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Chapter 27

Genetics of Sedentariness

Charlotte Huppertz, Eco J.C. de Geus, and Hidde P. van der Ploeg

Abstract The genetic investigation of sedentary behaviour is only recent and greatly lags behind that of other health behaviours. This section will review the available literature on the genetics of sedentary behaviour. First, the classical twin design will be outlined, and twin studies will be summarized that decompose the variance of sedentary behaviour into genetic and environmental variance. Second, it will be shown how twin studies can contribute to a better understanding of the consequences of sedentary behaviour by explicitly testing causality between this behaviour and health outcomes. Finally, molecular genetic studies will be outlined that aim to find the actual genetic variants that affect sedentary behaviour. We conclude that sedentary behaviour is partly heritable (~30%) but can also be affected by the environment that is shared between siblings. Paucity of studies and heterogeneity in the age ranges studied and measures used make it challenging to provide stable estimates for heritability and environmental influences. To date, no genetic markers have been reliably associated with sedentary behaviour.

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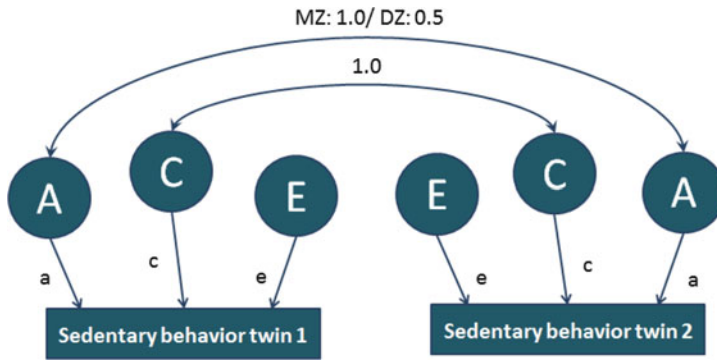
27.1 Introduction

Sedentary behaviour has been associated with premature mortality and the development of a range of non-communicable diseases, including cardiovascular disease and type 2 diabetes [1–3]. Sedentary behaviours are defined as activities incurring no more than 1.5 metabolic equivalents in sitting or reclining position during waking time [4]. This is distinctly different from inactivity, which is the lack of moderate to vigorous physical activity and is poorly correlated with sedentary behaviour [5].

Both in light of its high prevalence and its detrimental effects on health, changing sedentary behaviour patterns on a population level is a major public health priority. In order to develop interventions that decrease sedentary time, a better understanding of its underlying determinants is needed. The majority of studies that have been conducted to date have focused on cross-sectional associations [6], and it is usually ignored that even under identical circumstances, some individuals are—due to their genetic material—more likely to pursue a sedentary lifestyle than others. Research on these innate differences is of utmost importance.

27.2 Heritability

Innate individual differences in a trait are suggested if smaller within-family variation is observed compared to the between-family variation. A few studies that were based on nuclear families [7–9] and a three-generation study [10] have shown familial aggregation of total sedentary time as assessed by survey [9] and with accelerometers [7, 8], as well as self-reported computer use [9], television viewing and sitting time [9, 10]. However, this chapter focuses on twin studies to estimate heritability for two reasons: First, when comparing two twins of a pair, in contrast to, for instance, comparing parents and their offspring, generation-specific effects are taken into account. Second, compared to family studies, twin studies allow the disentanglement of familial resemblance into genetic (“nature”) and shared environmental (“nurture”) effects [11]. To this end, the resemblance of monozygotic (MZ) twin pairs is compared to the resemblance of dizygotic (DZ) twin pairs on a given phenotype (i.e. a trait, behaviour or characteristic). MZ twins originate from the same fertilized egg, meaning that they are (nearly) genetically identical, whereas DZ twins share on average 50% of their segregating genes. Environmental effects on the phenotype are expected to be equal for MZ and DZ twins, meaning that if the phenotypic correlation between MZ twins is larger than the correlation between DZ twins, this must be due to genetic influences. If the DZ correlation is larger than half the MZ correlation, this points towards shared environmental influences that make DZ twins more similar to each other than what would be expected based on their genes alone. These could be factors related to growing up in the same family and neighbourhood. Finally, there is a part of the environment that two twins of a pair do not share and that therefore makes them different from each other. Non-shared environmental influences can be inferred from MZ twin correlations that are smaller than one, as MZ twins share 100% of



MZ= monozygotic twin pair; DZ= dizygotic twin pair.

