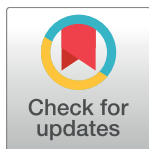


RESEARCH ARTICLE

# Genetic risk for neurodegenerative disorders, and its overlap with cognitive ability and physical function

Saskia P. Hagenaars<sup>1,2,3</sup>, Ratko Radaković<sup>1,2,4,5,6,7</sup>, Christopher Crockford<sup>2,6</sup>, Chloe Fawns-Ritchie<sup>1,2</sup>, International FTD-Genomics Consortium (IFGC)<sup>1</sup>, Sarah E. Harris<sup>1,8</sup>, Catharine R. Gale<sup>1,2,9</sup>, Ian J. Deary<sup>1,2</sup>✉\*

**1** Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, United Kingdom, **2** Department of Psychology, University of Edinburgh, Edinburgh, United Kingdom, **3** MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, Denmark Hill, London, United Kingdom, **4** Alzheimer Scotland Dementia Research Centre, University of Edinburgh, Edinburgh, United Kingdom, **5** Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, United Kingdom, **6** Euan MacDonald Centre for Motor Neurone Disease Research, University of Edinburgh, Edinburgh, United Kingdom, **7** Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, United Kingdom, **8** Medical Genetics Section, University of Edinburgh Centre for Genomic and Experimental Medicine and MRC Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh, United Kingdom, **9** MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom



**OPEN ACCESS**

**Citation:** Hagenaars SP, Radaković R, Crockford C, Fawns-Ritchie C, International FTD-Genomics Consortium (IFGC), Harris SE, et al. (2018) Genetic risk for neurodegenerative disorders, and its overlap with cognitive ability and physical function. PLoS ONE 13(6): e0198187. <https://doi.org/10.1371/journal.pone.0198187>

**Editor:** Lisa Chakrabarti, University of Nottingham, UNITED KINGDOM

**Received:** December 20, 2017

**Accepted:** May 14, 2018

**Published:** June 1, 2018

**Copyright:** © 2018 Hagenaars et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** Data from the UK Biobank ([www.ukbiobank.ac.uk](http://www.ukbiobank.ac.uk)) are third party and legal constraints do not permit public sharing of the data. The UK Biobank data used in this study can be accessed by applying through the UK Biobank Access Management System ([www.ukbiobank.ac.uk/register-apply](http://www.ukbiobank.ac.uk/register-apply)). The data generated by the International FTD-Genomics Consortium (IFGC) are available upon request to protect patient information; the IFGC can be

✉ These authors contributed equally to this work.

¶ Membership of the International FTD-Genomics Consortium (IFGC) is provided in the Acknowledgments.

\* [ian.deary@ed.ac.uk](mailto:ian.deary@ed.ac.uk)

## Abstract

Neurodegenerative disorders are associated with impaired cognitive function and worse physical health outcomes. This study aims to test whether polygenic risk for Alzheimer's disease, Amyotrophic Lateral Sclerosis (ALS), or frontotemporal dementia (FTD) is associated with cognitive function and physical health in the UK Biobank, a cohort of healthy individuals. Group-based analyses were then performed to compare the top and bottom 10% for the three neurodegenerative polygenic risk scores; these groups were compared on the cognitive and physical health variables. Higher polygenic risk for AD, ALS, and FTD was associated with lower cognitive performance. Higher polygenic risk for FTD was also associated with increased forced expiratory volume in 1s and peak expiratory flow. A significant group difference was observed on the symbol digit substitution task between individuals with high polygenic risk for FTD and high polygenic risk for ALS. The results suggest some overlap between polygenic risk for neurodegenerative disorders, cognitive function and physical health.

## Introduction

Alzheimer's disease (AD) is the most common form of dementia and it is expected that over one million people in the UK will be diagnosed with this disease by 2025 [1]. Approximately 10% of individuals over the age of 65 have AD, increasing in prevalence with age [2].

requested via <https://ifgcsite.wordpress.com/data-access/>.

**Funding:** The work was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1); funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. This report represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. CC is supported by the Euan MacDonald Centre for Motor Neurone Disease Research. CF-R is supported by Dementias Platform UK (DPUK), funded through the MRC (MR/L023784/2).

**Competing interests:** The authors have declared that no competing interests exist.

Pathological features of AD include amyloid B-plaques and neurofibrillary tangles [3], while degeneration of subcortical hippocampal regions and the medial temporal lobes is associated with the salient presenting memory impairment [4, 5].

Frontotemporal dementia (FTD), distinct from AD, is marked by degeneration of the frontal and anterior temporal lobes. FTD is the second most prevalent presentation of early onset dementia, accounting for approximately 3–26% of cases [6]. Behavioural variant FTD is the most common phenotype, and is defined by behaviour change and executive dysfunction (e.g., impairments in working memory, cognitive flexibility, response generation, and social cognition), with relative sparing of episodic memory and visuospatial skills [7]. FTD shares genetic, pathological, and neuropsychological overlap with Amyotrophic Lateral Sclerosis (ALS). ALS is a neurodegenerative disease marked by progressive loss of motor neurons in the brain and spinal cord, resulting in muscle wasting, spasticity, and death usually due to respiratory failure within three years [8]. Approximately 35% of ALS patients will present with mild cognitive and/or behavioural changes, of a similar nature to those seen in FTD, with an additional 15% meeting diagnostic criteria for both ALS and FTD [9]. Similarly, approximately 40% of FTD patients present with motor symptoms, and 15% meet ALS classification criteria [10].

The genetic aetiology of AD and FTD/ALS is heterogeneous. The *APOE* e4 allele is the strongest risk factor for late onset AD; however, numerous additional candidate and susceptibility loci have been established in recent years [11]. It has been suggested that late onset AD is due to susceptibility at multiple loci, and due to genetic and environmental interactions [12]. Conversely, early onset AD is autosomal dominant, accounting for approximately 1–5% of all cases, has been linked to variants in the *APP*, *PSEN1*, and *PSEN2* genes [13]. Autosomal dominant ALS accounts for approximately 5–10% of cases, with 85–90% of cases having no strong genetic linkage [14]. Familial ALS has been linked to the *SOD1*, *TARDBP*, *FUS*, and more recently *NEK1* genes [15, 16]. FTD shows a positive family history in up to 40% of cases, with mutations in the *MAPT* and *GRN* genes being amongst the most common [17]. The *C9ORF72* mutation has been most frequently associated with familial ALS and FTD [18, 19] but can also be found in sporadic forms of both diseases [20, 21], however the cause here is often unknown, and possibly due to environmental-genetic linkages [15]. A genome-wide association study (GWAS) of FTD [22] demonstrated that the *C9ORF72* mutation mainly associates with the ALS-FTD variant indicating a strong genetic overlap.

