RESEARCH PAPER

The phenotypic and genotypic association of grip strength with frailty, physical performance and functional limitations over time in older adults

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Abstract

Objectives: To replicate the phenotypic associations of grip strength with frailty, physical performance and functional limitations in older adults for longer follow-up periods and to examine whether these associations are due to shared genetic factors.
Methods: In total 2,262 participants 55 years and older with follow-up data up to 23 years ($N_{observations} = 8,262$) from the Longitudinal Aging Study Amsterdam were included. Weighted polygenic risk scores for grip strength (PRS-GS) were built using the genome-wide meta-analysis results from UK Biobank as reference. Grip strength was measured two times on each hand using a dynamometer. Frailty index (FI) and frailty phenotype were operationalised following standard procedures. Performance tests included a timed walk test, a repeated chair stands test and put on–take off cardigan test. Functional limitations were assessed using a questionnaire with six items.
Results: Higher grip strength was phenotypically associated with lower FI ($b = -0.013$, 95% CI (-0.016, -0.009)), better physical performance ($b = 0.040$, 95% CI (0.026, 0.054)) and less functional limitations (OR = 0.965, 95% CI (0.954, 0.977)) over time for follow-up periods up to 23 years. However, PRS-GS was not associated with any of the traits.
Conclusion: The phenotypic associations between grip strength, frailty, physical performance and functional limitations were replicated for follow-up periods up to 23 years. However, the associations between the traits could not be explained by shared genetics potentially indicating a more relevant involvement of non-genetic factors.

Keywords: polygenic risk score, grip strength, frailty, physical performance, functional limitations, older people

Key Points

- Higher grip strength was associated with lower frailty index, better physical performance and less functional limitations over long follow-up periods.
- Polygenic risk scores of grip strength were not associated with frailty, physical performance or functional limitations.
- The phenotypic association between the traits is mainly explained by non-genetic factors rather than shared genetics.

Introduction

Grip strength is an important indicator of physical functioning in old age and a predictor of morbidity and mortality [1–4]. It is associated with frailty, physical performance and functional limitations in older adults in cross-sectional [5, 6] and longitudinal studies [7]. Whether these phenotypic associations can be explained by shared genetic factors is not known, but may be likely. Exploring shared genetic factors between these traits can help shed light on the common aetiology and biological pathways involved as well as improve risk prediction and prevention of complex traits. To date grip strength is more used as a biomarker of the other conditions but the biological mechanisms of how it affects these traits remain unclear.

Grip strength is a complex trait with genetic heritability varying between 30 and 65% [8, 9]. The genetic architecture of grip strength is highly polygenic, characterised by multiple variants with small effect size scattered across the genome. The number of single-nucleotide polymorphisms (SNPs) associated with grip strength has increased from two in the first genome-wide association study (GWAS) [10], to 16 in a second GWAS [11], to 101 SNPs in the most recent GWAS [12] including 223,315 individuals from UK Biobank. Beyond these SNPs associated at stringent genome-wide significance level ($P = 5*10^{-8}$), modelling the joint additive effect of all measured SNPs explained between 13 and 24% in grip strengths variance (SNP-heritability) [11, 12], confirming the polygenic nature of the trait.

To date, there are no GWAS studies available for physical performance or functional limitations that would make it possible to pinpoint specific SNPs involved in all these traits. Also, GWAS studies on frailty are limited [13, 14]. The GWAS on frailty index (FI) from Atkins *et al*. [14] using data from UK Biobank and TwinGene study identified 14 loci, most of which were already known to be involved in traits like body mass index, cardiovascular diseases, depression, etc.

An alternative way to explore shared genetics between traits is by using polygenic risk scores (PRS) [15]. A PRS is a sum of all risk alleles associated with a trait (grip strength in this case) that takes into account the number of risk alleles and their effect estimates identified in previous GWAS studies. In the present study, we first aimed to replicate the phenotypic association between grip strength, frailty, physical performance and functional limitations in older adults measured over long follow-up periods up to 23 years. Then we used a PRS approach to test whether genetic variants that contribute to grip strength are also associated with frailty, physical performance and functional limitations over time in old age.

