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Polygenic Risk Scores and Physical Activity

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Polygenic Risk Scores and Physical Activity

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The funding sources had no roles in the study design, collection, analysis, or interpretations of the data or in the publication process.

The authors have no conflicts of interest to report. The results of the present study do not constitute endorsement by ACSM. All authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

ABSTRACT

Purpose: Polygenic risk scores (PRS) summarize genome-wide genotype data into a single variable that produces an individual-level risk score for genetic liability. PRSs have been used for prediction of chronic diseases and some risk factors. As PRSs have been studied less for physical activity (PA), we constructed PRSs for PA and studied how much variation in PA can be explained by these PRSs in independent population samples. **Methods:** We calculated PRSs for self-reported and objectively measured PA using UK Biobank genome-wide association study summary statistics, and analyzed how much of the variation in self-reported (MET-hours/day) and measured (steps and moderate-to-vigorous PA minutes/day) PA could be accounted for by the PRSs in the Finnish Twin Cohorts (FTC, N = 759-11,528) and the Northern Finland Birth Cohort 1966 (NFBC1966, N = 3,263-4,061). Objective measurement of PA was done with wrist-worn accelerometer in UK Biobank and NFBC1966 studies, and with hip-worn accelerometer in the FTC. **Results:** The PRSs accounted from 0.07% to 1.44% of the variation (R^2) in the self-reported and objectively measured PA volumes (*P*-value range 0.023 to < 0.0001) in FTC and NFBC1966. For both self-reported and objectively measured PA, individuals in the highest PRS deciles had significantly (11 to 28%) higher PA volumes compared to the lowest PRS deciles (*P*-value range 0.017 to < 0.0001). **Conclusions:** PA is a multifactorial phenotype and the PRSs constructed based on UK Biobank results accounted for statistically significant but overall small proportion of the variation in PA in the Finnish cohorts. Using identical methods to assess PA and including less common and rare variants in the construction of PRSs may increase the proportion of PA explained by the PRSs.

Key Words: GENE, EXERCISE, HERITABILITY, HIDDEN HERITABILITY

INTRODUCTION

Based on family and twin studies genetic factors underlie an individual's propensity to participate in physical activity (PA) (1-4). Genome-wide association studies (GWAS) have found a few loci that have genome-wide statistically significant association with PA but the found effect sizes are small (5-7).

Polygenic risk score (PRS) or also called polygenic score is a score based on variation in multiple genetic loci and their associated weights. It serves as the best prediction for the trait that can be made when accounting for variation in multiple genetic variants (8, 9). Genome-wide association analyses comparing disease cases with controls have identified thousands of genetic loci associated with complex disease risk and genomic information has become a potential candidate for improving disease risk assessment (10). While PRSs have been calculated for many chronic diseases and applied for their predictive value, there is limited amount of research for predicting PA levels using PRSs for PA (5, 6). In particular, we lack information on how the constructed PRSs for PA predict PA levels in independent cohorts with differing ancestry and with differing methods to assess self-reported and objectively measured PA levels. There has been much discussion on the genetic determinants underlying physical inactivity and it would be helpful to identify those individuals for whom PA participation is difficult. In exercise interventions these individuals may need tailored exercise programs with more support and supervision to gain the benefits of exercise therapy.

PA is a multifactorial behavior with many environmental and genetic factors influencing the volume of overall PA. Questionnaires and accelerometers are among the most used methods in

assessing PA levels although different methods have their strengths and challenges (11, 12). Self-reported leisure-time PA and measured overall PA levels may have same but also different determinants. Age, gender, obesity (13) and chronic diseases (14) are typical examples of other characteristics and traits associated with PA levels, which may modify also the size of the genetic effects on PA in a context-dependent manner.

The main aim of this study was to calculate PRSs for PA using UK Biobank GWAS summary statistics and then evaluate their out-of-sample predictive values in Finnish Twin Cohorts (FTC) and the Northern Finland Birth Cohort 1966 (NFBC1966) using different PA phenotypes. We hypothesized that the PRSs will account for a statistically significant proportion of the variation in PA. To deepen our understanding, we also compared the results between single nucleotide polymorphism (SNP) -based and pedigree-based PA heritability analyses. In addition, to evaluate the usability of PRSs for PA in clinical work, we compared how much of the variation in objectively measured PA is explained by simple questionnaire items compared to PRS.

METHODS

Study samples. FTC and NFBC1966 data, in addition to the open UK Biobank summary level data were used in this study.

Data on participants from three Finnish Twin Cohorts (FTC; Old twin cohort, Finntwin16 and Finntwin12) (15, 16) were included in this study (N = 11, 528 for both genetic and self-reported PA data, mean age 44 years [range 18-93], 46% males). From a subgroup of the Old twin cohort 765 individuals had both genetic and objectively measured PA data (MOBILETWIN study; mean

age 73 years [range 71-75], 46% males) (17). The twin studies were approved by the ethics committees of the University of Helsinki (113/E3/01 and 346/E0/05), Helsinki University Central Hospital (136/E3/01, 01/2011, 270/13/03/01/2008 and 154/13/03/00/2011), and Ethics Committee of the Southwest Finland (MOBILETWIN).