Fig. 27.1 Path diagram of a basic twin model depicting additive genetic factors (“A”), shared environmental factors (“C”) and non-shared environmental factors (“E”). *MZ* monozygotic twin pair; *DZ* dizygotic twin pair

both their genetic material and (by definition) of their shared environment. These influences could be twin-specific peer groups, work or life events. Measurement error would also be estimated as part of these non-shared environmental influences, as long as two twins of a pair do not systematically differ, because this random fluctuation would make twins of a pair more different from each other. A summary of virtually all existing twin studies of the past 50 years on a range of human phenotypes was recently published in *Nature Genetics* [12].

Figure 27.1 depicts the path diagram of a basic twin model. The rectangles depict the measured phenotypes (in this case sedentary behaviour) of twin 1 and twin 2, respectively. The circles contain the unmeasured, latent factors “A” (additive genetic effects), “C” (shared, or common, environmental effects) and “E” (non-shared environmental effects). The latent A components have a correlation of one for MZ twins (meaning that they share 100% of their genetic material), whereas the correlation is 0.5 for DZ twins (meaning that they share 50% of their genetic material). By definition, the shared environmental factors have a correlation of one, and the non-shared environmental factors are not correlated for both types of twins. Based on maximum likelihood estimation, structural equation software aims to find the path coefficients (a , c , e) that, given the imposed model, fit the data best. The *absolute* variance that is explained by A, C and E is obtained by squaring the path coefficients (a^2 , c^2 , e^2). Their *relative* contribution is obtained by dividing the result by the total variance [e.g. $a^2 / (a^2 + c^2 + e^2)$]. The relative contribution of genes is called heritability.

27.2.1 Heritability of Sedentary Behaviour

Table 27.1 depicts an overview of twin studies on the heritability of sedentary behaviour. The available studies have assessed a wide variation of sedentary

Table 27.1 Overview of twin studies on the heritability of sedentary behaviour under free-living conditions, age >5 years old, published in English, ordered by publication date

Reference	Sample	Sedentary behaviour phenotype	ACE (%) or twin correlations for sedentary behaviour
Kujala et al., 2002 [13]	The older Finnish twin cohort; $N = 15577$ twins (5133 complete pairs); 49% male; age range: 24–60 years	Self-reported sedentary work, dichotomized as “mainly sedentary work, which requires very little physical activity” versus more active categories	$A = 50$ (derived from twin correlations)
Nelson et al., 2006 [14]	National Longitudinal Study of Adolescent Health (Add Health); $N = 4782$ siblings that shared households in youth at baseline; 50% male; mean age (SD) at baseline/follow-up: 16.5 years (1.7)/22.4 (1.8); the sample included 1440 twin pairs of which some <i>live together</i> in adulthood and others <i>live apart</i>	Leisure screen time based on survey items assessing hours per week watching television/videos and/or playing video/computer games	Adolescence, cross-sectional $rMZ = 0.32$, $rDZ = 0.40$ Adulthood, cross-sectional <i>Live together:</i> $rMZ = 0.16$, $rDZ = 0.16$ <i>Live apart:</i> $rMZ = 0.40$, $rDZ = 0.09$ Change baseline to follow-up <i>Live together:</i> $rMZ = -0.06$, $rDZ = 0.31$ <i>Live apart:</i> $rMZ = 0.31$, $rDZ = 0.18$
Fisher et al., 2010 [15]	Twins Early Development Study (TEDS); $N = 234$ twins (117 complete pairs); 46% male; age range: 9–12 years	Total sedentary time measured with Actigraph accelerometers (<100 counts per minute)	Full model: $A = 24$, $C = 37$, $E = 39$ Best-fitting model: $A = 0$, $C = 55$, $E = 45$
van der Aa et al., 2012 [16]	Netherlands Twin Register (NTR); $N = 5090$ twins (2367 complete pairs) and 980 siblings; 44% male; age range: 12–20 years	Leisure screen time, based on survey items assessing weekly frequency of television viewing, playing electronic games, and personal computer/internet use	Age moderation Males: age 12 ($A = 35$, $C = 29$, $E = 36$) vs. age 20 ($A = 48$, $C = 0$, $E = 52$) Females: age 12 ($A = 19$, $C = 48$, $E = 34$) vs. age 20 ($A = 34$, $C = 0$, $E = 66$)
den Hoed et al., 2013 [17]	TwinsUK registry; $N = 1654$ twins (772 complete pairs); 2% male; age range: 17–82 years	Total sedentary time (≤ 1.5 metabolic equivalents of task) as derived from a combined heart rate and movement sensor (Actiheart)	Full model: $A = 31$, $C = 15$, $E = 55$ Best-fitting model: $A = 47$, $C = 0$, $E = 53$

