM = *r*DZF = *r*DOS). Finally, all sibling correlations were equal to the DZ correlations, showing that DZ twins do not resemble each other more than other first-degree siblings (i.e. there is no specific twin environment).

**Table 6.2.** *Maximum-likelihood estimates of twin and sibling correlations and the 95% confidence intervals.*

| | *r* | 95% CI | N[1] |
|---|---|---|---|
| Monozygotic male twins | 0.31 | 0.19 – 0.43 | 235 |
| Dizygotic male twins | -0.01 | -0.18 – 0.17 | 98 |
| Monozygotic female twins | 0.40 | 0.33 – 0.46 | 611 |
| Dizygotic female twins | 0.10 | 0.03 – 0.22 | 282 |
| Dizygotic opposite sex twins | 0.11 | 0.00 – 0.22 | 276 |
| Brothers | 0.18 | 0.00 – 0.49 | 55 |
| Sisters | 0.09 | -0.12 – 0.29 | 94 |
| Brother-sister | 0.01 | 0.00 – 0.17 | 165 |
| Male twin-brother | 0.05 | 0.00 – 0.17 | 281 |
| Female twin-sister | 0.10 | 0.02 – 0.18 | 689 |
| Male twin-sister | 0.11 | 0.03 – 0.19 | 333 |
| Female twin-brother | 0.11 | 0.03 – 0.19 | 468 |
| All monozygotic twins[2] | 0.38 | 0.33 – 0.44 | 846 |
| All first degree relatives[2] | 0.09 | 0.05 – 0.14 | 4055 |

*r, correlation; 95% CI, 95% confidence interval; n, number of complete pairs*
[1]*Correlations are based on complete and incomplete pairs.*
[2]*After constraining these correlations to be equal.*

To account for the heterogeneity in the variances of males and females, a scalar model was used in the variance decomposition models (Figure 6.1). In this model the total variance of the females is specified as a scalar times the variance of the males. The relative contributions of the variance components are equal for males and females, because there were no sex differences in the twin or sibling correlations. As expected, dropping the scalar from the model gave a significant deterioration of the fit ($p = 0.01$).

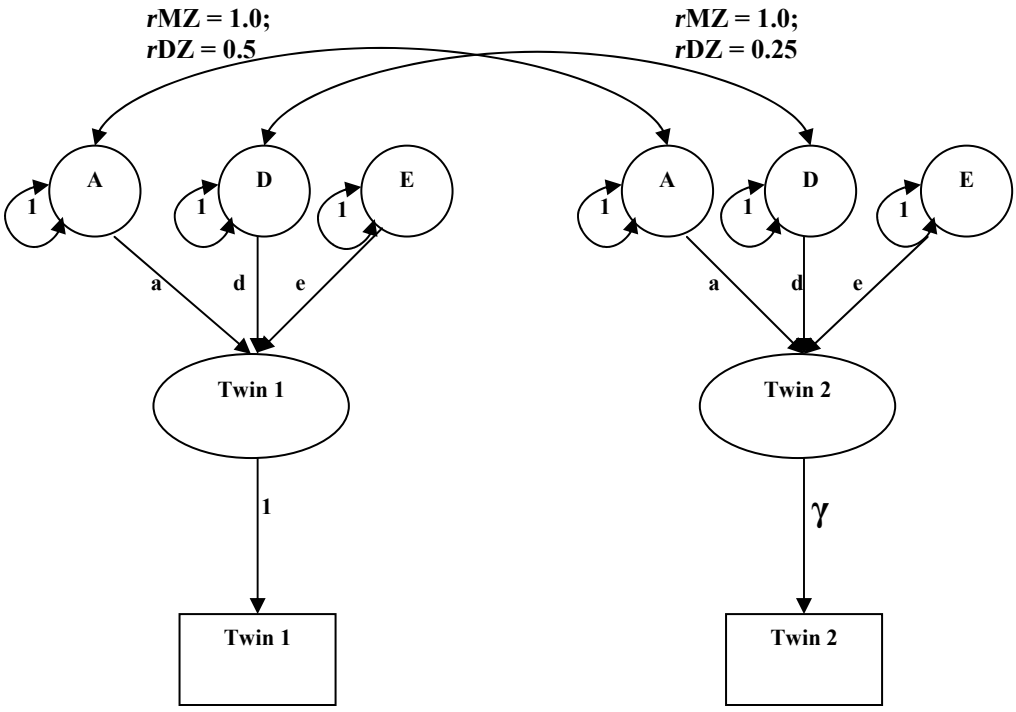


**Figure 6.1.** *ADE scalar model. The figure represents a dizygotic opposite-sex pair where the first-born twin is a male and the second-born twin is a female. Rectangles depict measured phenotypes and circles surround latent variables. A (additive genetic effects), D (non-additive genetic effects) and E (non-shared environmental effects) represent the sources of variance. The letter γ denotes the scalar parameter and accounts for the difference in variance between men and women. Path coefficients are represented by a, d and e.*

The results of genetic model fitting are summarized in Table 6.3. Compared to the saturated model, the ADE model gives a good fit to the data in this large dataset. Excluding non-additive (D) genetic influences from the model (AE model) resulted in a significant worsening of the fit ($p < 0.05$), and dropping both the additive and

dominance genetic variance components was also not allowed ($p < 0.05$). Thus, the ADE model without sex differences in heritability is the best-fitting model. Non-additive genetic factors explained 38% (95% CI = 20% – 44%) of the variance. The point estimate of the additive genetic effects was 0% (95% CI = 0% – 16%). The remaining 62% of the variance was attributed to unique environmental factors (including measurement error) (95% CI = 0.56% – 0.67%).

**Table 6.3.** *Univariate model fitting results for twins and siblings: goodness of fit ($\Delta\chi^2$) for saturated and genetic models.*

| Model | vs | -2LL | df | $\Delta\chi^2$ | $\Delta$df | p |
|---|---|---|---|---|---|---|
| 1. Saturated model | | 34931.46 | 5645 | | | |
| **2. ADE model** | **1** | **34947.13** | **5662** | **15.67** | **17** | **0.55** |
| 3. AE model | 2 | 34962.35 | 5663 | 15.22 | 1 | 0.00 |
| 4. E model | 2 | 35094.57 | 5664 | 132.22 | 1 | 0.00 |

*A, additive genetic effects; D, non-additive genetic effects; E, unique environmental effects; vs, versus and indicates with which model the submodel is compared to; -2LL, -2 log-likelihood; df, degrees of freedom; p, p-value. The most parsimonious solution is printed in boldface type.*

**Discussion**

Subjective well-being (SWB) can be partitioned into the components life satisfaction and affect. Research on factors influencing individual differences in these components of well-being has mainly focused on environmental characteristics. A few genetic studies mainly targeted the component of SWB as a whole. The aim of this study was to examine the relative contribution of genes to variation in the cognitive component of SWB (i.e. life satisfaction). In a large sample of Dutch twins and their siblings, genetic model fitting showed a significant contribution of genetic factors (38%) to life satisfaction. Environmental factors unique to the individual, rather than the environment shared by family members, explained the largest part of the variance in life satisfaction (62%).

To our knowledge, the sources of variance in the cognitive component (i.e. life satisfaction) of SWB have been studied only once before in a sample of elderly subjects from the Swedish Adoption/Twin Study of Aging (Harris *et al.*, 1992). In twins with an average age of 51 years, 32% of variation in life satisfaction could be attributed to genetic factors, which compares well to our finding in young adult to middle-aged twins and siblings. In their oldest age twin group (average age of 72 years)

genetic effects on life satisfaction were substantially larger (52%). We extended on these findings by including SWLS data from twins as well as from additional siblings present in the twin family. This provides an optimal design to test whether there are specific twin effects. Based on our results we conclude that the estimates of genetic and environmental contribution to variation in life satisfaction can be generalized to the general Dutch population.

A second advantage of using the extended twin design is that the statistical power to discriminate between additive genetic effects and common environmental and non-additive effects increases. We found that the genes underlying life satisfaction appear to act in a non-additive manner. This corresponds to the findings of Lykken and Tellegen (1996) on the affective component of well-being, who also found high MZ correlations and much lower DZ correlations. A further study by Tellegen and colleagues (1988) reported a heritability of 48% for SWB, and again non-additive genetic effects had to be included in the model. Taken together, these findings suggest that the genetic effect on well-being and life satisfaction is characterized by non-additive genetic variation, which can consist of dominance variation or epistatic variation or both.

The genetic architecture of well-being is relative unique compared to findings in other studies investigating typical personality traits like neuroticism. For example, in a large twin study on a sample of 45,850 Australian and American subjects individual differences were explained by large additive genetic effects and only very small non-additive effects were found (Lake *et al.*, 2000). Dominance variance of a trait refers to the variance due to the interaction effect of the two alleles that define the genotype at a locus. Dominance is distinct from the interaction that may occur between genotypes at separate loci (i.e. epistasis). The confidence interval for the additive (95% CI = 0% – 16%) and non-additive (95% CI = 20% – 44%) variance components are large, indicating that the estimate of the additive component could be anywhere between the 0% and 16%, whereas the non-additive variation lies between the 20% and 44%. Such large fluctuations in estimates were discussed by Eaves (1972) who used computer simulation to show that estimates of non-additive genetic influences and additive genetic influences are negatively correlated. The estimate of the broad heritability (i.e. the heritability due to additive and non-additive genetic influences) is stable, but large fluctuations in the estimates of the two components occur. Information from many different genetic relationships (e.g. twins, half siblings, parent-offspring) are needed to

reliably separate additive genetic influences from non-additive genetic influences reliably in non-experimental studies.

The mean level of SWLS score is relatively high compared to the findings in other countries. As information on life satisfaction was accumulated by mailed surveys, selective non-response to mailed surveys may have introduced bias if refusal to participate was not distributed randomly, being higher in those scoring low on the SWLS. However, the high level of SWLS is in agreement with results from a study comparing life satisfaction of people from 31 nations that showed Dutch persons tend to have higher average levels of life satisfaction compared to citizens of other countries (Diener and Diener, 1995). To investigate potential bias further, we exploited the genetic relatedness in our sample. Vink and colleagues (2004) proposed the use of data from respondents as a proxy for the data from their non-responding family members to estimate the non-response bias in a twin-family study. Results showed that scores of members from incomplete twin pairs tended to be more unfavorable (for example higher scores on anxious depression and neuroticism) than the scores from complete twin pairs. In our sample, no differences in life satisfaction between MZ twins from complete pairs versus incomplete MZ pairs were found ($p = 0.56$) and DZ twins from complete pairs also did not significantly differ in life satisfaction from incomplete DZ twins ($p = 0.89$).

We did not find effects of environmental factors that are shared by members of a sibship, for example socio-economic class of the parents. Generally the absence of an impact of socio-economic factors on life satisfaction is in good agreement with a recent study by Kahneman and colleagues (2004) who found that positive affect and enjoyment were strongly influenced by aspects of temperament and momentary environmental influences. General circumstances like income and education only had a small influence on the enjoyment of a regular day.

Two studies showed that the instrument used here (SWLS) can reliably detect changes over time, such as the increase or decrease of life satisfaction after positive or negative life events (Suh *et al.*, 1996; Vitaliano *et al.*, 1991). As discussed by Pavot and Diener (1993), these studies suggested that life satisfaction has a long-term component due to stable life circumstances (e.g. due to personality), a moderate-term component (e.g. due to recent life events or current work load), and a short-term state component (e.g. due to current mood). Our results are in agreement with such a model, and suggest that the individual differences in the long-term component of life satisfaction

may be caused by genetic factors, whereas the moderate-term and short-term state component may be caused by environmental factors specific to the subject.

# Chapter 7

# The association between exercise participation and well-being: What is causing it?

This chapter is based on:
Stubbe JH, Boomsma DI, and De Geus EJC (submitted). The association between exercise participation and well-being: What is causing it? Preventive Medicine.