In addition to the genetic complexity, the cognitive profiles of AD and FTD/ALS are heterogeneous, in that impairments in executive functions, language, visuospatial skills, and memory have been recorded in all three diseases [23]. Whereas evidence does exist that memory, visuospatial, and particularly language functions may be affected in FTD, the extent to which executive dysfunction explains these observations remains unclear [24, 25]. Previous research has suggested a preclinical phase of reduced cognitive functioning for older adults who subsequently develop AD [26] and for those at genetic risk of developing AD [27–31], with similar findings reported for FTD [32, 33]. Yet, not all those at genetic risk of developing AD or FTD/ALS go on to develop the disease, and these findings may suggest that genetic carriers may be at risk of developing preclinical symptoms without necessarily developing the disease itself. Furthermore, the genetic aetiology of AD, ALS, and FTD is multifactorial, and a significant proportion of genetic variance remains unexplained (that is, there is missing heritability [34]).

As such, polygenic risk scores are becoming increasingly useful in the study of genetically complex diseases. Polygenic risk scores are valuable in aggregating genetic markers that on their own do not reach significance [35]. Higher polygenic risk for AD, based on genome-wide significant single nucleotide polymorphisms (SNPs) [36] and all common SNPs [37], has been associated with lower general cognitive ability and memory. Some research has suggested that

healthy adults with a high polygenic risk for AD possess reduced brain cortical thickness [38]. Polygenic risk has been associated with cognitive performance in other diseases; for instance, a high polygenic risk of schizophrenia has been associated with a greater decline in cognitive functioning between childhood and older age [39], and reduced neural efficiency [40]. Similarly, high polygenic risk for autism has been associated with better cognitive ability in the general population [37, 41]. To date however, no identifiable research has explored whether polygenic risk for FTD or ALS is associated with cognitive, muscle, or respiratory function.

As such, the aim of this study is to extend the work accomplished in AD to FTD/ALS, and to further explore whether polygenic risk for AD, FTD, or ALS is associated with cognitive performance, or with physical function measures known to be affected by motor neuron degeneration.

## Materials and methods

### Sample

This study includes baseline data and data from a web-based cognitive follow-up from the UK Biobank study, a large resource for identifying determinants of human diseases in middle aged and older healthy individuals (<http://www.ukbiobank.ac.uk>) [42]. A total 502,655 community-dwelling participants aged between 37 and 73 years were recruited between 2006 and 2010 in the United Kingdom, and underwent extensive baseline testing including cognitive and physical assessments. All participants provided blood, urine and saliva samples for future analysis. For the follow up testing, participants completed cognitive tests remotely via a web-based assessment.

### Measures

**Cognitive measures.** Cognitive ability was measured using five different cognitive tests. These included tests of verbal-numerical reasoning ( $n = 36,035$ ), reaction time ( $n = 111,484$ ), memory ( $n = 112,067$ ), trail making (part A:  $n = 23,822$ , part B:  $n = 23,812$ ), and symbol digit substitution ( $n = 26,913$ ). The verbal-numerical reasoning test consisted of a 13-item questionnaire assessing verbal and arithmetical deduction (Cronbach  $\alpha$  reliability of 0.62). Reaction time was measured using a computerized ‘Snap game’, during which participants were asked to press a button as quickly as possible when two cards on the screen were matching. There were eight trials, four had matching cards and required the button to be pressed (Cronbach  $\alpha$  reliability of 0.85). Memory was measured using a pairs matching test, where participants were asked to memorize positions of matching pairs of cards, shown for 5s on a 3 by 4 grid. All cards were then placed face down and the participant had to identify the positions of the matching pairs as quickly as possible. The number of errors in this task was used as the (inverse) measure of memory ability. These tests have been previously described in more detail by Hagenaars et al. (2016)[37]. Executive functioning was measured using the trail making test parts A (TMT A) and B (TMT B), which were part of the follow up testing wave in UK Biobank, between 2014 and 2015. For TMT A, participants were instructed to connect numbers consecutively (which were quasi-randomly distributed on the touchscreen) as quickly as possible in ascending order by selecting the next number. TMT B is similar, but in this case letters and numbers had to be selected in alternating ascending order, e.g. 1 A 2 B 3 C etc. The difference between the raw scores for TMT A and TMT B was computed as TMT B minus TMT A (TMT B-A). Owing to positively skewed distributions, both TMT A and TMT B scores were log-transformed prior to further analyses. Further detail on these tests in UK Biobank has been published previously [43]. Processing speed was measured using the symbol digit substitution test, similar to the well-validated Symbol Digits Modalities Test [44], which was also

part of the follow up testing wave. In the UK Biobank symbol digit substitution test, participants are presented with symbols paired with digits and are asked to enter the digits that are paired with the symbols in the empty spaces. The score for processing speed was based on the number of correctly matched symbols. Participants who scored 0 ( $n = 61$ ) or above 40 ( $n = 3$ ) were removed from further analyses, as they scored more than 4 SD away from the mean.

**Physical measures.** Muscle weakening and respiratory dysfunction are physical symptoms characteristic of ALS and in a proportion of FTD patients. Muscle strength was measured via hand grip strength for both the right and left hand, using a Jamar J00105 hydraulic hand dynamometer. Participants were seated upright in a chair with their forearms on the armrests, and were asked to squeeze the handle of the dynamometer as strongly as possible for three seconds. The maximum grip strength for each hand was measured in whole kilogram force units. This study used maximum grip strength based on the dominant hand, as indicated by the participant.

Lung (respiratory) function was assessed using a Vitalograph Pneumotract 6800 spirometer. Participants were asked to record two to three blows, lasting for at least 6 seconds, within a period of 6 minutes. The following outcomes measures were calculated by the computer: forced expiratory volume in 1s (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF). FEV1 is the amount of air, in litres, that is forcibly exhaled in 1 second following full inspiration. FVC is the amount of air, in litres, that is exhaled followed full inspiration. PEF is the maximum speed of exhalation following full inspiration. All three measures were standardized and individuals with a Z-score  $> 4$  were excluded from FEV1 ( $n = 47$ ), FVC ( $n = 73$ ), and PEF ( $n = 28$ ).

## Genotyping and quality control

The interim release of UK Biobank included genotype data for 152,729 individuals, of whom 49,979 were genotyped using the UK BiLEVE array and 102,750 using the UK Biobank axiom array. These arrays have over 95% content in common. Quality control was performed by Affymetrix, the Wellcome Trust Centre for Human Genetics, and by the present authors; this included removal of participants based on missingness, relatedness, gender mismatch, and non-British ancestry. We only included individuals of White British ancestry to reduce population stratification and the other ethnic groups were underpowered on their own to detect effects. British ancestry was defined as individuals who both self-identified as White British and were confirmed as ancestrally White British using principal components analyses (PCA) of genome-wide genetic information, this information was provided by UK Biobank. Further details have been published elsewhere [37, 45]. Variants with a minor allele frequency of less than 0.01 and non-autosomal variants were excluded from further analysis. A sample of 112,151 individuals available for further analysis remained after quality control.

