

## A General Cognitive Ability Factor for the UK Biobank

Camille Michèle Williams, Ghislaine Labouret, Tobias Wolfram, Hugo Peyre, Franck Ramus

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ethical approval from the Research Ethics Committee (reference 11/NW/0382) and the present

study was conducted based on application 46 007.

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## 68 Highlights

- We provide 8 standardized cognitive scores relative to an age-matched UK population
- We provide general intelligence (g) scores relative to the UK population
- We estimate the quality of the g factor for individuals with missing data
- We ran a g factor GWAS on UK Biobank individuals without brain data (N = 187,288)
- We created g polygenic scores for subjects with brain data: 7.7% explained variance

### **Abstract**

Our aim was to create a standardized measure of general intelligence (g) relative to the UK population for UK Biobank participants and derive a g factor polygenic score for UK Biobank participants with neuroimaging data.

We first created standardized cognitive test scores that were relative to the UK population based on the participants' age, sex, and occupation. Using confirmatory factor analysis, we extracted a g factor score from eight cognitive tests for all individuals who completed at least one test (N= 501,650), explaining 29% of the variance in g. We estimated the quality of the g factor for individuals with missing data.

Our g factor was highly correlated (r > 0.85) with alternative measures of intelligence calculated in the UK Biobank and correlations between measures of intelligence and life and health outcomes were similar.

We conducted a Genome-Wide Association Study (GWAS) on UK Biobank participants with a g factor of good quality (N= 223,731) and identified 36 genetic loci that were not previously linked to intelligence or cognitive performance. We ran a another GWAS on UK Biobank participants with a g-factor of good quality but without neuroimaging data (N= 187,288). We used the results from the second GWAS to create a polygenic score for individuals with neuroimaging data and their siblings (N= 40,871), explaining 7.7% of the variance in g.

The present study provides cognitive and genetic scores for use by future UK Biobank studies as control variables or to examine the genetic, brain, and environmental factors underlying intelligence.

### Introduction

Intelligence – our ability to learn, reason and solve problems (Arvey et al., 1994) – has been of great interest to researchers in epidemiology, neuroscience, and genetics as it predicts a wide array of educational, health, and social outcomes (e.g., Calvin et al., 2017; Deary et al., 2007; Strenze, 2007). Given the numerous genetic, neural, and environmental factors that may contribute to intelligence, large-scale studies are needed to identify the respective contribution of these factors and their potential interactions on intelligence (for review see Deary et al., 2019, 2021).

The UK Biobank is an ideal database to study the causes and consequences of intelligence, with its cognitive, brain imaging, genetic, health, and environmental data on more than 500,000 British middle-aged and older adults. Yet, numerous factors make the use of cognitive tests in the UK Biobank difficult. First, not all participants completed the same number of tests, and more recent tests have fewer participants (e.g., word production). Second, those who completed the same number of tests did not necessarily complete the same combination of tests. Across 501,650 participants with data on at least one of the eight cognitive tests, we counted 80 different combinations of tests, with only 30,471 participants having usable data on all eight tests. Third, the age at which a test was completed varies by test and participant, with some participants completing a test as early as 38 years old and as late as 82 years old. Fourth, some participants completed certain tests several times. Finally, some tests or similar tests with slight variations (e.g., 14 instead of 13 questions for Fluid Intelligence) were completed at different locations: the assessment center on a touchscreen or autonomously online, with one's device.

To maximize the number of participants included in their studies on intelligence in the UK Biobank, some researchers estimated intelligence with a single test, either a Verbal Numerical Reasoning (aka Fluid Intelligence) score or a reaction time score (Davies et al., 2016; Kievit et al., 2018; Lee et al., 2018; Savage et al., 2018; Sniekers et al., 2017). Others created a general intelligence (g) factor from 3 to 5 cognitive variables using Principal Component Analysis (PCA) or Confirmatory Factor Analysis (CFA; (Cox et al., 2019a; Hepsomali & Groeger, 2021; Lyall et al., 2016; Navrady et al., 2017). Thus, while the UK Biobank test battery includes a diverse array of cognitive tests, these have been relatively under-exploited up to now. Furthermore, most studies used test scores that were neither adjusted for age nor standardized relative to a representative sample of the general population, despite the acknowledged lack of representativeness of the UK Biobank sample (Fry et al.,

2017). As the UK Biobank continues to accrue data and attract new researchers, access to a standardized general factor of intelligence for most UK Biobank participants will benefit future studies that consider intelligence as a variable of interest or as a confounder.

Our study's aim was therefore to create a standardized general (g) factor for all UK Biobank participants with at least one cognitive test that is relative to the UK population given the participant's age, sex, and occupation. We first created standardized cognitive tests scores relative to the UK population and then extracted a g factor score from these 8 cognitive tests with CFA for individuals with data on at least one cognitive test. We estimated the quality of the g factors for participants with missing data. We assessed the external validity of our g factor by examining the correlation between our g factor and life outcomes.