**Abstract**

We investigated the association between exercise participation and well-being (i.e. life satisfaction and happiness) and examined the causality underlying this association. The association between exercise participation and well-being was assessed in around 8,000 subjects, 18 to 65 years from the Netherlands Twin Registry. Causality was tested with the co-twin control method (Cederlof et al., 1977; Kendler et al., 1993) in 187 MZ twin pairs, 178 DZ twin and sibling pairs, and 2,848 unrelated individuals. Exercisers were more satisfied with their life and happier than non-exercisers at all ages. The odds ratio for life satisfaction given exercise participation was significantly higher than unity in unrelated pairs and DZ pairs but not in MZ twin pairs. The odds ratio for happiness given exercise participation was significantly higher than unity in unrelated pairs and a trend was visible in DZ pairs. In MZ pairs, the odds ratio was again close to unity. Exercise participation is associated with higher levels of life satisfaction and happiness. This association is non-causal and appears to be mediated by genetic factors that influence both exercise behavior and well-being.

**Introduction**

There is a large body of literature concerning the effects of exercise on mental health (Byrne and Byrne, 1993; Gauvin and Spence, 1996; Salmon, 2001; Scully *et al.*, 1998). Cross-sectional population studies have shown that non-exercisers are characterized by higher levels of anxiety and depression (Camacho *et al.*, 1991; De Moor *et al.*, in press; Farmer *et al.*, 1988; Gauvin and Spence, 1996; Steptoe and Butler, 1996; Strawbridge *et al.*, 2002). However, a serious limitation of these studies is that they almost exclusively used measures of negative affectivity or clinical outcomes. This may not be the best approach to understand effects of exercise in the population at large. The majority of people are not afflicted with psychopathology, but show large variation in the normal range of psychological well-being (Diener, 1984; Kahneman *et al.*, 2004; Koivumaa-Honkanen *et al.*, 2004). By focusing exclusively on the "bad" end of the distribution, we may have failed to use the information contained in the bulk of subjects in the middle.

To our knowledge, the association between exercise participation and positive measures of well-being remain unexplored in large population-based samples. In this paper, we investigate the association between exercise participation and well-being, where well-being is partitioned into its two components (i.e. life satisfaction and happiness). Furthermore, we test whether the association between exercise participation and well-being is more likely to be causal than non-causal by using the co-twin control method (Cederlof *et al.*, 1977; Kendler *et al.*, 1993). This method calculates the odds ratio (OR) of having high levels of well-being while exercising versus having high levels of well-being while not exercising in three specific groups: 1) MZ pairs in which one twin is an exerciser, while the co-twin is a non-exerciser, 2) DZ pairs similarly discordant for exercise participation, and 3) unrelated individuals in which about half of the subjects exercises and the other half does not.

Different hypotheses about the association between exercise participation and well-being lead to different expectations for the ORs in these three groups. This is illustrated in Figure 7.1. If the relationship is causal (i.e. exercise participation directly causes an increase in the level of well-being) the increase in well-being through exercising will be the same in the three groups (Figure 7.1: model 1). Exercisers will have a higher chance of having high levels of well-being than non-exercisers, regardless of the degree of genetic similarity between them.

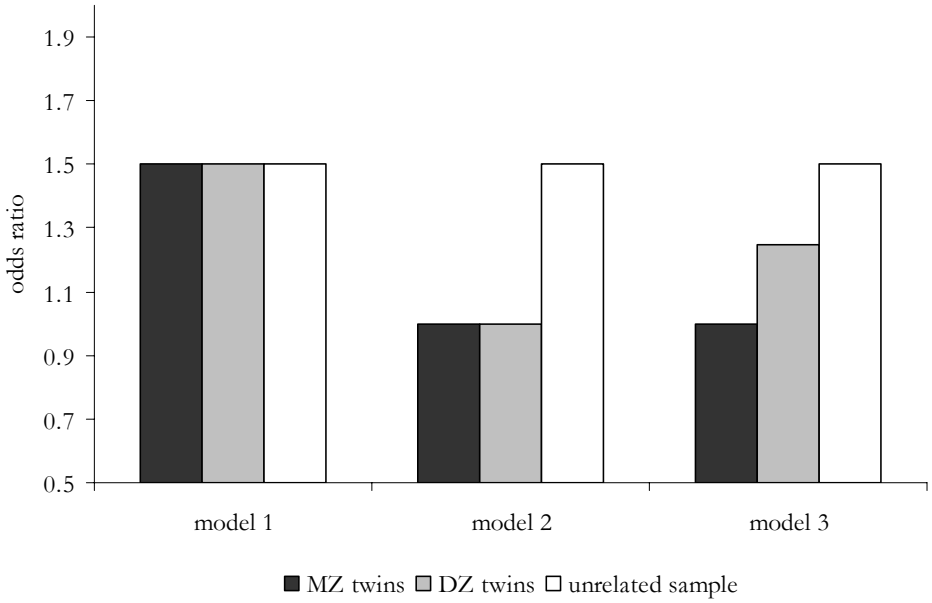


**Figure 7.1.** *The co-twin control method. The odds ratio for life satisfaction given exposure to exercise in the general population, in members of dizygotic (DZ) same-sex twin and sibling pairs discordant for exercise participation and in members of monozygotic (MZ) twins discordant for exercise participation as a function of whether the relationship between exercise participation and life satisfaction is truly causal (model 1), is non-causal and due to the family environment that predispose to both exercise participation and life satisfaction (model 2) or is non-causal and is due to genetic factors that predispose to both exercise participation and life satisfaction (model 3).*

If the association between exercise participation and well-being is non-causal and due to shared familial environmental factors (e.g. socio-economic status, neighborhood, parental rearing style), the expected OR for well-being given exercise participation will be significant in the group of unrelated individuals, but in the discordant MZ or DZ twin pairs it will be unity (Figure 7.1: model 2). Since the family environment is shared by both types of twins alike, its effect on well-being and exercise will make them resemble each other for both traits. To make sense, this model does require that well-being and exercise behavior are sensitive to shared environmental influences.

A non-causal association between exercise participation and well-being may also arise from genes influencing both exercise participation and well-being (Figure 7.1: model 3). Again, the OR for well-being, given exercise participation should be

significantly higher than unity in the unrelated pairs. In MZ twin pairs, however, the OR would be unity because the exercising and non-exercising members of a discordant MZ pair would completely share their genetic predisposition for well-being. In DZ twins, the OR would be intermediate because the exercising twin and non-exercising co-twin share on average only 50% of their genetic predisposition to well-being. To make sense, this model requires that both well-being and exercise behavior are heritable traits.

In summary, the co-twin control method can discriminate between a causal effect of exercise participation on well-being and an association brought about by familial effects (shared environment or shared genes) that influence both exercise participation and well-being.

## Method

*Subjects*

All subjects participate in a longitudinal study on health and lifestyle in twin families registered with the Netherlands Twin Registry (NTR) (Boomsma *et al.*, 2002b; Stubbe *et al.*, 2005b; Vink *et al.*, 2004). In the 2002 wave of this study, they received a survey by mail in which both exercise behavior and life satisfaction were assessed. A total of 10,344 individuals (4,541 twins, 1,458 siblings, 2,818 parents and 1,527 spouses of twins) from 3,463 families returned the survey. Participants with an injury or disease currently preventing participation in exercise (n = 1,344), participants with missing zygosity (n = 47), participants younger than 18 and older than 65 (N = 399) and participants with missing exercise data (N = 91) were excluded from the analyses. Participants with more than one item missing on life satisfaction (N = 99) were omitted, resulting in a total of 8,364 subjects in which the association between exercise participation and life satisfaction could be tested. Participants with one or more items missing on happiness (N = 387) were excluded, resulting in a total of 8,076 subjects in which the association between exercise participation and happiness could be tested.

For the co-twin control method, only the twins and siblings were used and three specific groups were formed with the maximum available data on life satisfaction and happiness. For life satisfaction, a group of 187 monozygotic twin pairs (MZ) was formed in which one member of the pair exercised regularly and the other did not (50 male MZ and 137 female MZ pairs). Secondly, 178 first-degree same-sex pairs were selected to be similarly discordant for regular exercise (26 dizygotic male twins pairs

(DZM), 93 dizygotic female twin pairs (DZF), 27 brother-brother pairs and 32 sister-sister pairs). Thirdly, 2,848 unrelated individuals were selected from the total sample of twins and siblings by randomly selecting one person from each family. Of these subjects, 49.8% were exercisers.

The same procedure was repeated for happiness resulting in groups of 172 MZ pairs, 172 DZ pairs and 2,807 unrelated subjects.

Approval of the study was obtained from the Medical Ethics Committee of the Vrije Universiteit.

*Instruments*

Exercise participation is a dichotomous variable primarily based on the question: "Do you participate in exercise regularly?", which could be answered with "yes" or "no". To further qualify exercise participation, those answering "yes" were asked what kind of exercise they were involved in, and how much time (minutes a week) they spent exercising. Ainsworth's Compendium of physical activity was used to recode each exercise activity into metabolic equivalents (METs), representing one MET as the rate of energy expenditure of an individual at rest which is approximately one kcal/kg/h (Ainsworth *et al.*, 2000). Twins were classified as exercisers if they were engaged in one or more leisure time exercise activities with a minimum intensity of four METs, and the total time spent on all activities was at least 60 minutes a week. They were classified as non-exercisers otherwise. To establish temporal stability of our classification, exercise participation was re-measured in 186 participants after about six months. The tetrachoric correlation between the two measurements was very high ($r$ = 0.91; 95% CI = 0.82 – 0.96).

Subjective well-being (SWB) is defined as the evaluative reaction of a person to his or her life and can be partitioned into the components *life satisfaction* (cognitive evaluation) and *affect* (emotional aspects of the construct, such as happiness) (Diener, 1984). Life satisfaction refers to the global assessment of a person's quality of life according to a person's own subjective judgment (Shin and Johnson, 1978). It was measured with the Satisfaction With Life Scale (SWLS: Diener *et al.*, 1985). This scale contains five items such as "In most ways my life is close to my ideal". It was translated into Dutch by Arrindell and colleagues (1991). Both the original and the Dutch version of the SWLS have demonstrated good psychometric properties (Arrindell *et al.*, 1991; Diener *et al.*, 1985; Pavot and Diener, 1993). In our sample,

Cronbach's alpha reliability was 0.85. For the co-twin control method, life satisfaction was partitioned into two categories (i.e. low and high), using the mean value of 27 as a cutoff-point.

Happiness was assessed with a Dutch adjusted version of the subjective happiness scale (Lyubomirsky and Lepper, 1999). This scale contains four items on happiness such as "In general, I consider myself a happy person". Reliability in our sample was high (Cronbach's alpha = 0.83). For the co-twin control method, happiness was partitioned into two categories (i.e. low and high), using the mean value of 22.5 as a cutoff-point.

*Statistical methods*

In the entire sample, linear mixed modeling in SPSS (Norusis, 2004) was used to test for differences in means on life satisfaction and happiness between exercisers and non-exercisers. This procedure allows for modeling statistical dependencies among observations by including random effects, such as dependencies due to nested sampling. The effects of exercise participation, gender and age (including interaction effects) on well-being were modeled by including them as fixed effects in the model. The model included a family effect that varied randomly over families, correcting for individuals nested within families. As expected, the variances of the family effect on life satisfaction and happiness significantly differed from zero, indicating that the correction for family structure was necessary.

To investigate whether the association between exercise participation and well-being was causal or non-causal, the co-twin control method (Cederlof *et al.*, 1977; Kendler *et al.*, 1993) was applied to the data. This design calculates the odds for an event, which is defined as the probability of occurrence over the probability of non-occurrence. For this method, life satisfaction and happiness were partitioned into two categories (i.e. low and high). In this paper, the odds ratio (OR) is calculated as the ratio between the chance of having high levels of well-being while exercising and the chance of having high levels of well-being while not exercising. The OR's were calculated separately for the discordant MZ pairs, discordant DZ pairs, and the unrelated individuals, and 95% confidence intervals were calculated using SPSS.