## Polygenic risk scores

The UK Biobank genotyping data required recoding from numeric (1, 2) allele coding to standard ACGT format before being used in polygenic profile scoring analyses, this was done using a bespoke program [37]. Polygenic risk scores were created for AD [11], ALS [21], FTD, [22] in all genotyped participants using PRSice software [46]. PRSice calculates the sum of alleles associated with the phenotype of interest across many genetic loci, weighted by their effect sizes estimated from a GWAS of the corresponding phenotype in an independent sample. The GWAS summary statistics for AD, ALS, and FTD were used as the training (base) dataset, while UK Biobank was used as the prediction (target) dataset. Clumping was used to obtain SNPs in linkage disequilibrium with an  $r^2 < 0.25$  within a 250kb window. Five

polygenic risk scores were then created for the three phenotypes (AD, ALS, FTD) containing SNPs selected according to the significance of their association with the phenotype, at thresholds of  $p < 0.01$ ,  $p < 0.05$ ,  $p < 0.1$ ,  $p < 0.5$ , and all SNPs. Polygenic risk scores were also created for AD excluding SNPs within a 500 kb window of apolipoprotein E (*APOE*) gene.

### Statistical analysis

All statistical analyses were performed in R version 3.4.0 [47]. The associations between the polygenic profiles and the target phenotype were examined in regression models, adjusting for age at measurement, sex, genotyping batch and array, assessment centre, and the first 10 genetic principal components to adjust for population stratification. The models including measures of lung function (FEV1, FVC, PEF) were also adjusted for smoking status and height, whereas the models for grip strength were additionally adjusted for height and weight. All models were corrected for multiple testing using the false discovery rate method [48].

Following calculation of each participant's polygenic risk score at each of the above-mentioned thresholds, participants were classified in terms of their high or low polygenic risk for each neurodegenerative disease (AD, ALS and FTD). High risk was defined by the participant's polygenic risk score falling within the top 10th percentile and low risk was defined by the participant's polygenic risk score falling within the bottom 10th percentile for any of the neurodegenerative diseases. These participants were then grouped based on High Risk for AD (top 10th percentile for AD and bottom 10th percentiles for ALS and FTD), High Risk for ALS (top 10th percentile for ALS and bottom 10th percentiles for AD and FTD) and High Risk for FTD (top 10th percentile for FTD and bottom 10th percentiles for ALS and AD) to homogenise pure polygenic risk for each neurodegenerative disease in these groups. There were no overlapping participants in each of these groups. These High Risk for AD, High Risk for ALS and High Risk for FTD groups were compared on cognitive and physical variables (chosen based on significant polygenic profile-target phenotype regression models from the previous analysis). Shapiro-Wilk tests were used to assess normality of the data, following which group comparisons were performed either using Kruskal-Wallis H or ANOVA tests on cognitive and physical variables, applying a Holm-Bonferroni correction. Significant Kruskal-Wallis H or ANOVA results were followed up with post hoc tests (Mann Whitney U tests, or Tukey's Honest Significant Differences, respectively), where effect size was estimated using Cohen's *d*.

## Results

For the present study, genome-wide genotyping data was available for 112,151 individuals (58,914 females), aged between 40 and 70 years (mean age = 56.9 years,  $SD = 7.93$ ) after the quality control process. Table 1 shows descriptive statistics for each of the measures used in this study.

### Polygenic risk analysis

The results for the polygenic risk analyses examining if polygenic risk for neurodegenerative diseases is associated with cognitive ability and physical health, using the best threshold (largest  $\beta$ ), are shown in Table 2 and Fig 1. Full results including all five thresholds can be found in S1 Table. Polygenic risk scores for AD significantly predicted verbal-numerical reasoning ( $\beta = -0.023$ ,  $p = 1.27 \times 10^{-5}$ ) [37], memory ( $\beta = 0.011$ ,  $p = 0.0001$ ) [37], symbol digit substitution ( $\beta = -0.015$ ,  $p = 0.0065$ ), and TMT B ( $\beta = 0.017$ ,  $p = 0.0047$ ). Thus, individuals with higher polygenic risk for AD answered fewer verbal-numerical reasoning questions correctly, made more errors on the memory task, completed fewer items on the symbol digit substitution test, and took longer to complete TMT B. When excluding *APOE* from the AD polygenic risk

**Table 1. Descriptive statistics for cognitive and physical function measures in UK Biobank.**

	N	mean (SD)
<b>Baseline cognitive tests</b>		
Verbal-numerical reasoning	36,035	6.16 (2.10)
Reaction time (time in ms)	111,483	555.10 (112.62)
Memory (errors)	112,067	4.06 (3.02)
<b>Follow-up cognitive tests</b>		
Symbol digit substitution (correct matches)	26,913	19.74 (5.13)
Trail making part A (time in s)	23,822	39.11 (14.73)
Trail making part B (time in s)	23,812	66.44 (24.89)
Trail making part B–part A (time in s)	23,769	27.22 (18.89)
<b>Physical function</b>		
Grip strength (in kg)	111,735	32.17 (11.35)
Forced expiratory volume in 1s (in litres)	104,722	2.79 (0.81)
Peak expiratory volume (in litres/min)	104,741	389.20 (135.42)
Forced vital capacity (in litres)	104,696	3.71 (1.01)
<b>Demographics</b>		
Age at baseline (in years)	112,151	56.91 (7.93)
Age at follow-up (in years)	27,429	63.00 (7.61)
Gender, female N (%)	112,151	58,914 (52.53)
College degree obtained, yes (%)	112,151	33,852 (30.20)

<https://doi.org/10.1371/journal.pone.0198187.t001>

score, the associations with symbol digit substitution attenuated to non-significance (S1 Table). Polygenic risk scores for ALS significantly predicted verbal-numerical reasoning ( $\beta = -0.019, p = 0.0004$ ). Individuals with higher polygenic risk for ALS had lower scores on verbal-numerical reasoning. Polygenic risk scores for FTD significantly predicted TMT B ( $\beta = 0.017, p = 0.0041$ ), FEV1 ( $\beta = 0.007, p = 0.0012$ ), and PEF ( $\beta = 0.011, p = 4.77 \times 10^{-6}$ ). Those with higher polygenic risk for FTD took longer to complete TMT B and had higher FEV1 and PEF scores. The associations between all scores at each threshold are shown in S2 Table.

