A twin study on the correlates of voluntary exercise behavior in adolescence

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Abstract

Objectives: To improve the success of interventions aimed to increase moderate to vigorous physical activity, we need to better understand the correlates of the extensive individual differences in voluntary exercise activities. Starting in adolescence, genetic effects become a dominant factor in explaining individual differences in voluntary exercise behavior. Here we aim to establish the prospective contribution of potential correlates of voluntary exercise behavior to its heritability.

Design: In a sample of adolescent and young adult twins, data on potential correlates of exercise behavior were collected using surveys (time point 1, N = 373) and a laboratory study (time point 2, N = 499). Information on personality, perceived barriers & benefits, subjective and objective exercise ability and the affective response to exercise were collected in a set of healthy adolescent twin pairs (16-18y) and their non-twin siblings (12-25y). Almost 3 years later, the subjects were sent an online follow-up survey on their current exercise status (time point 3, N = 423).

Methods: In bivariate models, the phenotypic (co)variance in these correlates and exercise behavior at all time points were decomposed in sources of genetic (co)variance and environmental (co)variance. The correlates that were significantly associated with exercise behavior at time point 1 or 2 and showed significant genetic correlations to exercise behavior at time point 3 were used in two further analyses: Multiple regression analysis to predict exercise behavior at time point 3, and a genetic analysis in a common 2-factor model, that tested the overlap in genetic factors influencing these correlates and exercise behavior.

Results: Personality (Extraversion), perceived benefits and barriers, exercise-induced affective response (Energy measured after the cycling test), and subjective and objective exercise ability (VO2max) showed significant phenotypic and genetic association with exercise behavior at time point 3. The genetic correlation between the two latent factors in the common 2-factor model was 0.51, indicating that part of the heritability in exercise behavior derives from genetic variants that also influence these correlates.

Conclusions: Given their shared genetic basis and predictive power we assert that individual differences in extraversion, perceived benefits and barriers, exercise-induced feelings of energy, and subjective and objective exercise ability can be used to develop stratified interventions for adolescent and young adult exercise behavior. In addition, our results provide the first clues on ‘where to look’ for specific genetic variants for voluntary exercise behavior.

1. Introduction

Despite the well-known benefits of physical activity, there is a growing number of adolescents and young adults with a less than optimal physically active lifestyle (Martinez-Gonzalez et al., 2001; Troiano et al., 2008), which puts them at risk for a large number of chronic diseases (Tremblay et al., 2011; Warburton, Nicol, & Bredin, 2006). Prospective cohort studies in adults suggest that increasing regular physical activity, especially moderate to vigorous physical activity, can protect against the onset of chronic disease and mortality (Ekelund et al., 2012; Gebel et al., 2015; Samitz, Egger, & Zwahlen, 2011) and it is a reasonable assumption that intervening early on this lifestyle reaps the largest benefits. In response, public health authorities worldwide have launched interventions aimed at physical activity during work/school time and transportation to work and school, and at physical activity in leisure time (e.g., the Global Recommendations on Physical Activity for Health by the World Health Organization (2010) and the EU Physical Activity Guidelines by the EU Working Group Sport...
and Health (2008)).

Because regular exercise in leisure time has become a major source of moderate to vigorous physical activity in industrialized societies (De Geus, Bartels, Kaprio, Lightfoot, & Thomis, 2014), increasing voluntary participation in regular exercise and sports activities is an important target for public health interventions. To improve the success of such interventions we need to better understand the determinants of the extensive individual differences that are found in voluntary leisure time exercise activities. Traditionally, research has focused on environmental factors that could either impede or facilitate participation in regular exercise of youngsters. Over the last decades, a growing number of studies have demonstrated that variation in voluntary exercise behavior (EB) has a strong heritable component, particularly during adolescence and young adulthood (e.g. De Moor et al., 2011; Huppertz et al., 2016a). This suggests that additional attention to biological characteristics in the research on determinants of EB is needed. In sharp contrast to a common misunderstanding, heritable traits can be excellent targets for intervention (Plomin & Haworth, 2010). Biological influences on the motivation to exercise do not impede attempts to increase the mean population level of that motivation, although they can be a cause of maintained variation around the increased post-intervention mean. Understanding the genetic pathways that lead to differences in voluntary EB may help identify specific biological and psychological determinants that would be solid targets for intervention. Such knowledge could exploit the genetic influences on EB in stratified or personalized interventions, rather than fighting an uphill battle against natural differences between individuals by using one-size-fits-all strategies.

The classical twin design, in which the resemblance of identical twins or monozygotic (MZ) and non-identical twins or dizygotic (DZ) is compared, decomposes all phenotypic variance of a trait in sources of genetic influences, shared environmental influences (influences shared with other family members e.g. upbringing) and person-specific influences (influences that are unique to the individual). Supplementary Fig. 1 shows the results of previous studies published on the relative influence of these factors on voluntary EB in children, adolescents and young adults up to 25 years old (Aaltenon, Ortega-Alonso, Kujala, & Kaprio, 2013; Beunen & Thomis, 1999; Boomsma, van den Bree, Orlebeke, & Molenaar, 1989; De Moor et al., 2011; Huppertz et al., 2016a; Koopmans, van Doornen, & Boomsma, 1994; Maia, Thomis, & Beunen, 2002; Mustelin et al., 2011; Stubbe, Boomsma, & de Geus, 2005; Van der Aa, de Geus, van Beijsterveld, Boomsma, & Bartels, 2010). In younger children, the shared environmental factors seem to explain a substantial part of the variation in EB, which is likely due to an important role of the parents; they provide their children with the opportunity to become active by means of transportation to exercise activities, give exercise activities priority over other leisure time activities, and provide motivation and encouragement to exercise. However, the importance of these shared environmental factors seems to decrease in adolescence and young adulthood, where genetic effects become the dominant factor explaining individual differences in voluntary EB.