**Results**

In testing the effects of exercise, gender and age on life satisfaction and happiness, all two-way interaction effects (exercise*age, exercise*gender, age*gender) were not significant ($p > 0.05$) and dropped from the model. Exercise had a significant effect on both life satisfaction and happiness ($p$'s $< 0.01$). At all ages, exercisers were more satisfied with their lives and happier than non-exercisers. Estimated marginal means for life satisfaction were 26.5 for non-exercisers and 27.2 for exercisers. Estimated marginal means for happiness were 22.4 for non-exercisers and 22.9 for exercisers. Life satisfaction and happiness decreased with increasing age and men were significantly more satisfied with their lives and happier than women ($p < 0.01$).

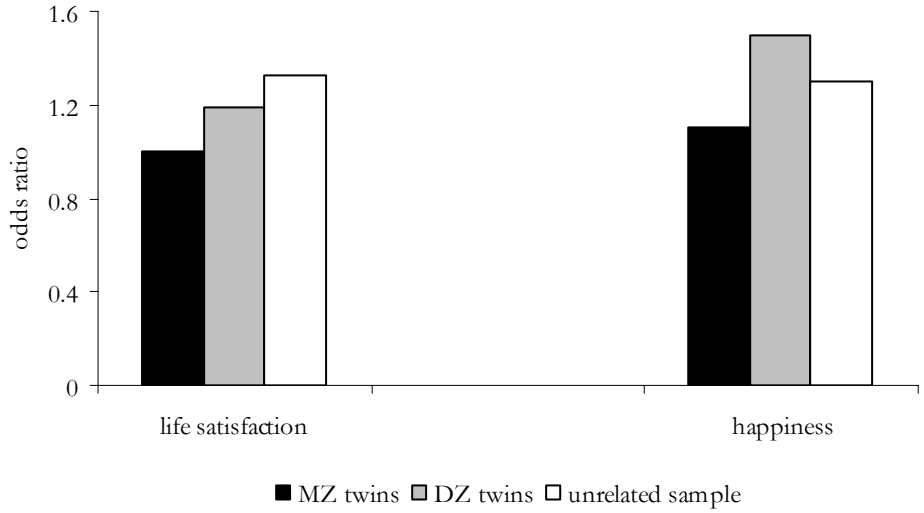


**Figure 7.2.** *The odds ratio for life satisfaction given exercise participation in MZ pairs discordant for exercise participation, in DZ pairs discordant for exercise participation, and in an unrelated sample.*

To examine whether the association between exercise participation and well-being was causal or non-causal, we computed the OR and its 95% CI for each of the three groups. These are depicted in Figure 7.2. For life satisfaction, the OR was significantly different from unity in the group of unrelated subjects (OR = 1.33; 95% CI = 1.14 – 1.55) but not in the group of DZ (OR = 1.19; 95% CI = 0.77 – 1.83) or MZ twin pairs (OR = 1.00; 95% CI = 0.65 – 1.53). For happiness, a similar pattern was found. The OR was significant in the group unrelated subjects (OR = 1.31; 95%

CI = 1.12 – 1.53) but not in the discordant DZ twins (OR = 1.54; 95% CI = 0.99 – 2.40) or MZ twin pairs (OR = 1.08; 95% CI = 0.70 – 1.67), although the OR of the DZ twins was close to significance. For both phenotypes, the OR for the MZ twins was close to unity and well outside the CI of the unrelated pairs.

**Discussion**

A primary finding from this study is that exercisers are on average more satisfied with their lives and happier than non-exercisers. Causal effects of exercise, however, do not seem a likely source of these associations. Instead, application of the co-twin control method (Cederlof *et al.*, 1977; Kendler *et al.*, 1993) argued strongly in favor of an "underlying factor" influencing both exercise participation and well-being in members of the same family. This factor may consist of shared environmental influences or a shared genetic make-up. The latter seems more likely on two accounts. First, the observed patterns in MZ, DZ and unrelated groups, in particular the ORs close to unity in the MZ twins, most closely resemble model 3 in figure 7.1, which obtains when genetic factors cause the association.

Second, the evidence for shared environmental influences on either well-being or exercise behavior is far less convincing than the evidence for genetic influences on both these traits. Previous results from a partly overlapping sample, for instance, concluded that exercise participation and life satisfaction are highly heritable and common environmental factors do not influences individual differences in these two traits (Stubbe *et al.*, submitted a; Stubbe *et al.*, 2005b). This is in good agreement with results in other adult twin samples that tested the cause of familial resemblance in exercise behavior (De Geus *et al.*, 2003; Frederiksen and Christensen, 2003; Lauderdale *et al.*, 1997) and well-being (Lykken and Tellegen, 1996; Røysamb *et al.*, 2002; Røysamb *et al.*, 2003; Tellegen *et al.*, 1988) and found significant heritability without evidence for shared environmental effects.

*Study limitations*

A first potential limitation to the co-twin control method is that the results from twin samples may not properly generalize to the population at large. There is, however, no current evidence to support a difference between twins and singletons with regard to well-being. In contrast, when twins and their singleton brothers and sisters were directly compared with regard to life satisfaction no such specific "twin

effects" were found (Stubbe *et al.*, 2005b). This was again replicated in the current sample in which we also did not find differences in the prevalence of exercise participation in twins and singletons.

Secondly, the co-twin control method does not identify the actual molecular mechanisms by which genetic variation causes individual differences in both well-being and exercise behavior. One attractive mechanism, although speculative at present, is the mesolimbic dopaminergic reward system. This system has been proposed to play a key role in a range of phenotypes related to rewarding mechanisms (Schulz, 1999) and is likely to influence well-being. Interestingly, Simonen and colleagues (2003a) have shown that a common variant in a gene for a key dopamine receptor (DRD2) was associated with exercise behavior. Clearly, the dopaminergic system is only one route along which genes may independently affect well-being and the drive to exercise. There are many plausible alternatives, including genetic variation in opioid and serotonergic systems (Chaouloff, 1997; Hara and Floras, 1995; Jarvekulg and Viru, 2002; McCubbin *et al.*, 1992; Schwarz and Kindermann, 1992). A complete mechanistic understanding of the "nature" of the association between well-being and exercise participation may well have to await progress in gene finding for either of these traits.

# Chapter 8

## Summary and discussion

## Introduction

The present thesis examined the genetics of exercise participation and well-being in twin families registered with the Netherlands Twin Registry (NTR). This final chapter summarizes the results that have been described in the previous chapters and discusses the implications for further research.

## Changes in genetic architecture of exercise behavior across the life span

A variety of twin studies have shown that genetic factors contribute to individual differences in exercise participation and quantity (i.e. frequency, duration and/or intensity) (Beunen and Thomis, 1999; Boomsma *et al.*, 1989; De Geus *et al.*, 2003; Frederiksen and Christensen, 2003; Heller *et al.*, 1988; Koopmans *et al.*, 1994; Lauderdale *et al.*, 1997; Maia *et al.*, 2002; Perusse *et al.*, 1989). Chapter two reviewed these studies and two striking findings stood out. First, the genetic architecture of exercise behavior changes strongly across the life span, most dramatically between the ages 15 and 20 years. Secondly, all studies in adult twins consistently suggest a significant genetic contribution to adult exercise participation. Both findings were corroborated by our own research, presented in chapters four and five.

In chapter four, we described the results of a study on the variation in exercise participation of Dutch male and female twins between the ages of 13 and 20 years. Up till age 13 – 16, genes are of no importance in explaining individual differences in exercise participation, and the large degree of familial resemblance is explained by common environmental effects. In late adolescence (from approximately age 17 onward), genetic factors start to appear and the role of common environment decreases. Genetic factors peak in their contribution to exercise behavior around age 18 – 20. In chapter five, we reported on the largest twin study on exercise behavior ever. The GenomEUtwin project ("Genome-wide analyses of European twin and population cohorts to identify genes predisposing to common diseases") entails one of the largest research consortia in genetic epidemiology in the world with a collection of over 0.8 million twins. Self-reported data on frequency, duration and intensity of exercise behavior from Australia, Denmark, Finland, Norway, The Netherlands, Sweden and United Kingdom were used to create an index of exercise participation in each country. Results obtained in 85,198 twins aged 19 – 40 years showed a median heritability of exercise participation of 62% across the seven countries, ranging, in males, from 27% in Norway to 67% in The Netherlands and, in females, from 48% in

Australia to 71% in the UK. Shared environmental effects played a role only in exercise participation of the Norwegian males (37%), but were of no importance in the other countries.

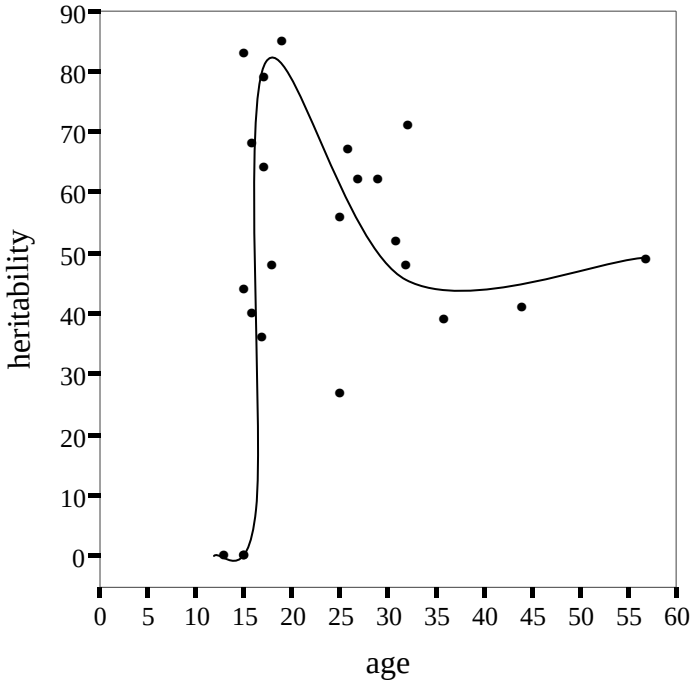


**Figure 8.1.** *Heritability estimates for exercise participation as a function of mean age of the twin sample.*

To summarize the outcomes of the twin studies reviewed in chapter two plus that of our own studies, we plotted the heritability estimates as a function of the mean age of the samples under investigation (Figure 8.1). The tentative curve drawn through this plot clearly shows that the genetic architecture changes across the life span. These changes have direct bearing on studies assessing heritability using parent-offspring correlations or younger-older sibling correlations. Such studies have systematically yielded lower heritability estimates than twin studies. We suggest that these lower heritability estimates may partly reflect the lower heritability in some age groups than in others or the expression of different genes at different ages.

**Common environment in adult exercise behavior**

A number of studies show low to moderate tracking from childhood exercise behavior to adult exercise behavior (Fortier *et al.*, 2001; Malina, 1996; Twisk *et al.*, 2000). Tracking, or stability, refers to the maintenance of relative rank or position over time. Inter-age correlations are generally used to estimate stability. It has been suggested that correlations < 0.30 are indicative of low stability, whereas those ranging from 0.30 to 0.60 are moderate, and those > 0.60 are high (Malina, 1996). A review by Malina (1996) shows that, although different indicators of physical activity and different methods of analysis are used, physical activity tracks at low to moderate levels during adolescence and adulthood. This is consistent with results from the longitudinal Amsterdam Growth and Health Study (Twisk *et al.*, 2000). In subjects with a mean age of 13.1 (± 0.8) years, total time spent on all habitual physical activities in relation to school, work, sports, and on other leisure time activities was measured with an interviewer administered activity questionnaire. During the first four years of the study, yearly measurements were carried out. Later on, two follow-up measurements took place after eight and fourteen years, respectively. The stability coefficient for daily activity, summarizing tracking across all intervals, was 0.34 (95% CI = 0.19 – 0.49) indicating that there was low to moderate tracking.

We essentially replicated this finding using existing and newly collected data from the Netherlands Twin Registry (NTR). Chapter three described in detail the newly data collection. Table 8.1 shows seven year tracking of exercise participation from ages 13 to 16 to ages 20 to 23. Low to moderate tracking coefficients were found ranging from 0.22 to 0.44. Model fitting results showed that these correlations did not significantly differ from each other ($p = 0.56$), resulting in an overall tracking coefficient of 0.37 from ages 13 – 20 to 16 – 23, which is in keeping with the stability coefficient of 0.34 found in the Amsterdam Growth and Health Study, even though our cohort was born more than 10 years later.