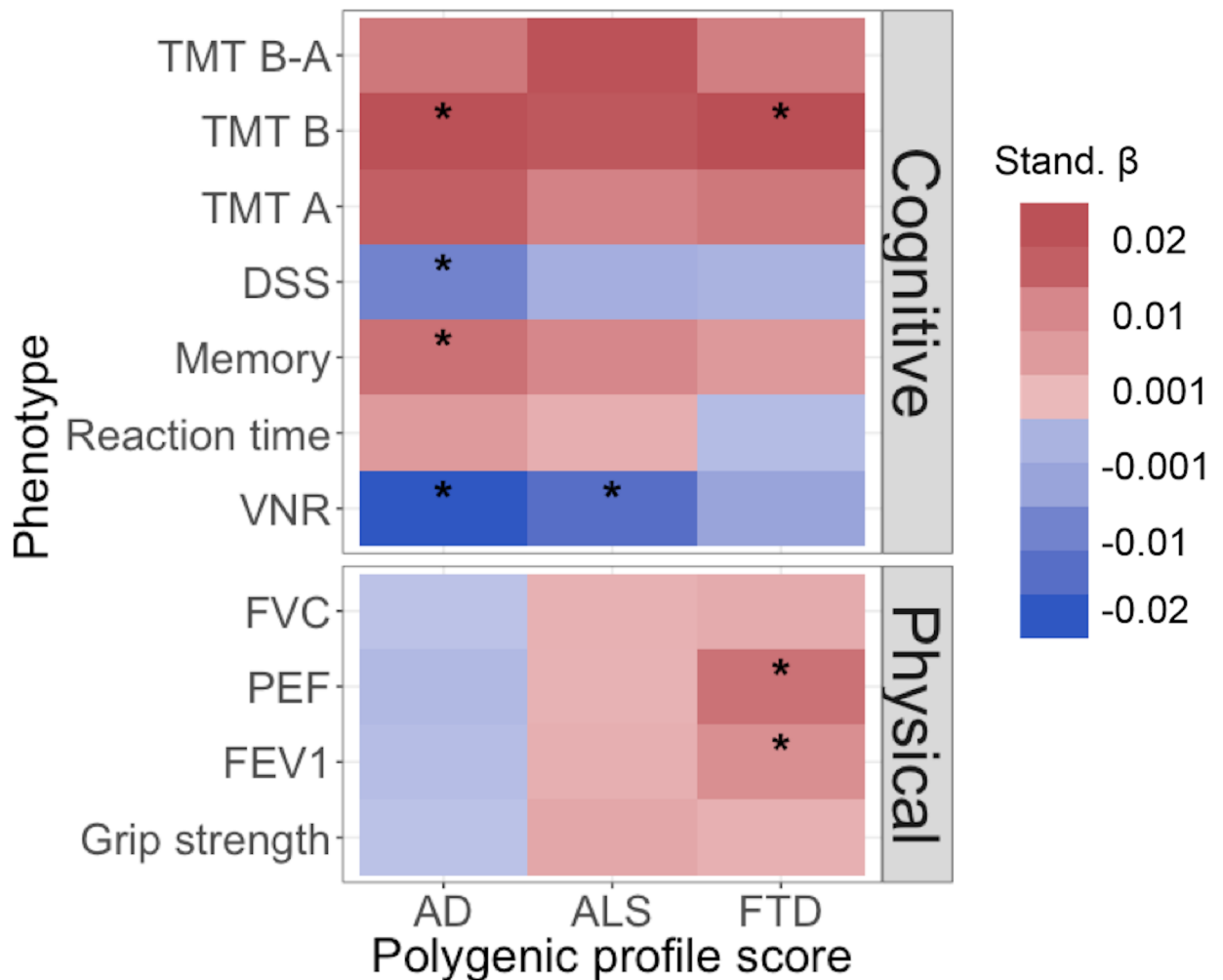
**Table 2. Associations between polygenic risk scores for Alzheimer’s disease (FDR p-value  $\leq 0.018$ ), amyotrophic lateral sclerosis (FDR p-value  $\leq 0.0024$ ), and frontotemporal dementia (FDR p-value  $\leq 0.0041$ ), and cognitive and physical measures controlling for age, sex, assessment centre, genotyping batch and array and 10 genetic principal components for population structure.**

	Alzheimer’s disease			Amyotrophic lateral sclerosis			Frontotemporal dementia		
	pT	$\beta$	p	pT	$\beta$	p	pT	$\beta$	p
Verbal-numerical reasoning	0.05	-0.0229	$1.27 \times 10^{-5}$ *	0.05	-0.0188	<b>0.0004</b>	1	-0.0085	0.1036
Reaction time	0.5	0.0052	0.0700*	1	0.0023	0.4315	0.5	-0.0033	0.2489
Memory	0.1	0.0114	<b>0.0001</b> *	0.1	0.0080	0.0074	0.05	0.0053	0.0737
Symbol digit substitution	0.5	-0.0150	<b>0.0065</b>	0.01	-0.0063	0.2613	0.01	-0.0053	0.3316
Trail making part A	0.05	0.0144	0.0195	0.01	0.0087	0.1609	0.1	0.0104	0.0900
Trail making part B	0.5	0.0168	<b>0.0047</b>	0.1	0.0155	0.0101	0.1	0.0171	<b>0.0041</b>
Trail making part B-A	1	0.0104	0.0965	0.1	0.0166	0.0091	0.1	0.0093	0.1410
Grip strength	0.1	-0.0016	0.3963	0.01	0.0032	0.0997	0.05	0.0020	0.2911
Forced expiratory volume in 1s	1	-0.0027	0.2018	0.01	0.0022	0.3066	0.05	0.0068	<b>0.0012</b>
Peak expiratory flow	1	-0.0039	0.1159	0.01	0.0017	0.4943	0.1	0.0113	$4.77 \times 10^{-6}$
Forced vital capacity	1	-0.0014	0.4817	0.01	0.0019	0.3158	0.05	0.0027	0.1628

pT, polygenic risk score threshold for best model

\*, previously published by Hagenaars et al., (2016) [37]

<https://doi.org/10.1371/journal.pone.0198187.t002>



**Fig 1. Heat map of associations between the polygenic profile scores for neurodegenerative disease and cognitive ability and physical health.** Stronger associations are indicated by darker shades, red indicates a positive association, blue indicates a negative association. AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; TMT B-A, trail-making part B–part A; TMT B, trail making part B; TMT A, trail making part A; DSS, digit symbol substitution; VNR, verbal numerical reasoning; FVC, forced vital capacity; PEF, peak expiratory flow; FEV1, forced expiratory volume in 1s. \*, significant association after FDR correction (p-value  $\leq$  0.018 (AD), 0.024 (ALS), or 0.0041 (FTD)). Full results can be found in S1 Table.

