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ABSTRACT

Purpose: Hand grip strength (HGS) is a widely used indicator of overall muscle strength and general health. We computed a polygenic risk score (PRS) for HGS, and examined, whether it predicted muscle strength, functional capacity and disability outcomes. **Methods:** Genome-wide association study summary statistics for HGS from the Pan-UK Biobank was utilized. PRSs were calculated in the Finnish Twin Study on Aging (N=429 women, 63–76 years). Strength tests included HGS, isometric knee extension, and ankle plantar flexion strength. Functional capacity was examined with the Timed Up and Go, six-minute and 10-meter walk tests, and dual-task tests. Disabilities in the basic (ADL) and instrumental activities of daily living (IADL) were investigated with questionnaires. The proportion of variation in outcomes accounted for by PRS HGS was examined using linear mixed models and extended logistic regression. **Results:** The measured HGS increased linearly over increasing PRS (β 4.8, SE 0.93, $P<0.001$). PRS HGS independently accounted for 6.1% of the variation in the measured HGS (β 14.2, SE 3.1, $P<0.001$), 5.4% of the variation in knee extension strength (β 19.6, SE 4.7, $P<0.001$), 1.2% of the variation in ankle plantar flexion strength (β 9.4, SE 4.2, $P=0.027$), and 0.1%–1.5% of the variation in functional capacity tests (P range 0.016–0.133). Further, participants with higher PRS HGS were less likely to have ADL/IADL disabilities (OR range 0.74–076). **Conclusions:** Older women with genetic risk for low muscle strength were significantly weaker than those with genetic susceptibility for high muscle strength. PRS HGS was also systematically associated with overall muscle strength and proximal and distal functional outcomes that require muscle strength.

Key Words: GENETICS, HERITABILITY, HAND STRENGTH, PHYSICAL CAPACITY, AGING

INTRODUCTION

Loss of muscle mass and strength is an inevitable part of the aging process and affected by interactions with genetic susceptibility and environmental and lifestyle factors. Muscle strength decreases gradually by1%–2% each year after 50 years of age, and this decline is associated with increased risk for chronic metabolic and musculoskeletal diseases and frailty. Further, low muscle strength is associated with increased risk for physical decline, traumatic events such as injuries and fractures, disability, loss of independence, and premature mortality (1).

Hand grip strength (HGS) is a strong predictor of adverse age-related health outcomes and a useful indicator of general health status, overall morbidities, all-cause mortality, and exceptional survival (2–4). It has been shown that HGS is a more capable single marker of frailty than chronological age (5) and that it is significantly associated with sarcopenia (1). Because changes in HGS across the life span imitate the changes in skeletal muscle mass and strength that occur over time, HGS is a widely used proxy of overall muscle strength and fitness (2). Although some studies have questioned its relationship to the strength of the lower extremities (6, 7), HGS seems to correlate with it strongly, especially knee extensor strength (8). In addition, it has been found that HGS correlates with both elbow flexion and trunk extension strength (9, 10) underlining shared physiological background. Research has also shown that HGS predicts mobility and balance disorders (11–13), fracture risk (14), difficulties performing the activities of daily living (15), and decreased engagement in social and leisure activities (16). As a convenient measure, HGS is commonly used in large-cohort studies, and it is the only measure of muscle strength available in some large biobanks, such as the UK Biobank (17).

According to twin studies, HGS is a moderately heritable phenotype (h^2=30–65%) (18). It has been shown that the heritability of HGS remains stable across the life span (19), but the candidate gene approaches have been able to identify only a few statistically significant hits, and studies have often failed to replicate these findings. Several genome-wide association studies (GWAS) have investigated the genetic determinants of variation in HGS (20–22). The largest one (21) (N=195,180) identified 16 statistically significant loci ($P<5x10^{-8}$). In the same study, common genetic variants (single-nucleotide polymorphisms, SNPs) accounted for 23.9% of variation in HGS – this measure is known as the SNP heritability. In the absence of variants with a major impact on HGS, the genetic background can be considered to be polygenic.

A polygenic risk score (PRS) estimates an individual's genetic liability to a trait or disease. It summarizes genome-wide genotype data as a single score based on the variation in multiple genetic loci and their associated effect-size weights. Thus, the use of PRSs is considered an effective method for predicting genetic variation in complex polygenic and omnigenic traits, that is, traits associated with hundreds or thousands of genetic variants each of which has a small effect size (23). PRSs can be used to investigate gene–environment interactions and to identify persons who are at high risk for certain clinical outcomes (24). In addition, according to a recent study of PRSs for physical activity (25), PRSs can act as proxies for phenotypes that have not been measured if the analysis dataset contains genome-wide genotypes. Studies have already determined PRSs for multiple common chronic diseases (24) and for physical activity (26). To the best of our knowledge, no epidemiological study has used a PRS for muscle strength.

A study that applied multivariate quantitative genetic analysis to older Finnish female twins suggested that some individuals might be genetically more susceptible to low muscle strength and thereby at increased risk for disability in old age (9). Building on that observation, the present study uses molecular genetic data and had three aims: (1) to construct and validate a PRS for hand grip strength (PRS HGS), (2) to test whether PRS HGS predicts the strength measurements of other muscle groups, and (3) to test whether genetic risk for low muscle strength associates with several measures of functional capacity and with disabilities in the basic activities of daily living (ADL) and instrumental activities of daily living (IADL) in older Finnish twin sisters.

METHODS

Study design

We used open GWAS summary statistics for HGS from the Pan-UK Biobank (27) to construct PRS for HGS. Validation of PRS HGS and predictive value for the other strength measurements as well as associations with functional test results and ADL, and IADL disabilities were analyzed in the *Finnish Twin Study on Aging (FITSA)* cohort (9).