NFBC1966 comprises of children born for mothers from Oulu and Lapland (Finland) and who had their expected date of birth between Jan 1st and Dec 31st, 1966 (18). Data on cohort members' self-reported PA and objectively measured PA was collected at the age of 46 years (19) and genome-wide data was obtained at the 31-year follow-up (20). Both genetic data and self-reported PA data were available for 4,061 individuals, and genetic data plus objectively measured data from 3,263-3,437 individuals (48% males). The Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland approved the study (94/2011).

Open UK Biobank GWAS summary level data was used in the generation of PRSs for PA. The UK Biobank comprises extensive phenotypic data on some 500,000 individuals of the general UK population between 40 and 69 years (21). Self-reported PA data for this study was available from 321,309 individuals and data on objective measurement for PA from 91,105 individuals (44% males). The North West Multi-Centre Research Ethics Committee approved the UK Biobank study.

In all study samples the individuals having data on age, sex, height, weight, genetic data, and data on objectively measured or self-reported PA were included in the analyses of this study. All

samples were collected and studies conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

PA variables. In FTC, the assessment of the leisure-time MET score was based on a series of structured questions on leisure-time physical activity (monthly frequency, mean duration, and mean intensity of sessions) and PA during commuting (22). The index was calculated by assigning a MET value to each activity and by calculating the product of that activity: intensity × duration × frequency. The MET score was expressed as the sum-score of leisure-time PA MET-hours/day (22). In the MOBILETWIN study PA was measured with a hip-worn triaxial accelerometer (Hookie AM20, Traxmeet Ltd, Espoo) during seven days and a mean duration of daily moderate-to-vigorous physical activity (MVPA) and mean number of daily steps was calculated, for details see Waller et al. (17).

In NFBC1966, the leisure-time PA was self-reported with questions on the frequency and duration of light and brisk physical activities during leisure time. Brisk PA was described as causing at least some sweating and breathlessness, while light PA was defined as causing no sweating or breathlessness. PA frequency had six response options: 1) once a month or less often, 2) 2–3 times a month, 3) once a week, 4) 2–3 times a week, 5) 4–6 times a week, and 6) daily. PA duration had the following response options: 1) not at all, 2) less than 20 min, 3) 20–39 min, 4) 40–59 min 5) 1–1.5 h, and 6) more than 1.5 h. Daily averages of MET-hour scores of light and brisk PA was calculated by multiplying the PA volume (duration×frequency) by its intensity (light PA 3 METs and brisk PA 5 METs) (23). PA was objectively measured with wrist-worn Polar Active monitors (Polar Electro Oy, Kempele, Finland) for 14 days. Polar Active is a waterproof

accelerometer providing MET values every 30 s based on daily PA (24). The participants were asked to wear the Polar Active monitor 24 h/day for at least 14 days on the non-dominant hand. Measured PA with intensity ≥ 3.5 METs was classified as MVPA and calculated as daily averages (min/day) (19). In addition, mean number of daily steps was calculated.

When constructing PRSs UK Biobank GWAS results of the self-report question on the "number of days/week of moderate PA 10+ minutes" ($PRS_{reported}$) and objectively measured overall activity measured with Axivity AX3 wrist accelerometer during seven days ($PRS_{measured}$) (6) were used. A basic linear regression with sex and the first 10 principal components (PCs) as covariates was performed on the GWAS used for the construction of the $PRS_{reported}$ and linear mixed model regression on the GWAS used for $PRS_{measured}$ (6). The mean "number of days/week of moderate PA" was 3.7 (SD 2.3) and the distribution of the variable, i.e. UK Biobank Data-Field 884, can be seen from the online showcase of UK Biobank resources (25). The objectively measured overall activity phenotype is a continuous phenotype based on 7-day wrist accelerometry and is the average vector magnitude for each 30-s epoch, and is described in more detail by Doherty et al (26). The SNP-based genetic correlation (r_g) of these UK Biobank PA variables has been reported to be 0.35 (6).