<https://doi.org/10.1371/journal.pone.0198187.g001>

### Polygenic inter-group comparison

Table 3 shows the comparison of polygenic risk groups on cognitive and physical variables. There was no significant difference between those categorised as having high polygenic risk for AD, ALS, or FTD on age or gender distribution. The only significant difference between these groups was observed with one of the cognitive variables, specifically, symbol digit substitution task. Follow up, post hoc analysis showed that participants with a high polygenic risk for FTD performed significantly worse on the symbol digit substitution task when compared to participants with a high polygenic risk for ALS ( $U = 396, p < 0.01, d = 0.85$ ). No significant differences were observed between other groups on cognitive and physical variables.

### Discussion

The present study aimed to explore whether polygenic risk for AD, FTD, or ALS is associated with cognitive performance, grip strength, or lung function measures. Using the large

**Table 3. Cognitive and physical variable comparison between high Alzheimer’s disease (AD) polygenic risk, amyotrophic lateral sclerosis (ALS) polygenic risk, and frontotemporal dementia (FTD) polygenic risk, N for each group is shown.**

	High Risk AD	High Risk ALS	High Risk FTD	p-value
Age	56.93 ± 7.81 (n = 389)	57.24 ± 7.75 (n = 386)	57.07 ± 7.95 (n = 343)	0.86
Gender (M/F)	179/210	188/198	157/186	0.67
Cognitive				
Trail making part B‡	4.10 ± 0.34 (n = 27)	4.05 ± 0.40 (n = 25)	4.15 ± 0.24 (n = 17)	1.00†
Verbal-numerical reasoning	6.50 ± 2.40 (n = 28)	6.22 ± 1.91 (n = 40)	6.42 ± 2.02 (n = 24)	1.00†
Memory	4.12 ± 3.26 (n = 107)	4.09 ± 2.98 (n = 112)	3.72 ± 2.73 (n = 103)	1.00†
Symbol digit substitution	19.77 ± 5.59 (n = 30)	22.16 ± 5.47 (n = 25)	17.57 ± 5.34 (n = 21)	<b>0.04†</b>
Physical				
FEV1	2.78 ± 0.70 (n = 112)	2.84 ± 0.84 (n = 93)	2.66 ± 0.72 (n = 84)	0.62†
PEF	383.09 ± 124.25 (n = 92)	398.06 ± 138.79 (n = 101)	394.27 ± 125.92 (n = 96)	0.62†

‡Log transformed

†Kruskal-Wallis H test; Chi Squared tests used for gender distribution comparison; Mean ± Standard Deviation shown for each high neurodegenerative disease polygenic risk group; bold text indicate significance adjusted for multiple comparisons (Holm-Bonferroni)

<https://doi.org/10.1371/journal.pone.0198187.t003>

cognitive, physical and genotypic data available in the UK Biobank, in concordance with the most up to date GWAS consortia of neurodegenerative disease (AD, ALS and FTD), our results showed a novel relationship between cognitive and physical function variables and polygenic risk for neurodegenerative conditions in a healthy population, particularly in the case of AD.

The findings of this study demonstrate that higher polygenic risk of AD is associated with numerous cognitive functions; specifically, reduced performance in verbal-numerical reasoning, memory, processing speed (symbol digit substitution), and executive functioning (TMT B). Sensitivity analysis indicated that the association between AD and cognitive ability (except symbol digit substitution) was not driven by the *APOE* gene. Although an association between polygenic risk of AD and cognitive ability—that is significant associations with verbal-numeric reasoning and memory—in UK Biobank have been reported previously [37], the present study extends these findings to measures of executive functioning and processing speed. Unlike AD, higher polygenic risk for ALS demonstrated only one significant relationship with cognitive function, namely verbal-numerical reasoning. Higher polygenic risk for FTD was only associated with reduced performance on the TMT B.

Physical function measures used in this study were chosen based on their relevance in clinical cases of FTD and ALS, in particular, measures of grip strength and lung function. Counter-intuitively higher risk of FTD was related to better respiratory functioning (FEV1 and PEF). Finally, a higher risk of ALS was not associated with grip strength or measures of lung function. It is worth noting, however, that the amount of variance explained by the polygenic risk scores was very small (< 0.01%). As such, these finding may be spurious.

In a small subset of participants, those with a high polygenic risk for FTD performed worse on a processing speed task (symbol digit substitution task) compared to those with high polygenic risk for ALS. There has been an emphasis on linkage and continuum-based relationship



between ALS and FTD, this finding based on pure genetic risk could provide insight towards sub-clinical cognitive impairment. The cognitive profile of ALS largely mirrors that of FTD, albeit in a milder form. Patients with FTD have demonstrated processing speed impairments, both cross-sectionally and longitudinally [49, 50]. However, studies of cognition in ALS have largely ignored tasks of processing speed due to the confounding presence of motor impairment in this patient group. That said, current research suggests unaffected processing speed in patients with ALS. As such, previous research combined with the findings herein may suggest a future avenue for detecting FTD syndromes in patients with ALS. However, further studies are needed to explore the reliability of differences between polygenic risk of FTD and ALS, and between people diagnosed with these diseases.

There are several limitations to note regarding the present study. While the cognitive tasks in the present study covered a number of domains, the measures are brief and non-standardized. As such, the sensitivity to detect small differences in cognitive ability are limited. Additionally, due to the nature of self-administration on a computer (in case of the measures for the symbol digit substitution test and the trail making test), the environment under which the tasks are performed could not be fully standardised. The trail making test could be confounded by the movement speed in older individuals, however subtracting completion time for TMT A from TMT B completion time (TMT B-A) will partially allow the relative contributions of movement speed to be parsed from the more complex executive functions in TMT B. Finally, a limitation is that the polygenic inter-group comparison yielded smaller sample sizes, which could be indicative of the rarity of 'pure' polygenic risk for each disease in healthy adults. The results in this area should therefore be interpreted with caution and require larger scale replication, despite building on previous research of a smaller sample size [49, 50].

Furthermore, while it is interesting to speculate how the findings of the present study may relate to those individuals who actually have AD, FTD, or ALS, it is important to remember that the participants of this study were healthy individuals. Those described as high polygenic risk for a particular disease are only at higher risk when compared to other participants of this study. It would be incorrect to describe these individuals as being at a high risk of developing a neurodegenerative disease more generally.

Future research may explore whether these findings replicate given more extensive and controlled measures of cognitive functioning. Provided that FTD is primarily a disease marked by changes in behaviour, the inclusion of such measures would be informative. Additionally, as previous research has suggested that reduction of cortical thickness was associated with polygenic risk for AD in healthy adults [38], it would be informative to further explore the neural correlates of polygenic risk for different neurodegenerative disorders (e.g. ALS and FTD) in this sample.