Participants

GWAS summary statistics from the Pan-UK Biobank (27) are based on genetic and phenotypic data from the UK Biobank, collected between 2006 and 2010, on nearly 500,000 members of the general UK population aged 40–69 years (17). HGS data were available for 482,074 individuals and were restricted to European ancestry (N=418,827) for PRS calculation. In the UK Biobank, maximal isometric HGS was measured using a calibrated hydraulic hand dynamometer (Jamar J00105, Lafayette Instrument Company, IN, USA). Additional details about these measurements

can be found in the UK Biobank online protocol (28). All the participants provided written consent. The North West Multi-Centre Research Ethics Committee approved the UK Biobank study.

The *Finnish Twin Study on Aging (FITSA)* investigated the role of the genetic and environmental factors in the disablement process (9). Only older women were recruited, because women are at a greater risk for disability and constantly underrepresented in health studies (29). The data were collected at the Gerontology Research Center in Jyväskylä, Finland, and the participants were recruited from the older Finnish Twin Cohort study (30) including both monozygotic (MZ) and dizygotic (DZ) twin pairs. The recruitment process has been described in detail elsewhere (9). Genetic data were available for 429 twin individuals (98 MZ and 114 DZ full twin pairs, and 5 MZ individuals) aged 63–76 years, and all of these participants had undergone HGS measurements. Before the laboratory examinations, the participants were informed about the study, and their written consent was obtained. The FITSA data collection was approved by the ethics committee of the Central Hospital District of Central Finland (KSSHP 24/2000). The studies were conducted in accordance with the Declaration of Helsinki.

Muscle strength tests

The *maximal isometric muscle strength* measurements were performed on each participant's dominant side in a sitting position using an adjustable dynamometer chair (Good Strength, Metitur, Palokka, Finland). After familiarization, the subjects performed three to five maximal efforts, separated by a one-minute rest. For each subject, the best performance with the highest value was accepted as the result. *HGS (N)* was measured using an isometric dynamometer fixed to the arm of the chair with the elbow flexed at 90°. *Knee extension strength (N)* was measured at a knee

angle of 60° from full extension, with the ankle fastened by a belt to a strain-gauge system. For the *ankle plantar flexion strength (N)* measurement, the ankle was set at an angle of 90° and fastened by a belt to a strain-gauge system. The leg was elevated to a horizontal position, and the knee was set at an angle of 20° from full extension. Among the participants, 403 had knee extension strength results and 391 had ankle plantar flexion strength results.

Functional capacity

The *Timed Up and Go (TUG) test (s)* measured the time it took participants to rise from a chair, walk 3 m at a normal pace, turn around, walk back to the chair, and sit down again. The participants were verbally and visually instructed. Each participant performed the test twice, and the faster performance was recorded as the result. In the *six-minute walk test (m)*, the participants were instructed to walk on a straight 50-m indoor track back and forth as fast as possible for six minutes. The distance (m) covered in that time was recorded. A standardized protocol and safety guidelines issued by the American Thoracic Society (31) were followed. The *10-meter walk test (s)* recorded the time it took participants to walk 10 m using a Digitest-1000 amplifier-time measurement system (Digi Test-1000; Digitest Ltd., Muurame, Finland). Photocells were placed 71 cm from ground level in the laboratory corridor, and 3 m were allowed for acceleration. The test was conducted twice for each participant, and the faster performance was documented as the result. Tests for dual-task performance during gait performance were conducted in the same way as the10-meter walk test, but a second task, such as carrying a glass full of water (manual task) or a verbal task, was added. To quantify the dual-task ability of the subjects, *dual-task cost*, that is, the effect of a second task on walking time, was calculated as the difference in time between walking with and walking without the second task (32). In all the walk tests, the participants were instructed to

walk as fast as possible without compromising their safety. Most of the participants had results for the TUG test (N=421), for the 10-meter walk test (N=414) and for the dual-tasks (N=410–411). 355 participants had results for the six-minute walk test.

Disabilities in basic and instrumental activities of daily living

ADL disabilities, such as difficulties in dressing, bathing, and toileting, and *IADL disabilities*, such as difficulties in light and heavy household work, were assessed through a self-reported, structured questionnaire. Participants were asked to assess their independence in ADL and IADL tasks with a 4-point Likert scale ranging from 0 (no difficulties) to 3 (need help/unable to perform). Due to small frequencies in the two last response categories, a dichotomous variable was created; it had a value 0 if the participant did not report any difficulties and a value of 1 if the participant reported difficulties, needed help, or was unable to perform the task. Four variables with the highest frequency of disabilities were included in the analysis. Responses regarding ADL and IADL disabilities were missing for two individuals (N=427). Missing data were related to various health problems, equipment failures, and other reasons. All maximal efforts were included into analyses, data did not include outliers. More detailed information about FITSA measurements has been provided elsewhere (9, 33–35).

Genotyping, quality control, and imputation

In the UK Biobank study, genome-wide genotyping was performed using the UK Biobank Axiom Array. It includes coding variants across a range of minor allele frequencies (MAFs), including both rare markers (<1% MAF) and markers that provide good genome-wide coverage for imputation in European populations in the common (>5%) and low-frequency (1%–5%) MAF

ranges. Details of genotyping, quality control, and imputation for the UK Biobank study and the FITSA are presented in the UK Biobank documentation (17, 28) and in our previous study (26), respectively.