In view of the striking shift in genetic architecture during adolescence, this tracking may seem puzzling. If common environmental factors influence exercise behavior among children and their exercise behavior tracks into adulthood, one would expect to find enduring effects of the environment they shared as youngsters even after they reach adulthood. In spite of this expectation, most of the studies in adults do not find evidence for common environment at all, including six of the seven samples in the GenomEUtwin study.

**Table 8.1.** *Seven-year tracking of exercise participation from adolescence into adulthood.*

| Initial age and age at follow-up | Number of subjects participating in the 2 surveys | Tetrachoric correlation |
|---|---|---|
| From age 13 to age 20 | 169 | 0.41 |
| From age 14 to age 21 | 184 | 0.22 |
| From age 15 to age 22 | 181 | 0.44 |
| From age 16 to age 23 | 214 | 0.36 |

A first potential explanation for the absence of C in adult samples is a lack of power to detect common environment in smaller sized twin studies. Most studies measured exercise behavior as a dichotomy, and at heritabilities between 30% and 70%, large samples are needed to detect additional common environmental influences of modest size as is shown in Table 8.2. (Neale *et al.*, 1994). However, at least three samples of the GenomEUtwin study (with heritability at 50%) easily exceed this sample size and yet did not detect common environment.

**Table 8.2.** *Sample size in subjects (N) needed to detect common environmental influences ($V_C$) on a dichotomous trait in full ACE models under varying levels of variation due to additive genetic sources ($V_A$).*

| | $V_A$ = 30% | | $V_A$ = 40% | | $V_A$ = 50% | | $V_A$ = 60% | | $V_A$ = 70% | |
|---|---|---|---|---|---|---|---|---|---|---|
| $V_C$ | 10% | 20% | 10% | 20% | 10% | 20% | 10% | 20% | 10% | 20% |
| N | 13,681 | 3,152 | 12,908 | 2,919 | 12,007 | 2,661 | 11,000 | 2,387 | 9,919 | 2,108 |

*MZ/DZ ratio = 1/1; significance level a = 0.05; power (1–β) = 0.80.*

A second potential explanation is that in adulthood common environmental factors interact with genetic make-up. Since twin studies cannot discriminate between main effects of genes and their interaction with common environmental influences (CxG); any CxG interaction would end up as a main effect of genetic factors in the classical twin model (Purcell, 2001). There is, in fact, a straightforward theoretical account for a CxG interaction on exercise behavior that would be compatible with such a scenario. It has been suggested that genetic influences on exercise ability, which are very strong both for strength and endurance phenotypes (Arden and Spector, 1997; Bouchard *et al.*, 1998; Thomis *et al.*, 1997), may explain part of the heritability of exercise behavior (Stubbe *et al.*, 2005a).The basic idea is that people, in particular

adolescents, will seek out the activities that they excel in. Hence, genes for exercise ability will become genes for adolescent exercise behavior. The parents and older siblings may be helpful to make sure the youngsters regularly get to the playing field in the first place, but after this their genotypes will determine whether they like exercising enough (by excelling in it) to maintain the behavior when guidance by family members ceases to be of importance in late adolescence.

**Different genes at different ages?**

The above CxG scenario would still leave unexplained why there is a peak in heritability around age 18 – 25. This peak was most clearly demonstrated in a study that assessed exercise behavior in an identical way in a cohort of 17 year old and a cohort of 45 year old twins (De Geus *et al.*, 2003). Heritability was found to be much higher in the adolescents (79%) than in the adults (41%). Does the impact of the unique environment on exercise habits increase after young adulthood, for instance due to factors like work stress and child care load? That is entirely possible, and would fit with data indicating that the most often reported barrier to exercise is "lack of time" (King *et al.*, 1992; Sallis and Hovell, 1990). Another, and potentially related, possibility is that in adolescence different genes play a role in exercise behavior than in adulthood. Genes that play a role in adolescent exercise behavior may be mainly related to exercise ability and the enjoyment related to self-perceived physical efficacy. Taken the strong positive cultural attitudes towards exercise, adolescents who are proficient in exercise may be more likely to adhere to a regular exercise regime because it gives them feelings of competence and mastery. The importance of exercise competence may decrease as subjects enter adulthood. As a consequence, genes influencing exercise ability may also loose their importance for exercise behavior.

In contrast genes that influence personality or the extent of mental and physical health effects of exercise may start to influence exercise behavior only in full adulthood. Neuroticism and extraversion show stable individual differences from an early age onward (Caspi and Roberts, 2001). In adult samples a robust association between both personality traits and exercise participation is found (De Moor *et al.*, in press) whereas the link is less clear in adolescence (Allison *et al.*, 2005). Thus, it is possible that in the transition from adolescence to adulthood the genes influencing personality become increasingly important for exercise. This may also apply to the genes that influence physical and mental health benefits of exercise. Such benefits are

systematically mentioned as the main reason to (plan to) engage in exercise in adult populations (Zunft *et al.*, 1999) but may not be of the same magnitude in all subjects. Standardized training programs have clearly shown that some persons are more responsive to the same exercise regime than others in terms of increased fitness, reduced body fat, reduced blood pressure or increased HDL. These individual differences in the health effects of exercise were shown to largely reflect differences in genetic make-up (An *et al.*, 2003; Bouchard *et al.*, 1999; Boule *et al.*, 2005; Lakka *et al.*, 2005; Perusse *et al.*, 2000; Rice *et al.*, 2002; Teran-Garcia *et al.*, 2005). Although currently unknown, mental benefits may well show a similar dependency on genotype. It seems a reasonable hypothesis that persons with the largest mental and/or physical benefits find it most easy to adhere to exercise. Thus, genes influencing the extent of the health effects may also be important determinants of adult exercise behavior.

As it stands, the idea that different genes influence exercise behavior across the life span remains hypothetical. This hypothesis can be fully tested, however, in longitudinal twin data.

**Assortative mating**

So far, we have suggested that twin studies on exercise behavior in adolescence may be characterized by the presence of common environment by gene interaction and by adolescence-specific genetic effects. Additional complexity may derive from assortative mating. In a three generation Finnish study (Aarnio *et al.*, 1997), intra- and intergenerational associations of leisure time physical activity among family members were examined. The sample consisted of 3,254 twins at the age of 16, their parents and grandparents. The correlation was 0.19 between parents, 0.33 between paternal grandparents and 0.43 between maternal grandparents, suggesting that assortative mating is present. In the Quebec family study, familial aggregation of physical activity phenotypes was investigated in 696 subjects from 200 families (Simonen *et al.*, 2002). For moderate to strenuous physical activity, the parental correlation was 0.22. Similar assortment was found in our own sample (Willemsen *et al.*, 2003). The tetrachoric correlation between exercise participation of spouses as a function of the duration of the relationship were 0.45, 0.42 and 0.49 for relations lasting $< 5$ years, $\geq 5$ years, and $> 15$ years, respectively.

How will assortment for exercise participation affect the estimates in twin studies? If the environment causes assortment no effects on genetic variance will be

seen. If the assortment is phenotypic, as we expect, it will act to both increase total genetic variance and heritability (Falconer and Mackay, 1996). In the classical twin design, however, phenotypic assortment will look like common environmental influences because it also increases the average amount of shared genes of DZ pairs above the theoretical 50%. Thus, the heritability in the population increases as a consequence of phenotypic assortment but use of the classical twin design will increase the estimate of common environmental influences.

Does the common environmental influence on exercise found in studies on adolescent twins in part reflect assortative mating? At first sight, the finding that common environmental effects disappear in later adulthood seems to argue against assortative mating since the higher than 50% genetic resemblance should stay in effect throughout the life span. However, above we argued that genes that are expressed in early adulthood may differ from the genes that influence exercise later in life. If the assortment is phenotypic, it will exclusively operate on the genes that are in effect during the main mating period (e.g. in late adolescence and young adulthood). In this case, the genes that affect exercise in later stages of life may still be under random mating. Future modeling of twins with their parents and their spouses may shed more light on these issues. As it stands, the conclusion that "familial resemblance is the result of environmental factors shared by members of the same generation rather than inherited factors" (Perusse *et al*, 1988), which was based entirely on the resemblance of young sibling-sibling and spousal correlations, seems rather premature.

**The association between exercise participation and well-being**

Several studies have focused on the association between exercise and negative affectivity. Lack of exercise was found to be associated with depression in population samples with a broad age range (Farmer *et al.*, 1988; Weyerer, 1992) and in samples consisting of young (Steptoe *et al.*, 1997; Steptoe and Butler, 1996) or older adults (Strawbridge *et al.*, 2002). De Moor *et al.* (in press) did not only examine the association of exercise with depression, but also investigated the relationship between exercise and anxiety and personality in a large population-based sample. They found that regular exercise was associated with lower neuroticism, anxiety and depression and higher extraversion and sensation seeking.

A limitation of these studies is that they focused, sometimes exclusively, on measures of negative affectivity. This may not be the best approach to understand

effects of exercise in the population at large. The World Health Organization defines health as "a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity" (World Health Organization, 1980). However, the link between exercise and the positive end of the mental health spectrum has not been studied extensively. According to a recent review by Lotan *et al.* (2005) many of the papers that do address this topic used small samples and vastly different definitions of well-being. To get more insight in the association between exercise participation and positive measures of well-being, we examined this relation in a large population-based sample, and defined well-being as its two components life satisfaction and happiness. Results from more than 8,000 subjects showed that exercisers were more satisfied with their life and happier than non-exercisers at all ages. This is the first large scale confirmation of the idea that exercise is also associated with variation in the good "end" of the well-being spectrum not just the "bad" end.

There are four different hypotheses regarding the underlying cause of the association between exercise participation and well-being. The most well-known hypothesis is that there might be a direct *causal effect of exercise on well-being* (i.e. exercise participation directly causes an increase in the level of well-being).Various randomized controlled training trials have shown that regular exercise has a beneficial effect in psychiatric populations or in subjects with high anxiety scores at the start of the study (Babyak *et al.*, 2000; Moore and Blumenthal, 1998; Steptoe *et al.*, 1989). This causal effect has not unanimously been replicated in the population at large (Gauvin and Spence, 1996) and caution has been suggested in the interpretation of studies in patient populations (Salmon, 2001). Also the few studies that addressed changes in positive mood did not find significant training effects (De Geus *et al.*, 1993). However, fairly consistent evidence has been found for a short-lasting beneficial effect directly following exercise activities, including reduced feelings of tension, anxiety and anger, and increased feelings of vigor (Gauvin, 1990; Gauvin and Spence, 1996; Steptoe *et al.*, 1989; Yeung, 1996).

Three competitive hypotheses have also been invoked to explain the association between exercise and well-being. First, the association may depend on *reversed causality*, i.e. well-being or a personality profile conducive to higher well-being may be a prerequisite for people to engage in exercise in the first place. Emotionally well-adjusted individuals may be more attracted to exercise, and have the necessary energy and self-discipline to maintain exercise regime (Dishman, 1988). As indicated

before, "personality-genes" may well play a role in the heritability of adult exercise behavior. Second, the association may be non-causal and due to an *underlying shared family factor* (e.g. socio-economic status, neighborhood, parental rearing style) influencing both exercise participation and well-being. Third, a non-causal association between exercise participation and well-being may also arise from *genes influencing both exercise participation and well-being*. Finally, any combination of these four different models may explain the association between exercise participation and well-being.

In chapter six, we first tested whether well-being met the necessary condition for each or either of the two non-causal models: that there is a significant effect of common environmental and/or genetic factors on well-being. The relative contribution of genes and environment to individual differences in life satisfaction was tested with the extended twin design in 5,668 Dutch twins and siblings. Broad-sense heritability was 38% and non-additive genetic factors explained all or most of the genetic influences. The remaining 62% of the variance in life satisfaction could be attributed to unique environmental factors, both persistent and transitory, plus measurement error. Shared environmental contribution was absent, which rules out the third of the above models.

