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The influence of genetic factors on physical functioning and exercise in second half of life

H. Frederiksen, K. Christensen

The Danish Twin Registry, Epidemiology, Institute of Public Health, University of Southern Denmark, DK-5000 Odense, Denmark
Corresponding author: Henrik Frederiksen, MD, The Danish Twin Registry, Sdr. Boulevard 23 A, DK-5000 Odense C, Denmark

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During the past decades, a number of studies of families and twins in particular have assessed the relative contribution of genetic and environmental factors to traits reflecting various aspects of physical functioning: maximal O_2 uptake, muscular endurance, muscular strength, muscle cross sectional area, flexibility, and trainability. Although the estimate of the size of the genetic component differs between the various studies, they point towards a moderate to substantial genetic influence on these phenotypes. Most of the studies have used only young and healthy study subjects, although in recent years phenotypes of particular importance to the elderly and the oldest-old (e.g., activities-of-daily living abilities) have also been shown to have substantial genetic component. Furthermore, behavioural studies have also revealed a genetic contribution to the disposition to level of leisure time physical activity. At present, there is still a few association studies on specific genetic variants, and the results have either been inconsistent or failed to show an association with physical functioning. Therefore, the mechanisms through which the genetic influence is expressed, is still an enigma. Here, we summarise the evidence currently available for a genetic influence on physical functioning and disposition to leisure time physical activity with a focus on recent Danish twin data.

Many traits – from health outcomes to behaviour have a tendency to run in families. Families share not only an environment, but also genetic factors. Epidemiologists have traditionally looked for environmental causes for variations in health outcome and behaviour, while geneticists have focused on tracing genetic factors of importance. During the past decades, a number of studies have assessed the relative contribution of genetic factors to traits involved in physical functioning (PF). Family, and in particular twin studies have provided evidence of a genetic contribution to a number of measures reflecting PF. In recent years, the focus is moving towards the molecular level with studies of specific genetic factors using different approaches (linkage studies, association studies, etc.). Although this field will probably contribute with remarkable results in the future, it is still in its infancy; and in a recent review on specific genetic variants associated with physical functioning Rankinen et al. (2001) concluded that "little has been accomplished to date". In particular, the PF phenotypes relevant for an ageing population have been poorly investigated. In this paper, we will review the evidence currently available for overall genetic contributions to phenotypes involved in physical functioning and exercise as well as introducing new data from Danish twins on the genetic influence of the disposition to sports participation. We will also briefly describe the few specific genetic variants that have been proposed to be associated with PF.

Methods to assess the overall influence of genetic factors

Traditional family studies

Traditional family studies of parent-offspring, sibs, etc. determine whether or not there is familial resemblance for the phenotype being studied, but they do not indicate whether this resemblance is due to genetic or shared environmental factors.

The heritability (h^2) is the proportion of the total phenotypic variance that can be attributed to genetic differences between individuals, and the values of h^2 ranges from 0 to 100%. A heritability close to zero indicates that genetic variance do not contribute to differences in the phenotype between individuals, but that the reasons for the phenotypic differences are primarily to be sought in differences in environmental exposures or in stochastic processes [e.g., handedness (Carlier, Spitz, Vacher-Lavenu, Villeger, Martin, Michel, 1996)], whereas a heritability close to 100% indicates that genetic factors are the key determinant of the variance [e.g., body height (Silventoinen, Kaprio, Lahelma, 2000)]. Being a proportion, the heritability is thus dependent on the effects from environmental factors (i.e., h^2 will increase if a trait is influenced both by genetic and environmental factors, and the environment will become more similar for the individuals in the population) and is therefore time and population-specific.

As families do not only share genes but also environment, traditional family studies can only provide the upper limit for

the heritability. Twin studies provide this opportunity to disentangle the effects of genes and environment.

Twin studies

The fact that twinning is relatively common, and nationwide twin registers exist in several countries, has made twin studies the most important tool for estimating the heritability of various traits in humans. Two types of twinning occur: monozygotic (MZ) twins share all their genetic material and dizygotic (DZ) twins, like ordinary siblings, share, on average, 50% of their genes. A greater phenotypic similarity in monozygotic than in dizygotic twins is to be expected, if genetic factors play an etiological role of the trait. The similarity in monozygotic and dizygotic twins can be assessed using probandwise concordance rates, odds ratios (OR) or tetrachoric correlations (Falconer, 1965; Neale & Cardon, 1992) for dichotomous outcomes (e.g., participation in sports (yes/no)) and intra-class correlations for continuous outcomes (e.g., grip strength).

