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

Schutte, N.M.

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CHAPTER 2

GENETICS OF PHYSICAL ACTIVITY & EXERCISE BEHAVIOR: REVIEW AND META-ANALYSIS

BASED ON

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ABSTRACT

Because regular physical activity and exercise behavior are key contributors to children's health, it is important to understand the sources of variation in these phenotypes seen among children and adolescents. Twin and family studies provide the ability to calculate the relative importance of genetic and environmental factors to the observed individual differences. Heritability estimates of physical activity and exercise behavior vary, depending on sample size and measurement instrument, but the overall importance of environmental factors on exercise behavior seems to decrease in adolescence, whereas genetic effects become more prominent in explaining individual differences. A sample size weighted meta-analysis in children, adolescents and late-adolescents showed increasing meta-analytic heritability estimates of 20% (95% CI: 13, 27), 35% (95% CI: 17, 52), and 53% (95% CI: 47, 59) respectively. Some evidence is found for specific genes coding for physical activity and exercise behavior, but in children and adolescents these studies are limited. This should be a priority for future research because knowledge on the source of individual differences in physical activity at different time points during childhood and adolescence can optimize the choice and timing of exercise intervention.

INTRODUCTION

Regular physical activity is key contributors to children's health (Janssen & Leblanc, 2010). However, the majority of the youth does not engage in regular exercise at the recommended level (Martinez-Gonzalez et al., 1999; Troiano et al., 2008). Traditionally, the individual differences in an active lifestyle of children and adolescents have been explained by environmental and social factors, such as socioeconomic status (of the parents), health beliefs and support by peers and family (Bergstrom et al., 1996; Dishman et al., 1985; Drenowatz et al., 2010; Sallis et al., 2000). However, as is the case for many human (behavioral) traits, (Polderman et al., 2015) another major source of variation in physical activity is innate biological differences.

The contribution of genes to the differences in physical activity is under study for many decades, since the first heritability study by Kaprio et al. (1981) published in 1981 in a large sample of adult male twins. Twin and family studies provide the ability to calculate the relative importance of genetic and environmental factors to the observed individual differences. Evidence of familial aggregation of a behavioral trait can be found when this specific trait occurs more in members of a family than can be readily accounted for by chance. A twin design exploits the known differences in genetic similarity in monozygotic and dizygotic twins (or siblings) to separate the genetic effects (the heritability) from other factors that are shared by the family members (e.g. family environment, school).

Studying the heritable components of a trait such as physical activity is referred to as quantitative genetics. Whereas these family and twin studies provide a starting point in exploring the effects of genetic and environmental variance on a phenotype, molecular genetic studies aim to detect the genes underlying the heritability. Studies in animals are used to identify the genetic mechanisms underlying physical activity by means of selective breeding and (fine) mapping of genomic regions. The progress in molecular genetics makes it feasible to collect and analyze DNA on a large scale also in humans.

In this chapter the principles of family, twin, animal and molecular genetic studies are shortly introduced followed by an overview of published studies on the quantitative genetics and molecular genetic findings for physical activity and exercise behavior.

THE PRINCIPLES OF FAMILY, TWIN, ANIMAL AND MOLECULAR GENETIC STUDIES

Family studies

Familial aggregation is seen when the occurrence of the trait among relatives is substantially higher than that among non-relatives.(Liang & Beaty, 2000) For quantitative traits (i.e. continuous traits: the trait has a quantitative value), such as amount of physical activity, familial aggregation can be investigated by computing correlations among relatives such as siblings, parents and their offspring, grandparents and grandchildren, nieces, et cetera, depending on the extent of the pedigrees from which data are available. Most family studies use sibling and parent-offspring correlations. Siblings among each other and parents and their offspring share on average half of their genes in common. They also share a household, the neighborhood, and various other aspects of belonging to the same family (the so-called shared environment). Therefore, evidence of familial aggregation may be due to shared exposure to a risk factor, due to genetic factors, or result from a mixture of both. Thus, this familial resemblance includes both genetic and shared environmental sources of covariance. If the effect of shared environment can be assumed zero, the familial resemblance in the trait can be ascribed to genetic factors and can be used to estimate its heritability. When familial environmental factors influence the trait of interest as well, familial resemblance only provides us with an indication of the upper value of the traits' heritability.