In this study we use a prospective twin design to test whether the heritability of EB in adolescents and young adults can be accounted for by potential correlates of EB from a number of domains that could be used to tailor future interventions: personality, affective response to exercise, exercise benefits and barriers, objective exercise ability, and subjective exercise ability. Previous evidence has already shown elements in these domains to be associated with voluntary EB (Allender, Cowburn, & Foster, 2006; Bonen & Shaw, 1995; Dishman et al., 2005; Rhodes & Kates, 2015; Rhodes & Smith, 2006). Furthermore, of these five domains, potential correlates in the first four were already proven to be heritable traits (Aaltenon et al., 2016; Bartels et al., 2012; Huppertz et al., 2014b; Schutte, Nederend, Hudziak, Bartels, & de Geus, 2016a; Schutte, Nederend, Hudziak, de Geus, & Bartels, 2016b; Schutte, Nederend, Hudziak, Bartels, & de Geus, 2017). However, no previous studies have examined these correlates jointly in a genetically informative design that can establish the extent to which the genetic factors that influence these determinants contribute to the heritability of EB.

A substantial body of evidence confirms personality to be a robust correlate of regular EB. Regular exercisers score lower on neuroticism and higher on extraversion, conscientiousness, and sensation seeking (De Moor, Beem, Stubbe, Boomsma, & de Geus, 2006; Rhodes & Smith, 2006; Wilkinson et al., 2013; Wilson & Dishman, 2015). Extraversion or sensation seeking are linked to individual differences in the functioning of the reward system, which can be activated in response to appetitive aspects of exercise (Eysenck, Nias, & Cox, 1982). Neuroticism may follow a different neurobiological route in that it is associated with higher activity of the punishment system (Gray & McNaughton, 1983; Gray & McNaughton, 2000). This punishment system can be activated in response to physical (pain, fatigue) and social (embarrassment) aversive aspects of exercise activities, and might thereby decrease their attraction on neurotic individuals. Conscientiousness may be an expression of stronger prefrontal connectivity to limbic reward and punishment areas needed for the self-control that is required to pursue regular exercise for its longer-term benefits, even when short-term reward value is attenuated e.g. by time pressure due to social or work-related obligations.

To maintain regular exercise participation, the net appetitive effects of exercise activities during and shortly after exertion need to outweigh the net aversive effects (De Geus & de Moor, 2008; De Geus & de Moor, 2011). If the exercise induced affective response is on balance positive, people are likely to maintain the behavior and become regular exercisers. Vice versa, if the net affective response is not favorable, people are at risk of dropping out and becoming non-exercisers. Strong individual differences are found in the affective responses during and after exercise (Ekkekakis, Hall, & Petruzzello, 2005; Ekkekakis, Parfitt, & Petruzzello, 2011). A more favorable affective response during exercise was found to be associated with the intention to engage in voluntary exercise (Kwan & Bryan, 2010; Ruby, Dunn, Perrino, Gillis, & Viel, 2011) as well as greater actual participation in (voluntary) moderate to vigorous exercise (Rhodes & Kates, 2015; Schneider, Dunn, & Cooper, 2009; Williams, Dunsiger, Jennings, & Marcus, 2012).

Although short term appetitive and aversive effects are important, longer term effects also weigh in. Social cognitive models of health behavior have consistently pointed to perceived benefits & barriers as a main determinant of the value of EB to a person (Allender et al., 2006; Hagger, Chatzisarantis, & Biddle, 2002; Huppertz et al., 2014b; Rhodes, Fiala, & Conner, 2009; Trost, Owen, Bauman, Sallis, & Brown, 2002). A positive attitude towards exercise and, consequently, the likelihood of maintaining EB increases when an individual perceives that the benefits of exercise outweigh the disadvantages. Huppertz et al. (2014b) demonstrated in a sample of adolescent twins that perceived benefits of and barriers to exercise are heritable and that exercise attitudes may have direct causal effects on EB.

A further important potential correlate of voluntary EB may be subjective exercise ability. People’s beliefs about their capabilities to produce designated levels of exercise performance lead to feelings of competence and mastery and this enhances the frequency of EB in leisure time. The self-determination theory (Deci & Ryan, 1985) assumes competence one of the psychological needs. Perception of competence can provide individuals with a sense of satisfaction when engaging in exercise activities. Teixeira et al. (2000) showed in a large review that perceived competence was positively associated with physical activity across different samples. However, the extent to which subjective exercise ability is influenced by genetic variation across individuals is currently unknown. Subjective exercise ability in part derives from objective exercise ability, although the relationship will be imperfect because individuals will base their judgments of their own performance in comparison to the peer groups. In adolescence, objective exercise ability is most directly observable by how individuals rank
in competitive performance in specific sports. Performance may be influenced by skills specific to a sport, but a number of general fitness characteristics including strength and endurance are strong predictors of performance across a variety of sports and exercise activities (McArdle and Katch, 2009). Both strength and endurance are known to be highly heritable traits (Schutte et al., 2016a; Schutte et al., 2016b) and could therefore contribute to the heritability of voluntary EB.