The probandwise concordance rate is defined as the proportion of 'affected' twin partners of probands. It reflects the probability of a trait for one twin, given that the partner twin is affected and is, thus, directly comparable to risk rates reported for other relatives (McGue, 1992). The OR utilises the additional information available from the concordant non-affected twin pairs and can be interpreted as the increased likelihood of the trait for one twin given the presence vs. the absence of the trait in the partner twin (Ramakrishnan et al., 1992). The tetrachoric correlations reflects the similarity in an assumed underlying liability to the dichotomous trait, whereas the intra-class correlation is a direct measure of the similarity of the twins within a pair of a trait measured on a continuous scale. The heritability of a phenotype can be estimated using structural equation modelling — a method that is standard in twin studies (Neale & Cardon, 1992; Neale, 1997) (for further details see Appendix).

Genetic factors and physical functioning

Physical functioning comprises of a number of phenotypes, e.g., muscular strength, muscular endurance, flexibility, balance, cardiopulmonary functioning, etc. In young people, it seems obvious that environmental factors (e.g., training efforts) influence some of these tasks, but genetic factors are also likely to explain some differences in physical capacities (not all of us can run equally fast or long despite the same training efforts). It is intuitively less clear to which degree genetic factors have an impact on physical functioning late in life. Differences in functioning with increasing age could also be explained by wear and tear or physical maintenance of heavy physical work, carrying weights at home, bringing up children or the contrary—a sedentary life style. As shown in Table 1, the studies addressing the resemblance of physical capabilities between members of nuclear families or twin pairs have used a wide variety of phenotypes: maximal O_2 uptake (VO_{2max}) (Fagard, Bielen, Amery, 1991; Sundet, Magnus, Tambs, 1994; Bouchard et al., 1998), muscular endurance [number of sit-ups in one minute (Perusse, Lortie, Leblanc, Tremblay, Theriault, Bouchard, 1987; Katzmarzyk, Gledhill, Perusse, Bouchard, 2001)], muscular strength (e.g., grip strength (Katzmarzyk et al., 2001; Reed, Fabsitz, Selby, Carmelli, 1991; Arden & Spector, 1997; Carmelli & Reed, 2000; Frederiksen et al., 2002a), knee extension strength (Perusse et al., 1987; Arden & Spector, 1997), elbow flexion strength (Thomis et al., 1997), and number of push-ups

Table 1. Family and twin studies reporting on the genetic contribution of physical functioning and exercise

First author	Year*	Phenotype	Type of study	N#	Heritability†
Physical functioning					
Bouchard	1998	VO_{2max}	Family	86	50%
Sundet	1994	VO_{2max}	Twin	1058	62%
Fagard	1991	VO_{2max}	Twin	48	20–66%
Katzmarzyk	2001	Muscular strength and endurance, flexibility	Family	502	48–59%‡
Arden	1997	Grip strength, knee extension strength	Twin	353	36%, 46%
Reed	1991	Grip strength	Twin	257	65%
Carmelli	2000	Grip strength	Twin	152**	22–35%
Frederiksen	2002	Grip strength	Twin	1757	52%
Perusse	1987	Knee extension strength and muscular endurance	Family	375	30%, 21%
Carmelli	2000	Lower extremity function	Twin	187	57%
Thomis	1997	Elbow flexion strength, muscle cross-sectional area	Twin	41	70%, 92%
Christensen	2000	ADL functioning	Twin	480	0–34%##
Christensen	2002	Rate-of-change of ADL functioning	Twin	127	9–16%††
Thomis	1998	Trainability of muscle strength	Twin	41	20%
Fox	1996	Trainability of motor skills	Twin	96	66%
Exercise					
Perusse	1989	Dominant physical activity for every 15 min of a day	Family	375	29%
Lauderdale	1997	Participation in leisure time physical activity	Twin	3344	38–50%
Koopmans	1994	Sports participation	Twin	1587	45%
Kaprio	1981	Participation in leisure time physical activity	Twin	5044	62%
Frederiksen	2002	Sports participation	Twin	1258	49%

*Year of publication. #Number of twin pairs or number of families. †The estimates of the heritability is often reported for more than one phenotype and after various adjustments and restrictions in the different studies. ‡Results at baseline. The heritability at a 7-year follow-up was reported to be 54–63%. **10-year follow-up on the study by Reed et al. (1991). ##Males: 0%, females: 34%. ††Males: 9%, females: 16%.