Methods

Data of the Longitudinal Aging Study Amsterdam (LASA) were used, an ongoing population-based cohort study of adults aged 55 years and older living in the Netherlands [16, 17]. The first cohort included 3,017 participants (55–84 years old) at baseline (1992–93) and two additional cohorts were added in 2002–03 and 2012–13 with, respectively, 1,002 and 1,023 participants (55–64 years old). Follow-up visits were conducted every 3 years and the follow-up period was 23, 13 and 3 years, respectively, for the first, second and third cohort. Trained interviewers collected data on cognitive, emotional, physical and social functioning during a home interview. Subsequently, all participants were invited for a medical interview during which further diagnostic examinations were done and blood samples were drawn.

The total sample in these analyses included 2,262 participants with 8,262 observations.

LASA has been approved by the Medical Ethics Committee of VU University Medical Center and all participants gave written informed consent.

Genotyping, quality control (QC) and imputation procedure are described in details elsewhere [18]. Genotyping was performed using the Axiom-NL array from Affymetrix (Avera Institute for Human Genetics, Sioux Falls, SD, USA) for 623 participants from cohort 1 and Infinium Global Screening Array-24 v.1.0 (GSA) from Illumina (Human Genomics Facility, Erasmus MC, Rotterdam, the Netherlands) for 1,779 participants from cohorts 1–3. Standard QC was performed and samples and SNPs that did not pass the QC were subsequently removed. Imputation was done with Minimac3 facilitated by the Michigan Imputation Server [19] using as reference the Haplotype Reference Consortium panel version 1.1 [20]. QC-ed, imputed data of non-related European-ancestry participants were available for 590 participants genotyped with Axiom-NL and 1,689 participants genotyped with GSA (cohort 1: $N = 491$, cohort 2: $N = 631$, cohort 3: $N = 567$).

Assessment of grip strength

Grip strength was assessed at baseline and follow-up visits during the medical interview using a grip strength dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd, Tokyo, Japan) from baseline for the first and second cohort until 2012. For the baseline of the third cohort and the follow-up measurements from 2012 onwards for all participants the Takei dynamometer was replaced with the JAMAR 5030J1 Hydraulic Hand Dynamometer, referred to as the gold standard in the literature [21]. Respondents performed two maximum grip strength trials per each hand, in standing position with arms along the body and grip strength was recorded to the nearest 1 kg. The average of both measurements in the right hand was used in line with the phenotype used in the GWAS from which the effect estimates for the genetic variants were derived. Participants who could not perform the test or refused to take the test were excluded from the analysis (<2%).

Assessment of frailty

The two most used tools to assess frailty are the frailty index (FI) and frailty phenotype (FP). FI is a widely used

frailty instrument. It involves the accumulation of diseases, symptoms, signs, disabilities or any deficiency in health with age, where more deficits indicate higher frailty. In LASA, the FI has been developed and validated by Hoogendijk *et al*. [22] according to the standard procedure described by Searle at al [23]. FI was measured at baseline and follow-up visits and was log-transformed to better fit normal distribution. FP was assessed at baseline only in a subgroup of participants at baseline using the Fried's criteria [24]: unintentional weight loss, muscle weakness, exhaustion, low gait speed and low physical activity [25]. Participants were considered frail if they fulfilled three or more criteria. Because of its components, FP is considered more a measurement of physical frailty contrary to FI, which includes cognitive and emotional items. However, since both measurements provide complementary information [26] they were both used in our analyses.

Assessment of physical performance

Performance tests were carried out at baseline and follow-up visits and included a timed walk test, a repeated chair stands test and a put on–take off cardigan test using a modified LASA protocol. For the walk test, participants were asked to walk 3 m, turn around and to walk back 3 m as quickly as possible. For the repeated chair stands, participants were asked to fold their arms across their chest and to stand up five times from a chair at usual pace. For testing the ability to put on and take off a cardigan, participants were asked to put on and take off a cardigan that was brought in by the interviewer [27, 28]. For all three tests the score ranged from 0 (unable to perform the test) to 4 (fastest quartile of time required doing the test). The scores of the three performance items were summed to a final score (range 0–12), where a lower score indicated a poorer physical performance.