Genotyping, quality control and imputation in FTC. Chip genotyping were done using Illumina Human610-Quad v1.0 B, Human670-QuadCustom v1.0 A, Illumina HumanCoreExome-(12 v1.0 A, 12 v1.1 A, 24 v1.0 A, 24 v1.1 A, 24 v1.2 A) and Affymetrix FinnGen Axiom arrays. The algorithm for genotype calling were Illumina's GenCall for all HumanCoreExome chip genotypes, Illuminus for 610k & 670k chip genotypes and AxiomGT1 for Affymetrix chip

genotypes. Genotype quality control were done in three batches (batch1: 610k+670k, batch2: HumanCoreExome, and batch3: Affymetrix chip genotypes) with removing variants with call rate below 97.5% (batch1 and batch3) and 95% (batch2), removing samples with call rate below 98% (batch1) or 95% (batch2 and batch3), removing variants with its minor allele frequency below 1% and Hardy-Weinberg Equilibrium *P*-value lower than 1×10^{-6}. Also samples from all batches with heterozygosity test method-of-moments F coefficient estimate value below -0.03 or higher than 0.05 (batch1 and batch2) or ±4SD from the mean (batch3) were removed along with the samples which failed sex check or were among the multidimensional scaling (MDS) principal component analysis outliers. Total amount of genotyped autosomal variants after quality control (QC) were 475,526 (batch1), 239,894 (batch2), and 388,673 (batch3) with following number of samples remaining for imputation: 2,617 (batch1), 5,328 (batch2), and 8,218 (batch3).

We then performed pre-phasing using Eagle v2.3 (27) and imputation with Minimac3 v2.0.1 using University of Michigan Imputation Server (28). Genotypes of all batches were imputed to Haplotype Reference Consortium release 1.1 reference panel (29).

Genotyping, quality control and imputation in NFBC1966. Genotyping was performed using Illumina Human CNV370-Duo DNA bead chip as described previously in Sabatti et al. (20). The following quality control steps were applied; SNPs with call rate <95% or minor allele frequency <0.05 were excluded from the study along with individuals with genotyping success rate <95%. Imputation to 1000 Genomes phase 3 reference panel (30) was performed using pre-phasing software SHAPEIT v2 (31) and imputation software IMPUTE2 v2.3.0 (32).

Polygenic scoring. PRSs were constructed for self-reported ($PRS_{reported}$) and objectively measured PA ($PRS_{measured}$), see above in 'PA variables' paragraph. To obtain PRSs we implemented a Bayesian approach taking account the linkage disequilibrium between each variant (LDpred) (33) and therefore any pruning or thresholding method to select variants was not used. The infinitesimal model for polygenic scoring were adjusted with LD reference panel which consists of 27,284 unrelated Finnish samples from the national FINRISK study (34). GWAS summary statistics from the UK Biobank for the risk score calculation were obtained from Neale lab repository of summary statistics (35) (questionnaire based data) or from the data sharing repository of GWAS of PA measured by accelerometer (6). There were weights from 91,105 to 321,309 samples for the risk score calculation. The LD reference panel, summary statistics and the target study samples of FTC and NFBC1966 were restricted to HapMap3 (36) variants with European MAF>5% and excluding the MHC region from chromosome 6 (GRCh37: 6p22.1-21.3), representing the whole genome capturing the polygenic signal and which tends to be well imputed for samples of European or Finnish ancestry. Total number of variants used for risk score calculation varied from 1,140,182 to 1,142,416 in FTC and from 1,140,159 to 1,142,392 in NFBC1966.

Associations between PRSs and self-reported or measured PA. On the basis of previous knowledge on the different types of self-reported and objectively monitored PA variables and their heritability we focused in analyzing whether $PRS_{reported}$ predicts self-reported PA and whether $PRS_{measured}$ predicts either self-reported or objectively measured PA in the Finnish Cohorts. The proportion of total variation of PA outcomes explained by the model (R^2) was estimated by generalized linear regression models. All PRSs were scaled to obtain standardized normal

distribution with a mean of zero and standard deviation of 1. Basic models were adjusted for four genetic principal components and sex in FTC and NFBC1966 and also for age in FTC. We also report the change in R^2 (ΔR^2) when PRS was included in the model after the other predictors. Square root-transformation of MVPA was used due to violation of the assumption of normal distribution both in FTC and NFBC1966 and of daily MET score in NFBC1966. In the linear mixed model regression of the FTC data, the within-pair dependency was accounted for by using the family identifier as the random effect of the models. Individuals were divided to PRSs deciles and daily MET score, MVPA, and steps were compared between first and last deciles with independent samples t-test or Mann-Whitney's test. The level of significance was set at $P < 0.05$.

Pedigree and SNP-based heritabilities in FTC. We estimated pedigree- and SNP-based heritabilities simultaneously using the same set of SNPs that were used in the PRS calculations. We implemented a method (GCTA-GREML) according to Zaitlen et al. (37) and Yang et al. (38) where the heritability is calculated using two genetic relatedness matrices where the first takes into account only the heritability caused by family structure and the second takes into account only the genetic part of the heritability so that in the first matrix the off-diagonals below 0.05 were set to 0 letting the second matrix to have values below 0.5 indicating possible distant genetic relationships between samples. Both of the matrices were used as the fixed effect of the linear mixed model. Using this method there were no need to drop any related samples from the analysis. The difference between these two heritabilities is called missing (or hidden) heritability (37). SNP-based heritabilities for the UK Biobank PA measures were obtained from association results using LD Score Regression (39) restricted to same set of HapMap3 SNPs that were used for PRS calculations.