(Katzmarzyk et al., 2001), time to five chair stands (Carmelli et al., 2000), muscle cross sectional area (Katzmarzyk et al., 2001), activities-of-daily living (ADL) functioning (Christensen, McGue, Yashin, Iachine, Holm, Vaupel, 2000; Christensen, Gaist, Vaupel, McGue, 2002), flexibility and balance (Katzmarzyk et al., 2001; Carmelli et al., 2000), and trainability of skills (Fox, Hershberger, Bouchard 1996; Thomis et al., 1998). Although the size of the genetic component differs somewhat between the studies the overall result is a moderate to substantial genetic influence on these phenotypes (Table 1).

Familial clustering of physical functioning

In a recent study of 502 nuclear families Katzmarzyk et al. (2001) studied the familial aggregation of a large number of phenotypes (grip strength, number of push-ups, number of sit-ups, and a sit-and-reach test) involved in musculoskeletal functioning (strength, endurance, and flexibility). The study furthermore provided data from the same tests at a 7-year follow-up on 66% of the original sample. When comparing the within-family with the between-family variability, membership of a family accounted for 48%–59% of the variance in these phenotypes at baseline and 54%–63% in the 7-year changes (Katzmarzyk et al., 2001). The performance of the spouses in these families did not correlate significantly in grip strength and trunk flexibility but did correlate in push-ups and sit-ups. This pattern suggests a role for genes in explaining the familial resemblance of the two former phenotypes, and that familial non-genetic factors play a role of the two latter, although the study design suffers from difficulties in separating common environmental contribution from genetic effects as previously mentioned.

Bouchard et al. (1998) studied the VO_{2max} in the sedentary state in 86 families. They found significant correlation of this phenotype in various parent–offspring and sibling relations, but also among the spouses. A heritability estimate of approximately 50% was reported but is likely to be inflated from familial environmental effects. Interestingly the mother–offspring correlations were somewhat higher than the father–offspring correlations, and by modelling these results it was estimated that the maternal 'heritability' was approximately 30%. This result could suggest a genetic influence expressed through genes solely of maternal descent (e.g., mitochondrial DNA) but effects from exclusive maternal environmental influence (e.g., *in utero*) cannot be ruled out. From another study of 375 families including twins, the heritability of muscular strength (knee extension strength) and endurance (number of sit-ups in 1 minute) were reported to be 30% and 21%, respectively (Perusse et al., 1987).

In a recent family study of more than 9000 Danes aged 45–102 the effect of parental life span to muscular strength in ageing offspring was studied. In this study Frederiksen et al. (2002b) found that among 70 + year olds, the grip strength in offspring increased by 0.32 kg for every 10-year increment in parental life span. Although the effect is small in absolute terms, this finding suggests that factors that promote longevity among parents are associated with preserved muscular strength in ageing offspring.

Influence of genetic factors on VO_{2max}

The genetic influence on VO_{2max} has been studied in two twin studies. Fagard et al. (1991) estimated VO_{2max} on the basis of measured O_2 uptake and recorded workload using a bicycle test in 48 young male pairs (29 MZ and 19 DZ). They found heritability estimates for peak O_2 uptake, and O_2 uptake at sub-maximal exercise (at heart rate of 150 beats min^{-1} and at respiratory exchange ratio (CO_2 output/O_2 uptake) of 0.95) between 20% and 66%. Likewise the heritability of peak workload (work load just prior to exhaustion) and workload at sub-maximal exercise ranged between 48% and 76% (Fagard et al., 1991). In a large study of 1058 Norwegian young twin pairs, the VO_{2max} was estimated from a nomogram on the basis of body weight and workload after a bicycle test. The heritability of this VO_{2max} estimate was reported to be 62% and the rest of the variance could be attributed to the effects from individual-specific environment (Sundet et al., 1994).

Genetic correlation of more than one phenotype

Studies of genetic influence on PF tend to decompose PF into several phenotypes that are studied separately. However, the genetic influence on correlated phenotypes can be studied using multivariate analysis, which furthermore can be used for assessing whether the genetic influence results from the same genetic factors. Thomis et al. (1997) that studied elbow flexion isometric strength and mid-arm muscle cross-sectional area among 41 male twin pairs age 17–30. When determined separately, additive genetic factors accounted for 66–78% of the variance of strength and 92% of the variance of cross-sectional area, the rest of the variances being explained by unique environmental factors. In addition, the genetic correlation between these two traits was high (76–90%) suggesting that one common genetic factor explained the largest part of the covariation and that the same genes were important for both phenotypes (Thomis et al., 1997).