(continued)

Table 27.1 (continued)

Reference	Sample	Sedentary behaviour phenotype	ACE (%) or twin correlations for sedentary behaviour
Piirtola et al., 2014 [18]	The older Finnish twin cohort; $N = 6713$ twins (1940 complete pairs); 46% male; age range: 53–67 years	Total sitting time, summed over survey items on sitting time (min/d) (1) in office or similar places, (2) at home watching television or videos, (3) at home at the computer, (4) in a vehicle and (5) elsewhere	$A = 35, C = 1, E = 64$ (derived from twin correlations)
Haberstick et al., 2014 [19]	MacArthur Longitudinal Twin Study (MALTS) and the Colorado Twin Registry (CTR); $N = 2847$ twins (1418 complete pairs); 48% male; mean age (SD): 15.1 years (2.2)	Self-reported “passive activities” during leisure time, consisting of “total hours watching television—weekday plus weekend”, “sitting around doing nothing” and “sitting and listening to music”	Males: full model ($A = 3, C = 21, E = 76$), best-fitting model ($A = 0, C = 23, E = 77$) Females: full model ($A = 30, C = 23, E = 46$), best-fitting model ($A = 35, C = 19, E = 46$)

A additive genetic effects; C shared environmental effects; E non-shared environmental effects; rMZ monozygotic twin correlation; rDZ dizygotic twin correlation

behaviour outcomes based on self-report, namely, leisure screen time [14, 16], “passive activities” during leisure time [19], sedentary work [13] and total sitting time [18], whereas two studies have objectively assessed total sedentary time with accelerometry [15] and a combined heart rate and movement sensor [17]. It is usually tested whether the structural equation model that includes all possible parameters can be reduced to a model that includes fewer parameters without a significant deterioration of the model fit. If available, both the results of the full model and the results of the best-fitting model are reported. Two studies [13, 18] relied on manual calculations of variance components based on the MZ and DZ twin correlations.

The large diversity of studies makes it difficult to draw overall conclusions. Based on the available evidence, it seems that up till adolescence, both shared environmental and genetic factors play a role. For instance, Nelson and colleagues [14] report (1) twin correlations on leisure screen time for adolescents, as well as (2) separate twin correlations for young adult pairs that kept living together and pairs that separated. In general, they find higher congruence between MZ and DZ twins that are living together, favouring the environment as the source of twin resemblance, whereas the MZ correlations are higher than the DZ correlations when they are living apart, favouring a genetic cause of twin resemblance. Across all studies, the relative role of the shared environment seems to decrease from childhood to adulthood, whereas heritability remains fairly stable.

The estimates in Table 27.1 differ widely, however, and it is unclear whether this is due to age differences or due to the large variety of sedentary behaviour measures.

In the current literature, including twin studies, sedentary behaviour is sometimes mistaken for inactivity, which is a distinct behaviour, and both behaviours should be studied separately. More high-quality data are needed from large twin cohorts with objective- as well as domain-specific self-report measurements of sedentary behaviour that allow the analysis of sex- and age-specific effects. Apart from studying the heritability of different types of sedentary behaviour, we also need to understand the distinctiveness and overlap between the variance components that affect these different types. Once we have a clearer picture of the relative contribution of genes and the environment to individual differences in sedentary behaviour, we need to focus on the underlying mechanisms. A larger contribution of the shared environment in childhood may be due to parental influences, the availability of screen-viewing opportunities at home and/or the influence of the school environment. In adults, the determinants of sedentary behaviour during leisure time are probably highly complex, as this is a time of free choice, while sedentary time at work is often predetermined by job type and specific tasks.