Twin Studies

A more powerful design to disentangle the relative importance of environmental and genetic influences on a trait or behavior is the classical twin design. This design compares the intrapair resemblance between two types of sibling relationships; genetically identical twins or monozygotic (MZ), a result of division of a single fertilized egg during an early stage in embryonic development, and non-identical twins or dizygotic (DZ), resulting from two separate fertilized eggs. Consequently, MZ twins are genetically identical and the differences between the twins are due to person-specific environmental factors: experiences that one of the twins has and the co-twin does not. DZ twins share on average 50% of their genetic make-up. If MZ-resemblance for the trait of interest is higher than DZ-resemblance, this constitutes evidence for genetic influences (referred to as 'A') on the trait.

Twin studies decompose all phenotypic variance of the trait of interest in sources of genetic influences (A), shared environmental influences (influences shared with other family members e.g. upbringing; referred to as 'C') and person-specific influences (influences that are unique to the individual; referred to as 'E'). An important assumption is that the shared environmental effects are independent of zygosity (and thus equal for both MZ and DZ twins). Thus: the correlation between MZ twins (r_{MZ}) comprises A+C, whereas the DZ twin correlation (r_{DZ}) is an estimate of ½A+C. Following from this, a simple formula by Falconer (1960) computes the relative contribution of genetic influences (A) to the total variance, as twice the difference in MZ/DZ resemblance:

$$\text{Heritability} = 2(r_{MZ} - r_{DZ})$$

An alternative to this simple formula is the use of structural equation modelling to obtain a more precise estimate of heritability (Neale & Cardon, 1992). In contrast to familial aggregation studies that cannot separate genetic and familial environmental sources of variance, the classic twin design can separate how much of the variance in a trait is due to genetic effects (the heritability; A) and how much appears to be due to shared environmental effects (the shared environment; C).

Animal Studies

Artificial selection practices in animals have long provided proof of genetic influences on phenotypes. For example farmers selectively interbreed cattle that produce the most milk to increase production in offspring generations. The increased milk production in the offspring provides evidence of this trait being influenced by genetic factors and can be used to estimate its heritability. With regard to physical activity, Swallow *et al.* (Swallow et al., 1998) used selective breeding to create four lines of mice with high activity levels: 10 generations of selective breeding of voluntary wheel-running behavior resulted in an increase of approximately 75% in activity level compared with mice from control lines (Swallow et al., 1998).

Another way to show heritability of a trait is measuring this trait in different strains of inbred mice, growing up in identical environments. Systematically mating brother and sisters for 20 consecutive generations will results in isogenic (genetically identical strains) groups of mice

allowing the mean of the trait to be compared across different strains. With regard to daily wheel running Lightfoot et al. (2004) detected significant interstrain differences in 13 strains of inbred mice, which suggests that genetic background indeed plays a role in determining spontaneous daily wheel running activity in mouse strains.

Molecular Genetic Studies

After establishing heritability of a trait, the next step is to identify the genomic regions that contribute to the heritable trait variation. For quantitative traits it is likely that heritability reflects the additive effects of thousands of genetic variants in a manifold of different genes. Molecular genetic studies such as linkage analysis and association studies provide an opportunity to localize genetic variants and confirm its association with the trait of interest.

Linkage analysis examines whether specific genetic markers, positioned strategically across the entire genome, segregate jointly with traits in clusters of related individuals. The markers that are linked to the genomic region that influences the trait will be seen to segregate more frequently with the occurrence of this trait. The genomic region carrying such markers is likely to harbor causative genetic variants for the trait. Genetic linkage can easily demonstrated in breeding experiments in mice, when two mice that differ genetically for a trait of interest are crossed (parental line) and the segregation of genetic markers, along with phenotypic characteristics, can be followed in each of the offspring.

Genes of interest found in these animal studies can provide the first clues for conducting association studies in both animals and humans. Alternatively candidate genes can be selected based on known or inferred biological function that makes it plausible that they may predispose to the trait of interest. Association studies are similar to traditional epidemiological approaches in which an a priori hypothesis between exposure to a given factor, in this case, a genotype at a given locus, and trait is formulated: Candidate gene studies test the association of quantitative traits with the frequency of specific genetic variants, or compare the frequency of such variants in selected groups of low-scoring (unaffected controls) and high-scoring (affected cases) individuals.