## Conclusion

The present study confirmed and extended previous findings that polygenic risk for AD is associated with multi-domain cognitive functioning in healthy adults. Additionally, the findings of this study demonstrate that polygenic risk for ALS is associated with verbal-numeric reasoning, while polygenic risk for FTD was associated with executive functioning. Physical function measures commonly affected in patients with ALS, were not associated with polygenic risk of ALS in healthy adults. However, higher polygenic risk significantly predicted better lung function.

## Supporting information

**S1 Table. Associations between polygenic risk scores for Alzheimer's disease (FDR p-value < = 0.0118), amyotrophic lateral sclerosis (FDR p-value < = 0.0024), frontotemporal dementia (FDR p-value < = 0.0041), and Alzheimer's disease (no APOE) (FDR p-value < = 0.0080), and**

**cognitive and physical measures controlling for age, sex, assessment centre, genotyping batch and array and 10 genetic principal components for population structure.**

(XLSX)

**S2 Table. Correlation matrix of polygenic risk scores for amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and Alzheimer's disease (AD) at each threshold.**

Correlations with a p-value < 0.05 are in bold.

(XLSX)

**S1 File. Supplementary information for genetic risk for neurodegenerative disorders, and its overlap with cognitive ability and physical function.**

(DOCX)

## Acknowledgments

This research was conducted using the UK Biobank Resource. UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382). This study has been completed under UK Biobank application 10279. The work was undertaken in The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1); funding from the BBSRC and Medical Research Council (MRC) is gratefully acknowledged. This report represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. CC is supported by the Euan MacDonald Centre for Motor Neurone Disease Research. CF-R is supported by Dementias Platform UK (DPUK), funded through the MRC (MR/L023784/2). The authors would like to thank the Project MinE GWAS Consortium. The authors thank the International FTD-Genomics Consortium (IFGC) for providing phase I summary statistics data for these analyses. This consortium includes the following authors: R Ferrari (lead author, [r.ferrari@ucl.ac.uk](mailto:r.ferrari@ucl.ac.uk)); D G Hernandez; M A Nalls; J D Rohrer; A Ramasamy; J B J Kwok; C Dobson-Stone; P R Schofield; G M Halliday; J R Hodges; O Piguet; L Bartley; E Thompson; I Hernández; A Ruiz; M Boada; B Borroni; A Padovani; C Cruchaga; N J Cairns; L Benussi; G Binetti; R Ghidoni; G Forloni; D Albani; D Galimberti; C Fenoglio; M Serpente; E Scarpini; J Clarimón; A Lleó; R Blesa; M Landqvist Waldó; K Nilsson; C Nilsson; I R A Mackenzie; G-Y R Hsiung; D M A Mann; J Grafman; C M Morris; J Attems; T D Griffiths; I G McKeith; A J Thomas; P Pietrini; E D Huey; E M Wassermann; A Baborie; E Jaros; M C Tierney; P Pastor; C Razquin; S Ortega-Cubero; E Alonso; R Perneckzy; J Diehl-Schmid; P Alexopoulos; A Kurz; I Rainero; E Rubino; L Pinessi; E Rogaeva; P St George-Hyslop; G Rossi; F Tagliavini; G Giaccone; J B Rowe; J C M Schlachetzki; J Uphill; J Collinge; S Mead; A Danek; V M Van Deerlin; M Grossman; J Q Trojanowski; J van der Zee; C Van Broeckhoven; S F Cappa; I Leber; D Hannequin; V Golfier; M Vercelletto; A Brice; B Nacmias; S Sorbi; S Bagnoli; I Piaceri; J E Nielsen; L E Hjerminde; M Riemenschneider; M Mayhaus; B Ibach; G Gasparoni; S Pichler; W Gu; M N Rossor; N C Fox; J D Warren; M G Spillantini; H R Morris; P Rizzu; P Heutink; J S Snowden; S Rollinson; A Richardson; A Gerhard; A C Bruni; R Maletta; F Frangipane; C Cupidi; L Bernardi; M Anfossi; M Gallo; M E Conidi; N Smirne; R Rademakers; M Baker; D W Dickson; N R Graff-Radford; R C Petersen; D Knopman; K A Josephs; B F Boeve; J E Parisi; W W Seeley; B L Miller; A M Karydas; H Rosen; J C van Swieten; E G P Dopper; H Seelaar; Y A L Pijnenburg; P Scheltens; G Loggrosino; R Capozzo; V Novelli; A A Puca; M Franceschi; A Postiglione; G Milan; P Sorrentino; M Kristiansen; H-H Chiang; C Graff; F Pasquier; A Rollin; V Deramecourt; T Lebouvier; D Kapogiannis; L Ferrucci; S Pickering-Brown; A B Singleton; J Hardy; P Momeni.

Further acknowledgments for IFGC, e.g. full members list and affiliations, can be found in [S1 File](#).

## Author Contributions

**Conceptualization:** Saskia P. Hagenaars, Ratko Radaković, Christopher Crockford.

**Data curation:** Saskia P. Hagenaars.

**Formal analysis:** Saskia P. Hagenaars, Ratko Radaković, Chloe Fawns-Ritchie.

**Investigation:** Saskia P. Hagenaars.

**Methodology:** Saskia P. Hagenaars.

**Project administration:** Catharine R. Gale, Ian J. Deary.

**Supervision:** Sarah E. Harris, Catharine R. Gale, Ian J. Deary.

**Writing – original draft:** Saskia P. Hagenaars, Ratko Radaković, Christopher Crockford.

**Writing – review & editing:** Saskia P. Hagenaars, Ratko Radaković, Christopher Crockford, Chloe Fawns-Ritchie, Sarah E. Harris, Catharine R. Gale, Ian J. Deary.