To establish the role of personality, perceived benefits & barriers, exercise-induced affective response, and subjective and objective exercise ability in the heritability of voluntary EB we performed a study in a sample of adolescents and young adult twins. We hypothesized that the genetic factors contributing to many of these potential correlates overlap with the genetic factors that are responsible for the individual variation seen in EB in late adolescence/young adulthood. Three different waves of data collection were used. Personality, perceived benefits & barriers, and subjective exercise ability were measured at time point 1 by survey in a sample of 16 to 18-year-old twins and their siblings. These participants, and additional twins and siblings, were invited at time point 2 for an experimental assessment of affective response to exercise, by repeated measurements during and after (sub) maximal exercise tests. Objective exercise ability was assessed in parallel by tests of muscle strength, balance and flexibility and by VO2max testing on a cycle ergometer. Regular voluntary EB was measured in the survey and by interview during the experimental session, and at time point 3, after a 3-year follow-up period by an online/telephone interview at age 20. When a potential correlate showed a significant association with EB measured at either time point 1 or 2, we further tested whether it shared genetic variance with EB, by computing their genetic correlation (rG) in bivariate twin designs. When this correlation was significant, we tested how well these correlates jointly predicted EB at the 3-year follow-up. A two-factor model was used to test the hypothesis that genetic variants that influence these correlates significantly contribute to the heritability of EB. Such correlates can be prioritized in developing stratified interventions on adolescent and young adult EB.

2. Method

2.1. Participants

A set of healthy adolescent twin pairs aged between 16 and 18 and their siblings (age range 12–25) from the Netherlands Twin Register (NTR, Van Beijsterveldt et al., 2013) were invited to participate in a study on the determinants of adolescent EB. Selection for invitation was based on the availability of longitudinal survey data on zygosity and regular leisure time EB. The aim was to have sufficient twins present from the entire spectrum of sedentary to vigorous leisure time exerciser and for each zygosity group. We started with a random selection, but if a zygosity group was underrepresented or if there were too little sedentary or vigorous exercisers, invitations were biased towards the underrepresented groups. This was mainly the case for dizygotic twins, siblings, and sedentary subjects. Regarding the latter, we selected twin probands who reported no engagement in EB on a previously filled out survey. The co-twin was then selected as well, regardless of exercise status. Huppertz (2016b) made an effort to compare EB in multiples versus singletons based on data within the NTR. The percentage of non-exercisers and the means and variances in weekly MET hours between first-born multiples and siblings in narrow age groups (at the age of 13, 14, 15, 16, 17, and 18) showed no systematic differences (Huppertz, 2016b). In order to be eligible for the study, participants had to have no history of cardiovascular or respiratory disease, and being physically capable of engaging in exercise activities. Participants were invited by sending a letter advertising the opportunity to test their fitness in addition to earning a gift voucher. All invitees had to be able and willing to visit the VU University in Amsterdam for lab testing. All participants provided written informed consent and if the participants were under 18 consent was given by both of their parents/guardians. All study procedures submitted to and approved by the Medical Ethics Review Committee of the VU University Medical Center Amsterdam (NL35634.029.10).

2.2. Study design

Variables that were in previous studies associated with exercise behavior and shown to be heritable traits were identified. Measurements on these variables were collected at three time points. Fig. 1 shows type of data collected, the sample sizes and mean age at every time point. At time point 1, part of the twins and their non-twin siblings received an online self-report survey. The survey contained items about regular EB, personality, exercise attitudes and subjective exercise ability. The mean age at completion of the survey was 16.9 ± 0.8 (N = 373).

At time point 2, regular EB was queried by interview during an extended experimental protocol including tests of affective responses to exercise and subjective exercise ability. Protocol details of the exercise tests are described elsewhere (Schutte et al., 2016a; Schutte et al., 2016b; Schutte et al., 2017). Briefly, on arrival at the laboratory, height and weight were measured and a short lifestyle interview was completed, including detailed questions on current levels of regular exercise. Next, four fitness tests were administered to measure balance, hand grip strength, flexibility and vertical jump height. Thereafter, two
exercise tests were conducted (in fixed order) on an electro-
mechanically braked Lode cycle ergometer (type Corival) and a Lode
treadmill (type Valiant) at fixed loads that are below the intensity of
the ventilatory threshold for most adolescents. Both submaximal tests
consisted of 4 incremental stages of 5 min each followed by a 1-min
cooling-down phase and by a 5-min recovery period. To ensure that
the intensity of every stage was below the intensity of the ventilatory
threshold for most adolescents, the ratio of the oxygen consumption
and carbon dioxide production ($\dot{V}CO_2/\dot{V}O_2$) was monitored. This re-
spiratory exchange ratio (RER) can be used to estimate the ventilatory
threshold. This threshold is passed when exhalation of $CO_2$ exceeds
inhalation of $O_2$, which is visualized by a RER $> 1.00$. For each test, the
load of each stage was adjusted when necessary to keep the intensity
below an RER of 1.00. Finally, an incremental maximal exercise test
was conducted on a cycle ergometer to establish $V_{O2\text{max}}$. The work rate
was increased every minute until exhaustion. After cessation of the test,
every participant completed a mandatory cool-down phase on the cycle
ergometer of 5 min on a low, individually chosen work rate.