QUANTITATIVE GENETICS OF PHYSICAL ACTIVITY & EXERCISE BEHAVIOR

Since the first twin study by Kaprio et al. (1981) on the heritability of physical activity, several studies provided evidence for genetic influences on physical activity. A number of studies measured total physical activity objectively with accelerometers, in a respiration chamber or with the double labelled water method. However, most twin and family studies used physical activity questionnaires (self-report) to quantify total physical activity. Surveys are a more convenient tool for epidemiological-scaled research, even though the correlation with accelerometry or doubly labelled water varies to a great extent (Chinapaw et al., 2010). The phenotypes used in these survey studies often captured rather different constructs: some measured sport participation specifically, with questionnaires including items such as: 'Do you participate in (moderate to vigorous) sports regularly?'. Others used questionnaires such as an activity record, in which subjects are asked to note the energy expenditure of the dominant activity of every 15 minutes using a list of categorized activities.

When discussing twin and family studies on physical activity, a distinction will be made between physical activity due to all possible sources (total physical activity) and physical activity due to sports participation in leisure time (voluntary exercise behavior). The distinction is not always clear. A large part of total physical activity is classified as light to moderate and will be due to transportation (walking, biking, standing) or many light work or household activities. This will typically not contain sports activities. Moderate to vigorous intensity (MVPA) activities are more ambiguous and may often include voluntary sports activities in leisure time. Therefore, studies reporting on moderate to vigorous physical activities will be discussed together with studies on voluntary exercise behavior.

All twin and family studies on the heritability of total physical activity in childhood or adolescent samples are summarized in Table 2.1, ordered by age. All twin and family studies on the heritability of MVPA or voluntary exercise behavior are summarized in Table 2.2.

Total physical activity

The heritability estimates found in family studies include both genetic and familial environmental sources of variance, and are therefore listed in a separate column in Table 2.1. Especially in younger children (up until the age of 11), accelerometers or doubly labelled

water were used to quantify physical activity (Butte et al., 2006; Cai et al., 2006; Fisher et al., 2010; Franks et al., 2005; Saudino & Zapfe, 2008; Wood et al., 2008). The family studies by Cai et al. (2006) and Butte et al. (2006) were largest in sample size and reported moderate to high estimates of familial aggregation. In addition, Saudino and Zapfe (Saudino & Zapfe, 2008) showed that 32% of the variation in total physical activity in 2 year old twins could be explained by genetic factors. The twin studies by Franks et al. (2005) and Fisher et al. (2010) did not find significant genetic factors, perhaps because the sample size was modest and the study could be underpowered to find small genetic influences. Indeed the MZ correlations in the study by Fisher et al. (2010) were slightly higher than DZ correlations. A more robust finding is the substantial part (35% to 73%) of the variance in physical activity in these twins that could be attributed to shared environmental factors: 35% to 73%.

Four studies reported heritability estimates of physical activity measured by surveys (de Chaves et al., 2014; Maia et al., 2002; Perusse et al., 1989; Seabra et al., 2014). The mean age in these studies was 13 to 17 years old; indicating that self-report of physical activity is feasible in adolescence. The heritability estimates range from 6% for work-related physical activity (Seabra et al., 2014) to 63% for leisure time physical activity (Maia et al., 2002).

Table 2.1 Heritability of physical activity: an overview of twin and family studies. *Note.* A = variance explained by genetic factors; C = variance explained by shared environmental factors; TPA = Total Physical Activity; PAEE = Physical Activity Energy Expenditure; PAL = Physical Activity Level; LPA = Low Physical Activity; MPA = Moderate Physical Activity; WPA = Work Physical Activity; LTPA = Leisure Time Physical Activity; [a] Adjusted for age; [b] Adjusted for sex; [c] Adjusted for body weight; [d] Adjusted for SES; [e] boys/girls.