27.3 Health Effects of Sedentary Behaviour: Causality or Genetic Pleiotropy?

The main reasons for the current interest in sedentary behaviour are well-documented detrimental health effects of too much sitting. Twin studies can contribute to a better understanding of these as they can explicitly test the hypothesis of causality between two phenotypes. What is often interpreted as a negative causal effect of sedentary behaviour on health might partly be explained by underlying factors that influence both phenotypes in the absence of causality. Causality can be supported (but not proven) or falsified by using (1) bivariate models that decompose genetic and environmental effects on the covariance between two phenotypes [20, 21] and (2) the MZ twin intra-pair differences design [20].

The rationale behind causality testing based on bivariate genetic models is that if sedentary behaviour causally influences a health outcome, then everything that influences sedentary behaviour will also, through the causal chain, influence the health outcome (if 1 causes 2 and 2 causes 3, then 1 causes 3). Let us assume that sedentary behaviour is affected by genetic effects (A), shared environmental effects (C) and non-shared environmental effects (E). Under the hypothesis of causality, the effects of A, C and E on sedentary behaviour also need to affect the health outcome. This can be tested by calculating the genetic and environmental cross-trait correlations between sedentary behaviour and the health outcome in a bivariate twin model. Figure 27.2 depicts the path diagram of such a model. As before, the measured phenotypes are depicted in rectangles, whereas the unmeasured latent factors are depicted in circles. The genetic, shared environmental and non-shared environmental (co-)variances are decomposed into (1) effects on sedentary behaviour (a_{11} , c_{11} , e_{11}), (2) effects on the health outcome that are not shared with sedentary behaviour (a_{22} , c_{22} , e_{22}) and (3) effects that overlap between the two

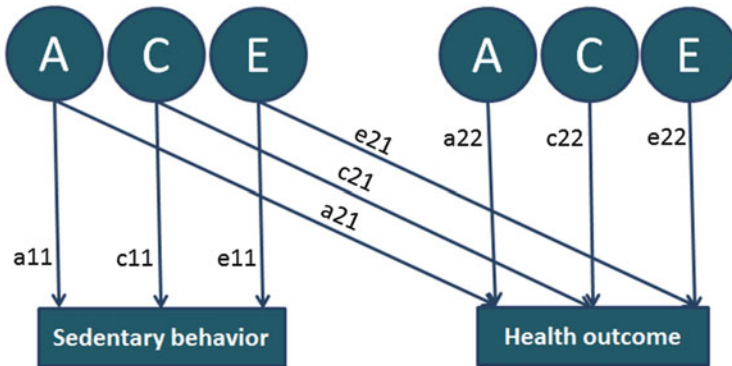


Fig. 27.2 Path diagram of a bivariate twin model with only one of the twins depicted, for clarity

phenotypes (a_{21} , c_{21} , e_{21}). According to the rationale that was outlined before, a_{21} , c_{21} and e_{21} —given sufficient power—all need to be significantly different from zero. If, for instance, only a_{21} was significantly different from zero and c_{21} and e_{21} were not, this would point towards underlying genetic effects that affect both phenotypes (“genetic pleiotropy”) in the absence of causality. The power of this test can be increased by using repeated measures or multiple indicators of sedentary behaviour and the health outcome.

The MZ twin intra-pair differences design is based on the assumption that if there is a negative causal association between sedentary behaviour and a health outcome, the twin who is more sedentary should have a worse health compared to the genetically identical co-twin who is less sedentary. As MZ twins are perfectly matched for age, genetic background and for their shared environment, no difference in the health outcome would imply that some of these underlying factors explain the association that is only found on a population level.