Influence of genetic factors on trainability

In close relation with physical function is the trainability of skills. The role for genetic factors in the trainability of muscle strength have been investigated in a study of 41 young male twin pairs (Thomis et al., 1998).

The intra-class correlation for the strength gain achieved through training in upper extremity muscles was 0.49 for MZ and 0.22 for DZ twins indicating a genetic influence on this phenotype. In a study of twins reared apart, Fox et al. (1996) investigated the acquisition of a fine motor skill (keeping a stylus on a rotating target). Even after an intense training (15 practice sessions with 25 trials in each) the MZ twin correlation remained high while the DZ correlation was unchanged, low, or even decreased slightly. Along with the trials, the level of skills of the participant improved considerably: the least gifted participant attained levels of skills after practice that were superior to the most gifted in the initial trials. This demonstrates that even when applying the training for a physical task where not many have a prior skill, the genetic factors play a considerable role and that the 'ceiling' for this performance is mostly genetically determined (Fox et al., 1996).

Genetics of performance phenotypes especially relevant for the elderly

Many of the previous studies have used young healthy study subjects. In recent years, some of the phenotypes of particular importance to the elderly and the oldest-old (e.g., physical and cognitive functioning) have been shown to have substantial genetic component. Studying the elderly and the old using phenotypes that require transportation of the participants to laboratory facilities are likely to limit the participants to the best functioning individuals. This constraint makes measures that can be applied in attractive household settings.

Self-reported abilities in the elderly

Particularly among the old and the oldest-old, self-report of abilities and limitations in ADL have this property and have proven to discriminate functioning well (Schultz–Larsen, Avlund, Kreiner, 1992; Nybo, Gaist, Jeune, McGue, Vaupel, Christensen, 2001). In a study of 2401 Danish twins (480 pairs) aged 75 and older, we found a genetic contribution to ADL functional abilities using self-report measured as a summary score on an 11-item scale (Christensen et al., 2000). Among females, one-third to one-half of the variation could be attributed to genetic variation whereas among males heritability estimates were low. Thus when determined cross-sectionally the heritability of this trait was substantial among females. Some 127 of these twin pairs were reassessed after two and four years. Even at single item level, the functional abilities showed a systematic decline over time, and the pattern was even clearer for the summary score (Christensen et al., 2002). The heritability of the rate-of-change in ADL score was however only 16% among women and 9% among men, both non-significant indicating that it is the level rather than the rate-of-change in ADL functioning that is influenced by genetic factors.

Upper and lower extremity function in the elderly

Although reliable and valid among the elderly and the oldest-old, the ADL scale has an inherent ceiling effect that results in lack of variation among the younger old. Therefore phenotypes, which discriminates physical functioning in a broader age span, have also been studied. For this purpose grip strength is an attractive phenotype as it is easy, inexpensive, and reliable to measure, and it correlates with strength in other muscle groups (elbow flexion, knee extension, trunk extension, and trunk flexion, $r = 0.44$–0.64) among 75 year olds (Rantanen et al., 1994). Four previous papers based on three twin populations have addressed the issue of the genetic influence on this phenotype. Among women aged 45–70, one study found a grip strength heritability of 30% (Arden & Spector, 1997) whereas another study of 257 male twin pairs aged 45–59, the grip strength heritability was 65% (Reed et al., 1991) but dropped to 22–35% at a follow-up 10 years later (Carmelli & Reed, 2000). We conducted a large scale study of grip strength among 1757 twin pairs aged 45–96 and found that the variance could be attributed to additive genetic and unique environmental effects, and that the heritability was 52% (Frederiksen et al., 2002a).

The genetic influence on lower extremity function was studied among 187 old (mean age mid-seventies) male twin pairs (Carmelli et al., 2000). Lower extremity function was determined by the chair stand test (time to complete five chair stands), 8-foot walking speed, and a balance test. Each test was evaluated on a 0–4 scale, where 0 was assigned to those unable to complete the test and 1–4 corresponded to quartiles of the actual performance. A summary scale ranging 0–12 was constructed by summing the score from the three categories, and this summary index as well as the three subscales were used for the twin analysis. The heritability of these measures were 46% for the chair stands, 42% for the walking speed, 0% for balance and 57% for the summary score (Carmelli et al., 2000).