Questionnaire items vs $PRS_{measured}$ in explaining variation in objectively measured PA. In the MOBILETWIN study (17) complete data from 640 individuals was available to analyze how much of the variation in objectively measured PA (MVPA and steps) could be accounted for by questionnaire-based data (age, sex, body-mass index, self-reported distance walked or jogged outdoors, self-reported fitness, self-reported mobility restricting disease, and self-reported PA category) and by $PRS_{measured}$. This methodology and results are described in more detail in Supplemental Digital Content 1, Questionnaire items vs $PRS_{measured}$ in explaining variation in objectively measured PA, http://links.lww.com/MSS/B929.

RESULTS

Polygenic risk scores. The $PRS_{reported}$ accounted for 0.24% and 0.25% of the variation (R^2) in the reported daily MET scores in NFBC1966 and FTC (*P*-values 0.0017 and < 0.0001, respectively) (Table 1). The $PRS_{measured}$ accounted from 0.07% to 1.44% of the variation in the self-reported and objectively measured PA (*P*-value range 0.023 to < 0.0001) (Table 1). For all studied PA volume variables, individuals in the highest PRS deciles compared to the lowest PRS deciles had significantly (11 to 28%) higher PA volume both in FTC and in NFBC1966 (*P*-values 0.017 to < 0.0001) (Table 2). Figure 1 shows the means of the objectively measured PA variables in MOBILETWIN and NFBC1966 according to $PRS_{measured}$ deciles. The associations are quite similar despite differences in age and measurement method between MOBILETWIN and NFBC1966 studies.

Pedigree and SNP heritabilities in FTC. The pedigree heritabilities (37 to 56%) and heritability explained by SNPs in FTC are shown in Table 3. The results show that the missing (or hidden)

heritability estimates (34 to 40%) are higher than those of SNP-heritabilities (7 to 19%). The SNP-based heritability (SNP-h^2 [LD Score Regression]) obtained from UK Biobank PA association results was 0.040 (SE 0.002), $P < 0.0001$ for reported "number of days/week of moderate PA 10+ minutes" and 0.143 (SE 0.008), $P < 0.0001$ for measured overall PA.

Questionnaire items vs $PRS_{measured}$ in explaining variation in measured PA in the MOBILETWIN study. For details of the results see Supplemental Digital Content 1; Questionnaire items vs $PRS_{measured}$ in explaining variation in objectively measured PA, http://links.lww.com/MSS/B929. Self-reported weekly walking or running distance outdoors accounted for the highest amount of variation in objectively measured MVPA (R^2= 44%) and daily steps (R^2=36%). BMI, self-reported fitness level, mobility restricting disease, and PA category accounted for lower amounts of variation (R^2 from 11 to 23%). Multivariable model including age, sex, body-mass index, and the physical fitness and activity related self-reports accounted for 57% of the variation in MVPA and 47% in daily steps. Adding the $PRS_{measured}$ into the models increased the proportion of total variation explained by the model only by 0.03% for MVPA and 0.31% for daily steps.

DISCUSSION

Our study adds to the understanding on the out-of-sample predictive value of PRSs for PA using different self-report and objectively measured PA methods. PRSs constructed on the basis of UK Biobank results explained statistically significantly PA in the Finnish cohorts but the variation accounted for was small compared to some questionnaire-reported parameters such as physical fitness or health status.

Leisure-time or total PA is influenced by sex, body-mass index, education, occupation, family commitments, physical fitness, occurrence of chronic diseases, environmental factors, and many other factors, which influence also varies with age and with study area (14, 40). These variables may mediate or modify the relationship of genetic liability to PA with the observed phenotype.

In addition to the above determinants of PA, there may be other reasons why our observed explanation rates of PRSs constructed based on UK Biobank results to account for the variation in the Finnish cohorts were low. First, UK Biobank and the Finnish cohorts used differing methods both to assess self-reported and to assess objectively measured PA. Secondly, there may be genetic differences between the studied populations as we are predicting from a general European population to a genetic isolate (41). Thirdly, as the SNP heritabilities were statistically significant but low compared to pedigree heritabilities, there may be hidden genetic factors not covered by the variants used in the calculation of PRSs. Among the proposed explanations for this missing (hidden) heritability is the existence of many unidentified common variants with very small effect sizes, rare variants not captured by current genotyping platforms, structural variants, epistatic interactions, gene-environment interactions, or parent-of-origin effects (35, 42, 43). Interestingly, new research (43) showed that pedigree heritability for height and body-mass index appeared to be fully recovered from whole-genome sequence data in the analysis including also rare variants. These hidden genetic factors may also contribute to the differences between the pedigree and SNP heritabilities for PA in our study, as well as the low explanation rates of the constructed PRSs to explain variation in PA. SNP heritabilities obtained from UK Biobank association results using only the effect sizes were statistically significant but low compared to pedigree heritabilities obtained from the FTC subjects using the whole genome and phenotypic information together. The

SNP heritabilities in FTC were at a similar or slightly higher level compared to those calculated for the UK Biobank PA variables using the same set of SNPs (5).