In chapter seven, we have started with the actual investigation of the causality of the association between exercise participation and well-being (i.e. life satisfaction and happiness). Based on the logic of the co-twin control method (Cederlof *et al.*, 1977; Kendler *et al.*, 1993), we concluded that the association between exercise participation and well-being was non-causal. Instead, both traits seemed to be influenced by a common set of genetic factors. This phenomenon is called "genetic pleiotropy", which refers to the finding that a single gene can independently influence variance in multiple and very diverse traits.

Admittedly, the co-twin control method is not the optimal test for investigating the causality between two phenotypes. Duffy and Martin (1994) introduced a bivariate extension of the classical twin design that models the direction of causation between two correlated traits solely by using cross-sectional data. However, a current practical limitation of this method is its application to a dichotomous trait like our measure of exercise participation. A second theoretical limitation is that this method has limited power if the heritabilities of the two phenotypes under investigation do not differ by a substantial amount. Indeed, if both traits are moderately heritable, i.e. 38% for well-being and 67% for exercise participation as we have found, the power to distinguish

bidirectional causation from pleiotropy is extremely low. This is aggravated by the fact that the association between exercise and well-being, although highly significant, is only modest in size. It is uncertain, therefore, whether this method will ever resolve the issue of causality in the association between exercise and well-being. Instead, a complete mechanistic understanding of the "nature" of the association between well-being and exercise participation may have to await progress in gene finding for either of these traits. If, for instance, an actual genetic variant is identified that influences exercise behavior the test of pleiotropy becomes fairly straightforward: we then expect this same genetic variant to also predict well-being and to do so to the same extent in exercisers and non-exercisers.

**Direction of future research**

The prevailing theoretical perspective in preventive medicine now holds that social and environmental factors largely account for variation in voluntary lifestyle choices. In this thesis, it is shown that in adulthood some of the choices for a healthy lifestyle reflect differences in genetic make-up, although potentially in interaction with shared environment. This requires a change in our perspective, such that we change from "population-based" intervention strategies to "personalized" intervention strategies. Currently, this concept of "personalized medicine" is increasingly being applied to curative medicine and pharmacotherapeutic intervention. We suggest extending this concept to preventive medicine.

Crucial to such personalized preventive medicine is a mechanistic understanding of the genetic pathways that underlie the genetic contribution to individual variation in this behavior. Such understanding may not only help to improve intervention strategies but may impact on research on health in general. Randomized controlled training trials have clearly shown that regular exercise has a causal effect on physical health (Berlin and Colditz, 1990). It is possible, therefore, that the well-known heritability of many health parameters like obesity (Schousboe *et al.*, 2003), thrombosis (Dunn *et al.*, 2004), hypertension (Kupper *et al.*, 2005b), diabetes (De Lange *et al.*, 2003) and even cardiovascular mortality (Zdravkovic *et al.*, 2004) may partly reflect the genetic factors causing the adoption and maintenance of regular exercise behavior. In that case, finding the genetic disposition that underlies individual differences in exercise might immediately translate to finding genetic factors for these traits. Furthermore, once actual exercise genes have been identified, it will be much

easier to tackle the causality issue of the association between exercise and psychological well-being as argued above.

Which genes could explain the heritability of exercise behavior? Unfortunately, this is a vastly underexplored question. For exercise *ability* coordinated efforts exist world wide and a number of genes for endurance and strength have been identified and replicated a number of times (Rankinen *et al.*, 2004; Wolfarth *et al.*, 2005). For exercise *behavior*, no such coordinated effort exists although a number of the studies with a primary interest in exercise ability occasionally also examined exercise habits. This has led to three of the five genes associated with exercise so far. In the Quebec Family study, the Melanocortin-4 receptor gene (MC4R-C-2745T variant) showed significant associations with moderate-to-strenuous activity scores and with inactivity scores (Loos *et al.*, 2005). In 331 early postmenopausal women, physical activity was associated with a polymorphism in the CYP19 (aromatase) gene (Salmen *et al.*, 2003). Finally, in 97 healthy girls, physical activity was associated with polymorphisms in a calcium-sensing receptor gene (Lorentzon *et al.*, 2001).

Two strategies are available to identify genes underlying genetic variation in exercise participation: linkage analysis and candidate gene association studies. In linkage analysis, a number of DNA markers of known location are measured in individuals from multiple generations. For each DNA marker, evidence for linkage is obtained through statistical procedures that trace the co-segregation of the trait and the DNA marker along familial lineages in extended pedigrees. If such a relationship can be established with sufficient statistical confidence, then one or more genes in those regions are possibly involved in trait similarity among individuals. Linkage analysis thus serves to detect the regions of the genome where genetic variants with a quantitative effect on the trait must be located. To our knowledge, only one whole genome scan based on linkage analysis exists for physical exercise (Simonen *et al.*, 2003b). Several putative genomic regions were identified that might harbor genes influencing participation in regular exercise, but the evidence was only suggestive, as the power for linkage in this relatively small and unselected sample was small.

In association analysis, known "candidate" genes are selected based on a theoretical notion about the possible motives to engage in regular exercise. Allelic variation in these genes is measured and tested for association with exercise behavior. The measured allelic variants can be either the functional variant that changes the gene's effect on exercise behavior, or non-functional variants that are closely

correlated with the true (but unmeasured) functional allelic variant. Only two genes have been identified so far that fit in a meaningful theoretical framework.

The mesolimbic dopaminergic reward system has been proposed to play a key role in a range of phenotypes related to rewarding mechanisms (Schulz, 1999) and may influence diverse traits like sensation seeking and extraversion as well as general well-being. As detailed earlier, sensation seeking, extraversion and well-being have all been associated with exercise (De Moor *et al.*, in press; Stubbe *et al.*, submitted b). Interestingly, Simonen and colleagues (2003a) have shown that a common variant in a gene for one of the key receptors in the dopaminergic system (DRD2) was associated with exercise behavior, although exclusively in women.

The second gene is the Angiotensin Converting Enzyme (ACE) that may influence exercise behavior through its effects on exercise ability. The idea here is that people, perhaps adolescents more so than adults, generally like doing what they are good at, and will pursue those activities in leisure time as much as possible. Taking this one step further, we may reasonably assume that people feel specifically competent when they notice themselves to gain more in performance compared to others who nonetheless follow the same exercise regime. The large scale HERITAGE family study has clearly shown that the gain in exercise performance in response to a standardized exercise program is a heritable trait, i.e. in the prime exercise ability trait, aerobic fitness, there is clear evidence of gene by exercise interaction (An *et al.*, 2003; Bouchard *et al.* 1999; Boule *et al.*, 2005; Lakka *et al.*, 2005; Perusse *et al.*, 2000; Rice *et al.*, 2002; Teran-Garcia *et al.*, 2005). In a landmark paper, Montgomery and colleagues (Williams *et al.*, 2000; Woods *et al.*, 2000) identified one of the genes responsible for this interaction. An insertion/deletion (I/D) polymorphism in the ACE was determined in British army recruits who were tested for a number of fitness traits before and after a 10 week training program. Efficiency of the muscles, or delta efficiency, computed as the increase in power output for a given increase in oxygen consumption, was found to increase almost nine fold more in subjects homozygous for the I allele. Almost no training effect was found in those homozygous for the D allele. In more mundane terms this gene-by-exercise interaction meant that the maximum duration for which recruits could perform repetitive biceps flexion with a 15 kilo barbell increased with training 11-fold more among those with an ACE II genotype compared to those with a DD genotype.

Can such favorable trainability genes, in turn, become genes that predispose to exercise behavior? In support of this "competence hypothesis" a multicentre study in Italian borderline hypertensives (Winnicki *et al.*, 2004) showed that the ACE polymorphism accounted for 21% of the variance in exercise participation. The most sedentary group had a clear excess of the genotype (DD) that caused the lowest increase in muscle efficiency after training in the British recruits. Here, at least, low exercise *ability* indeed coincided with low exercise *drive*.

Clearly there must be many other genes that influence exercise behavior through, as yet, unknown pathways. There simply has not enough work been done in this area. Combining the importance of exercise for health to the strong evidence for its heritability I strongly recommend that large scale gene finding studies start targeting this crucial behavior.

# Samenvatting

Dutch summary

# De erfelijkheid van sportgedrag en psychologisch welbevinden

## Inleiding

Waarom vinden sommige mensen het heerlijk om uren door het bos hard te lopen, terwijl andere mensen veel liever computeren of tv kijken? Worden deze verschillen tussen mensen bepaald door verschillen in hun omgeving (bijvoorbeeld sportgedrag van je partner, werk, school of opvoeding) of door verschillen in de erfelijke aanleg? Deze vragen vormen de kern van dit proefschrift. In dit proefschrift wordt verder onderzocht of er een relatie is tussen sportgedrag en psychologisch welbevinden en hoe die relatie tot stand komt. Een belangrijke hypothese daarbij, die tegen de volkswijsheid ingaat, is dat er wel een relatie bestaat maar dat deze niet oorzakelijk is. Verschillen tussen individuen in sportgedrag en psychologisch welbevinden zouden bijvoorbeeld deels verklaard kunnen worden door dezelfde set onderliggende genen. Eerst wordt nagegaan of er erfelijke invloeden op welbevinden zijn. Ten slotte wordt getest of deze genetische invloeden op welbevinden overlappen met de erfelijke invloeden op sportgedrag. Hieronder wordt een samenvatting gegeven van de belangrijkste resultaten.

## Familieonderzoek naar gezondheid en leefgewoonten

Voor dit onderzoek is gebruik gemaakt van tweelingfamilies die geregistreerd zijn bij het Nederlands Tweelingen Register (NTR). Deze tweelingfamilies zijn ruim tien jaar geleden voor het eerst benaderd om mee te doen aan een grootschalig familieonderzoek naar gezondheid en leefgewoonten. Om de twee jaar krijgen tweelingen en hun familieleden een vragenlijst toegestuurd, waarin onderwerpen aan bod komen zoals rookgedrag, alcoholgebruik, sport en lichamelijke activiteit. Tweelingfamilies vormen voor de wetenschap een unieke groep, want met hun hulp kan onderzocht worden in welke mate een bepaalde eigenschap erfelijk is. Eeneiige tweelingen zijn genetisch 100% identiek. Twee-eiige tweelingen delen gemiddeld de helft van hun erfelijk materiaal. Stel nu dat erfelijke aanleg van belang is voor het hebben van een hoog welbevinden. Dan zullen eeneiige tweelingen vaker allebei ongeveer dezelfde score op de schaal voor welbevinden hebben dan twee-eiige tweelingen. Eeneiige tweelingen hebben immers dezelfde erfelijke aanleg.

**Erfelijkheid van sportgedrag**

Verschillende kleinschaliger tweelingstudies hadden al laten zien dat genetische factoren bijdragen aan individuele verschillen in sportgedrag. Hoofdstuk 2 geeft een overzicht van deze studies en twee belangrijke bevindingen springen eruit. Ten eerste is de invloed van genen gedurende het leven niet gelijk. Dit betekent dat individuele verschillen in sportgedrag tussen kinderen andere oorzaken hebben dan verschillen in volwassen sportgedrag. Ten tweede tonen alle volwassen tweelingstudies aan dat genetische factoren verschillen in sportgedrag verklaren. In hoofdstuk vier en vijf worden beide bevindingen bevestigd door ons eigen onderzoek.

In hoofdstuk vier beschrijven we de resultaten van het onderzoek naar oorzaken van verschillen in sportgedrag van Nederlandse mannelijke en vrouwelijke tweelingen tussen de 13 en 20 jaar. Tot en met het 16e levensjaar zijn genen niet van belang in het verklaren van individuele verschillen in sportgedrag, terwijl gedeelde familie-invloeden (bijvoorbeeld opvoeding, sociaal economische status en school) van grote invloed zijn. Vanaf 17 – 18 jaar gaan genen voor het eerst optreden en de rol van gedeelde omgeving neemt af. Rond de leeftijd van 19 – 20 jaar zien we dat de invloed van genetische factoren op het sportgedrag zijn hoogtepunt bereikt. Meer dan 80% van verschillen tussen mensen in sportgedrag wordt op die leeftijd bepaald door genen. Na deze leeftijdspiek neemt de invloed van genen af.