## References

1. Prince M, Knapp M, Guerchet M, McCrone P, Prina M, Comas-Herrera A, et al. Dementia UK: Update 2014. Available from: [http://www.cfes.ac.uk/files/2015/07/P326\\_AS\\_Dementia\\_Report\\_WEB2.pdf](http://www.cfes.ac.uk/files/2015/07/P326_AS_Dementia_Report_WEB2.pdf)
2. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*. 2017; 13(4):325–73.
3. Hardy J, Selkoe DJ. The Amyloid Hypothesis of Alzheimer's Disease: Progress and Problems on the Road to Therapeutics. *Science*. 2002; 297(5580):353–6. <https://doi.org/10.1126/science.1072994> PMID: 12130773
4. Jack CR, Petersen RC, Xu Y, O'Brien PC, Smith GE, Ivnik RJ, et al. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. *Neurology*. 2000; 55(4):484–90. <https://doi.org/10.1212/wnl.55.4.484> PMID: 10953178
5. Jack JCR, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain*. 2009; 132(5):1355–65. <https://doi.org/10.1093/brain/awp062> PMID: 19339253
6. Vieira RT, Caixeta L, Machado S, Silva AC, Nardi AE, Arias-Carrión O, et al. Epidemiology of early-onset dementia: a review of the literature. *Clinical practice and epidemiology in mental health: CP & EMH*. 2013; 9:88.
7. Rascofsky K, Salmon DP, Ho GJ, Galasko D, Peavy GM, Hansen LA, et al. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. *Neurology*. 2002; 58(12):1801–8. <https://doi.org/10.1212/wnl.58.12.1801> PMID: 12084880
8. Al-Chalabi A, Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment and time. *Nat Rev Neurol*. 2013; 9(11):617–28. <https://doi.org/10.1038/nrneurol.2013.203> PMID: 24126629
9. Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology*. 2005; 65(4):586–90. <https://doi.org/10.1212/01.wnl.0000172911.39167.b6> PMID: 16116120
10. Burrell JR, Kiernan MC, Vucic S, Hodges JR. Motor Neuron dysfunction in frontotemporal dementia. *Brain*. 2011; 134(9):2582–94. <https://doi.org/10.1093/brain/awr195> PMID: 21840887
11. Lambert J-C, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 2013; 45(12):1452–8. <https://doi.org/10.1038/ng.2802> PMID: 24162737
12. Alonso Vilatela ME, López-López M, Yescas-Gómez P. Genetics of Alzheimer's Disease. *Archives of Medical Research*. 2012; 43(8):622–31. <https://doi.org/10.1016/j.arcmed.2012.10.017> PMID: 23142261

13. Van Cauwenbergh C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. *Genetics in Medicine*. 2016; 18(5):421–30. <https://doi.org/10.1038/gim.2015.117> PMID: 26312828
14. Turner MR, Hardiman O, Benatar M, Brooks BR, Chio A, de Carvalho M, et al. Controversies and priorities in amyotrophic lateral sclerosis. *The Lancet Neurology*. 2013; 12(3):310–22. [https://doi.org/10.1016/S1474-4422\(13\)70036-X](https://doi.org/10.1016/S1474-4422(13)70036-X) PMID: 23415570
15. Chen S, Sayana P, Zhang X, Le W. Genetics of amyotrophic lateral sclerosis: an update. *Molecular Neurodegeneration*. 2013; 8(1):28. <https://doi.org/10.1186/1750-1326-8-28> PMID: 23941283
16. Brenner D, Müller K, Wieland T, Weydt P, Böhm S, Lulé D, et al. NEK1 mutations in familial amyotrophic lateral sclerosis. *Brain*. 2016; 139(5):e28–e. <https://doi.org/10.1093/brain/aww033> PMID: 26945885
17. Tang SS, Li J, Tan L, Yu JT. Genetics of Frontotemporal Lobar Degeneration: From the Bench to the Clinic. *Journal of Alzheimer's disease: JAD*. 2016; 52(4):1157–76. Epub 2016/04/23. <https://doi.org/10.3233/JAD-160236> PMID: 27104909.
18. DeJesus-Hernandez M, Mackenzie Ian R, Boeve Bradley F, Boxer Adam L, Baker M, Rutherford Nicola J, et al. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. *Neuron*. 2011; 72(2):245–56. <https://doi.org/10.1016/j.neuron.2011.09.011> PMID: 21944778
19. Majounie E, Renton AE, Mok K, Dopper EGP, Waite A, Rollinson S, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *The Lancet Neurology*. 2012; 11(4):323–30. [http://dx.doi.org/10.1016/S1474-4422\(12\)70043-1](http://dx.doi.org/10.1016/S1474-4422(12)70043-1). PMID: 22406228
20. van Blitterswijk M, DeJesus-Hernandez M, Rademakers R. How do C9ORF72 repeat expansions cause ALS and FTD: can we learn from other non-coding repeat expansion disorders? *Current Opinion in Neurology*. 2012; 25(6):689–700. <https://doi.org/10.1097/WCO.0b013e32835a3efb> PubMed PMID: PMC3923493. PMID: 23160421
21. van Rheenen W, Shatunov A, Dekker AM, McLaughlin RL, Diekstra FP, Pulit SL, et al. Genome-wide association analyses identify new risk variants and the genetic architecture of amyotrophic lateral sclerosis. *Nat Genet*. 2016; 48(9):1043–8. <https://doi.org/10.1038/ng.3622> PMID: 27455348
22. Ferrari R, Hernandez DG, Nalls MA, Rohrer JD, Ramasamy A, Kwok JBJ, et al. Frontotemporal dementia and its subtypes: a genome-wide association study. *The Lancet Neurology*. 2014; 13(7):686–99. [https://doi.org/10.1016/S1474-4422\(14\)70065-1](https://doi.org/10.1016/S1474-4422(14)70065-1) PMID: 24943344
23. Hutchinson AD, Mathias JL. Neuropsychological deficits in frontotemporal dementia and Alzheimer's disease: a meta-analytic review. *Journal of Neurology, Neurosurgery & Psychiatry*. 2007; 78(9):917–28. <https://doi.org/10.1136/jnnp.2006.100669> PMID: 17371908
24. Taylor LJ, Brown RG, Tsermentseli S, Al-Chalabi A, Shaw CE, Ellis CM, et al. Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis? *Journal of Neurology, Neurosurgery & Psychiatry*. 2013; 84(5):494–8. Epub 2012/10/04. <https://doi.org/10.1136/jnnp-2012-303526> PMID: 23033353.
25. Silveri MC, Salvigni BL, Cappa A, Della Vedova C, Puopolo M. Impairment of Verb Processing in Frontal Variant-Frontotemporal Dementia: A Dysexecutive Symptom. *Dementia and Geriatric Cognitive Disorders*. 2003; 16(4):296–300. <https://doi.org/10.1159/000072816> PMID: 14512727
26. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of alzheimer disease: A 22-year prospective study of the framingham cohort. *Archives of Neurology*. 2000; 57(6):808–13. <https://doi.org/10.1001/archneur.57.6.808> PMID: 10867777
27. Bookheimer SY, Strojwas MH, Cohen MS, Saunders AM, Pericak-Vance MA, Mazziotta JC, et al. Patterns of Brain Activation in People at Risk for Alzheimer's Disease. *New England Journal of Medicine*. 2000; 343(7):450–6. <https://doi.org/10.1056/NEJM200008173430701> PMID: 10944562.
28. MacPherson SE, Parra MA, Moreno S, Lopera F, Della Sala S. Dual task abilities as a possible preclinical marker of Alzheimer's disease in carriers of the E280A presenilin-1 mutation. *Journal of the International Neuropsychological Society: JINS*. 2012; 18(2):234–41. Epub 2011/12/03. <https://doi.org/10.1017/S1355617711001561> PMID: 22133015.
29. MacPherson SE, Parra MA, Moreno S, Lopera F, Della Sala S. Dual memory task impairment in E280A presenilin-1 mutation carriers. *Journal of Alzheimer's disease: JAD*. 2015; 44(2):481–92. Epub 2014/10/30. <https://doi.org/10.3233/JAD-140990> PMID: 25352452.
30. Caselli RJ, Locke DEC, Dueck AC, Knopman DS, Woodruff BK, Hoffman-Snyder C, et al. The neuropsychology of normal aging and preclinical Alzheimer's disease. *Alzheimer's & Dementia*. 2014; 10(1):84–92. <https://doi.org/10.1016/j.jalz.2013.01.004> PMID: 23541188
31. Thai C, Lim YY, Villemagne VL, Laws SM, Ames D, Ellis KA, et al. Amyloid-Related Memory Decline in Preclinical Alzheimer's Disease Is Dependent on APOE epsilon4 and Is Detectable over 18-Months.