At time point 3, the participants to the exercise tests were sent an
online follow-up survey on their current exercise status. When partici-
pants failed to take the survey online, the survey was done by tele-
phone. Five participants unsubscribed from the NTR and were therefore
not available for the follow-up survey. 59 participants were lost to
follow-up due to missing contact information or did not respond to the
questionnaire after several reminders or refused to participate by tele-
phone. This resulted in a response rate of 88%. Complete follow-up data
were available for 423 participants; 50 MZM pairs (of which 11
participated with a sibling); 26 DZF pairs (of which 1 participated with
a sibling); 46 MZF pairs (of which 11 participated with a sibling); 28 DZM
pairs (of which 2 participated with a sibling); 26 DOS pairs, 2 (non-
twin) sibling pairs and 26 singletons. Mean age at time of the follow-up
test, of which 2 participated with a sibling); 28 DOS pairs, 2 (non-
twin) sibling pairs and 26 singletons. Mean age at time of the follow-up
test, was 19.7 ± 1.1.

2.3. Measurements

Regular exercise behavior The participants were asked to indicate
what types of regular sports or exercise activities they were involved in.
Participants were asked to indicate for each activity for how many years
the subject participated in the activity, for how many months a year,
how many times a week, and how many minutes each time. Each ac-
tivity was recoded into a metabolic equivalent (MET) score, based on
the compendium of energy expenditure for youth published by
Ainsworth et al. (Ainsworth et al., 2000). By multiplying the MET score,
the frequency, and the duration of each exercise activity, weekly MET-
hours spent on exercise activities were calculated for each participant.
We only included activities that were conducted for at least 3 months a
year and since at least half a year (thereby excluding ski holidays,
sailing camps, and similar). EB was quantified in the same way at all
three time points, but surveys were used at time points 1 and 3, whereas
an interview was conducted at time point 2. Tracking coefficients
(Pearson $r$) were 0.67 from time points 1 to 2, 0.57 for time points 2 to
3, and 0.49 for time points 1 to 3.

Personality Personality traits were measured by the short version of
the NEO, reliability and validity of which are well-established (NEO-
FFI: Costa & McCrae, 1992). The NEO-FFI consists of 60 items that are
rated on a 5-point scale (1–5: “totally disagree”,” disagree”, “neutral”,
“agree”, “totally agree”) and gives a score for the traits neurotism,
agreeableness, conscientiousness, extraversion and openness to ex-
perience. For each trait 12 items are summed to obtain a total score.

Affective response Affective responses to exercise were assessed by the
Dutch versions of the Feeling Scale (Hardy & Rejeski, 1989) and the
Activation-Deactivation Adjective Checklist (Thayer, 1986). The
Feeling Scale (FS) is an 11-point bipolar measure of pleasure-dis-
pleasure. The scale ranges from −5 “very bad” to +5 “very good” and
has been used in many studies on the affective response to exercise
(Ekkekakis, Hall, & Petruzzello, 2008; Ekkekakis et al., 2011; Parfitt,
Rose, & Burgess, 2006; Schneider & Graham, 2009). As the Feeling
Scale scores were recorded at baseline (before the tests) and during
every incremental step of the submaximal exercise tests, scores were
plotted and the area above the curve was calculated for every partici-
 pant during exercise (using the polyarea function in Matlab
(Matlab 2014a; The MathWorks Inc., Natick, Massachusetts, USA).
For details see Schutte et al., 2017. The Activation-Deactivation Adjective Check-
list (ADACL) is a multidimensional test of transitory arousal states
using a four-point self-rating system: “definitely feel” (4), “slightly feel”
(3), “cannot decide” (2) or “definitely do not feel” (1). As the partici-
pants experienced some trouble with understanding three of the items
“placid” and “favorable” and “intense”, these items were left out the
analyses. This questionnaire is scored by averaging five items to create
5 subscales: Energy, Tiredness, Tension, and Calmness. A previous
cross-sectional study showed the heritability of these measurements of
affective responses to exercise and its correlation to regular EB (Schutte
et al., 2017). Scores on the Feeling Scale (during the cycle ergometer
test), Energy (after the cycle ergometer test), Tiredness (after cycle
ergometer test), and Calmness (after cycle ergometer, treadmill and
maximal exercise test) proved to be heritable and showed a significant
phenotypic correlation to EB and were therefore included in the current
analyses.

Perceived benefits & barriers Perceived benefits of EB were measured
by 10 items with a 4-point response scale, ranging from “strongly
disagree” (1), “disagree”, “agree”, to “strongly agree” (4). Seven items
were derived from a questionnaire by Devereaux Melillo, Williamson,
Futrell, and Chamberlain (1997). The remaining three items were taken
barriers towards EB were measured by 23 items derived from a ques-
tionnaire by Sallis et al. (1989) (Van Sluijs, van Poppel, Twisk, Brug, &
v van Mechelen, 2005). Each item could be answered on a five-point
response scale (ranging from “never” (1) to “very often” (5)). All items
were combined into six components, according to Huppertz et al.
(2014b): Benefits; Lack of skills, support and/or resources; Time con-
straints, Lack of energy; Lack of enjoyment; and Embarrassment.