PRS calculation

Detailed description of PRS HGS calculation pipeline and commands is presented in Supplemental Digital Content 1 (http://links.lww.com/MSS/C655). To obtain polygenic risk scores from existing Pan-UK Biobank GWAS summary statistics (27) we implemented a method based on weighting GWAS summary statistics using linkage disequilibrium (LD) reference panel (SBayesR) (36). The methodology is based on Bayesian multiple regression models and it extends standard linear-mixed models by re-scaling the GWAS SNPs effect estimates using a mixture of four alternative genetic effort distributions as the prior (36, 37). SBayesR has better prediction accuracy over other commonly used summary statistic-based methods (37) and it also allows to calculate SNP-h2 simultaneously. According to Lloyd-Jones et al. (2019), SBayesR methodology produces optimal estimates of weights when the reference panel consists of mostly same samples which have been usen in original GWAS. Therefore, we used a sparse LD matrix generated by SBayesR authors, constructed from random sample of 50,000 UK Biobank individuals. In this study, we restricted the variants to ~1.1 million HapMap3 (38) SNPs (excluding major histocompatibility complex region from chromosome 6 (6p22.1-21.3)), which are common (MAF >5%) in European samples. These variants are likely well imputed and represent the whole genome while the restriction reduces the computational burden when handling the whole genome at once. A total 418,827 of individuals and 1,006,473 variants were used for PRS calculation. PRS HGS was computed as a sum of risk alleles weighted by the risk allele effect sizes to the FITSA dataset.

Missing heritability

Missing heritability, that is, the number of heritable factors that cannot be measured with SNPs included in PRS HGS, was investigated using the GCTA-GREML method following Zaitlen et al. (39) and Yang et al. (40). The heritabilities were calculated using two genetic-relatedness matrices; the first took into account only the heritability caused by family structure, and the second took into account only the heritability explained by SNP genotypes. The difference between these two heritabilities is called missing (or hidden) heritability (39). In addition, SNP-based heritability for the Pan-UK Biobank HGS measures was derived by LD score regression and was restricted to the European HapMap3 (38) variants, as in the PRS calculations. Quantitative genetic estimates of heritability using a twin design have been published earlier in the FITSA (9).

Associations between PRS HGS and outcomes

Distribution of PRS HGS in the FITSA cohort is shown in Supplemental Figure 1 (see Supplemental Digital Content 2, http://links.lww.com/MSS/C656). Individuals were divided into PRS deciles to illustrate the linear association between PRS HGS and HGS. The association between PRS HGS deciles and measured HGS was analyzed using linear regression. The proportion of variation in measured muscle strength and functional-capacity outcomes accounted for by PRS HGS was examined using linear mixed models. For linear mixed modeling, the PRS value was scaled to obtain standardized normal distribution, with a mean of zero and a standard deviation (SD) of 1. The model predictors included age, 10 genetic principal components, and PRS HGS. Genetic principal components (PCs) were used to adjust for potential population stratification which may occur in Finnish sample due to bottleneck effect and genetic drift of the initial Finnish population (41, 42). 10 PC's were generated from the underlying FITSA SNP

genotypes using the PLINK software (43). Adjusting for PC's minimizes the possible confounding caused by any geographical strata in the data. The within-pair dependency was accounted for by using the family identifier as the random effect in all the models. The results are reported as the proportion of total variation in outcomes explained by the model (R^2) and as the change in R^2 (ΔR^2) when PRS HGS was included in the model after the other predictors. Extended logistic regression models were used to examine the association of PRS HGS with ADL and IADL disabilities. The level of significance was set at $P \leq 0.05$.

RESULTS

The FITSA participants' baseline characteristics are presented in Table 1. The participants were older women with a mean age of 68.6 years, and their BMI was 27.9 kg/m^2 (±4.7). Most of them (83.7%) had never been smokers, and the prevalence of chronic diseases was relatively low. The frequencies and percentages for ADL and IADL disability variables are presented in Supplemental Table 1 (see Supplemental Digital Content 3, http://links.lww.com/MSS/C657).

The measured HGS increased linearly over PRS HGS deciles in the FITSA (R^2 0.058, β 4.774, SE 0.93, $P < 0.001$) (Figure 1). The mean HGS in the highest and lowest PRS deciles was 204 N and 161 N, respectively.

The heritability calculated using the PRS gene variants (SNP-h^2, 21.2%) was approximately half of the heritability estimated using the GCTA-GREML method and pedigree-based analysis (41.7%) (Table 2); thus, the amount of missing heritability was 20.6%. The high value was obtained from SNP-h2 GCT-analysis, but due to the small sample size, the statistical power of the analysis was low. The value for SNP-based heritability obtained with LD score

regression from the Pan-UK Biobank HGS association results was 11.7% (SE 0.004, 95% CI [0.109, 0.125]).

PRS HGS independently accounted for 6.1% of the variation (ΔR^2) in the measured HGS in the FITSA cohort (Table 3). PRS HGS explained 5.4% of the variation in knee extension strength and 1.2% of the variation in ankle plantar flexion strength. Regarding functional capacity, PRS HGS explained 1.5% of the variation in the TUG test and 1.1% of the variation in the 10-meter walk test. PRS HGS hardly explained the variation (0.1%) in the six-minute walk test. In addition, PRS HGS explained 1.4% of the variation in dual-task cost in the 10-meter walk test with a verbal task but less so of the variation in dual-task cost in the 10-meter walk test with a manual task (0.7%).

As PRS HGS increased, the odds of ADL and IADL disabilities in opening a jar (OR 0.74, 95% CI [0.57, 0.97]), cutting toenails (OR 0.75, 95% CI [0.57, 1.0]), and heavy household work (OR 0.76, 95% CI [0.57, 1.0]) decreased. No association of PRS HGS with rising from a chair was seen (OR 0.98, 95% CI [0.69, 1.39]).

DISCUSSION

The purpose of this study was to construct and validate a polygenic risk score for hand grip strength (PRS HGS) and to test whether this score predicts proximal and distal functional-capacity outcomes in older people. Our study shows that PRS HGS statistics derived from Pan-UK Biobank data predicts variation both in HGS and in lower limb muscle strength almost to a similar extent.

The results suggest that genetic inheritance of muscle strength could be a noteworthy predictor of functional capacity and future disabilities among older Finnish women.