The outlined designs have been frequently applied to regular exercise behaviour. For instance, de Moor and colleagues [20] have shown that the negative association between regular exercise behaviour and symptoms of anxiety and depression that is seen on a population level can most likely be explained by underlying genes that affect both phenotypes in the absence of causality. Unfortunately, applications to sedentary behaviour are scarce. Kujala and colleagues [13] investigated the effect of persistent discordance in sedentary work on mortality in both adult MZ and DZ twins. Sedentary workers had a lower mortality risk than non-sedentary workers. However, the effect was attenuated when controlling for income level, education, smoking, heavy use of alcohol and participation in vigorous leisure physical activity. There was no difference between MZ and DZ twins, supporting a causal association between sedentary work and mortality. The National Aeronautics and Space Administration (NASA) Johnson Space Center conducted two 30-day bed rest studies with MZ twins, where one of the pair served as sedentary control and the other performed exercises to counteract bed rest-induced bone loss [22, 23]. They concluded that the exercises counteracted bone resorption, especially

in men. These kinds of interventions offer stronger support for causality than experiments with non-twin individuals as treatment effects are less confounded due to better matching of experimental and control group. However, bed rest is an extreme form of sedentary behaviour that rarely occurs in daily life, especially for prolonged periods of time. Future studies on phenotypes that are relevant to the population at large should fully exploit the power of causality testing based on twin data.

27.4 Molecular Genetics

Heritability of complex behavioural phenotypes derives from the summed effects of allelic variants at hundreds or thousands of loci. In the past two decades, mapping of the human genome and rapid technological advances have made it feasible to identify these specific variants. There are, roughly, two approaches to study the effects of allelic variation on a phenotype such as sedentary behaviour: *linkage studies* and *association studies*.

27.4.1 Linkage Studies

The method underlying linkage studies is outlined by Ferreira [24]. Briefly put, if individuals that share a greater proportion of alleles identical by descent (IBD) on a given genetic variant (a marker) are also more similar to each other on a given phenotype, it is concluded that there is linkage between the marker and the phenotype. One genome-wide linkage study has been conducted with sedentary behaviour as the outcome variable. Cai and colleagues [7] assessed awake time spent in sedentary activities with Actiwatch accelerometers in 1030 Hispanic children and 631 parents of the Viva La Familia Study and found significant linkage ($p < 0.0001$) with markers on chromosome 18q. Simonen and colleagues [25] combined sedentary behaviour and inactivity as assessed by 3-day activity diaries in 767 subjects of the Québec Family Study. Participants indicated their dominant activity for each 15-min period of a day. The activities were categorized into one of nine classes according to their energy expenditure level, and the scores of the first four classes were summed to reflect resting or very light activities. The authors found promising linkage with two markers on chromosome 2p22-p16 ($p < 0.0023$). The main limitation of linkage studies is that they do not identify actual DNA variation related to a phenotype. Instead, they identify chromosomal regions that harbour these variants, and subsequent fine mapping by association testing is needed to identify the allelic variants causing the linkage signal.

27.4.2 Association Studies

Association studies compare variation in a phenotype across groups of people with different combinations of alleles in *specific* genetic variants. The variants to be tested are either selected based on a priori hypotheses (candidate gene study) or hundreds of thousands of variants are tested simultaneously without any hypotheses (genome-wide association study).

Klimentidis and colleagues [26] have recently published a candidate gene study on sedentary behaviour. They found a significant association between a variant in the FTO¹ gene and self-reported time spent sitting (number of hours a day) in participants of the Framingham Heart Study (FHS; $N = 7318$; mean age 45 years; 48% males), but only a trend was found in their replication sample that was derived from the Women's Health Initiative (WHI; $N = 4756$; mean age 61 years; females only). The FTO gene has been frequently related to body mass index in previous research. Two additional studies were, again [25], based on a combined measure of sedentary behaviour and physical inactivity as assessed from a 3-day activity diary in French Canadian parents and their offspring from the Québec Family Study. Simonen and colleagues [27] investigated a polymorphism in the DRD2² gene ($N = 712$) and found no association with the phenotype. Based on the same measure, Loos and colleagues [28] investigated nine polymorphisms in seven genes coding for neuropeptides and receptors of the arcuate and paraventricular nucleus of the hypothalamus and molecules in downstream pathways ($N = 669$) and found an association with a variant of the MC4R³ gene which has previously been related to feeding behaviour and energy homeostasis. However, they did not correct for multiple testing. In general, stringent alpha levels and replication are of utmost importance with these kinds of studies as significant associations are often found by mere chance or due to confounding [29].