Age Mean (±SD)	Reference	Sample	Instrument	Pheno-type	Familial aggregation	A	C
2.1 (±0.1)	Saudino & Zapfe, 2008	144 MZ pairs / 168 DZ pairs	Accelerometer	TPA		31%	55%
6.8 (±1.4)	Franks et al., 2005	62 MZ pairs / 38 DZ pairs	Doubly labeled water	PAEE[ab]		41%	35%
			Doubly labeled water	PAEE[abc]		0%	69%
			Doubly labeled water	PAL[ab]		0%	65%
8.5 (±0.4)	Wood et al., 2008	150 MZ pairs / 113 DZ pairs	Accelerometer	TPA		35%	40%
10.9 (±0.2)	Butte et al., 2006	319 families	Accelerometer	TPA[ab]	60%		
11.0 (±3.9)	Cai et al., 2006	319 families	Accelerometer	TPA[ab]	55%		
				LPA[ab]	46%		
				MPA[ab]	49%		
11.2 (±0.5)	Fisher et al., 2010	57 MZ pairs / 60 DZ pairs	Accelerometer	TPA		0%	73%
12.7 (±3.5)	Chaves et al., 2014	260 families	Baecke Questionnaire	TPA[abd]	24%		
14.6 (±3.3)	Perusse et al., 1989	375 families; 55 MZ pairs / 56 DZ pairs	3-day activity record	TPA[abd]		29%	0%
14.5 (±2.8)	Santos et al., 2014	339 families	Baecke Questionnaire	TPA[ab]	23%		
16.1 (±4.0)	Seabra et al., 2008	2375 families	Baecke Questionnaire	TPA[abd]	23%		
				WPA[abd]	6%		
				LTPA[abd]	25%		
16.9 (±5.6)	Maia et al., 2002	203 MZ pairs / 208 DZ pairs	Baecke Questionnaire	LTPA		63%/32%[f]	0%/38%[f]

Voluntary exercise behavior

Fifteen twin and/or family studies reported heritability estimates for voluntary exercise behavior or moderate to vigorous physical activity. Heritability estimates vary widely, ranging from 0% to 85%. Possible sources of this variation are differences in the age, differences in measurement instrument and sample size. The age of all studies shown in Table 2.2 ranges from 4 (Cai et al., 2006) to 25 (Maia et al., 2002). Up to 12 years of age, heritability estimates are low to moderate (Cai et al., 2006; Fisher et al., 2010; Huppertz et al., 2016). In adolescence, heritability estimates of voluntary exercise behavior are moderate to high with the exception of two studies in which heritability estimates are low or zero (Stubbe et al., 2005). Nevertheless, the importance of shared environmental factors seems to decrease in adolescence, whereas genetic effects become more prominent in explaining individual differences in voluntary exercise behavior. In adults, heritability of voluntary exercise behavior levels off to about 40% (de Geus et al., 2003; de Moor et al., 2011). The changing genetic architecture of voluntary exercise behavior across the life span has been described before (Huppertz et al., 2016; Stubbe et al., 2005; Stubbe & de Geus, 2009). The notion that shared environmental factors play a greater role in childhood than adolescence can be explained by the important role of the parents; they provide the children with the opportunity to become active, by means of transportation to exercise activities, give exercise activities the priority over other leisure time activities and motivation and encouragement to exercise.

Two studies employed accelerometers (Actiwatch or Actigraph) to quantify moderate to vigorous physical activity in children (~11 year olds) (Cai et al., 2006; Fisher et al., 2010). The heritability estimates were low, but Fisher et al. (2010) demonstrated significant influences of shared environmental factors (61%). Two studies using prospective 3-day activity recording, which may be more accurate then retrospective surveys, reported no significant influence of genetic factors (Perusse et al., 1989; White et al., 2014) However, the majority of the studies specifically measured voluntary exercise behavior by starting their surveys with items similar to “Do you participate in sports regularly?” These studies generally found evidence of significant genetic influences. By comparing the heritability estimates of voluntary exercise behavior (Table 2.2) with the estimates for total physical activity (Table 2.1) one can conclude that the part of the variation in adolescents that can be attributed to genes appears higher in

voluntary exercise behavior than in total physical activity. It is important to note that such a finding could be driven in part by higher measurement error in self-reported total physical activity compared to in self-reported voluntary exercise behavior. Consciously planning of exercise activities is easier to recall than how much energy is spent on activities at school or commuting. This might introduce more measurement error in self-reported total physical activity surveys, which will inflate the environmental contribution (E) to the variance in this trait. Consequently, the relative contribution of genetic contribution to the total variance, i.e. the heritability decreases.