Assessment of functional limitations

To assess functional limitations participants were asked if they could perform the following six activities without difficulty: walk up and down a staircase of 15 steps without resting, use public transportation without help, cut own toenails, dress and undress yourself, sit down and stand up from a chair and walk outside for 5 min without stopping [29]. The functional limitations variable counts the number of activities that are done with difficulty or cannot be done by the participant and ranges from 0 (has no difficulty with any activity) to 6 (has difficulties with all activities).

Polygenic risk scores

Ten polygenic risk scores for grip strength (PRS-GS) were built using as reference summary statistics from UK Biobank data (available at: http://www.nealelab.is/uk-biobank) following the method described by Purcell *et al*. [30]. *P*-value threshold for SNP inclusion varied between 5×10^{-8} and 1. A detailed description on how PRS-GS were built, the number of SNPs included for each threshold value and

the power calculations of the PRS-GS can be found in the Supplementary Methods and Table S1. PRS-GS were standardised (mean = 0, SD = 1) to help the interpretation of the scores.

Covariates

The following covariates were taken into account: age at baseline, sex and 10 ancestry-informative principal components (PC). PCs were generated from the genetic data and were included in the analysis to adjust for potential population stratification. Longitudinal analyses were also adjusted for the follow-up time.

Statistical analysis

Descriptive statistics of the baseline characteristics of the participants were assessed per cohort and per genotyping array (for the first cohort). We tested the phenotypic association between grip strength, FI, physical performance and functional limitations over time using Generalized Estimating Equations (GEE). Tuning of the PRS was performed by checking the proportion of variance in grip strength explained by each PRS-GS using linear regression in the group genotyped with the GSA array (largest group). The best performing PRS-GS was carried forward in subsequent analyses. The association of PRS-GS with FI, physical performance and functional limitations over time was tested using GEE. The associations of PRS-GS with FP and its components were tested using logistic regression. Models were adjusted for age, sex and PCs. The analyses were done separately per cohort (and per genotyping array for the first cohort). Then the results were pooled using variance weighting, random-effect meta-analysis in R with the meta package.

Analysis was performed using PLINK 1.9 [31], R software version 3.5.3 and SPSS Statistics for Windows, version 24 (IBM Corp.).

Results

Baseline sample characteristics per cohort and genotyping array are presented in Table 1. Participants in the first cohort were on average older, had lower grip strength and had more functional limitations (Table 1).

Phenotypically, higher grip strength was associated with lower FI, better physical performance and less functional limitations over time (Table 2).

The *P*-value threshold for PRS-GS and the number of SNPs included for each threshold can be found in Table S1. The analysis reported in the manuscript is for the *P*-value threshold of 0.001 since this PRS-GS explained the highest variation in grip strength (Figure S1). Overall, higher PRS-GS was associated with higher grip strength over time ($b = 0.666$, 95% CI 0.413–0.918).

We did not find an association between PRS-GS and FI, physical performance and functional limitations, respectively.

Table 1. Baseline characteristics of the study sample

	LASA 1	LASA 1	LASA 2	LASA 3
Genotyping array	Axiom-NL	GSA	GSA	GSA
Number of participants	590	465	631	576
Age (years)	73.6 (7.6)	71.5 (8.2)	60.0 (3.0)	60.5 (2.9)
Females, N (%)	299 (50.7%)	260 (55.9%)	333 (52.8%)	292 (51.5%)
Grip strength (kg)	27.21 (9.67)	28.16 (10.15)	35.73 (12.31)	33.88 (11.82)
FI	0.18 (0.11)	0.16 (0.10)	0.13 (0.09)	0.14 (0.09)
FP, Frail, N (%)	55 (10.8%)	43 (12.3%)	26 (4.5%)	30 (6.1%)
Physical performance	8.03 (2.5)	8.37 (2.56)	8.17 (2.31)	8.33 (2.34)
Functional limitations, Yes, N (%)	298 (51.2%)	227 (47.5%)	181 (28.7%)	168 (29.6%)

Mean (SD) or N (%).