Subjective exercise ability Subjective ability was measured using four
items. The first three asked to compare a participant’s own sport per-
formance, endurance capacity and muscle strength to their peers.
Responses were measured with a 5-point response scale ranging from “I
perform much worse than my peers” (1) to “I perform much better than
my peers” (5). The final item asked the participant to indicate on a 10-
point scale, ranging from “very bad” (1) to “really good” (10) how well
they performed at sport activities. This final item was rescaled to a 5-
point response scale by dividing the score by two. All four items were
combined into one measure (a mean was calculated) for subjective
exercise ability (Cronbach’s alpha = .78).

Objective exercise ability As detailed elsewhere, tests of muscle
strength as well as a maximal exercise test on a cycle ergometer were
used to test exercise ability in these participants (Schutte et al.,
2016a; Schutte et al., 2016b). Briefly, explosive strength was measured with
a vertical jump test. To measure handgrip strength, participants were
instructed to hold a dynamometer (Baseline Digital Smidley Hand dy-
amometer, Fabrication Enterprises Inc., USA) in the dominant hand
and when ready, the subject was encouraged to squeeze the dynamo-
 meter once with maximum effort (in kg). Flexibility was measured
using a standard sit-and-reach box (Baseline Sit-and-reach Trunk Flex-
ibility Box, Fabrication Enterprises Inc., USA). The Balance Error
Scoring System (BESS) was used to assess balance (Bell, Guskiewicz,
Clark, & Padua, 2011), which we recorded as such that a better balance
was associated with a higher score. Finally, to obtain maximal oxygen
take-up ($\dot{V}O_{2\text{max}}$), oxygen take-up ($\dot{V}O_2$) and carbon dioxide production
($\dot{V}CO_2$) were recorded breath-by-breath by means of a telemetric gas
exchange system (Cosmed K4b2, Cosmed Benelux, Nieuwegein,
The Netherlands). To obtain $V_{O2\text{max}}$, only $V_{O2}$ data with a corresponding
respiratory exchange ratio of at least 1.10 were selected to ensure good
effort above the intensity of the ventilatory threshold. Breath-by-breath
VO2 data was cut into 20-s blocks. For every 20-s block, we calculated the mean VO2, after discarding deviant breaths. VO2max was determined as the highest mean value of VO2 of all the 20 s blocks. VO2max is expressed in mL/min/kg.

2.4. Statistical analysis

Statistical analyses were performed in R (R Development Core Team, 2017). For all analyses, a threshold of $p < .05$ was considered for statistical significance. Genetic modeling was done in the OpenMx package (Boker et al., 2011) with the raw-data ML procedure for estimation of parameters. Since (non-twin) siblings share, like DZ twins, on average 50% of their segregating genes, parameter estimates were constrained to be equal for DZ twins and siblings. Means were estimated separately for males and females.

Analysis of the data was done in three steps. First, saturated bivariate models including EB and one potential correlate were fitted in which phenotypic correlations, MZ and DZ/sibling correlations, as well as cross-trait/cross-twin correlations were estimated to explore their association. Next, total phenotypic variation in these variables was decomposed into additive genetic variance and covariance (A), variance and covariance that can be ascribed to sources that are shared by the twins (e.g. family environment, C) and sources of variance and covariance that are person-specific (unique environment, E). This latter component also includes measurement error. Posthuma and Boomsma (2000) showed that to detect additive genetic influences in full bivariate models with a power of 80% and an alpha of .05 a sample size of up to 678 participants is required, depending on the presence of C. As the influences of the C component were previously found to be low at late adolescence in a comparable Dutch sample (Huppertz et al., 2016a), we expected the influences of C to be small, therefore the sample size of the current study should suffice to detect additive genetic influences. The significance of these A, C and E components was examined by comparing the bivariate model including these components to a model in which A, C or E is constraint to be equal to zero. These nested submodels were compared by hierarchic chi-squared tests. The chi-squared statistic is computed by subtracting log-likelihood (-2LL) for a reduced model from the -2LL for the full model ($\chi^2 = -2LL_{full \ model} - -2LL_{reduced \ model}$). This chi-squared statistic is distributed with degrees of freedom (df) equal to the difference in the number of parameters estimated in the two models ($df = df_{full \ model} - df_{reduced \ model}$). If the difference test is significant the constraints on the reduced model cause a significant deterioration of the fit of model. In the second step, we selected the heritable correlates that had shown a significant correlation to EB at time point 1 or 2 for further testing of the genetic covariance. By constraining the genetic correlation ($r_G$) to zero (Fig. 2), it was tested whether there is substantial overlap in genetic variants underlying the correlate and EB at either of these time points. If this was the case, we repeated this bivariate analysis for this correlate with regular EB at time point 3.

The correlates that proved to be significantly associated with EB at time point 1 or 2, were heritable, and showed significant genetic correlations to EB at time point 3 were included multiple regression analyses in Stata/SE (version 14.1, StataCorp LP, USA). This analysis was performed to determine how much of the variance in EB could be explained by these correlates. First, EB at time point 1 was taken as dependent variable and the correlates were entered simultaneously as independent variables. Family was modeled as a random effect to take familial relatedness into account. Subsequently, the analysis was repeated with EB at time point 2 and finally EB at time point 3 as dependent variable.