A meta-analysis on exercise behavior

All heritability estimates in Table 2.3, based on a twin sample, were included in three meta-analyses: 7 to 12 year olds (childhood), 13 to 15 year olds (adolescence) and 16 to 18 year olds (late-adolescence). By weighing these heritability estimates from all studies by the number of subjects, the weighted average heritability can be computed using Microsoft Excel (2010) (Li et al., 2003; Neyeloff et al., 2012). When the standard errors (SEs) or confidence intervals (CIs) of the heritability estimates were not reported, these were calculated using the standard errors (SEs) or CIs from studies who did report these statistics (Li et al., 2003). Some studies reported one (equated) heritability estimate for boys and girls; others estimated the heritability of exercise behavior for boys and girls separately. These heritability estimates for boys and girls were treated as if these were independent samples. The I^2 statistic was used to assess heterogeneity and was calculated as (Q – df)/Q, where Q is Cochran's heterogeneity statistic and df the degrees of freedom (Higgins & Thompson, 2002).

Results of the meta-analyses are presented in Table 2.3. In childhood, the meta-analytic weighted average heritability was 20% (95% CI: 13, 27). Table 2.3 shows that the confidence intervals for the results of individual studies do show overlap with the confidence interval for the meta-analytic average, indicating the presence of statistical homogeneity. This meta-analytic average increased to a heritability estimate of 35% (95% CI: 17, 52) in adolescence, with an I^2 value of 22, which suggests that a percentage of the variability in the heritability estimates in adolescents is due to heterogeneity rather than sampling error (chance). Table 2.3 shows higher heritability estimates for boys than for girls in the studies by van der Aa et al (2010) and Beunen & Thomis (1999), which may explain this heterogeneity. In late-

adolescence, a meta-analytic weighted average heritability of 53% (95% CI: 47, 59) was found, and the studies included in this meta-analysis were less heterogeneous (I^2 = 10). The results from these meta-analyses confirm increasing influence of genetic factors with age on exercise behavior.

Table 2.2 Heritability of exercise behavior: an overview of twin and family studies. *Note.* A = variance explained by genetic factors; C = variance explained by shared environmental factors; EB = Voluntary Exercise Behavior; VPA = Vigorous Physical Activity; MVPA = Moderate to Vigorous Physical Activity; [a] Adjusted for age; [b] Adjusted for sex; [c] Adjusted for SES; [d] boys/girls.