Expectedly there were simple questions which accounted for more of the variation in measured PA in the MOBILETWIN individuals than PA PRSs calculated based on the findings from another cohort. The questionnaire items also contribute to the understanding why PRSs account for only a small proportion of the variation of the PA measures.

PA measurements differed between the studied populations, which can be considered either as a limitation or as a strength in our study. From UK Biobank results we selected clinically relevant self-report and objectively monitored PA variables based on which calculation of PA PRSs were possible. Then we used clinically relevant variables (self-reported PA volume and measured daily MVPA minutes and steps) from the Finnish cohorts to study the associations of PRSs and PA. Although all these indicators of PA describe PA volumes, they are not identical. We did not have access to the original UK Biobank data to construct new PA variables. However, to evaluate the additional value of combining information from the different self-reports we performed a joint analysis of the UK Biobank GWAS results for reported moderate and reported vigorous activity using multi-trait analysis of GWAS (MTAG). However, this new $PRS_{reported\ MTAG}$ predicted reported daily MET score in FTC only slightly better than the $PRS_{reported}$ with ΔR^2–values 0.32% vs. 0.25% (for details see Supplemental Digital Content 2, Polygenic scoring on multi-trait analysis of GWAS (MTAG)-estimated effects, http://links.lww.com/MSS/B930). The PRSs constructed on the basis of UK Biobank self-reported PA questions did not predict statistically significantly objective measured PA variables in FTC (results not shown). The used objective PA measurements

do not differentiate between leisure-time and work-related or household activities and thus indicate total PA volume in a different way than self-reports. Differing genetic factors may predict work-related and leisure-time PA. An additional difference between self-reported and objectively measured PA volumes is that self-reports take the subjective intensity into account while accelerometer data usually is transformed to PA without considering the individual fitness level (44). Individuals with chronic diseases, low fitness or advanced biological ageing process usually move less and more slowly than healthy and high-fit individuals, although their PA intensity relative to their fitness level may be the same (44), which again may cause challenges in the analysis of genetic factors predicting PA. Despite the above factors PRSs constructed based on UK Biobank data predicted PA in the Finnish cohorts, which is good news for scientists who are applying Mendelian Randomization methods and do not have the exactly same PA phenotypes in their cohorts as the UK Biobank study has.

In conclusion, PRSs constructed based on UK Biobank results accounted for statistically significant but overall small proportion of the variation in PA in the Finnish cohorts. However, there were significant differences in the PA levels between the individuals who were in the highest PRS deciles compared to those in the lowest PRS deciles. In future studies, using identical questions or objective measurement methods to assess detailed PA behaviors and possibly including rare variants in the construction of PRSs may increase the proportion of PA explained by the PRSs, which may increase the usability of PRSs for identifying individuals at risk for physical inactivity.

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Figure legends

FIGURE 1 - Means and SEMs of the objectively measured daily MVPA minutes (upper panel) and daily steps (lower panel) in MOBILETWIN and NFBC1966 studies according to $PRS_{measured}$ deciles. $PRS_{measured}$ constructed based on the objective measurement of overall activity in UK Biobank. Dotted line is the trend line and R-squared is from the bivariate decile mean-decile model to illustrate trend linearity between the PA decile means and the PRS deciles.