Specific genetic factors associated with physical functioning

The substantial heritabilities found in twin and family studies thus indicates that differences in PF can partly be ascribed to a number of specific genetic variants. One of the most extensive studied genetic variants associated with physical functioning and trainability is the I/D polymorphism in the ACE gene. The genotype accounts for approximately half of the variance in the circulating ACE level and from the II to the DD genotype the presence of each D allele is associated with an additive effect on ACE activity (50% higher in the DD

compared to the II genotype) (Rigat, Hubert, Alhenc, Cambien, Corvol, Soubrier, 1990). Since the ACE gene through the renin–angiotensin system is involved in cardiovascular and renal homeostasis, and ACE activity and angiotensin receptors can be demonstrated in various peripheral tissues including skeletal muscle, (Dragovic, Minshall, Jackman, Wang, Erdos, 1996) it seems conceivable that the I/D polymorphism could be associated with physical function. A number of studies have suggested an increased performance associated with the II genotype (Montgomery et al., 1998; Williams et al., 2000; Montgomery et al., 1999; Myerson, Hemingway, Budget, Martin, Humphries, 1999) among young healthy males or elite athletes in endurance sports. However, in another study, the DD genotype were more prevalent among short distance elite swimmers (Woods et al., 2001) and yet others have found no skewed distribution of ACE genotype in athletes compared to controls (Taylor, Mamotte, Fallon, van Bockxmeer, 1999; Rankinen et al., 2000c). Two studies have explored the association among fitness phenotypes in the general population and ACE genotype and found no association (Rankinen et al., 2000b; Frederiksen et al., 2002c). Although the association is biologically plausible and studies are feasible even with few subjects, (approximate allele distribution: 50% of each) the results from many association studies on this variant have been inconsistent. Most of the studies that have found increased performance among participants with a certain allele or skewed allele distribution between athletes and controls have used highly selected populations in small samples. Inconsistent results from association studies on the I/D polymorphism and risk of ischemic heart disease have also been reported, and publication bias (i.e., lower association measure in studies with larger sample size) have been shown to be a likely contributor to this discrepancy (Keavney et al., 2000).

Other genetic variants have been investigated mainly in association studies. No association was found between genetic variants in the vitamin D receptor and oestrogen receptors genes and muscle strength in two studies of post-menopausal women (Geusens, Vandevyver, Vanhoof, Cassiman, Boonen, Raus, 1997; Vandevyver et al., 1999) while variants in the $Na \pm K \pm ATP_{ase}$ $\alpha 2$ gene explained approximately 2% of the variability in the trainability of VO_{2max} among offspring but not parents in a association study among nuclear families (Rankinen et al., 2000a).

In the coming years, an increasing number of studies will suggest association between specific genetic variants or markers and various traits (e.g., physical functioning). If the objective is to identify unknown variants, the approach will often be linkage studies among families or just sib-pairs. In a study of 99 families who received a 14-week training program linkage analysis was subsequently performed to identify chromosomal markers containing specific genetic factors associated with either VO_{2max} at baseline or the training response of VO_{2max} (Bouchard et al., 2000). Weak evidence for linkage was found in chromosomes 4, 8, 11, and 14 for baseline VO_{2max} and in chromosomes 1, 2, 4, 6, and 11 for training response in VO_{2max}. However, the statistical power to detect differences in this study was low. A statistically and logistically appealing approach is the use of sib-pairs that are either extremely discordant or extremely concordant for the trait (Risch & Zhang, 1995). The problem here is to find a phenotype that can be measured in large samples and subsequently collect such data in a large sample. In our previously mentioned large twin study on grip strength, we identified dizygotic pairs that are either extremely discordant or extremely concordant and found 77 and 28 such pairs, respectively (Frederiksen et al., 2002a). These will be the basis for a search for genetic variants associated with grip strength.

Genetic factors and exercise

In intimate relation with functioning is the physical activity and exercise, which can be regarded as a behaviour associated with performance or functioning (DiPietro, 1996). Physical activity can be regarded as any voluntary movement produced by the skeletal muscles, whereas exercise is a planned, structured and repetitive activity with the intent of improving or maintaining one or more aspects of function (DiPietro, 1996). The genetic contribution to these phenotypes has been studied in relatively few populations, although among a large numbers of twin pairs (Table 1). We therefore provide new data on the genetics of the disposition to sports participation among 1258 middle-aged Danish twin pairs.

Familial clustering

Based on 375 families Perusse et al. (1989) assessed the physical activity of the participants from self-reported records of the energy expenditure (on a 1–9 scale) of the dominant activity for every 15 minute period of a day on three different days. They concluded that the habitual level of physical activity rather than exercise participation was influenced by genetic factors with a heritability estimate of 29%.

Disentangling genetics and familial environmental factors of activity and exercise

Three large twin studies have reported on genetic factors of physical activity and exercise. In a study from the Vietnam era twin registry 3344 male twins aged 33–51 provided information about their participation in moderate as well as intense physical activity.