Table 2. Longitudinal association between grip strength and frailty, physical performance and functional limitations over time

	FI B (95% CI)	Physical performance B (95% CI)	Functional limitations OR (95% CI)
LASA 1	−0.012 (−0.015, −0.009)	0.028 (0.012, 0.044)	0.975 (0.961, 0.989)
LASA 1	−0.018 (−0.022, −0.014)	0.061 (0.043, 0.080)	0.953 (0.934, 0.972)
LASA 2	−0.009 (−0.013, −0.006)	0.038 (0.022, 0.053)	0.967 (0.951, 0.983)
LASA 3	−0.011 (−0.017, −0.005)	0.033 (0.012, 0.054)	0.971 (0.951, 0.991)
Pooled results	−0.013 (−0.016, −0.009)	0.040 (0.026, 0.054)	0.965 (0.954, 0.977)

Adjusted for age, sex and follow-up time.

Table 3. Longitudinal association of PRS-GS with frailty, physical performance and functional limitations over time

	FI, B (95% CI)	Physical performance, B (95% CI)	Functional limitations, OR (95% CI)
LASA 1	−0.005 (−0.048, 0.038)	0.060 (−0.098, 0.218)	1.103 (0.951, 1.280)
LASA 1	−0.015 (−0.061, 0.030)	0.009 (−0.152, 0.170)	1.057 (0.893, 1.250)
LASA 2	0.0001 (−0.049, 0.048)	0.024 (−0.117, 0.165)	1.008 (0.885, 1.148)
LASA 3	0.022 (−0.034, 0.079)	−0.004 (−0.181, 0.173)	1.048 (0.893, 1.232)
Pooled results	−0.002 (−0.026, 0.022)	0.024 (−0.055, 0.103)	1.050 (0.974, 1.132)

Adjusted for age, sex, 10 ancestry-informative PCs and follow-up time. P-value threshold for SNP inclusion in PRS-GS is 0.001.

Extra analyses using different P-value thresholds for PRS-GS showed similar results. The results for P-value threshold 0.1, the PRS-GS explaining the second highest variance, are presented in Table S2.

Moreover we tested the cross-sectional association between PRS-GS, being frail based on the FP and FP components. Overall, PRS-GS was associated with muscle weakness, but we found no association with being frail, weight loss, exhaustion, low gait speed or low physical activity (Table S3).

Discussion

In this study, we found that higher grip strength is associated with lower FI, better physical performance and less functional limitations over time. PRS-GS was associated with grip strength over time but there was no association between PRS-GS and frailty, physical performance and functional limitations over time. This suggests that the phenotypic association between the traits is not explained by shared genetic factors captured by currently available PRS-GS. The

phenotypic association may be explained by a combination of factors, such as lifestyle factors, morbidity, early life factors (weight at birth, socioeconomic status of the family, etc. [32, 33]) and the ageing process itself. Exploring these factors further was outside the scope of this study.

In line with the previous literature, grip strength was associated with frailty over time even for long follow-up periods up to 23 years [34]. Furthermore our results support earlier studies on the association between grip strength and physical performance and grip strength and functional limitations and provide evidence that this association remains over long time [7, 34, 35].

Studies on the genetic association between grip strength and frailty are limited. Tikkanen et al. [12] studied the cross-sectional association between PRS-GS and components of FP in a subset of UK Biobank participants. Contrary to our results, they found that a higher PRS-GS was associated with slower walking speed and less feeling of tiredness/lethargy. However, our population was older than in the study of Tikkanen et al. (age range 55–85 years vs. 40–69 years). This may indicate that effect of the genetic factors might

decrease with age and that at older age mainly non-genetic factors are driving the association between the traits. Also, the frailty components were measured differently; slower walking speed, for example, was measured by asking the participants 'How would you describe your walking speed?' in the study of Tikkanen *et al.*, whereas in our sample, it was derived from the walking test. Also, the PRS-GS in the study of Tikkanen *et al.* was slightly different from the one used in our study and included only 101 SNPs derived from the GWAS described in the same article.