Finally, a common two-factor model was fit to the data. This model specified two latent factors; one latent factor for regular EB measured at three time points and one underlying latent factor for all correlates of EB. In this model part of the covariation between the different measures of EB is assumed to be influenced by a single phenotypic latent factor. Similarly, part of the covariation between the different measured correlates is assumed to be influenced by one single phenotypic latent factor. Our twin data allows estimation of the relative importance of genetic and environmental effects on the variance in these latent factors and can also detect the genetic correlation ($r_G$) between the ‘exercise’ and ‘correlates’ factor. Genetic and environmental factors specific to the measured variables are also estimated, to account for the remaining variance.

3. Results

3.1. General descriptives

Table 1 shows the means and standard deviations (SDs) for EB measured at the 3 time points for males and females separately. METs spent on EB reported by survey at the youngest age were higher than those measured by interview in the lab study and by survey at 3-year follow-up. Females had lower MET scores compared to males at all three time points. Table 1 also shows the means and SDs of the potential determinants in the five different domains. Males had lower scores on the Personality subscales Neuroticism and Agreeableness. Females felt more energetic after the submaximal exercise test, whereas males reported higher feelings of tiredness. Regarding the perceived benefits & barriers, females scored lower on ‘lack of energy’ higher on ‘embarrassment’. As expected, males score higher on all four measures of objective exercise ability, but no significant differences were seen for subjective exercise ability. The (univariate) heritability of regular EB was 67% (95% CI: 55%–76%) for EB at time point 1, 81% (95% CI: 73%–86%) at time point 2 and 60% (95% CI: 42%–72%) for EB at time point 3.

3.2. Bivariate genetic analyses

Fig. 3 displays phenotypic correlations of the measured variables to EB across the three time points. Higher scores of Extraversion and Conscientiousness were associated with higher amounts of EB at all three time points (0.19 < r < 0.25 and 0.09 < r < 0.13 respectively). Exercise-induced affective responses showed low, but significant phenotypic correlations with EB at time point 2 (0.11 < r < 0.17). However, only Energy measured after the submaximal test on the cycle ergometer showed significant phenotypic correlation with EB at time point 3 ($r = 0.12$). All phenotypic
The objective exercise ability quantified heritability estimate of 66%. Finally, a substantial part of variation in constraints to 59% for Embarrassment. Subjective exercise ability showed a well as better vertical jumping scores at time point 2 (vertical jump performance, balance and

3.3. Multivariate regression analyses

These potential correlates were included multiple regression analyses to determine how much of the total variance in EB could be explained by these correlates. This was done for completeness on all time points, but the most critical test is the prospective regression analyses were the correlates measured at time point 1 or 2 are used to predict EB at the 3-year follow-up. Twenty-nine percent of the variance in EB at time point 1 could be explained by these potential correlates (Extraversion, Energy measured after submaximal exercise, perceived benefits, all five perceived barriers, subjective ability and VO2max). When repeating the analysis with EB at time point 2 as dependent variable, this was 26%. Finally, at the 3-year follow up, 18% of the variance in EB was explained by these correlates.

3.4. Common factor model

Extraversion, Energy measured after submaximal exercise, perceived benefits, all five perceived barriers and subjective ability showed substantial phenotypic correlation (see Supplementary Table 1). For VO2max, the phenotypic associations with the other correlates was low, except for the association with Embarrassment and subjective exercise ability (both \( r = -0.31 \)). All these correlates were included in a common two-factor analysis including one latent factor accounting for their covariances and one latent factor for EB at the three time points (Supplementary Fig. 2) This showed that specific genetic factors explained 20% (time point 1), 14% (time point 2) and 20% (time point 3) of the variance in EB. The largest part of the variance in EB was explained by the genetic effects on the latent factor (50%, 67% and 39% for the three time points respectively). Likewise, the environmental variance in EB was largely due to effects on the latent factor.

For the correlates, the latent factor explained around half (43%-66%) of the total variance in all the perceived barriers, except for Time constraints (29%). Most of this variance was accounted for the by genetic effects on the latent factor (31%-46%). For the remaining correlates the latent factor explained between 5% (VO2max) and 31% (subjective exercise ability), however, most of this variance was accounted for by the genetic effects on the latent factor. The genetic correlation between the two latent factors was 0.51 (95% CI: 0.35-0.65) indicating that these latent factors are for a large extent influenced by the same genetic variants.

4. Discussion

In the current study, heritability estimates of regular voluntary EB were 67% (time point 1), 81% (time point 2) and 60% (time point 3) and confirm the high heritability estimates in adolescents and young adults reported in previous studies (Supplementary Fig. 1). The peak at time point 2 might be partly attributed to the use of a lifestyle interview instead of an online survey; this might have resulted in lower measurement error compared to online surveying and a relative increase of the estimate of genetic effects.

A twin design was used to test whether the heritability of EB in these age groups could be accounted for by a number of potential correlates of EB: personality, affective response to acute exercise, perceived benefits & barriers, objective exercise ability as well as subjective exercise ability. The first four of these correlates of EB had been shown to be heritable in previous studies with strongest evidence for objective exercise ability (for meta-analyses see Schutte et al., 2016a and Schutte et al., 2016b). We now also provide evidence for substantial heritability (66%) of subjective exercise ability: one’s self-reported ranking of physical fitness compared to peers.