Figure 1

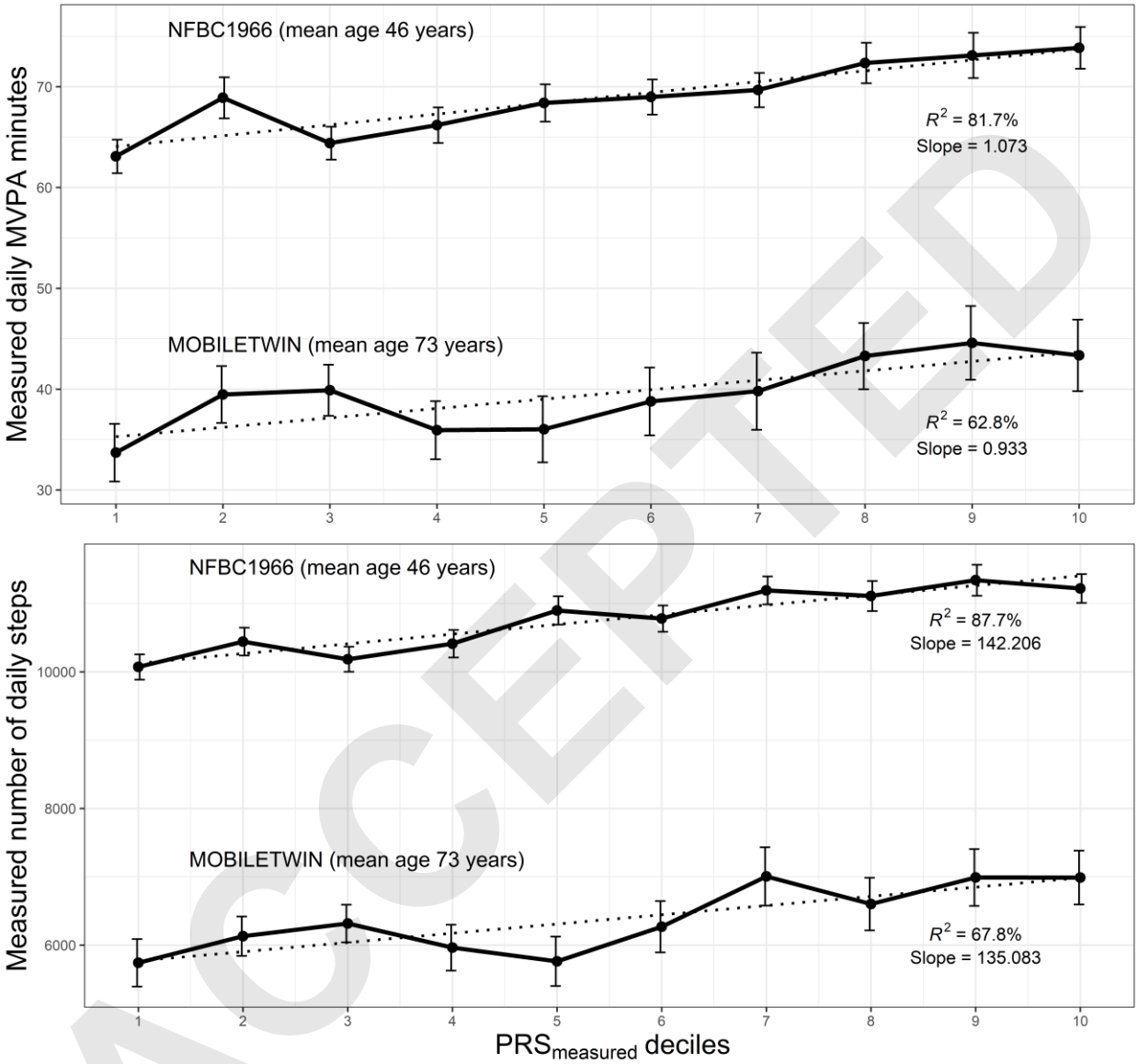

TABLE 1. Associations between PRSs and PA variables in FTC and NFBC1966.

Variables	β (SE)*	*P**	R^2% (95% CI)†	ΔR^2%‡	N
PRS for number of days/week of moderate PA 10+ minutes in UK Biobank ($PRS_{reported}$)					
Reported daily MET score in FTC	0.1717 (0.0323)	<0.0001	5.38 (4.50-6.25)	0.25	11,528
Reported daily MET score in NFBC1966	0.0355(0.0113)	0.0017	1.07 (0.52 – 1.62)	0.24	4,061
PRS for measured overall activity in UK Biobank ($PRS_{measured}$)					
Reported daily MET score in FTC	0.0908 (0.0321)	0.0046	5.20 (4.45-6.04)	0.07	11,528
Reported daily MET score in NFBC1966	0.0405 (0.0112)	0.0003	1.15 (0.58-1.71)	0.32	4,061
Measured daily MVPA in MOBILETWIN	2.497 (1.093)	0.0227	3.73 (0.85-6.60)	0.90	759
Measured daily MVPA in NFBC1966	0.1620 (0.0335)	<0.0001	8.54 (7.11-9.96)	0.62	3,437
Measured daily steps in MOBILETWIN	369.8 (123.3)	0.0028	2.71 (0.14-5.28)	1.44	759
Measured daily steps in NFBC1966	365.82 (64.04)	<0.0001	3.71 (2.72-4.69)	0.96	3,263

PRS; polygenic risk score.

*Effect and *P* value adjusted for age, sex and 4 genetic principal components.

†Variation accounted for by age, sex and the PRS with family number as random effect of the linear mixed model in FTC.

‡ΔR^2 = difference of R-squared between models with and without PRS included.

TABLE 2. Physical activity volumes of Finnish individuals in the lowest and highest PRS deciles.