Even when analysed as single items Lauderdale et al. (1997) found evidence for a genetic contribution to both moderate and intense physical activities. Based on 1587 adolescent Dutch twin pairs the genetics of the disposition to sports participation were assessed by a single question (Koopmans, van Doornen, Boomsma, 1994). Koopmans et al. (1994) found that a model containing additive genetic and unique environmental factors (AE model) explained variation in this trait, and that the heritability was 45%. In a large Finnish study of 5044 male twin pairs, the leisure time physical activity was assessed using questions on amount, intensity and duration (Kaprio, Koskenvuo, Sarna, 1981). From these, a composite activity score was constructed. The intraclass correlations for this score were 0.57 among MZ twins and 0.26 among DZ twins resulting in a heritability estimate of 62%.

New data

In a study of Middle Aged Danish Twins (MADT) the participants provided data on leisure time physical activity. The study that have been described in detail elsewhere (Gaist et al., 2000) were conducted by lay interviewers from the Danish National Institute of Social Research. The study was home-based and included a structured interview, as well as physical and cognitive testing. The study was conducted in a period of six months in 1998 and the participation rate was 83% and consisted 4314 participants of whom 1884 were intact pairs (both twins in a pair participated) and 546 were single twins. For this study, we used the same-sex dizygotic (DZ) pairs ($n = 642$ pairs) and the monozygotic (MZ) pairs ($n = 616$ pairs) that provided information on their leisure time sports participation 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 volley ball". The active participants were defined as those indicating participation in any of these sports ($n = 979$ individuals), whereas the sedentary participants ($n = 1537$ individuals) did not report any participation in any sport. To test the hypothesis that MZ twins were more similar for this dichotomous trait (active vs. sedentary) we used the probandwise concordance rates, odds ratios (OR) and tetrachoric correlation. Table 2 shows the probandwise concordance rates, the OR's and the correlations for being active in leisure time sports across zygosity, age and sex. All these statistics are consistently higher in the MZ twin pairs than in the corresponding DZ twin pairs, indicating that genetic factors are of importance for this trait. Subsequent biometrical analysis revealed that differences related to age and sex were not needed to account for the data, and that the best fitting model was a model attributed variation in sports participation entirely to dominant genetic effects and unique environmental effects (DE model, Table 3). However, the more biologically plausible model containing additive genetic effects and unique environment effects (AE model) also fitted data well and resulted in highly comparable estimates (Table 3). From this model, it can be estimated that the contribution of genetic effects to the variation on this trait is 49% (95% Cl, 39–58%) and conversely 51% (42–61%) of the variation to unique environmental effects. In order to rule out effects from any recent change in physical activity (e.g., due to illness), we

Table 2. Probandwise concordance rate, odds ratio (OR) and tetrachoric correlation for sports participation (see notes below) among Danish 1258 twin pairs aged 45–68

Zygosity	Sex	Age	Concordant pairs (both participates in sports of)	Discordant pairs (one participates in sports and one does not)	Concordant pairs (both do not participate in sports)	Probandwise concordant rate 95% CI[a]	OR (95% CI[a])	Tetrachloric correlation (95% CI[a])
Monozygotic	Male	45–56	47	47	71	0.67 (0.59–0.74)[b]	6.1 (3.1–11.9)[c]	0.61 (0.42–0.76)[†]
		57–68	26	55	88	0.49 (0.39–0.58)	3.0 (1.5–6.2)	0.40 (0.16–0.60)
		All	73	102	159	0.59 (0.53–0.65)	4.5 (2.8–7.2)	0.52 (0.38–0.65)[†]
	Female	45–56	41	55	68	0.60 (0.52–0.68)	3.8 (1.9–7.3)	0.47 (0.25–0.66)[†]
		57–68	49	47	67	0.68 (0.60–0.75)	6.0 (3.0–11.7)	0.61 (0.41–0.76)[†]
		All	90	102	135	0.64 (0.58–0.69)	4.7 (2.9–7.5)	0.54 (0.40–0.67)[†]
	All monozygotic		163	204	294	0.62 (0.57–0.66)	4.6 (3.3–6.4)	0.54 (0.44–0.63)[†]
Dizygotic	Male	45–56	28	69	62	0.45 (0.36–0.54)	1.5 (.7–3.2)	0.15 (−0.10–0.38)
		57–68	16	52	83	0.38 (0.28–0.48)	2.1 (0.9–4.0)	0.25 (−0.03–0.50)
		All	44	121	145	0.42 (0.35–0.49)	1.7 (1.0–2.9)	0.21 (0.03–0.38)
	Female	45–56	28	73	47	0.43 (0.35–0.52)	1.0 (0.9–1.0)	0.00 (−0.26–0.25)
		57–68	24	65	52	0.42 (0.33–0.52)	1.2 (0.4–3.5)	0.07 (−0.20–0.33)
		All	52	138	99	0.42 (0.37–0.49)	1.1 (0.5–2.3)	0.04 (−0.15–0.21)
	All dizygotic		96	259	244	0.43 (0.38–0.47)	1.4 (1.0–2.0)	0.13 (0.00–0.26)