HGS is a complex polygenic trait, and the score used in our study summarizes the variation of over one million genetic variants. In this study, PRS HGS independently accounted for 6.1% of the variation in HGS. The amount of variation in measured HGS explained by PRS HGS is significantly larger than that explained by previous genetic methods (44) and about five times more than the variation explained by chronological age. Hence, PRS HGS seems to have a relatively high predictive value compared to other PRSs for physical-activity-related traits. For example, in a recent study, we found that two PRSs for physical activity explained only 0.07%–1.4% of the variation in different physical activity phenotypes (26). In the present study, we used a recently developed SBayesR method (36) to derive PRS HGS. This method has proven more powerful than other commonly used methods for computing PRS scores (37). Compared to other physical-activity and function-related measurements, HGS is also easier to standardize, which may explain its good predictive value across cohorts.

Whether HGS can be used as a proxy of overall muscle strength is under debate (2, 6, 7) but at least some of the genetic variance is shared. The multivariate genetic analysis in a previous study suggested that HGS and knee extensor strength are explained by shared genetic factors accounting for 14% of the variance in HGS in the FITSA cohort (9). In this study we observed that PRS HGS predicted the variation in isometric knee extension strength almost to the same extent as for HGS (5.4% vs. 6.1%) but that its predictive value for ankle plantar flexion strength was lower, which may have been caused in part by practical difficulties in standardizing the maximal

strength effort for this task (9). However, in our study, the proportion of variance in measured strength of lower extremities explained by PRS HGS was rather large, indicating that PRS HGS may be a useful tool for addressing certain issues in future research, such as controlling for underlying genetics. The genetic variants identified by large-scale HGS GWAS associates with the structure and function of skeletal muscle fibers and with central and peripheral neural regulation (21). These mechanisms are shared and essential in all muscle force production and support our conclusion that PRS HGS can be considered as an overall genetic predictor of muscle strength.

In our study, we determined SNP heritability, which indicates the extent to which measured genetic variants affect phenotypic variation (44) and because we had twin data available, we were also able to compare this heritability estimate to pedigree based h^2. SNP heritability was calculated using SNPs that were included in the PRS HGS. These SNPs accounted for 21% of the variation in measured HGS, which is larger than observed for many traits and diseases. The pedigree-based heritability observed in our study (h^2=42%) is in line with several family-based studies (18) that have suggested rather high heritability (h^2=30–65%) for HGS. However, it must be noted that our sample size was small for heritability calculations in the FITSA cohort. Despite the rapid development of designs and methodology in polygenic scoring methods, PRSs still have a limited ability to capture full genetic loading for diseases or traits at the same level compared to genetic variance estimated from family-based studies. It has been suggested that the difference between SNP and pedigree-based heritabilities, that is, missing heritability, originates from a failure to identify common variants with small effect sizes or due to rare variants, copy number variants and structural variants, gene–environment interactions, or insufficient sample size (39, 40, 44). In

addition, SNP-based heritability estimates should be unbiased, such that increases in sample size impact only the precision (i.e., the standard error of the estimates decreases with increasing sample size) (39, 44). On the other hand, some researchers have pointed out that it is also possible that classical twin studies have overestimated heritability, due to genetic interactions, gene–environment interactions, or of the twin studies assumptions about the equal environment, suggesting less heritability actually is missing (44).

Compared to men, women are at a greater risk for living with disabilities due to their longer life expectancy and generally lower muscle strength. To successfully prolong the duration of a healthy and disability-free life, it is important to identify the factors that may act as barriers to achieving the goal. Muscle strength has a specific role being one of the key components of functional capacity (1). In addition, muscle strength may represent a physiological reserve in later life (45). Although the FITSA participants were relatively healthy and reported low levels of ADL and IADL disabilities, lower PRS HGS seemed to increase the risk of disabilities in opening a jar, cutting one's toenails, and heavy household work. At the hierarchical level, heavy household work requires more functional capability than do other IADLs and ADLs, and it is generally one of the first abilities to be lost, as well as the abilities requiring manual dexterity, such as cutting one's toenails. Difficulties in opening a jar may indicate a weak HGS, and all these tasks may predict a decline in ADL and IADL abilities at the next stage (46). We also found that PRS HGS accounted for 1.1% –1.5% of the variation in functional capacity tests, such as the TUG and the 10-meter walk test, which require a good level of muscle strength and are well-known predictors of disability (1, 47). The results are in line with previous findings which showed that genetics effects are common to strength, power and maximal walking speed in older women (48). Our results confirm

that muscle strength, functional capacity, and ADL and IADL disabilities are partly regulated by the same genetic background, which supports the potential role of PRS HGS as a predictor of functional limitations and disability.

Performing a dual-task test requires attentional and cognitive resources. A previous study showed that in a test with a verbal task, walking speed is partially explained by test-specific genetic influences among older women (33). In the present study, PRS HGS accounted for 1.4% of the variance in assessing dual-task cost during the 10-meter walk test with a verbal task, which may indicate that HGS plays an important role in cognitive-function decline. This may be explained by the previous finding that part of the variants explaining the maximum HGS are located within or close to genes implicated in neuronal maintenance, and signal transduction in the central and peripheral nervous systems or are associated with genes implicating in psychomotor impairments (21).

The HGS measurements differed between participants in the UK Biobank study and those in the FITSA. In the Pan-UK Biobank HGS measurements were conducted with the right hand, whereas in the FITSA HGS was measured from the dominant side. However, consistent with calculations of the Neale Lab (49), differences between left and right HGS SNP heritabilities were not found in our analysis (data not shown). Hence, there was no need to account for handedness in the analysis. The reliability of the HGS measurement can be influenced by equipment, body posture, joint position as well as introductions and encouragement, density and duration of testing, time of day, and training of the assessor (50). In the UK Biobank study, HGS was measured with the Jamar hand dynamometer, whereas in the FITSA, it was measured with an isometric

dynamometer in a dynamometric chair. The measurements were performed in a similar body and joint position and a standardized protocol was followed in both studies. Despite the differences in the equipment used in these two studies, PRS HGS seemed to be a robust predictor of HGS across the various protocols.