Ten of the potential correlates proved to be significantly associated with EB at time point 1 or 2 and showed significant genetic correlations to EB at time point 3: Extraversion, Energy measured after the submaximal exercise tests, the perceived benefits and five perceived barriers, subjective exercise ability and VO2max. When including these correlates in a common two-factor model, we showed that a large part of the covariation between EB and a latent ‘correlates factor’ was due to genetic causes. Hence, the substantial heritability of EB (60%) in our sample of young adolescents and adults overlaps with the genetic variation shared by these ten correlates. This finding inevitably reflects

Table 1

Means and SDs for males and females for exercise behavior and its potential correlates.

<table>
<thead>
<tr>
<th>Exercise behavior (METS/week)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point 1†</td>
<td>33.3</td>
<td>28.4</td>
</tr>
<tr>
<td>Time point 2†</td>
<td>25.2</td>
<td>22.8</td>
</tr>
<tr>
<td>Time point 3†</td>
<td>23.6</td>
<td>27.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personality</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroticism</td>
<td>28.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Extraversion</td>
<td>42.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Openness to experience</td>
<td>35.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>42.7</td>
<td>4.7</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>42.4</td>
<td>6.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Affective Response</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling Scale - cycle</td>
<td>3.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Tiredness - cycle</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Calmness - cycle</td>
<td>2.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Calmness - treadmill</td>
<td>2.9</td>
<td>0.8</td>
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</table>

<table>
<thead>
<tr>
<th>Perceived benefits</th>
<th>Males</th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td>Calmness - max test</td>
<td>3.3</td>
<td>0.6</td>
</tr>
<tr>
<td>31.4</td>
<td>4.9</td>
<td>32.2</td>
</tr>
<tr>
<td>Lack of skills, support and/or resources</td>
<td>13.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Time constraints</td>
<td>9.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>8.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Lack of enjoyment</td>
<td>6.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Embarrassment</td>
<td>4.5</td>
<td>1.7</td>
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</table>

<table>
<thead>
<tr>
<th>Subjective ability Objective ability</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>0.6</td>
<td>3.4</td>
</tr>
<tr>
<td>VO2max</td>
<td>46.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Hand grip (kg)</td>
<td>40.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Vertical Jump (cm)</td>
<td>45.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Flexibility (cm)</td>
<td>19.7</td>
<td>10.4</td>
</tr>
<tr>
<td>Balance</td>
<td>44.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

* Significant mean difference between males and females correlations of the perceived benefits & barriers with EB were significant at all three time points. Subjective exercise ability was consistently correlated to EB (0.28 < r < 0.40). Finally, higher VO2max and flexibility were associated with a higher amount of EB at time point 2 and 3 (r = 0.18 and 0.34 for VO2max, and r = 0.14 for flexibility) as well as better vertical jumping scores at time point 2 (r = 0.12).

Fig. 4 shows the heritability estimates of the measured variables. The five personality traits showed heritability estimates of 41%-59%. Heritability estimates for exercise-induced affective responses ranged from 15% to 37%. For perceived benefits the heritability was 47%, and for perceived barriers, the estimated ranged from 30% for Time constraints to 59% for Embarrassment. Subjective exercise ability showed a heritability estimate of 66%. Finally, a substantial part of variation in objective exercise ability quantified by VO2max, handgrip strength, vertical jump performance, balance and flexibility could be explained by genetics (44%-80%). Fig. 4 also displays the genetic correlation of the heritable correlates that showed a significant phenotypic correlation to regular EB at time point 1 or 2. Ten potential correlates met the final requirement to be included in subsequent analyses: Extraversion, Energy measured after submaximal exercise, perceived benefits, all five perceived barriers for EB, subjective ability and VO2max proved to be significantly associated with EB at time point 1 or 2, were heritable, and showed significant genetic correlations to EB at time point 3. These ten correlates were selected for the analyses below.
some overfitting and independent replication is direly needed. Nonetheless, it is unlikely that these ten correlates would cease to be of importance for the genetics of EB. This study therefore provides a valuable glimpse on the factors that give rise to the high heritability estimates reported in late-adolescents and young adults.

EB is, like many other behaviors, a complex polygenic trait; whether people perform exercise activities in leisure time and how often are the result from variation within multiple genes (and their interaction with environmental factors). Each of these genetic variants will explain only a very small percentage of the variance (Flint, 2013). To detect them, a major collaborative effort is needed that collects DNA with genome-wide genotyping in a sample large enough to perform genome-wide

![Correlate vs Phenotypic correlation chart]