The current state-of-the-art are genome-wide association studies (GWAS) that allow a hypothesis-free, exploratory approach to the detection of relevant DNA markers as hundreds of thousands of variants covering most of the common genetic variation across the genome are tested simultaneously [30]. The main challenge of a GWAS is that very small p -values (e.g. $\alpha = 5 \times 10^{-8}$) need to be handled to correct for multiple testing. Most behavioural phenotypes, including sedentary behaviour, are thought to be influenced by many genetic variants with very small effects, however, meaning that large samples are needed to identify associations and significant effects need to be confirmed in independent samples to make sure they do not represent chance findings. Unfortunately, collecting, genotyping and processing DNA data of hundreds of thousands of individuals is still an expensive undertaking. Therefore, the Genetic Investigation of ANthropometric Traits (GIANT) consortium has recently pooled data of cohorts that have measured both

¹FTO gene: fat mass and obesity-associated gene

²DRD2 gene: dopamine receptor D2 gene

³MC4R gene: melanocortin 4 receptor gene

genome-wide DNA and sedentary behaviour, and the first GWAS for sedentary behaviour is underway.

Once specific genetic variants are clearly associated with sedentary behaviour, it becomes feasible to identify their function and to understand how they could affect sedentariness [31]. Furthermore, the test of causality based on bivariate genetic twin models that was outlined before can then be performed with measured genetic variants instead of latent genetic variance components, using Mendelian randomization [32].

27.5 Summary

Although behaviour genetics has tackled many behavioural and health phenotypes [12], sedentary behaviour, a relative “newcomer”, has not been widely studied. The available evidence from family and twin studies does suggest, based on both subjective and objective data, that sedentary behaviour is partly heritable (~30%), but no genetic markers have been reliably associated with this phenotype. The environment that is shared between siblings plays an important role in childhood and adolescence, but its influence seems to wane in adulthood. In the present section, we have outlined genetic methods that could be applied to test the causal effects of sedentary behaviour on health. Bigger twin- and family-based datasets, the use of better measurement instruments for sedentary behaviour as well as enrichment of datasets with molecular genetic marker data will further help to advance this field of research.

References

1. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, et al. Daily sitting time and all-cause mortality: a meta-analysis. *PLoS One*. 2013;8(11):e80000.
2. Proper KI, Singh AS, van Mechelen W, Chinapaw MJ. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. *Am J Prev Med*. 2011;40(2):174–82.
3. Thorp AA, Owen N, Neuhaus M, Dunstan DW. Sedentary behaviors and subsequent health outcomes in adults: a systematic review of longitudinal studies, 1996–2011. *Am J Prev Med*. 2011;41(2):207–15.
4. Sedentary Behaviour Research N. Letter to the editor: standardized use of the terms “sedentary” and “sedentary behaviours”. *Appl Physiol Nutr Metab*. 2012;37(3):540–2.
5. Van der Ploeg HP, Chey T, Ding D, Chau JY, Stamatakis E, Bauman AE. Standing time and all-cause mortality in a large cohort of Australian adults. *Prev Med*. 2014;69:187–91.
6. Rhodes RE, Mark RS, Temmel CP. Adult sedentary behavior: a systematic review. *Am J Prev Med*. 2012;42(3):e3–28.
7. Cai G, Cole SA, Butte N, Bacino C, Diego V, Tan K, et al. A quantitative trait locus on chromosome 18q for physical activity and dietary intake in Hispanic children. *Obesity (Silver Spring)*. 2006;14(9):1596–604.