In addition to measurement protocols, for example age, sex, presence of chronic diseases, lifestyle and environmental factors, and socioeconomic status may be sources of bias by affecting variation in HGS and functional phenotypes (1, 24). In HGS, mean absolute values are generally higher in men than in women, and men tend to have better results than women in most functional-capacity measurements (51). Women and men differ also in terms of age-related decline in muscle strength. In men, HGS decline after midlife is steeper than in women, but the differences in slope narrow slightly with age (19, 52, 53). Differences in age-related trajectories have been assumed to originate from gender-specific patterns in the environmental factors (54), but twin studies have also suggested that genetic components exhibit differences with age. It has been observed that the heritability of HGS is higher in men than in women (19), and the difference seems to be relatively constant across the life span (19, 53). The studies that have investigated sex-differences in genetic determinants of the HGS, have found that although the effects of individual genetic variants on HGS do not differ between sexes, the genetic score summarizing 16 SNPs has shown to be stronger predictor of phenotype in men than in women (21). However, the role of sex-specific genetic variants in genetic architecture of human traits has shown to be in general small (55, 56). In the future sex-stratified GWASs may increase understanding of sexual dimorphism in the autosomal level. Gene by sex interactions may also be more relevant in the context of common diseases than in HGS (56). The Pan-UKBB GWAS that we used for summary statistics was adjusted for age and

sex. Thus, based our current knowledge, the PRS HGS calculated in this study can be used to investigate genetic impacts of the muscle strength on the phenotype level both men and women in the further studies. However, in this study, the FITSA participants in our association sample were older women, which limits the generalizability of our association results.

Last, the predictive value of PRS is dependent on genetic ancestry and other participant characteristics in the original GWAS, and differences in cohort characteristics may limit portability across groups of different genetic ancestries (23, 24). In this study, the GWAS summary statistics derived from Pan-UK Biobank data were restricted to European ancestry. Although the Finnish population differs from that of other Europeans in terms of the frequency of less common and rare variants due to genetic isolation and bottlenecks, the Finnish population is highly comparable to other European populations with respect to common variants (41). In both datasets, the participants were volunteers; thus, the samples may represent individuals who were healthier than people of the same age from the general population (57). Missing data, potentially caused by worse health, can lead to biased results among studies conducted in older participants. In this study, missing data ranged from 2% to 9% and was mainly due to equipment or measurement failure, or other reasons such as scheduling problems. The most missing data were in the six-minute walk test (17%), where the missing values occurred primarily because of contraindications determined by the study physician who then recommended not to do the test. However, in case of our analyses, missingness due to poor health will most likely decline the statistical power of the analysis because of smaller variation in test results. The actual association between PRS HGS and functional capacity could be stronger had all those with worse health been able to take part. Overall, PRS HGS seemed to have a good predictive value in the Finnish population, probably because measurement validation

is rather easy and because HGS, compared to other measures of human performance, is less influenced by health behaviors such as physical activity.

CONCLUSIONS

PRS HGS seems to be a useful predictor of muscle strength and functional capacity among older women. After careful validation using larger cohorts that include both men and women of different ages, PRS HGS could be used to expand our understanding of how genetic inheritance of muscle strength is associated with adverse age-related outcomes and whether inherited muscle strength predicts survival after adverse health events. Knowledge about genetic susceptibility could also be used to improve personalized risk prediction with regard to functional limitations and to identify individuals who would benefit from targeted therapies.

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The funders were not involved in the study design, the collection, analysis, or interpretation of the data, or the publication process. The authors have no conflicts of interest to report. All the authors declare that the results of the study are presented clearly and honestly and without fabrication, falsification, or inappropriate data manipulation. The results of the study do not constitute endorsement by the American College of Sports Medicine.

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FIGURE LEGENDS

Figure 1. Association between a polygenic score for hand grip strength (PRS HGS) deciles and measured hand grip strength (HGS). Fitted values from a linear regression of HGS on PRS HGS deciles.

SUPPLEMENTAL DIGITAL CONTENT

SDC 1: Supplemental Digital Content 1. docx - Description of PRS HGS pipeline and commands

SDC 2: Supplemental Digital Content 2. eps - Figure 1. Histogram of PRS HGS with overlaid density plot

SDC 3: Supplemental Digital Content 3. Docx - Table 1. Proportion of women reporting ADL and IADL disabilities in the FITSA cohort.