Participants were categorised as sports participants if they reported participating in any of the following in their leisure time: jogging, gymnastics, swimming, tennis, badminton, football, handball, aerobics, rowing, table tennis, or volleyball. [a]CI = Confidence interval. [b]Based on SE for a proportion. [c]Test-based ($OR^{1\pm1.96/\sqrt{\chi^2}}$). [†]MZ correlation larger than the corresponding DZ correlation ($P < 0.05$).

Table 3. Biometrical models for sports participation (see notes below) among Danish 1258 twin pairs aged 45–68

Model	χ^2	df	*P*	AIC	Variance component			
					a^2	c^2	d^2	e^2
ACE	18.6	18	0.42	−17.4	0.49 (0.34–0.58)	0.00 (0.00–0.10)	–	0.51 (0.42–0.61)
AE	18.6	22	0.67	−25.4	0.49 (0.39–0.58)	–	–	0.51 (0.42–0.61)
CE	38.8	22	0.02	−5.2	–	0.34 (0.26–0.42)	–	0.66 (0.58–0.74)
E	98.0	23	0.00	52.0	–	–	–	1.00 (1.00–1.00)
ADE	13.8	18	0.74	−22.1	0.00 (0.00–0.44)	–	0.52 (0.06–0.62)	0.47 (0.38–0.58)
DE	13.9	22	0.91	−30.1	–	–	0.53 (0.42–0.62)	0.47 (0.38–0.58)

Participants were categorised as sports participants if they reported participating in any of the following in their leisure time: jogging, gymnastics, swimming, tennis, badminton, football, handball, aerobics, rowing, table tennis, or volleyball. The two best fitting models according to AIC (Akaike's Information Criterion $= \chi^2 - 2\times$df) is given in bold. A = additive genetic effects; D = genetic effects due to dominance; C = shared environmental effects; and E = non-shared environmental effects. All results are based on models where age and sex are fixed resulting in common estimates across the age and sex groups since there were no statistical significant difference between the full model and the models constraining the effects of age and sex.

Table 4. Probandwise concordance rate, odds ratio (OR) and tetrachoric correlation for sports participation (see notes below) among Danish 1258 twin pairs aged 45–68. Populations restricted as noted in table

Zygosity	Concordant pairs (both participates in sports)	Discordant pairs (one participates in sports and one does not)	Concordant pairs (both do not participate in sports)	Probandwise concordance rate (95% CI[a])	OR(95% CI[a])	Tetracholoric correlation (95% CI[a])
All (n = 1258 pairs)						
Monozygotic	163	204	294	0.62 (0.57–0.66)	4.6 (3.3–6.4)	0.54 (0.44–0.63)[†]
Dizygotic	96	259	244	0.43 (0.38–0.47)	1.4 (1.0–2.0)	0.13 (0.00–0.26)
No change in habitual level of physical activity last six months (n = 879 pairs)						
Monozygotic	124	137	201	0.64 (0.60–0.69)[b]	5.4 (3.6–8.0)[c]	0.58 (0.46–0.68)[†]
Dizygotic	75	171	168	0.47 (0.41–0.52)	1.7 (1.1–2.6)	0.21 (0.05–0.36)
No health related limitations in being physical active (n = 797 pairs)						
Monozygotic	116	129	177	0.64 (0.59–0.69)	5.0 (3.3–7.5)	0.56 (0.43–0.67)[†]
Dizygotic	71	162	139	0.47 (0.41–0.52)	1.5 (1.0–2.4)	0.16 (0.00–0.31)
Twins within pairs with rare contact (n = 770 pairs)*						
Monozygotic	82	115	169	0.59 (0.53–0.65)	4.2 (2.7–6.6)	0.50 (0.36–0.63)[†]
Dizygotic	60	180	158	0.40 (0.34–0.46)	1.2 (0.7–1.9)	0.06 (−0.10–0.22)