8. Butte NF, Cai G, Cole SA, Comuzzie AG. Viva la Familia study: genetic and environmental contributions to childhood obesity and its comorbidities in the Hispanic population. *Am J Clin Nutr.* 2006;84(3):646–54. quiz 73–4
9. Santos DM, Katzmarzyk PT, Diego VP, Blangero J, Souza MC, Freitas DL, et al. Genotype by sex and genotype by age interactions with sedentary behavior: the Portuguese healthy family study. *PLoS One.* 2014;9(10):e110025.
10. Diego VP, de Chaves RN, Blangero J, de Souza MC, Santos D, Gomes TN, et al. Sex-specific genetic effects in physical activity: results from a quantitative genetic analysis. *BMC Med Genet.* 2015;16:58.
11. Falconer DS, Mackay TF. Introduction to quantitative genetics. 4th ed. Essex: Pearson Education; 1996. 280 p.
12. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet.* 2015;47(7):702–9.
13. Kujala UM, Kaprio J, Koskenvuo M. Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *Am J Epidemiol.* 2002;156(11):985–93.
14. Nelson MC, Gordon-Larsen P, North KE, Adair LS. Body mass index gain, fast food, and physical activity: effects of shared environments over time. *Obesity (Silver Spring).* 2006;14(4):701–9.
15. Fisher A, van Jaarsveld CH, Llewellyn CH, Wardle J. Environmental influences on children's physical activity: quantitative estimates using a twin design. *PLoS One.* 2010;5(4):e10110.
16. Van der Aa N, Bartels M, te Velde SJ, Boomsma DI, de Geus EJ, Brug J. Genetic and environmental influences on individual differences in sedentary behavior during adolescence: a twin-family study. *Arch Pediatr Adolesc Med.* 2012;166(6):509–14.
17. Den Hoed M, Brage S, Zhao JH, Westgate K, Nessa A, Ekelund U, et al. Heritability of objectively assessed daily physical activity and sedentary behavior. *Am J Clin Nutr.* 2013;98(5):1317–25.
18. Piirtola M, Kaprio J, Ropponen A. A study of sedentary behaviour in the older Finnish twin cohort: a cross sectional analysis. *Biomed Res Int.* 2014;2014:209140.
19. Haberstick BC, Zeiger JS, Corley RP. Genetic and environmental influences on the allocation of adolescent leisure time activities. *Biomed Res Int.* 2014;2014:805476.
20. De Moor MHM, Boomsma DI, Stubbe JH, Willemsen G, de Geus EJC. Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Arch Gen Psychiatry.* 2008;65(8):897–905.
21. Huppertz C, Bartels M, Jansen IE, Boomsma DI, Willemsen G, de Moor MHM, et al. A twin-sibling study on the relationship between exercise attitudes and exercise behavior. *Behav Genet.* 2014;44(1):45–55.
22. Smith SM, Davis-Street JE, Fesperman JV, Calkins DS, Bawa M, Macias BR, et al. Evaluation of treadmill exercise in a lower body negative pressure chamber as a countermeasure for weightlessness-induced bone loss: a bed rest study with identical twins. *J Bone Miner Res.* 2003;18(12):2223–30.
23. Zwart SR, Hargens AR, Lee SM, Macias BR, Watenpaugh DE, Tse K, et al. Lower body negative pressure treadmill exercise as a countermeasure for bed rest-induced bone loss in female identical twins. *Bone.* 2007;40(2):529–37.
24. Ferreira MA. Linkage analysis: principles and methods for the analysis of human quantitative traits. *Twin Res.* 2004;7(5):513–30.
25. Simonen RL, Rankinen T, Perusse L, Rice T, Rao DC, Chagnon Y, et al. Genome-wide linkage scan for physical activity levels in the Quebec family study. *Med Sci Sports Exerc.* 2003;35(8):1355–9.
26. Klimentidis YC, Arora A, Chougule A, Zhou J, Raichlen DA. FTO association and interaction with time spent sitting. *Int J Obes (Lond).* 2016;40(3):411–6.

27. Simonen RL, Rankinen T, Perusse L, Leon AS, Skinner JS, Wilmore JH, et al. A dopamine D2 receptor gene polymorphism and physical activity in two family studies. *Physiol Behav.* 2003;78(4–5):751–7.
28. Loos RJ, Rankinen T, Tremblay A, Perusse L, Chagnon Y, Bouchard C. Melanocortin-4 receptor gene and physical activity in the Quebec family study. *Int J Obes (Lond).* 2005;29(4):420–8.
29. Tabor HK, Risch NJ, Myers RM. Candidate-gene approaches for studying complex genetic traits: practical considerations. *Nat Rev Genet.* 2002;3(5):391–7.
30. Pearson TA, Manolio TA. How to interpret a genome-wide association study. *JAMA.* 2008;299(11):1335–44.
31. Van Dongen J, Slagboom PE, Draisma HH, Martin NG, Boomsma DI. The continuing value of twin studies in the omics era. *Nat Rev Genet.* 2012;13(9):640–53.
32. Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet.* 2014;23(R1):R89–98.