Figure 1

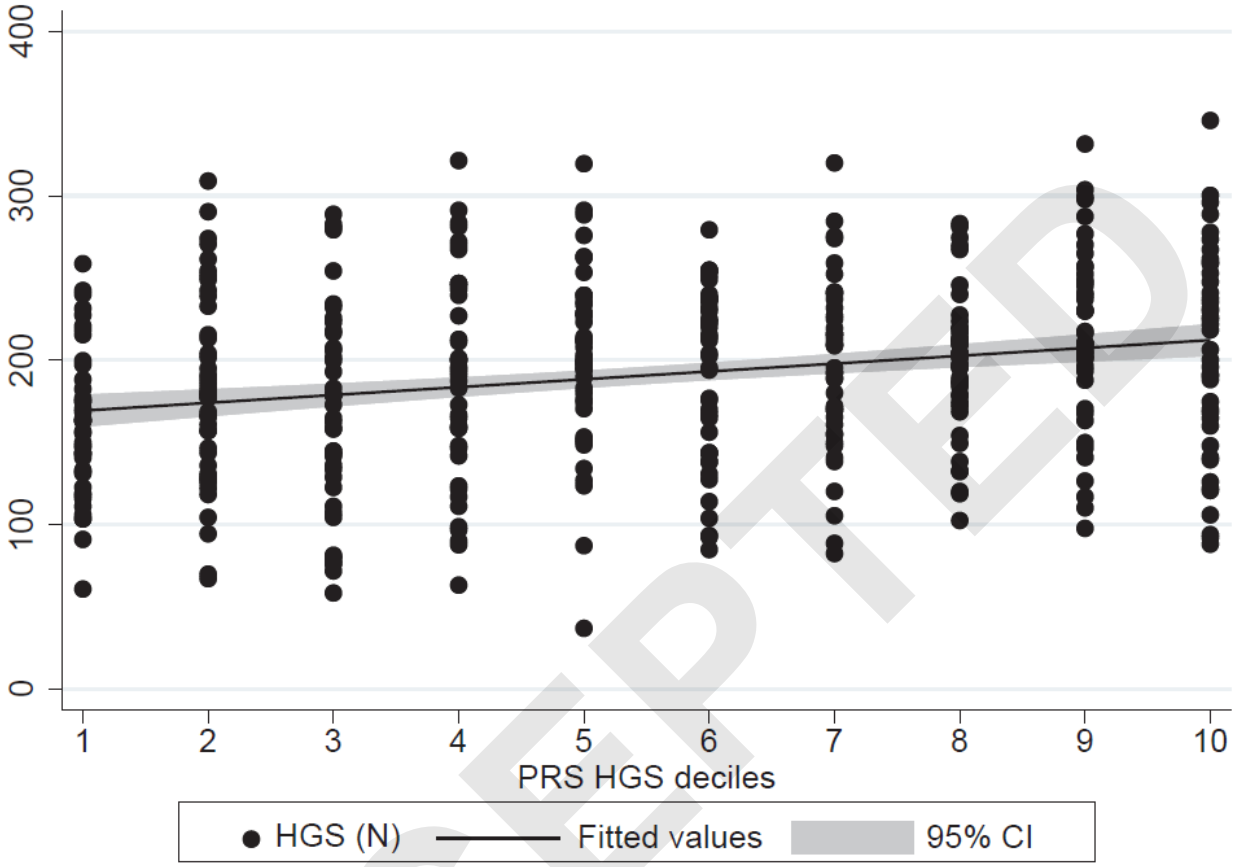

TABLE 1. Characteristics and functional capacity outcomes in the FITSA cohort.

	n (%)	mean (SD)	N
Age (y)		68.6 (3.4)	429
Body mass index (kg/m^2)		27.9 (4.7)	429
Never smoker	359 (83.7)		409
Selected diseases			429
Coronary heart disease	52 (12.1)		
Heart failure	45 (10.5)		
Myocardial infarction	16 (3.7)		
Hypertension	182 (42.4)		
Stroke	11 (2.6)		
Claudication	19 (4.4)		
Type 2 diabetes	25 (5.8)		
Isometric muscle strength (Newtons)			
Hand grip strength		190.7 (57.1)	429
Knee extension strength		292.8 (83.1)	403
Ankle plantar flexion strength		218.8 (83.8)	391
Functional capacity tests			
Timed Up and Go (s)		9.3 (1.9)	421
Six-minute walk (m)		529.7 (7.57)	355
10-meter walk (s)		6.0 (1.3)	414
10-meter walk with manual task (s)		6.8 (1.4)	411
10-meter walk with verbal task (s)		7.7 (1.9)	410

FITSA=Finnish twin study on aging, SD=standard deviation.

TABLE 2. Pedigree, SNP, and missing heritability in the FITSA cohort.

Variable	**Pedigree- h^2**	**SNP-h^2**	**Missing Heritability (Pedigree-SNP-h^2)**
Hand grip strength	*0.417 (SE 0.070)* *95% CI [0.280, 0.551]*	0.212 (SE 0.715) 95% CI [-1.19, 1.61]	0.206 (SE 0.717) 95% CI [-1.21, 1.61]

SNP=single-nucleotide polymorphism, FITSA=Finnish Twin Study on Aging, h^2= heritability. See methods for details of estimation.

TABLE 3. Associations between a polygenic score for hand grip strength (PRS HGS) and isometric muscle strength and functional capacity in the FITSA cohort.

	zPRS HGS			Full model			
	beta	SE	*P*	R^2 (%)	*P*	ΔR^2 (%)	N
Isometric muscle strength							
Hand grip strength (N)	14.159	3.062	**<0.001**	9.4	**0.002**	6.1	429
Knee extension strength (N)	19.573	4.672	**<0.001**	13.2	**0.001**	5.4	403
Ankle plantar flexion strength (N)	9.352	4.203	**0.027**	7.4	**0.022**	1.2	391
Functional capacity							
Timed Up and Go (s)	- 0.238	0.099	**0.017**	7.1	**0.015**	1.5	421
Six-minute walk (m)	1.783	4.464	0.069	8.2	**0.050**	0.1	355
10-meter walk (s)	- 0.141	0.073	0.055	8.6	**0.001**	1.1	414
Dual-task cost with manual task (s)	- 0.055	0.036	0.133	3.5	0.379	0.7	411
Dual-task cost with verbal task (s)	- 0.147	0.061	**0.016**	6.0	0.057	1.4	410

Note: Results are shown for the full model including zPRS HGS as a predictor and adjusted for age and 10 principal genetic components. Family number was included in the models as a random factor. ΔR^2 describes difference in coefficient of determination (R^2) between adjusted model with and without PRS HGS. Bold type indicates statistical significance at the level of $P \leq .05$. z=standardized for normal distribution, FITSA=Finnish Twin Study on Aging, SE=standard error.