Variables	**Lowest PRS decile**	**Highest PRS decile**	***P****
	Mean (95% CI)		
PRS for number of days/week of moderate PA 10+ minutes in UK Biobank ($PRS_{reported}$)			
Reported daily MET score in FTC, MET-hours	2.76 (2.59 – 2.93)	3.45 (3.23 – 3.67)	<0.0001
Reported daily MET score in NFBC1966, MET-hours	2.19 (2.0 - 2.38)	2.68 (2.44 - 2.91)	0.017
PRS for measured overall activity in UK Biobank ($PRS_{measured}$)			
Reported daily MET in FTC, MET-hours	3.12 (2.94 – 3.30)	3.51 (3.29 – 3.73)	<0.0001
Reported daily MET score in NFBC1966, MET-hours	2.18 (1.99 - 2.38)	2.69 (2.46 - 2.93)	0.002
Measured daily MVPA in MOBILETWIN, minutes	33.7 (28.1 – 39.3)	43.3 (36.3 – 50.3)	<0.0001
Measured daily MVPA in NFBC1966, minutes	63.1 (59.8 - 66.4)	73.9 (69.8 – 77.9)	<0.0001
Measured daily steps in MOBILETWIN, steps	5742 (5062 - 6422)	6989 (6216 - 7762)	<0.0001
Measured daily steps in NFBC1966, steps	10070 (9705 – 10435)	11219 (10803 – 11634)	<0.0001

PRS; polygenic risk score.

**P* for difference between the highest and lowest deciles.

TABLE 3. Pedigree, SNP-, and missing heritabilities in FTC.

Variables	**Pedigree-h^2**	**SNP-h^2**	**Missing heritability (Pedigree – SNP h^2 difference)**
Reported daily met score in FTC	0.416 (SE 0.017), *P* = 0.0026	0.071 (SE 0.027), *P* = 0.0026	0.345 (0.032)
Measured daily MVPA in MOBILETWIN	0.564 (SE 0.061), *P* = 0.326	0.191 (SE 0.413), *P* = 0.326	0.374 (0.417)
Measured daily steps in MOBILETWIN	0.481 (SE 0.062), *P* = 0.432	0.0776 (SE 0.418), *P* = 0.432	0.403 (0.423)

SNP; single nucleotide polymorphism.

h^2; heritability

Supplemental Digital Content 1

Questionnaire items vs $PRS_{measured}$ in explaining variation in objectively measured PA

Methods: In the MOBILETWIN study (1) comprehensive data from 640 individuals was available to analyze how much of the variation in objectively measured PA (MVPA and steps) could be accounted for by questionnaire items and by $PRS_{measured}$. The basic characteristics and questionnaire items used in this analysis were age, sex, body-mass index (BMI) calculated based on self-reported height and weight, self-reported distance walked or jogged outdoors, self-reported fitness, self-reported mobility restricting disease, and self-reported PA category. In more detail, we asked the participants to estimate with 0.5 km accuracy how many kilometers altogether they had walked or jogged outdoors during the past 7 days (2). Self-reported fitness was based on a question "Is your current physical fitness in your opinion?" 1) Very good, 2) Fairly good, 3) Satisfactory 4) Fairly poor, 5) Very poor. Due to low number of answers to categories four and five, these two were combined for the analyses and called poor (3). The response alternatives in the question 'Do you have any physician-diagnosed disease which restricts your mobility?' were 'no' and 'yes' (2). The overall PA category was based on the question: "How much do you move/exercise or participate in physical loading activities?" The response alternatives were: 1) I read, watch TV and do daily routines which do not load me physically (=Inactive), 2) I walk, bike or do light home or yard work many hours per week (=Moderately active), 3) I participate in conditioning exercises or sports such as running, skiing, skating or ball-games, several hours a week (=Highly active).

The proportion of total variation of outcomes explained by the model (R^2) was estimated by linear regression. Basic models were adjusted for 4 genetic principal components, sex and age. Multivariable models were constructed by entering potential predictors into the basic models one at a time. Finally, full models including all potential predictors were constructed and the change in R^2 (ΔR^2) was calculated. Square root-transformation of MVPA was used due to violation of the assumption of normal distribution. In all regression models within-pair dependency of twin individuals was taken into account in standard errors yielded by cluster variance estimator which were robust to non-independent observations within families (cluster option in Stata). The statistical analyses were executed using IBM SPSS Statistics for Windows, Version 24 (IBM

Corp. Armonk, NY, USA) and Stata version 15 (Stata Corp, College Station, TX, USA). The level of significance was set at $P < 0.05$.

Results: Self-reported weekly walking or running distance accounted for highest amount of variation in objectively measured MVPA (R^2= 44%) and daily steps (R^2= 36%, Supplemental Table 1). BMI, self-reported fitness level, mobility restricting disease, and PA category accounted for lower amounts of variation (R^2 from 11% to 23%). Multivariable model including age, sex, BMI, and the above physical fitness and activity related self-reports accounted for 57% variation in MVPA and 47% in daily steps. Adding $PRS_{measured}$ into these models increased the proportion of total variation explained only by 0.03% in MVPA and 0.31% in daily steps.

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Supplemental Table 1. Clinical questionnaire items and $PRS_{measured}$ as determinants of measured daily MVPA and steps in the MOBILETWIN study (N=640).