Participants were categorised as sports participants if they reported participating in any of the following in their leisure time: jogging, gymnastics, swimming, tennis, badminton, football, handball, aerobics, rowing, table tennis, or volley ball. [a]CI = Confidence interval. [b]Based on SE for a proportion. [c]Test-based ($OR^{1\pm1.96/\sqrt{\chi^2}}$). [†]MZ correlation larger than the corresponding DZ correlation ($P < 0.05$). *Twins within pairs who had not been living together for the past 30 years and who were currently in contact only monthly or more rarely.

repeated the analyses using only twin pairs where none of the twins had changed there habitual level of physical activity during the past six months (Table 4). A number of the diseases that potentially results in functional limitations have been shown to have a genetic component [diabetes (Poulsen, Kyvik, Vaag, Beck–Nielsen, 1999), cardiovascular disease (Marenberg, Risch, Berkman, Floderus, de Faire, 1994) and some cancers (Lichtenstein et al., 2000)]. We therefore also repeated the analyses restricted to pairs where none of the twins indicated health related problems in being physically active. As shown in Table 4 these restrictions resulted in highly comparable estimates. The equal environmental assumption as described in the appendix was in this study tested by restricting the analyses to pairs where the twins had not been living together for the past 30 years and who were currently in contact only monthly or more rarely (Table 4). This also resulted in highly comparable estimate indicating that the equal environment assumption is not violated in our study.

Conclusion and perspectives

Evidence gathered through the past two decades from a number of family and twin studies suggests that genetic factors account for a moderate to substantial proportion of the phenotypic variability of physical functioning and physical activity. This provides some optimism for subsequent studies at the molecular level. Yet, there is currently very little insight into the mechanisms through which genetic factors influence these phenotypes and nor have any specific genetic variant

consistently proven to influence physical functioning or the associated behaviour on a population level. In an ageing population interventions that increase the non-disabled life expectancy will be of major importance. In this respect the identification of specific genetic factors through which aspects of physical functioning in old age is expressed is important for understanding these mechanisms and could form a potential basis for such interventions.

Key words: twin studies; epidemiology; ageing; genetics; grip strength; physical activity.

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Appendix

According to standard biometric practice, it is assumed that the total variance (V) in a trait can be decomposed as $V = A + D + C + E$, where A refers to the variance contribution from additive genetic effects (the sum of average effects of alleles within and across loci), D refers to the variance contribution from genetic effects due to dominance (interaction of alleles within loci), C refers to the variance contribution of shared environmental effects, and E refers to the variance contribution from non-shared environmental effects. Shared environmental effects (i.e., environmental factors that are shared by reared-together twins such as prenatal and early shared family influences) are a source of their similarity, whereas non-shared environmental effects (i.e., environmental factors that are not shared by reared-together twins) are a source of their dissimilarity. In the full standard biometric model D and C cannot be simultaneously estimated. Therefore separate ACE and ADE models are fitted. Other, simpler models might explain data equally well. Therefore also AE, DE, CE, and E models are fitted. Thus, six different models, the ACE, ADE, AE, DE, CE, and E models, are fitted to the data (exemplified in Tables 2 and 3). The genetic and environmental variance components (A, C, D, E) and the likelihood-based confidence intervals can be estimated by structural equation modeling using the Mx software package (Neale, 1997). Each model is evaluated in terms of whether it both fits the data well (i.e., has a non-significant χ^2 goodness-of-fit test statistic) and is parsimonious (i.e., none of the parameters in the model can be deleted without a significant increase in χ^2). The Akaike information criterion (AIC) (Akaike, 1987) which corresponds to χ^2 minus twice the degrees of freedom provides a summary index of both fit and parsimony to compare non-nested models. Models

with the lowest AIC are preferred. For comparison of nested models the Chi-squared difference test are used. The difference in Chi-squared of the models is itself distributed as a Chi-squared statistic with the degrees of freedom equal to the difference in the degrees of freedom of the models being compared. Firstly, analyses of the different models, allowing the variance components to vary across sex and age, are carried out (age strata in Table 2). Then, submodels of the best-fitting model, in which the variance components are constrained to be equal across sex and/or age groups, are analysed to test the effect of sex and age on the parameters. Finally, the heritability of the trait is derived from the best-fitting model.

A number of assumptions underlie the biometrical models including: no epistasis (genetic inter–locus interaction), no gene–environment interaction or correlation, no assortative mating (the tendency to "like marrying like"), and intrapair equal environment (Kendler & Gardner, 1998) some of which can be tested.