Description of PRS HGS pipeline and commands

Methods

SBayesR summary statistics methodology (1) was used in the GCTB software (2) to derive PRSs from Pan-UK Biobank (Pan-UKBB) GWAS summary statistics (3). This methodology is based on a Bayesian multiple regression models likelihood and the sparse reference linkage disequilibrium (LD) correlation matrix, presuming GWAS SNPs effects as a flexible mixture of four priors for normal distribution with different variances (1, 4, 5). For SBayesR, each distribution has mean of 0 and the variance is some product of the common marker effect variance σ_β^2 and the variance weight γ_c ,where γ_c = 0, 0.01, 0.1, 1. for c = 1, 2, 3, 4. SBayesR replaces LD clumping and p-value thresholding steps by taking into account of the joint effects of all SNPs, and no external tuning data is required (1). The sparse LD matrix generated by SBayesR authors (6) was built from 50,000 random individuals of UKBB cohort for HapMap3 (7) variants. SBayesR methodology produces optimal estimates of weights when the reference panel consists of mostly same samples which have been usen in original GWAS (1). PRS validation and association analysis were performed in the *Finnish Twin Study on Aging (FITSA)* cohort (8) with PLINK 1.9 software (9). All required datasets used for PRS HGS calculation is shown in Table 1.

Table 1. Datasets used in PRS HGS calculation

Dataset	Information available
Pan-UKBB GWAS summary statistics for HGS	https://pan.ukbb.broadinstitute.org/downloads
Sparse 50k LD matrix generated by SBayesR authors	https://zenodo.org/record/3350914
Genotype and phenotype data of the FITSA cohort	Tiainen et al. 2004
SNP list of ~1.1M HapMap3 SNPs (without MHC region)	https://ldsc.broadinstitute.org/

PRS HGS= Polygenic risk scores for hand grip strength, Pan-UKBB= Pan-UK Biobank, GWAS= Genome-wide association study, LD= linkage disequilibrium, FITSA= the Finnish Twin Study of Aging, SNP= single nucleotide polymorphism, MHC= The major histocompatibility complex

Genotyping, quality control, and imputation

The quality of the base and target data has a crucial impact to the statistical power and validity of the PRS (10). In this study, the quality of SNP variants had been confirmed in both used datasets. Details of genotyping, quality control, and imputation for the UK Biobank study and the FITSA are presented in the UK Biobank documentation (11, 12) and in our previous study (13), respectively. Briefly, in the FITSA cohort, genotype quality control was done in three batches. SNPs were excluded if call rate was less than 98% (batch1) or 95% (batch2 and batch3), minor allele frequency was less than 1%, and Hardy–Weinberg equilibrium (HWE) *P* value lower than 1×10^{-6}. Samples from all batches with heterozygosity test method-of-moments *F* coefficient estimate value less than −0.03 or higher than 0.05 (batch1 and batch2) or ±4 SD from the mean (batch3) were removed. Further, samples that failed sex check or were among the multidimensional scaling principal component analysis outliers were excluded. Genotyping imputation of all batches were performed using Haplotype Reference Consortium release 1.1 reference panel (14). Pan-UKBB summary statistics and the target study samples of the FITSA cohort were restricted to the European HapMap3 (7) variants with minor allele frequency >5% and excluding the major histocompatibility complex region from chromosome 6 (GRCh37: 6p22.1–21.3). HapMap3 SNPs set represents the whole genome as well as tends to be well

imputed for samples of European or Finnish ancestry and is used to reduce the computational burden in the genome-wide studies. A total of 418,776 European individuals and 1,006,473 variants were used for PRS calculation.

Extracting of Pan-UKBB GWAS summary statistics

Pre-existing GWAS summary statistics for right hand grip strength including both the per-phenotype and the variant manifest flat files were downloaded from Pan-UK Biobank (2). The per-phenotype file (phenocode 47) contained GWAS results, and the variant manifest file included information on each variant such as rs ids. Flat files were pasted and restricted to European samples (34,263,104 variants) in the local Linux Cluster. Selected fields from Pan-UKBB flat files used to extract the GWAS results are presented in the Table 2. Further, GWAS summary statistics were restricted to ~1.1 million HapMap3 (3) and filtering out variants with duplicate position. Finally, the GWAS summary statistics were transformed to input GCTA-COJO format required for the GCTB (4) by renaming the columns as follows: SNP identifier (SNP), the effect allele (A1), the other allele (A2), frequency of the effect allele (freq), effect size (b), standard error (se), p-value (p) and sample size (N) (Table 2). As a result, GWAS summary statistics text file in the GCTA-COJO format was created containing a total 1,006,473 variants.

Table 2. Selected fields from Pan-UKBB flat files to extract GWAS results

Fields		Meaning
in Pan-UKBB flat files	**in GCTA-COJO format**	
chr		chromosome of the variant
pos		position of the variant in GRCh37 coordinates
ref	A2	reference allele on the forward strand
alt	A1	alternate allele, used as effect allele for GWAS
af_EUR	freq	alternate allele frequency for European samples
beta_EUR	b	estimated effect size of alternate allele of European samples
se_EUR	se	estimated standard error of beta_EUR
pval_EUR	p	log p-value of beta_EUR significance test
rsid	SNP	reference SNP cluster id for the variant
	N	sample size

Pan-UKBB= Pan-UK Biobank, GWAS= Genome-wide association study, GCTA-COJO= Genome-wide Complex Trait Analysis - Conditional and Joint analysis

Calculating the re-weighted effect size estimates of summary statistics with the sparse LD matrix

The re-weighted effect sizes of summary statistics were computed using the downloaded sparse 50k LD matrix (6). First, the re-weighted effect size estimates by chromosome {1…22} were calculated in the local Linux Cluster using GCTB software (4). SBayesR commands and their meanings used for re-weighting calculation are presented in the Table 3. Detailed information of the commands can be found in GCTB-tutorial (4). The output out.snpRes files of posterior statistics of SNP effects of each chromosome were then concatenated to one dataset (ALL.snpRes) and extracted by the columns "Name" (rsid), "A1" (effect allele) and "A1Effect".