- PLoS one. 2015; 10(10):e0139082. Epub 2015/10/03. <https://doi.org/10.1371/journal.pone.0139082> PMID: 26430784; PubMed Central PMCID: PMC4592244.
32. Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Doppler E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *The Lancet Neurology*. 2015; 14(3):253–62. [https://doi.org/10.1016/S1474-4422\(14\)70324-2](https://doi.org/10.1016/S1474-4422(14)70324-2) PMID: 25662776
  33. Stokholm J, Teasdale TW, Johannsen P, Nielsen JE, Nielsen TT, Isaacs A, et al. Cognitive impairment in the preclinical stage of dementia in FTD-3 CHMP2B mutation carriers: a longitudinal prospective study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2013; 84(2):170–6. <https://doi.org/10.1136/jnnp-2012-303813> PMID: 23142962
  34. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorf LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. *Nature*. 2009; 461:747. <https://doi.org/10.1038/nature08494> PMID: 19812666
  35. Chatterjee N, Shi J, Garcia-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nature Reviews Genetics*. 2016; 17(7):392–406. <https://doi.org/10.1038/nrg.2016.27> PMID: 27140283
  36. Verhaaren BFJ, Vernooij MW, Koudstaal PJ, Uitterlinden AG, van Duijn CM, Hofman A, et al. Alzheimer's Disease Genes and Cognition in the Nondemented General Population. *Biological Psychiatry*. 2013; 73(5):429–34. <http://dx.doi.org/10.1016/j.biopsych.2012.04.009> PMID: 22592056
  37. Hagenaars SP, Harris SE, Davies G, Hill WD, Liewald DCM, Ritchie SJ, et al. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N = 112 151) and 24 GWAS consortia. *Mol Psychiatry*. 2016; 21(11):1624–32. <https://doi.org/10.1038/mp.2015.225> PMID: 26809841
  38. Sabuncu MR, Buckner RL, Smoller JW, Lee PH, Fischl B, Sperling RA. The Association between a Polygenic Alzheimer Score and Cortical Thickness in Clinically Normal Subjects. *Cerebral Cortex*. 2012; 22(11):2653–61. <https://doi.org/10.1093/cercor/bhr348> PMID: 22169231
  39. McIntosh AM, Gow A, Luciano M, Davies G, Liewald DC, Harris SE, et al. Polygenic Risk for Schizophrenia Is Associated with Cognitive Change Between Childhood and Old Age. *Biological Psychiatry*. 2013; 73(10):938–43. <https://doi.org/10.1016/j.biopsych.2013.01.011> PMID: 23419543
  40. Walton E, Geisler D, Lee PH, Hass J, Turner JA, Liu J, et al. Prefrontal Inefficiency Is Associated With Polygenic Risk for Schizophrenia. *Schizophrenia Bulletin*. 2014; 40(6):1263–71. <https://doi.org/10.1093/schbul/sbt174> PMID: 24327754
  41. Clarke TK, Lupton MK, Fernandez-Pujals AM, Starr J, Davies G, Cox S, et al. Common polygenic risk for autism spectrum disorder (ASD) is associated with cognitive ability in the general population. *Mol Psychiatry*. 2016; 21(3):419–25. <https://doi.org/10.1038/mp.2015.12> PMID: 25754080
  42. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLoS Medicine*. 2015; 12(3):e1001779. <https://doi.org/10.1371/journal.pmed.1001779> PMID: 25826379
  43. Hagenaars SP, Cox SR, Hill WD, Davies G, Liewald DCM, Charge consortium Cognitive Working Group, et al. Genetic contributions to Trail Making Test performance in UK Biobank. *Mol Psychiatry*. 2017. <https://doi.org/10.1038/mp.2017.189> PMID: 28924184
  44. Smith A. The symbol-digit modalities test: a neuropsychologic test of learning and other cerebral disorders. *Learning disorders*. 1991:83–91.
  45. Wain LV, Shrine N, Miller S, Jackson VE, Ntalla I, Artigas MS, et al. Novel insights into the genetics of smoking behaviour, lung function, and chronic obstructive pulmonary disease (UK BiLEVE): a genetic association study in UK Biobank. *The Lancet Respiratory Medicine*. 2015; 3(10):769–81. [https://doi.org/10.1016/S2213-2600\(15\)00283-0](https://doi.org/10.1016/S2213-2600(15)00283-0) PMID: 26423011
  46. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics*. 2015; 31(9):1466–8. <https://doi.org/10.1093/bioinformatics/btu848> PMID: 25550326
  47. R Core Team. R: A language and environment for statistical computing. 2013.
  48. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological)*. 1995; 57(1):289–300.
  49. Geschwind DH, Robidoux J, Alarcón M, Miller BL, Wilhelmsen KC, Cummings JL, et al. Dementia and neurodevelopmental predisposition: Cognitive dysfunction in presymptomatic subjects precedes dementia by decades in frontotemporal dementia. *Annals of Neurology*. 2001; 50(6):741–6. <https://doi.org/10.1002/ana.10024> PMID: 11761471
  50. Jiskoot LC, Doppler EGP, Heijer Td, Timman R, van Minkelen R, van Swieten JC, et al. Presymptomatic cognitive decline in familial frontotemporal dementia: A longitudinal study. *Neurology*. 2016; 87(4):384–91. <https://doi.org/10.1212/WNL.0000000000002895> PMID: 27358337