	Measured daily MVPA					**Measured daily steps**				
			Full model					Full model		
	β (SE)	*P*	R^2	*P*	ΔR^{2a}	β (SE)	*P*	R^2	*P*	ΔR^{2a}
Model 1										
Age	-0.39 (0.79)	0.634	0.0203	0.005		-109 (142)	0.442	0.0078	0.1278	
Sex	-4.96 (1.52)	0.001				-532 (275)	0.054			
Model 1 and BMI	-1.77 (0.18)	<0.001	0.1586	<0.001	0.1383	-283 (31)	<0.001	0.1158	<0.001	0.1080
Model 1 and self-reported distance walked or jogged	0.85 (0.06)	<0.001	0.4606	<0.001	0.4403	140 (11)	<0.001	0.3722	<0.001	0.3644
Model 1 and self-reported fitness										
Very good (ref.)	1		0.2483	<0.001	0.2280	1		0.2047	<0.001	0.1969
Good	-10.67 (1.70)	<0.001				-1902 (326)	<0.001			
Satisfactory	-21.00 (1.94)	<0.001				-3572 (348)	<0.001			
Poor	-34.85 (2.48)	<0.001				-5907 (443)	<0.001			
Model 1 and mobility restricting disease										
No (ref.)	1		0.1308	<0.001	0.1105	1		0.1162	<0.001	0.1084
Yes	-13.62 (1.61)	0.104				-2438 (289)	<0.001			
Model 1 and self-reported PA category										
Highly active (ref.)	1		0.1707	<0.001	0.1504	1		0.1292	<0.001	0.1214
Moderately active	-8.72 (2.05)	<0.001				-1325 (360)	<0.001			
Inactive	-25.75 (2.64)	<0.001				-4159 (425)	<0.001			
Model 1 and $PRS_{measured}$	1.70 (0.78)	0.030	0.0296	0.0038	0.0093	409 (140)	0.004	0.0244	0.0099	0.0166
Model 2			0.5697	<0.001				0.4695	<0.001	
Model 2 and $PRS_{measured}$	0.34 (0.50)	0.0497	0.5700	<0.001		178 (101)	0.078	0.4726	<0.001	

Model 1: Age (in years) and sex (men coded as 1 and women as 2) as independent variables in the regression model.

Model 2: Body-mass index (BMI, kg/m^2), self-reported distance walked or jogged, self-reported fitness, self-reported mobility restricting disease, and self-reported physical activity (PA) category as independent variables in the regression model.

$PRS_{measured}$ scaled to obtain standardized normal distribution with a mean of zero and standard deviation of 1.

[a]ΔR^2 shows the additional R^2 compared to Model 1.

Supplemental Digital Content 2

Polygenic scoring on multi-trait analysis of GWAS (MTAG)-estimated effects

Methods: We constructed a new $PRS_{reported\ MTAG}$ for self-reported PA using UK Biobank GWAS for "number of days/week of moderate PA 10+ minutes") and for "number of days/week of vigorous PA 10+ minutes" (N=321,533) as another set of summary statistics to estimate the genetic correlation between these two PA measures and used it to obtain the new multi-trait analysis of GWAS (MTAG)-estimated effect sizes for PRS calculation (1). The new effective sample size for this new GWAS estimated by MTAG was 352,429. MTAG analyses were ran using Complex-Traits Genetics Virtual Lab –platform (Complex-Traits Genetics Virtual Lab (CTG-VL) — https://genoma.io).

Results: Compared to the $PRS_{reported}$ (as also reported also in our manuscript) constructed on the basis of the self-reported "number of days/week of moderate PA 10+ minutes" question, the new $PRS_{reported,\ MTAG}$ accounted for slightly higher variation (ΔR^2 0.32% vs. 0.25%) in the reported daily MET score in FTC (Supplemental Table 2).

Reference

1. Turley P, Walters RK, Maghzian O, et al. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nature Genetics.* 2018;50(2):229-237.

Supplemental Table 2. Associations between PRSs constructed on the basis of reported PA variables in UK Biobank and reported daily MET score in FTC.

Variables	β (SE)*	*P**	R^2% (95% CI)†	ΔR^2%‡	N
PRS for number of days/week of moderate PA 10+ minutes (variable 884) in UK Biobank ($PRS_{reported\ moderate\ activity}$)					
Reported daily MET score in FTC	0.1717 (0.0323)	<0.0001	5.38 (4.50-6.25)	0.25	11,528
PRS for number of days/week of vigorous PA 10+ minutes (variable 904) in UK Biobank ($PRS_{reported\ vigorous\ activity}$)					
Reported daily MET score in FTC	0.1924 (0.0321)	<0.0001	5.40 (4.56-6.33)	0.03	11,528
PRS for reported moderate and vigorous PA 10+ minutes ($PRS_{reported\ MTAG}$)					
Reported daily MET score in FTC	0.1934 (0.0323)	<0.0001	5.45 (4.55-6.34)	0.32	11,528

PRS; polygenic risk score.
*Effect and *P* value adjusted for age, sex and 4 genetic principal components.
†Variation accounted for by age, sex and the PRS with family number as random effect of the linear mixed model in FTC.
‡ΔR^2 = difference of R-squared between models with and without PRS included.