The study of Atkins *et al.* [14] also showed a cross-sectional association between PRS-GS and FI in UK Biobank. The two-sample Mendelian Randomization, however, did not show a casual effect. They used 16 SNPs derived from the GWAS of Willems *et al.* [11] to build the PRS-GS, including part of the data from UK Biobank. Also, here the overlap in age and other characteristics of the participants included in the discovery GWAS and PRS study (part of UK Biobank participants) could have driven the results.

We examined whether the lack of association in our study could be because of the lack of statistical power. Our power calculations (see Supplementary Material) showed that we have at least 80% power to detect a significant association given a small genetic covariance between the traits of 0.1 and SNP heritability is 13%, the lowest heritability estimates reported in the literature [12]. Although the lack of association seems unlikely because of lack of statistical power it is important to remark that the PRS-GS captured only a small proportion of the overall grip strength variance and the true genetic covariance amongst the study traits is unknown. Our results indicate that in the phenotypic association between grip strength and frailty, physical performance and functional limitation the contribution of shared genetic factors is limited, whereas other non-genetic factors such as physical activity, diet, smoking status and comorbidities may play a more prominent role.

Another plausible explanation is that frailty, physical performance and functional limitations have shared genetic factors with age-related loss of muscle strength, also known as dynapenia, rather than grip strength as a continuum. Indeed, a recent GWAS showed that only three of the genetic variants associated with continuous grip strength were significantly associated with dynapenia [36]. Their findings imply that muscle weakness in older adults has distinct genetic drivers and mechanisms from continuous grip strength. Additionally, in this study, the lower (unweighted) genetic risk score of dynapenia were associated with increases FI.

Strengths of our study include its prospective design and long follow-up. PRS-GS were based on the largest independent discovery sample available. To our knowledge, this is the first study investigating the association of PRS-GS with frailty, physical performance and functional limitations over time. Moreover, this is the first study to assess the phenotypic association of grip strength with frailty, physical performance and functional limitations during a follow-up period up to 23 years.

Nonetheless, this study has some limitations. First, the sample size was not suitable to detect very small effect estimates for genetic covariance between the traits smaller than 0.1. Second, data on FP and its components were not available for every wave, which made only cross-sectional analyses possible. Third, the study population is of European ancestry and generalizability of the results in other ancestries should be taken with caution. Fourth, there were also some methodological limitations that could not properly be accounted for. For example, medical data on important musculoskeletal diseases such as rheumatoid arthritis, osteoarthritis and osteoporosis that might affect grip strength measurement were not available for all participants and therefore were not accounted for in the analysis. This might have been relevant as the presence of these diseases may have caused confounding in the association between grip strength and the functional outcomes. However, given the prevalence of 1% of rheumatoid arthritis [37] and ∼11% of osteoarthritis of the hand [38] reported in previous LASA substudies, we do not believe that they have significantly impacted the results. Also, the change of the dynamometers from 2012 in LASA could have introduced a slight measurement error. A comparison of the two dynamometers is not available in LASA. A recent study in older adults from geriatric and internal medicine outpatient clinic in Turkey [39] showed similar results between two dynamometers (interclass correlation coefficient 0.9) with a slight overestimation of the Takei dynamometer versus the JAMAI dynamometer used as gold standard.

In conclusion, the phenotypic association between grip strength, frailty, physical performance and functional limitations is present even after long follow-up periods. Shared genetic mechanisms between these traits are either minimal or involve different variant from the ones currently identified in GWAS studies of grip strength.

interpretation of results, writing or publishing of the manuscript.

Data Availability: Data are available upon request following the guidelines for data access of the LASA study. For more information please check the website of LASA (https://lasa-vu.nl/en/request-data/).

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