Wat is de oorzaak van deze piek in erfelijkheid rond de leeftijd van 19 – 20 jaar? Ten eerste kunnen unieke omgevingsfactoren zoals werkdruk en een gebrek aan tijd toenemen na de pubertijd, waardoor de invloed van genen wordt verminderd. Een andere mogelijkheid is dat tijdens de adolescentie andere genen een rol spelen dan tijdens de volwassenheid. Genen die een rol spelen bij hoe goed je bent in sporten spelen mogelijk vooral tijdens de adolescentie een rol, maar steeds minder tijdens de volwassenheid. Genen die de acute mentale of langdurigere lichamelijke effecten van sporten beïnvloeden zijn mogelijk vooral van invloed in de volwassenheid en nog niet op jeugdige leeftijd. Op dit moment blijven dit echter speculaties en is een longitudinale onderzoeksopzet nodig om deze hypothesen te toetsen.

Hoofdstuk 5 geeft een beschrijving van het GenomEUtwin project. Dit project is het grootste tweelingonderzoek naar sportgedrag dat ooit uitgevoerd is en bestaat uit een verzameling van meer dan 0.8 miljoen tweelingen. Gegevens over hoe vaak, hoe lang en hoe intensief tweelingen sporten in Australië, Denemarken, Finland, Noorwegen, Nederland, Zweden en Groot-Brittannië zijn gebruikt om een index van

sportgedrag te creëren in elk land. In totaal hebben we sportgegevens van meer dan 85.000 jong volwassen tweelingen (19 – 40 jaar) geanalyseerd. In deze zeven landen blijken genen gemiddeld voor 62% individuele verschillen in sportgedrag te verklaren. Gedeelde familie-omgevingseffecten speelden alleen een rol in sportgedrag van Noorse mannen (37%), maar waren niet van belang in andere landen.

Erfelijkheid speelt dus in Europese landen een belangrijke rol bij de keuze voor een lichamelijk actief leven. Welke genen kunnen deze robuuste bevinding verklaren? Tot nu toe zijn er vijf genen gevonden die geassocieerd zijn met sportgedrag. Het CYP19 (aromatase) gen, een calcium receptor gen en een receptor in het dopamine systeem blijken sportgedrag van vrouwen te beïnvloeden. Het is nog niet duidelijk of deze drie genen ook een rol spelen bij het sportgedrag van mannen. Voor zowel mannen als vrouwen geldt dat het melanocortin-4 receptor gen (MC4R-C-2745T variant) is geassocieerd met matige tot inspannende lichamelijke activiteit en met inactiviteit en ten slotte blijkt het angiotensin converting enzym (ACE) sportgedrag te beïnvloeden. Het aantal studies naar dit onderwerp is wereldwijd echter nog zeer beperkt. Gegeven de rol van sportgedrag in de gezondheid is dit een ongewenste situatie.

**De relatie tussen sportgedrag en welbevinden**

In dit proefschrift wordt tevens gekeken naar het verband tussen sportgedrag en het psychologische welbevinden. Is het zo dat mensen die veel sporten, lekkerder in hun vel zitten dan mensen die weinig sporten? In hoofdstuk zeven worden verschillende studies beschreven die zich richten op de relatie tussen sportgedrag en negatief welbevinden. Uit deze studies komt naar voren dat mensen die regelmatig sporten minder last hebben van depressies, angstige gevoelens en neuroticisme dan mensen die lichamelijk inactief zijn. Een beperking van deze studies is dat ze zich alleen richten op negatieve metingen van welbevinden. Om meer inzicht te krijgen in de relatie tussen sportgedrag en positief welbevinden, hebben we vragen gesteld over geluk en tevredenheid met je leven. Uit hoofdstuk 6 blijkt ten eerste dat verschillen in positief welbevinden tussen mensen deels verklaard kunnen worden door genen (38%). Uit hoofdstuk 7 blijkt verder dat sporters meer tevreden zijn met hun leven en zich gelukkiger voelen dan mensen die niet sporten. Dit resultaat werd gevonden voor alle leeftijden. Dit is het eerste grootschalige onderzoek dat het idee bevestigd dat sporten gerelateerd is aan positief welbevinden en niet alleen met negatief

welbevinden. Verder is onderzocht hoe deze relatie tot stand komt. Het blijkt dat beide eigenschappen worden beïnvloed door dezelfde genen. Dit betekent dat de genen die individuele verschillen in sportgedrag verklaren ook gedeeltelijk individuele verschillen in positief welbevinden verklaren.

**Toekomstig onderzoek**

Het beeld dat heerst in de huidige gezondheidszorg is dat sociale factoren en omgevingsfactoren grotendeels verschillen in leefstijl bepalen. Sommige mensen leven ongezond omdat dat een keuze is, ze kunnen immers gaan sporten of op dieet gaan. Dit proefschrift maakt duidelijk dat keuzes voor een gezonde leefstijl mede bepaald worden door de genen die iemand meekrijgt van de ouders. Er zou eigenlijk een verandering moeten plaatsvinden in de hedendaagse geneeskunde naar een meer persoonlijk gericht behandelingsplan. Dit concept wordt in toenemende mate toegepast op curatieve geneeskunde en farmacotherapeutische interventies. Wij stellen voor om dit concept uit te breiden naar preventieve geneeskunde.

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# Appendices

## Appendix I: Dutch exercise and physical activity items (survey six)

**Sport**

38. Doet u regelmatig aan sport? ☐ nee → *door naar effecten van sporten (vraag 40)*
☐ ja

39. Geef hieronder aan welke sport(en) u beoefent. Geef aan hoeveel jaren, hoeveel maanden per jaar, hoe vaak per maand en hoelang u gemiddeld per week deze sport(en) beoefent. Tel de tijd van de trainingen en wedstrijden bij elkaar op.

| **naam van de sport** | **aantal jaren** | **aantal maanden per jaar** | **aantal keren per maand** | **gemiddelde tijd per week** |
|---|---|---|---|---|
| 1. _____ | _____ jaren | _____ maanden | _____ keer | ____ minuten |
| 2. _____ | _____ jaren | _____ maanden | _____ keer | ____ minuten |
| 3. _____ | _____ jaren | _____ maanden | _____ keer | ____ minuten |
| 4. _____ | _____ jaren | _____ maanden | _____ keer | ____ minuten |
| 5. _____ | _____ jaren | _____ maanden | _____ keer | ____ minuten |

**Lichamelijke activiteit**

41. Neem een normale week in de afgelopen maand in uw gedachten. Wilt u aangeven hoeveel dagen per week u de onderstaande activiteiten verrichtte en hoelang u daar dan gemiddeld op zo'n dag mee bezig was? Indien u een bepaalde activiteit niet heeft gedaan kunt u deze activiteit overslaan.

| | | **aantal dagen per week** | **gemiddelde tijd per dag** |
|---|---|---|---|
| **I.** | **Fietsen** | | |
| a. | doordeweeks (maandag tot en met vrijdag) | ___ dagen | ___ minuten |
| b. | in het weekend | ___ dagen | ___ minuten |
| **II.** | **Wandelen** | | |
| a. | doordeweeks (maandag tot en met vrijdag) | ___ dagen | ___ minuten |
| b. | in het weekend | ___ dagen | ___ minuten |

| | | aantal dagen per week | gemiddelde tijd per dag |
|---|---|---|---|
| **III.** | **Lichamelijke activiteit in het huishouden** | | |
| a. | licht en matig inspannend huishoudelijk werk (staand werk zoals koken, afwassen, strijken, kind in bad doen en/of lopend werk zoals stofzuigen) | ___ dagen | ___ minuten |
| b. | zwaar inspannend huishoudelijk werk (vloer schrobben en met zware boodschappen lopen) | ___ dagen | ___ minuten |
| **IV.** | **Lichamelijke activiteit op werk en/of school** | | |
| a. | matig inspannend werk (staand werk met af en toe lopen, zoals baliewerk, kapper en schilder) | ___ dagen | ___ minuten |
| b. | zwaar inspannend werk (werk waarbij regelmatig zware dingen worden opgetild, zoals verhuizer en stukadoor) | ___ dagen | ___ minuten |
| **V.** | **Overige lichamelijke activiteiten** | | |
| a. | tuinieren | ___ dagen | ___ minuten |
| b. | klussen/doe-het-zelven | ___ dagen | ___ minuten |
| c. | dansen | ___ dagen | ___ minuten |

42. Bent u tenminste één keer per week in uw vrije tijd zo lichamelijk actief dat u ervan gaat zweten?
☐ nee
☐ ja, nl: →
☐ één keer per week
☐ twee keer per week
☐ drie keer per week
☐ meer dan drie keer per week

43. Als u terugdenkt aan de **afgelopen 6 maanden**, hoe vaak bent u in uw vrije tijd tenminste 20 minuten achter elkaar lichamelijk actief geweest (bijvoorbeeld fietsen zwemmen, dansen en tuinieren)?
☐ nooit
☐ minder dan 1x per maand
☐ ongeveer 1x per maand
☐ ongeveer 2-3x per maand
☐ 1-2x per week
☐ 3x per week of vaker

## Appendix II: Letter survey six (November 2002)

Geachte heer, mevrouw,

Wij nodigen u uit om deel te nemen aan het grootschalige familieonderzoek naar gezondheid en leefgewoonten van het Nederlands Tweelingen Register (NTR). Dit onderzoek is in 1991 aan de Vrije Universiteit te Amsterdam van start gegaan en richt zich op het belang van erfelijke aanleg voor gezondheid en leefgewoonten. U kunt meedoen door de bijgevoegde vragenlijst in te vullen en deze naar ons op te sturen in de antwoordenvelop (geen postzegel nodig). De vragenlijst is bedoeld voor tweelingen en hun broers, zussen, ouders en partners. In de informatiefolder kunt u meer lezen over de achtergronden en het doel van dit onderzoek.

Mocht u na het lezen van deze brief en de informatiefolder nog vragen hebben over het onderzoek dan kunt u contact opnemen met de uitvoerder van dit onderzoek drs. J.H. Stubbe (***020-4448776***, b.g.g. ***020-4448787*** of mailen naar ***jh.stubbe@psy.vu.nl***). Indien u vragen heeft die u liever niet aan de onderzoeker zelf stelt, dan is het mogelijk om een onafhankelijke arts te raadplegen (dr. W.J.G. Hoogendijk, donderdagochtend: 020-5736509).

Wij hopen dat u bereid bent om aan dit onderzoek mee te werken. Met het invullen van deze vragenlijst levert u een belangrijke bijdrage aan het wetenschappelijk onderzoek van het NTR. Uw deelname is echter geheel vrijwillig. Als u vragen te indringend of te vervelend vindt hoeft u deze, als u daar tegenop ziet, beslist niet in te vullen.

Wij willen u bij voorbaat hartelijk danken voor uw medewerking.

Met vriendelijke groet,
mede namens mevr. prof. dr. D.I. Boomsma en
prof. dr. E.J.C. de Geus,

mevr. drs. J.H. Stubbe

## Appendix III: Letter survey six (March 2003)

Geachte heer, mevrouw,

Enige tijd geleden heeft u van het Nederlands Tweelingen Register (NTR) een vragenlijst ontvangen betreffende het familieonderzoek naar gezondheid en leefgewoonten. Door het invullen van deze vragenlijst levert u een belangrijke bijdrage aan het wetenschappelijk onderzoek van het Nederlands Tweelingen Register (voor meer informatie: zie bijgevoegde folder). Ook als u in het verleden al eens een vragenlijst heeft teruggestuurd, wordt uw herhaalde medewerking zeer op prijs gesteld.