Age Mean (±SD)	Reference	Sample	Instrument	Phenotype	Familial aggregation	A	C
7.5 (±0.3)	Huppertz et al., 2016	2535 MZ pairs / 4796 DZ pairs	Multiple survey items	EB		14%/12%[d]	80%/80%[d]
9.8 (±0.4)	Huppertz et al., 2016	2784 MZ pairs / 5223 DZ pairs	Multiple survey items	EB		26%/26%[d]	68%/65%[d]
11.0 (±3.9)	Cai et al., 2006	319 families	Accelerometer	VPA[ab]	18%		
11.2 (±0.5)	Fisher et al., 2010	57 MZ pairs / 60 DZ pairs	Accelerometer	MVPA[ab]		0%	61%
12.3 (±0.4)	Huppertz et al., 2016	5281 MZ pairs / 9348 DZ pairs	Multiple survey items	EB		31%/27%[d]	62%/65%[d]
12.4 (±1.4)	White et al., 2014	72 MZ pairs / 76 DZ pairs	3-day activity record	MVPA		0%/0%[d]	66%/33%[d]
13/14	Stubbe et al., 2005	276 MZ pairs / 370 DZ pairs	Multiple survey items	EB		0%	84%
14.5 (±0.3)	van der Aa et al., 2010	554 MZ pairs / 948 DZ pairs	Multiple survey items	EB		85%/38%[d]	0%/46%[d]
14.6 (±3.3)	Perusse et al., 1989	375 families; 55 MZ pairs / 56 DZ pairs	3-day activity record	MVPA[abc]		0%	12%
14.6 (±0.6)	Huppertz et al., 2016	3325 MZ pairs / 5705 DZ pairs	Multiple survey items	EB		43%/40%[d]	36%/43%[d]
15.0	Beunen & Thomis 1999	43 MZ pairs / 61 DZ pairs	Single survey item	EB		83%/44%[d]	0%/54%[d]
15/16	Stubbe et al., 2005	321 MZ pairs / 442 DZ pairs	Multiple survey items	EB		0%	78%
16.1 (±4.0)	Seabra et al., 2014	2375 families	Baecke Questionnaire	EB[abc]	50-60%		
16.2	Aaltonen et al., 2013	769 MZ pairs / 1743 DZ pairs	Single survey item	EB		52%/52%[d]	19%/24%[d]
16.2 (±0.6)	van der Aa et al., 2010	662 MZ pairs / 969 DZ pairs	Multiple survey items	EB		80%	0%
16.4 (±1.1)	de Moor et al., 2011	1736 families; 656 MZ pairs / 1628 DZ pairs	Multiple survey items	EB		42%/36%[d]	44%/52%[d]
16.7 (±2)	de Geus et al., 2003	69 MZ pairs / 88 DZ pairs	Multiple survey items	MVPA[a]		79%	0%
16.9 (±0.6)	Huppertz et al., 2016	2320 MZ pairs / 3698 DZ pairs	Multiple survey items	EB		56%/49%[d]	27%/31%[d]
16.9 (±5.6)	Maia et al., 2002	203 MZ pairs / 208 DZ pairs	Baecke Questionnaire	EB		68%/40%[d]	20%/28%[d]
17.0 (±2.1)	Boomsma et al., 1989	44 MZ pairs / 46 DZ pairs	Single survey item	EB		64%	0%
17.1	Aaltonen et al., 2013	724 MZ pairs / 1614 DZ pairs	Single survey item	EB		44%/50%[d]	24%/26%[d]
17/18	Stubbe et al., 2005	248 MZ pairs / 395 DZ pairs	Multiple survey items	EB		36%	47%
18.8 (±0.5)	Huppertz et al., 2016	1118 MZ pairs / 1641 DZ pairs	Multiple survey items	EB		79%/49%[d]	4%/19%[d]
18.0 (±2.3)	Koopmans et al., 1994	1593 families: 578 MZ pairs / 1000 DZ pairs	Single survey item	EB		45%	44%
18.1 (±0.7)	van der Aa et al., 2010	488 MZ pairs / 747 DZ pairs	Multiple survey items	EB		72%	0%
18.6	Aaltonen et al., 2013	715 MZ pairs / 1603 DZ pairs	Single survey item	EB		46%/51%[d]	23%/21%[d]