Table 3. GCTB commands and functions for the re-weight effect sizes calculation

Command	Function
--SBayes R	Specifies the Bayesian alphabet model
--ldm	Loads the LD matrix
--pi 0.95,0.02,0.02,0.01	Determines the number of components of a finite mixture of normal distribution
--gamma 0.0,0.01,0.1,1	Specifies the gamma values
--gwas-summary	Path to the GWAS summary statistics
--chain-length 10000	Specifies the total number of iterations in MCMC
--burn-in 2000	Specifies the number of iterations to be discarded
--out-freq 10	Displays the intermediate results for every 10 iterations

GCTB= Genome-wide Complex Trait Bayesian analysis, LD= linkage disequilibrium, MCMC= Monte Carlo Markov Chain

Calculating the individual polygenic risk scores

As well as summary statistics, the samples of the FITSA cohort were adapted in variant call format (vcf file) rsid as SNP identifier. Individual sum scores for the FITSA participants were calculated in the PLINK 1.9 software using commands presented in Table 4. Allelic scoring results were generated as an allele average in the plink.profile format.

Table 4. PLINK commands for polygenic risk scores calculation

Command	Function
--vcf	Extracts the variant call format information of the target genotype data
--double-id	Converts both family and within-family IDs to be set to the sample ID
--score	Performs allelic scoring, writes results to plink.profile

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Supplemental Digital Content 2

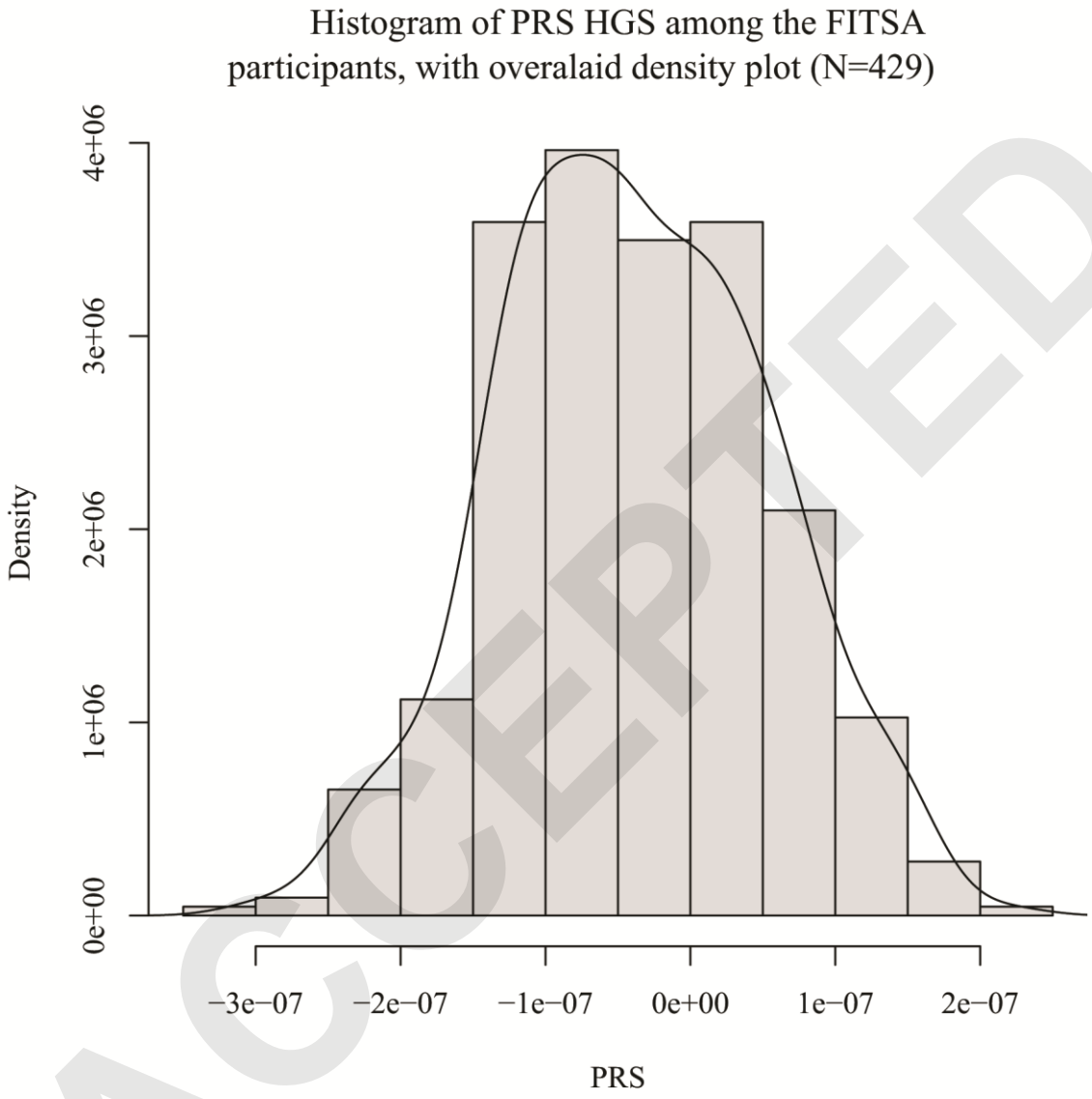

TABLE 1. Proportion of women reporting ADL and IADL disabilities in the FITSA cohort.

	n (%)	N
ADL disabilities (self-report)		
Opening a jar	170 (39.6)	429
Cutting toenails	147 (34.3)	429
Getting into/ out of bed	32 (7.5)	428
Bathing or showering	17 (4)	429
Toileting	6 (1.4)	429
Rising from a chair	70 (16.3)	429
Dressing	38 (8.9)	429
Eating	13 (3.0)	429
Transfers	18 (4.2)	429
IADL disabilities (self-report)		
Heavy household work	195 (45.0)	427
Opening a door with a key	19 (4.4)	429
Managing medication	7 (1.6)	429
Using a telephone	12 (2.8)	429
Preparing meals	23 (5.4)	429
Doing the laundry	25 (5.8)	429
Managing finances	18 (4.2)	428
Light household work	24 (5.6)	429

FITSA=Finnish twin study on aging, ADL= activities of daily living, IADL= instrumental activities of daily living.