Uit onze administratie blijkt dat we uw vragenlijst nog niet retour ontvangen hebben. Bijgaand krijgt u opnieuw de vragenlijst toegestuurd. Wij verzoeken u vriendelijk om deze lijst zo volledig mogelijk in te vullen. De vragenlijst kan in de meegestuurde antwoordenvelop (geen postzegel nodig) naar ons worden teruggestuurd.

Als u dit keer niet mee wilt doen aan het onderzoek of hulp wilt bij het invullen van de vragenlijst, kunt u gebruik maken van het bijgevoegde antwoordkaartje (geen postzegel nodig). Dit antwoordkaartje kunt u ook opsturen als u een tweeling bent en een partner heeft die mee wil doen aan het onderzoek.

We realiseren ons dat het invullen van de vragenlijst enige tijd zal kosten. In het belang van het onderzoek hopen we toch dat u bereid bent om mee te werken, zodat onze kennis over gezondheid en leefgewoonten in Nederland wordt vergroot.

Als u vragen heeft over het onderzoek of over de vragenlijst, kunt u contact opnemen met mevrouw J.H. Stubbe, medewerker van het project. Onderaan de brief vindt u het telefoonnummer en e-mailadres.

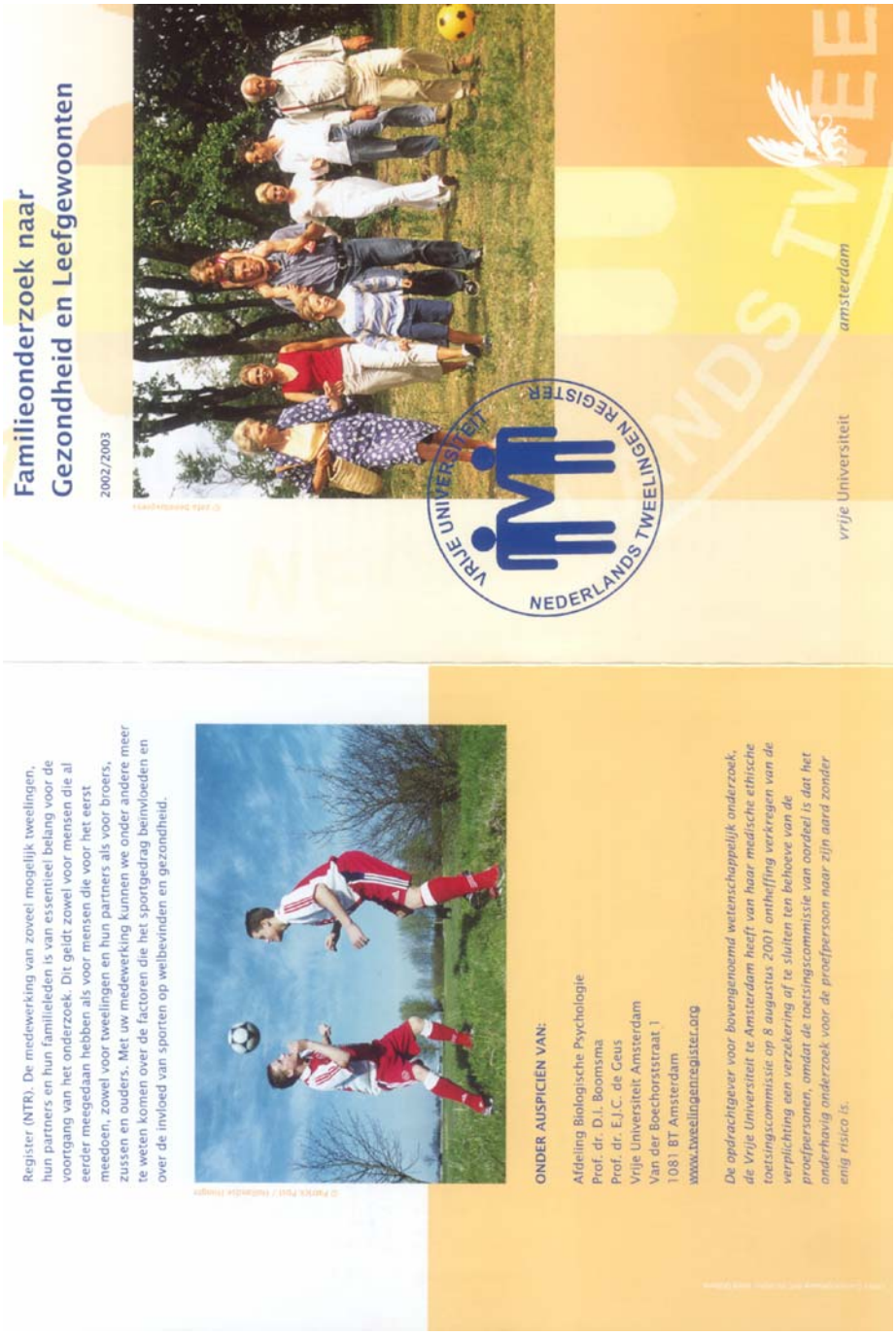
Als u de vragenlijst inmiddels al heeft ingevuld en opgestuurd willen wij u hartelijk bedanken voor uw medewerking. U kunt deze brief dan als niet verstuurd beschouwen. Meer informatie over de achtergrond van het onderzoek vindt u op www.tweelingenregister.org.

Met vriendelijke groet,

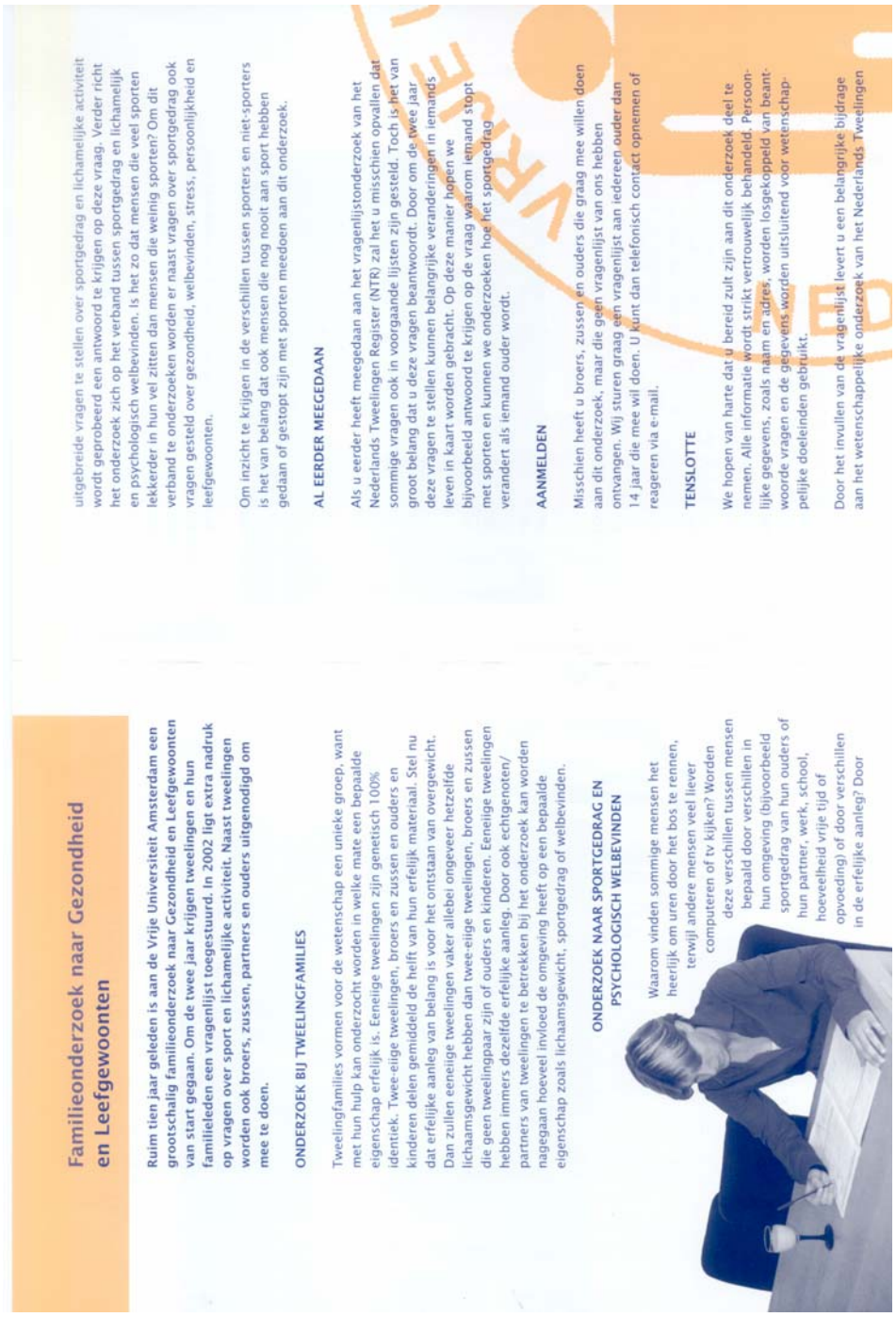
Prof. dr. D.I. Boomsma, Hoogleraar  Prof. dr. J.C.N. de Geus, Hoogleraar

Met vragen of opmerkingen over dit onderzoek kunt u terecht bij:
mevrouw. drs. Janine Stubbe, onderzoeker Nederlands Tweelingen Register
tel: 020-4448776 (b.g.g. 020-4448787)
e-mail: jh.stubbe@psy.vu.nl

## Appendix IV: Brochure (cover)



## Appendix V: Brochure (interior)



Familieonderzoek naar Gezondheid en Leefgewonten

**Ruim tien jaar geleden is aan de Vrije Universiteit Amsterdam een grootschalig familieonderzoek naar Gezondheid en Leefgewonten van start gegaan. Om de twee jaar krijgen tweelingen en hun familieleden een vragenlijst toegestuurd. In 2002 ligt extra nadruk op vragen over sport en lichamelijke activiteit. Naast tweelingen worden ook broers, zussen, partners en ouders uitgenodigd om mee te doen.**

ONDERZOEK BIJ TWEELINGFAMILIES

Tweelingfamilies vormen voor de wetenschap een unieke groep, want met hun hulp kan onderzocht worden in welke mate een bepaalde eigenschap erfelijk is. Eeneiige tweelingen zijn genetisch 100% identiek. Twee-eiige tweelingen, broers en zussen en ouders en kinderen delen gemiddeld de helft van hun erfelijk materiaal. Stel nu dat erfelijke aanleg van belang is voor het ontstaan van overgewicht. Dan zullen eeneiige tweelingen vaker allebei ongeveer hetzelfde lichaamsgewicht hebben dan twee-eiige tweelingen, broers en zussen die geen tweelingpaar zijn of ouders en kinderen. Eeneiige tweelingen hebben immers dezelfde erfelijke aanleg. Door ook echtgenoten/ partners van tweelingen te betrekken bij het onderzoek kan worden nagegaan hoeveel invloed de omgeving heeft op een bepaalde eigenschap zoals lichaamsgewicht, sportgedrag of welbevinden.

ONDERZOEK NAAR SPORTGEDRAG EN PSYCHOLOGISCH WELBEVINDEN

Waarom vinden sommige mensen het heerlijk om uren door het bos te rennen, terwijl andere mensen veel liever computeren of tv kijken? Worden deze verschillen tussen mensen bepaald door verschillen in hun omgeving (bijvoorbeeld sportgedrag van hun ouders of hun partner, werk, school, hoeveelheid vrije tijd of opvoeding) of door verschillen in de erfelijke aanleg? Door uitgebreide vragen te stellen over sportgedrag en lichamelijke activiteit wordt geprobeerd een antwoord te krijgen op deze vraag. Verder richt het onderzoek zich op het verband tussen sportgedrag en lichamelijk en psychologisch welbevinden. Is het zo dat mensen die veel sporten lekkerder in hun vel zitten dan mensen die weinig sporten? Om dit verband te onderzoeken worden er naast vragen over sportgedrag ook vragen gesteld over gezondheid, welbevinden, stress, persoonlijkheid en leefgewonten.