Age group	Refence		Age mean	(SD)	Sample size	Heritability (95% CI)	
7 - 12	Huppertz et al., 2016	boys	7.5	(±0.3)	3694	14	(6, 22)
	Huppertz et al., 2016	girls	7.5	(±0.3)	3637	12	(3, 21)
	Huppertz et al., 2016		9.8	(±0.4)	8006	26	(20, 32)
	Fisher et al., 2010		11.2	(±0.5)	234	0	(-34, 34)
	Huppertz et al., 2016	boys	12.3	(±0.4)	7185	31	(25, 37)
	Huppertz et al., 2016	girls	12.3	(±0.4)	7443	27	(21, 33)
	White et al., 2014		12.4	(±1.4)	518	0	(-23, 23)
	Meta-analysis				**30717**	**20**	**(13, 27)**
13 - 15	Stubbe et al., 2005		13/14		1332	0	(-14, 14)
	van der Aa et al., 2010	boys	14.5	(±0.3)	1162	85	(78, 90)
	van der Aa et al., 2010	girls	14.5	(±0.3)	1476	38	(22, 57)
	Perusse et al., 1989		14.6	(±3.3)	244	0	(-33, 33)
	Huppertz et al., 2016	boys	14.6	(±0.6)	3998	43	(35, 51)
	Huppertz et al., 2016	girls	14.6	(±0.6)	5031	40	(33, 47)
	Beunen & Thomis 1999	boys	15		92	83	(66, 89)
	Beunen & Thomis 1999	girls	15		91	44	(21, 91)
	Stubbe et al., 2005		15/16		1526	0	(-13, 13)
	Meta-analysis				**14952**	**35**	**(17, 52)**
16 - 18	Aaltonen et al., 2013		16.2		5024	52	(42,55)
	van der Aa et al., 2010		16.2	(±0.6)	2726	80	(76, 84)
	de Moor et al., 2011	boys	16.4	(±1.1)	1636	42	(29, 55)
	de Moor et al., 2011	girls	16.4	(±1.1)	1889	36	(24, 48)
	de Geus et al., 2003		16.7	(±2.0)	314	79	(69, 85)
	Huppertz et al., 2016	boys	16.9	(±0.6)	2624	56	(46, 66)
	Huppertz et al., 2016	girls	16.9	(±0.6)	3393	49	(40, 58)
	Maia et al., 2002	boys	16.9	(±5.6)	361	68	(42, 89)
	Maia et al., 2002	girls	16.9	(±5.6)	461	40	(-10, 73)
	Boomsma et al., 1989		17	(±2.1)	180	64	(26, 102)
	Aaltonen et al., 2013	boys	17.1		2137	44	(37, 53)
	Aaltonen et al., 2013	girls	17.1		2539	50	(44, 53)
	Stubbe et al., 2005		17/18		1286	36	(11, 64)
	Huppertz et al., 2016	boys	18.8	(±0.5)	1040	79	(63, 95)
	Huppertz et al., 2016	girls	18.8	(±0.5)	1719	49	(37, 61)
	Koopmans et al., 1994		18	(±2.3)	3156	45	(36, 54)
	van der Aa et al., 2010		18.1	(±0.7)	1864	72	(65, 77)
	Aaltonen et al., 2013	boys	18.6		2105	46	(40, 53)
	Aaltonen et al., 2013	girls	18.6		2551	51	(42, 63)
	Meta-analysis				**37005**	**53**	**(47, 59)**

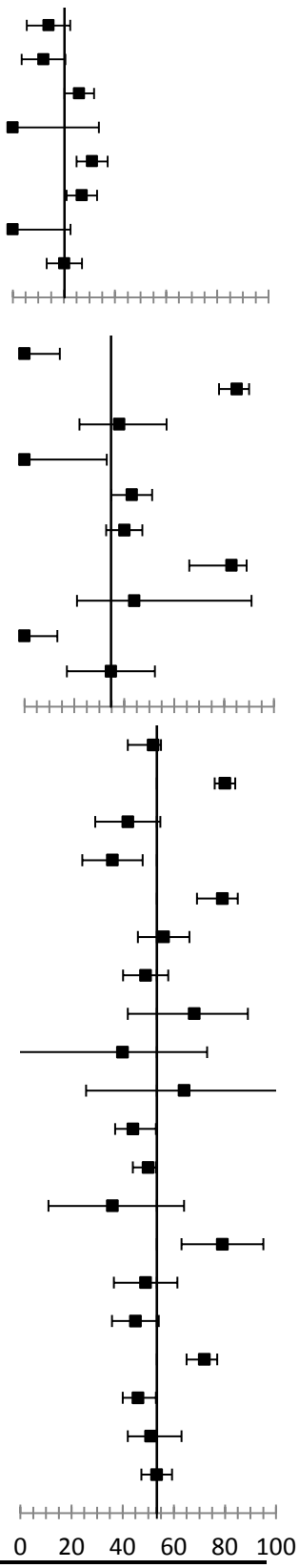

Table 2.3 Results meta-analyses of exercise behavior in three age groups: 7 – 12 year, 13 – 15 year and 16 – 18 year

MOLECULAR GENETIC FINDINGS FOR PHYSICAL ACTIVITY & EXERCISE BEHAVIOR

Studies with spontaneous wheel-running inbred mice-strains and selective breeding in mice for high voluntary wheel-running activity resulted in numerous genomic regions that were associated with physical activity in mice. For instance, Lightfoot et al. (2008) identified four genomic regions that were associated with the distance, duration, and speed of voluntary wheel-running on chromosomes 9 and 13, with the genomic locus for running speed (on chromosome 9) accounting for the largest percentage of phenotypic variance. The research group by Garland found even more loci to be associated with these phenotypes, (Kelly et al., 2010; Nehrenberg et al., 2010) but the only overlap they reported were loci close to the *TYR* gene on chromosome 7 coding for tyrosinase, a precursor for the neurotransmitter dopamine, found be involved in voluntary movement and reward (Rhodes et al., 2005).