Fig. 3. Phenotypic associations of all potential correlates with exercise behavior at time point 1, time point 2 and time point 3. *significant at $p > .05$ level.
association (GWA) study on regular voluntary EB. In parallel, a candidate gene approach could be used based on genetic variants influencing some of the correlates detected by our analyses. Such an approach could help establish that the correlates have a causal effect on variation in EB (and might genuinely be labeled determinants) rather than a consequence of EB (reverse causality). A source of candidate genes repeatedly implicated in voluntary wheel running in animal models is the mesolimbic dopaminergic...
reward system (Rhodes, Gammie, & Garland, 2005). However, attempts to link dopaminergic candidate genes to voluntary EB in humans has showed mixed results (Huppertz et al., 2014a; Jozkow, Slowinska-Lisowska, Laczmanski, & Medras, 2013; Simonen et al., 2003). This does not, of course, rule out individual differences in the neurobiology of reward seeking or sensitivity. At least one other reward system, the endocannabinoid system, has long been implicated in exercise (Raichlen, Foster, Gerdeman, Seillier, & Giuffrida, 2012; Sparling, Giuffrida, Piomelli, Roskopf, & Dietrich, 2003). In general, genetic variants increasing the balance of appetitive over aversive experiences during and after exercise should be regarded potential candidate genes for EB. Bryan, Hutchison, Seals, and Allen (2007) reported that a single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (BDNF) gene (G/A at nucleotide 196; Rs6265) moderated the effect of exercise on positive mood and perceived exertion in a sample of healthy exercisers (Bryan et al., 2007). Karoly et al. (2012) found two SNPs (rs8044769 and rs3751812) in the fat mass and obesity-associated protein gene (FTO) gene to be related to positive affect change during exercise (Karoly et al., 2012). The FTO gene is strongly linked with body mass index. The risk alleles within this gene seem to act on appetite ratings and satiety, but not on resting energy expenditure or physical activity (Speakman, 2015). The FTO gene effect could be related to the ‘embarrassment’ component of the exercise attitudes linked to voluntary EB in this study might. Feelings of shame or embarrassment during exercise are known to be larger in overweight adolescents (e.g. Gillison, Standage, & Skevington, 2006).

Exercise ability was a further correlate of EB, but VO2max was shown to be more consistently (genetically) associated with EB than muscle strength. Participants were late-adolescents and young adults and a large portion of their weekly MET hours was dedicated to aerobic sports activities performed in teams, such as hockey and soccer. These METs are therefore for a substantial part based on aerobic activities, which might explain the lower correlations to hand grip strength and vertical jump. A number of candidate genes for exercise ability also exist. In addition, below 5000 twin pairs, the power to detect a significant environmental correlation between EB and a correlate is very poor (Stubbe & de Geus, 2009). Here we find no significance for the person-specific environmental correlations between EB and the correlates of EB. Following the logic of De Moor, Boomsma, Stubbe, Willemsen, and de Geus (2008) this could be taken to falsify a true causal effect of these determinants. However, taking the power-issue into account, the non-significance in the current study should not be interpreted.

As a further limitation, we did not take into account the possibility that, as part of maturation, different genes were expressed at baseline and follow-up. Modeling longitudinal data on EB in 7–18-year olds by Huppertz et al. (2016a) showed that genetic effects on EB were marked by both transmission (the same genetic influences EB at all ages) as well as innovation (newly emerging genetic effects on EB at all time points). At the age of 18 this was about fifty-fifty; half of the genetic variants is explained by the same genetic effects influencing EB at age 16, whereas the other half is explained by newly emerging genetic effects. When new genetic factors come into play only at follow-up they would act to reduce the genetic correlation with correlates measured at an earlier time point. However, in our study, all genetic variation most of the genetic variance in EB could be explained by one latent factor, suggesting more transmission than innovation at these ages. The age range in our sample is wider than the age ranges in the study by Huppertz et al. (2016a), suggesting that genetic factors that come into play during late-adolescence may be already picked up by our study at the first time point. Maturation might also have consequences for other variables. Our sample had a fairly wide age range and might comprise individual differences in maturation as the younger siblings may still be pubertal, compared to the rest of the subjects. However, we tested for possible effects of these maturational differences between the twins and siblings by repeating the analysis with a restriction on age (no siblings) and the results showed comparable heritability estimates.

A limitation of our experimental protocol, a consequence of logistic and feasibility constraints, was that submaximal and maximal exercise testing was done in a single session on one day. This prevented us from measuring the affective response at a fixed percentage of VO2max. In addition, our participants could anticipate having to pedal until exhaustion during the maximal exercise test. This may have biased our results because individuals who have a low tolerance for vigorous exercise activities or feel embarrassed when exercising vigorously could be underrepresented in our sample of volunteers.

Finally, the factors we have included in the currently study are not all-embracing. Multiple regression analyses showed that 18%–29% of the variance in EB could be explained by the correlates used here. Other potential correlates of EB such as intentions, susceptibility to injuries, levels of stress (e.g. Rhodes et al., 2013; Sherwood & Jeffery, 2000; Aldana, Sutton, Jacobson, & Quirk, 1996; Bauman et al., 2012), might also be heritable and may explain part of the heritability of EB. Here, we included only potential correlates of EB that were available within the NTR and proven to be heritable.

In conclusion, all five main classes of potential determinants examined showed significant associations with EB: Extraversion, positive affect after exercise, perceived benefits & barriers (lack of skills, support and/or resources, time constraints, lack of energy, lack of enjoyment, embarrassment), subjective exercise ability and objective exercise ability, quantified by maximal oxygen uptake. Multivariate modeling
showed a large proportion of variance that is shared between EB and its correlates is due genetic causes. Demonstrating such high levels of heritability in correlates of (un)desirable health behaviors can appear intimidating. Heritability sounds like sentence for a life. It is not.

Genetic variants are a route to increased future understanding of the actual biological pathways leading to the heritability of EB. These can provide a rational basis for stratified or personalized interventions on EB.

Conflicts of interest
None.

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Supplementary data
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