Om inzicht te krijgen in de verschillen tussen sporters en niet-sporters is het van belang dat ook mensen die nog nooit aan sport hebben gedaan of gestopt zijn met sporten meedoen aan dit onderzoek.

AL EERDER MEEGEDAAN

Als u eerder heeft meegedaan aan het vragenlijstonderzoek van het Nederlands Tweelingen Register (NTR) zal het u misschien opvallen dat sommige vragen ook in voorgaande lijsten zijn gesteld. Toch is het van groot belang dat u deze vragen beantwoordt. Door om de twee jaar deze vragen te stellen kunnen belangrijke veranderingen in iemands leven in kaart worden gebracht. Op deze manier hopen we bijvoorbeeld antwoord te krijgen op de vraag waarom iemand stopt met sporten en kunnen we onderzoeken hoe het sportgedrag verandert als iemand ouder wordt.

AANMELDEN

Misschien heeft u broers, zussen en ouders die graag mee willen doen aan dit onderzoek, maar die geen vragenlijst van ons hebben ontvangen. Wij sturen graag een vragenlijst aan iedereen ouder dan 14 jaar die mee wil doen. U kunt dan telefonisch contact opnemen of reageren via e-mail.

TENSLOTTE

We hopen van harte dat u bereid zult zijn aan dit onderzoek deel te nemen. Alle informatie wordt strikt vertrouwelijk behandeld. Persoonlijke gegevens, zoals naam en adres, worden losgekoppeld van beantwoorde vragen en de gegevens worden uitsluitend voor wetenschappelijke doeleinden gebruikt.

Door het invullen van de vragenlijst levert u een belangrijke bijdrage aan het wetenschappelijke onderzoek van het Nederlands Tweelingen

## Appendix VI: Reply card

Registratienummer:

☐ Ik wil graag meer informatie / ik wil hulp krijgen bij het invullen van de vragenlijst (het Nederlands Tweelingen Register zal telefonisch contact met u opnemen)

☐ Ik ben zelf een tweeling en mijn partner wil graag een vragenlijst ontvangen (het Nederlands Tweelingen Register zal zo spoedig mogelijk een partnerlijst naar u toesturen)

☐ Ik wil dit keer niet meedoen aan het vragenlijstonderzoek

Overige opmerkingen:

_____

_____

_____

# List of publications

## Papers:

**Stubbe JH**, Boomsma DI, and De Geus EJC (2005). Sports participation during adolescence: a shift from environmental to genetic factors. *Medicine and Science in Sports and Exercise* 37(4): 563-70.

**Stubbe JH**, Posthuma D, Boomsma DI, and De Geus EJC (2005). Heritability of life satisfaction in adults: A twin-family study. *Psychological Medicine* 35: 1581-1588.

**Stubbe JH**, Boomsma DI, Cornes BK, Martin NG, Skytthe A, Kyvik KO, Rose RJ, Kujala U, Kaprio J, Harris JR, Pedersen NL, and De Geus EJC (submitted). Genetic and environmental influences on exercise participation: A comparative study in twin samples from six countries. *International Journal of Epidemiology*.

**Stubbe JH**, Boomsma DI, and De Geus EJC (submitted). The association between exercise participation and well-being: what is causing it? *Preventive Medicine*.

Boomsma DI, Vink JM, Van Beijsterveldt CEM, De Geus EJC, Beem AL, Mulder EJCM, Derks EM, Riese M, Willemsen GHM, Bartels M, Van den Berg M, Kupper HM, Polderman JC, Posthuma D, Rietveld MJH, **Stubbe JH**, Knol LI, Stroet TH, Van Baal GCM. Netherlands Twin Register: A Focus on Longitudinal Research. *Twin Research, 5, 401-406,* 2002

De Moor, MHM, Beem AL, **Stubbe JH**, Boomsma DI, and De Geus EJC (in press). Regular exercise, anxiety, depression and personality: a population-based study. *Preventive Medicine*.

Hillman CH, Motl RW, Pontifex MB, Posthuma D, **Stubbe JH**, Boomsma DI, and De Geus EJC (in press). Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals, *Health Psychology*.

Ligthart L, Boomsma DI, Martin NG, **Stubbe JH**, and Nyholt, DR (in press). Migraine with aura and migraine without aura are not distinct entities: further evidence from a large Dutch population study. *Twin Research*.

Middeldorp CM, **Stubbe JH**, Cath DC, and Boomsma DI (2005). Familial clustering in burnout: a twin family study. *Psychological Medicine* 35: 113-120.

Vink JM, Willemsen G, **Stubbe JH**, Middeldorp CM, Ligthart RSL, Baas KD, Dirkzwager HJC, De Geus EJC, and Boomsma DI (2004). Estimating non-response bias in family studies: Application to mental health and lifestyle. *European Journal of Epidemiology,* 19, 623-630.

## Book chapters:

**Stubbe JH,** and De Geus EJC (accepted). Genetics of Exercise behavior. *Handbook of Behavior Genetics.*

De Geus EJC, and **Stubbe JH** (in press). Aerobic exercise and stress reduction. *Encyclopedia of Stress.*

## Abstract:

**Stubbe JH**, Vink JM, Boomsma DI and De Geus EJC (2005). Heritability of exercise participation and the amount of weekly energy expended in exercise. *Behavior Genetics*, 35(6):831.

De Geus EJC, Willemsen G, Posthuma D, Hottenga JJ, Kupper N, **Stubbe JH**, Vink JM and Boomsma DI (2004). Can the comorbidity of physical inactivity and cardiovascular risk factors help us find genes? *Twin Research.* 7:682

De Moor MHM, Beem AL, **Stubbe JH**, Boomsma DI and De Geus EJC. The association between regular exercise and negative affect in twins, siblings and other family members: A study from the Netherlands Twin Registry. *Twin Research*, 8(4):417

**Stubbe JH**, Boomsma DI, Harris JR, Kaprio J, Rose RJ, Kujala U, Martin NG, Cornes BK, Pedersen NL, Kyvik KO, Skytthe A and De Geus EJC. Genetic and environmental influences on exercise participation: A comparative study of twin cohorts in six countries. *Twin Research*, 8(4):421

# Dankwoord

Met het WK voetbal voor de boeg ben ik tot de conclusie gekomen dat een promotietraject doorlopen veel overeenkomsten vertoont met de voorbereidingen van sporters op een belangrijk toernooi. Zonder hulp van anderen is het niet mogelijk om uiteindelijk de finale te bereiken. De volgende personen wil ik dan ook op sportieve wijze bedanken:

*Mijn jeugdtrainers:* Sandra en Anuschka, jullie hebben mij kennis laten maken met de wetenschap door mij aan te nemen als student-assistent voor jullie eigen promotieonderzoeken. In deze periode heb ik ontzettend veel van jullie geleerd.

*Mijn hoofdtrainers:* Ik heb de afgelopen twee jaar niet één, maar twee begeleiders gehad. Dit had verwarrend kunnen werken, maar juist door jullie aanvullende kwaliteiten vond ik dit zeer prettig. Eco, als eerste promotor was jij mijn eerste aanspreekpunt. Volgens mij bestaat een dag bij jou uit meer dan 24 uur. Of ik nu 's avonds om 22.00 uur een mail stuurde of in het weekend, altijd had ik binnen een paar uur antwoord. Door jouw inzet, deskundigheid en je schrijfvaardigheid is het gelukt om dit proefschrift af te ronden. Dorret, jouw wetenschappelijke kennis en analytische blik bleken van grote waarde op de momenten dat ik dacht dat het er hopeloos uit zag. Jij wist altijd weer een nieuwe invalshoek te bedenken, waardoor ik de analyses uiteindelijk toch kon uitvoeren. De artikelen zijn hierdoor steeds naar een hoger wetenschappelijk niveau getild.

*Overige leden van de technische staf:* Judith Koopmans, Mireïlle van den Berg en Jacqueline Vink waren verantwoordelijk voor de eerdere dataverzamelingen en hebben ervoor gezorgd dat er al een schat aan informatie lag toen ik hier kwam werken. Zonder de hulp van Gonneke was het niet mogelijk geweest om deze data te analyseren. Jacqueline, van jou heb ik alle informatie over het onderzoek naar gezondheid en leefgewoonten gekregen. Ondanks je eigen drukke werkzaamheden, heb je altijd voor mijn vragen tijd vrijgemaakt en daarvoor wil ik je bedanken. Gelukkig hoefde ik niet alle administratieve taken met betrekking tot de versturing en ontvangst van de zesde vragenlijst zelf te doen, maar stonden Marijn Distel en Suzanne Thijs altijd klaar om bij te springen waar dat nodig was. Kim Baas heeft mij geholpen met het bellen van de tweelingen en hun familieleden. Het secretariaat mag ik in dit dankwoord niet vergeten. Jaqueline, Michiel en Natascha bedankt voor jullie hulp! Voor het non-

response onderzoek is bergen werk verzet door medewerkers van LASA. Jan Smit, Reen Halkema, Angelique Verbruggen en alle interviewers wil ik heel hartelijk danken. Furthermore, I would like to thank dr. Martin, dr. Kyvik, dr. Kaprio, dr. Harris, dr. Pedersen, and dr. Spector for their valuable contributions to chapter five and for their collaboration. I would also like to thank the reading committee for their time and effort.

*Mijn sponsors:* Zonder sponsors geen sportwedstrijd, zonder tweelingen geen data. Ik wil alle tweelingen en hun familieleden graag bedanken voor het invullen van alle vragenlijsten door de jaren heen. Zonder hun belangeloze inzet had ik geen gegevens gehad om te analyseren.

*Mijn medespelers:* Mijn collega's wil ik graag bedanken voor alle steun door de jaren heen. De deur van iedereen staat altijd open en dat maakt het gemakkelijk om even bij elkaar naar binnen te lopen. Mijn kamergenoten Marleen en Irene wil ik in het bijzonder bedanken voor de prettige werksfeer. Door jullie gezamenlijke interesse voor M-plus en datasimulatie voelde ik mij soms een buitenbeentje. Gelukkig hebben we genoeg andere gezamenlijke raakvlakken waardoor het altijd erg gezellig was op onze kamer en geen dag saai.

*Mijn publiek:* Als je er even door zit is het belangrijk dat je terug kunt vallen op de twaalfde man. De tennismeiden Astrid, Heleen, Jet, Marleen B., Marleen S. en Rita wil ik bedanken voor alle gezelligheid. Heleen, jou wil ik in het bijzonder bedanken. Door jou ben ik mij al snel in Amsterdam thuis gaan voelen. Een vriendschap tussen een Tukker en een Groninger is heel veel waard! Ondanks het feit dat ik Groningen verlaten heb, heb ik contact gehouden met een aantal dierbare vrienden: Erik, Gepke, Marieke, Natasja en Tom bedankt voor jullie vriendschap door de jaren heen.

*Mijn thuisfront:* Pap en mam, altijd staan jullie voor mij klaar. Ik wil jullie dan ook bijzonder graag bedanken voor de enorme steun en het onvoorwaardelijke vertrouwen dat jullie mij altijd gegeven hebben. Arjan, je tomeloze energie en doorzettingsvermogen zijn voor mij van kleins af aan een inspiratiebron geweest. Een leukere en lievere broer kan ik mij niet voorstellen! Marloes Stubbe (ja eindelijk mag ik je zo noemen!), sinds kort ben je getrouwd met mijn broer, maar eigenlijk hoor je al

jaren bij de familie. Bedankt voor je interesse in mijn onderzoek. Ten slotte Marloes, zo sta je in de rij voor een kroeg en zo sta je in mijn dankwoord. Het is niet altijd gemakkelijk om iemand te leren kennen die in de afrondingsfase van haar proefschrift is. Ineens heb je een relatie met iemand die het alleen maar kan hebben over deadlines, reviewers, pedel, paranimfen en lekenpraatje. Ongelooflijk hoe jij daar mee om bent gegaan. Bedankt voor je steun en begrip het afgelopen jaar.

Samen met jullie allemaal heb ik mijn eigen finale bereikt en ik hoop dat ik deze 14 juni met jullie steun winnend af zal sluiten!

Janine, 18 april 2006