In spite of the evidence for a contribution of heritable factors to physical activity from twin and family studies, surprisingly little work has been done to identify the actual genes contributing to this heritability of physical activity and exercise behavior in humans. Even less candidate gene studies have specifically addressed physical activity in children. Lorentz et al. (Lorentzon et al., 2001) found that in a sample of 97 healthy Caucasian girls (mean age 16.9) the A986S polymorphism in the calcium sensor receptor gene (*CASR*) was significantly associated with self-reported physical activity level. This *CASR* gene is involved in the regulation of calcium homeostasis and bone resorption. *CASR* mRNA is also expressed in the hypothalamus of the rat brain, a region that had been associated with regulating motivation. In 7 year old boys, self-reported physical activity level was associated with the Gln223Arg polymorphism in the leptin receptor (*LEPR*) gene, (Richert et al., 2007) known to regulate food intake and energy balance (Elmquist et al., 1998). Physical activity measured for 3 days with an Actiwatch accelerometer in 10 year-olds was associated with variants within the Melanocortin 4 Receptor Gene (*MC4R*), (Cole et al., 2010) a gene associated with weight-related phenotypes. Two studies in 15 and 16 year old children did not find a significant

association of a common variant in the *FTO* gene (rs9939609) and self-reported physical activity, as well as physical activity objectively measured with Actigraphs (Hakanen et al., 2009; Liu et al., 2010).

Candidate genes suffer from the shortcoming that they are based on our current biological knowledge. A more agnostic and open study design to find genetic variants associated with a trait of interest is a genome wide association (GWA) study. Using millions of measured or imputed SNP markers the entire genome is searched for SNP variants that occur more frequently in people with higher levels of the trait of interest compared to people with lower trait level. However, no GWA study in children has been conducted to date. The only GWA study conducted on exercise behavior published by de Moor et al. (De Moor et al., 2009) was entirely based on an adult sample. In 1644 unrelated Dutch and 978 unrelated American adults of European ancestry several novel variants were associated with exercise behavior, mainly in the *PAPSS2* gene. The effect sizes were small, such that these variants did not contribute much to the heritability of exercise behavior and would not have reached significance according to the current GWA standards (Clarke et al., 2011). In hindsight, lessons learned from GWA studies on other complex traits make it likely that this study on exercise behavior was underpowered to detect the many small genetic effects causing heritability (Klein, 2007). Meta-analyses across a total sample size of tens of thousands of individuals will be needed for successful detection of the association of specific genetic variants with a physically active lifestyle.

IMPLICATIONS FOR PEDIATRICS

The evidence that the variance in physical activity and especially exercise behavior are under substantial genetic control does not mean that it is impossible to increase the amount of physical activity and exercise activities to improve sports performance and health in children and adolescents. These findings should, however, contribute to the acknowledgment that the substantial range in physical activity and exercise behavior in population-based samples of children and adolescents will *not* be erased by exercise intervention. We argue that this should never be a goal to begin with: intervention is about shifting the mean of the distribution towards a more favorable value, not about reducing its variance.

To encourage adolescents to stay active, the innate individual differences can be used as a starting point. Children may experience rather different 'gains' when exercising or adopting a physically active lifestyle: by being good at sports some adolescents may gain self-esteem, whereas others who are less good at sports but greatly enjoy the activity or its social aspects reap a different benefit. Acknowledgement of these differences in gains may aid in abandoning population-based strategies and moving towards personalized or family-based intervention strategies. Information on the source of individual differences at different time points during childhood and adolescence can inform type and timing of the optimal intervention approaches. To achieve the same aim of optimizing the appetitive aspects that are specific for that individual and generating realistic person-specific goals, different genotypes may require entirely different exercise programs.

Within the last decades, we have already discovered much on the genetic characteristics of physical activity and exercise behavior. Taken the fast increase in knowledge of genomics and the enhanced technological aids for prolonged physical activity recordings in large scale samples we can expect even more progress in the coming decade. This will lead to better understanding of the genetic and environmental determinants of physical activity and exercise behavior in the young, which in turn will expand our capability to improve pediatric health.