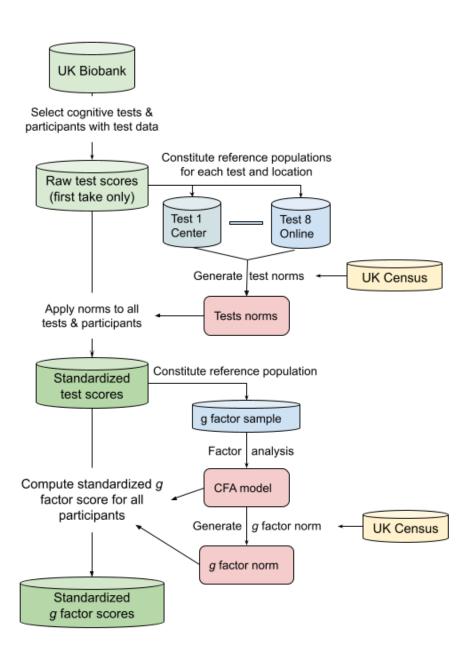
Finally, we conducted genetic analyses to create a general intelligence polygenic score (PGS) in the UK Biobank: We conducted a genome-wide association study (GWAS) of the g factor score on the UK Biobank participants with a g factor of good quality and without neuroimaging data (N = 187,288), and we assessed its predictive validity in the participants with neuroimaging data (N = 39,131). We additionally conducted a GWAS of the g factor score on the entire UK Biobank sample with a g factor of good quality to identify SNPs and genomic loci that were not previously associated with intelligence or cognitive abilities.

By creating cognitive and polygenic scores in the UK Biobank, we offer more robust measures of intelligence that foster homogeneity in intelligence research within the UK Biobank, and deliver summary statistics and PGS for future studies interested in examining the genetic associations of intelligence with neuroimaging, behavioral, and environmental measures.

### 1. Methods

All analyses were performed in R (R Core Team, 2022). Supplemental Information, supplemental data, and code are anonymously available on the Open Science Framework (OSF): https://osf.io/49scv/?view\_only=29e0ee6a1420461d81d234d94d549751.

The standardization of cognitive test and g factor scores relative to the UK population are summarized in Figure 1.



*Figure 1. G factor Creation Pipeline*. Cylinders represent datasets; inputs are UK Biobank and UK census data; blue cylinders are subsets of data (standardization samples). Boxes represent produced norms and models. Arrows represent computations.

### 2.1. UK Biobank dataset and participants

The UK Biobank is an open-access large prospective study with phenotypic, genotypic, and neuroimaging data from more than 500,000 participants. Participants were recruited between 2006 and 2010, from the vicinity of 22 assessment centers in England, Wales, and Scotland, with an age range for inclusion of 40–69 years (Sudlow et al., 2015). Data collection continues up to date.

All participants provided informed consent ("Resources tab" at https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200). The UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382) and the present study was conducted based on application 46007.

Participants performed a variety of cognitive tests, either when visiting a UK Biobank assessment center, or online during the online follow-up. Participants who did not complete any of the cognitive tests retained for this study were excluded, yielding 501,650 participants (excluded 843 participants).

The UK Biobank participants differ from the general UK population: they tend to be healthier and to have a higher socioeconomic status (e.g., more likely to own property; Fry et al., 2017; Keyes & Westreich, 2019), women are overrepresented and the distribution across ages differs from the general population (ages 50-59 in 2001 overrepresented, while 30-39 are underrepresented). To obtain an IQ score standardized with respect to the general population, one needs to compensate for the difference between UK Biobank participants and the general UK population.

### 2.2. Census data

UK 2001 census data (Office for National Statistics, 2011) was obtained from Casweb (casweb.mimas.ac.uk). We selected tables ST033 and ST034, which provide occupation categories for people currently in employment (ST033) and unemployed or economically inactive (ST034), between 16 and 74 (ST033) or 64 (ST034) years of age, by sex.

Occupation was retained as a stratification variable because of its correlation with intelligence (Schmidt & Hunter, 2004) and because it is available with a similar coding in the UK Biobank and in the 2001 census (Standard Occupational Classification 2000 - SOC2000; Office for National Statistics, 2000). We did not use the 2011 census because occupation was coded using SOC2010, which differs notably from SOC2000, with no easy correspondence.

We matched participants to census characteristics using their age, country, and occupation on the day the census was conducted (April 29, 2001; Supplemental Section 1.1).

### 2.3. Cognitive Tests

### 2.3.1. Test Selection

UK Biobank participants could complete several cognitive tests every time they visited the UK Biobank assessment centers (category 100026) and during the online follow-up (category 116). We used 8 cognitive tests to create the *g* factor (bolded tests in Table 1). Some participants completed some tests several times. We only considered the first occurrence of each test to best reflect the stable part of general intelligence, before aging and cognitive decline.

**Table 1.** *UK Biobank Cognitive Tests Considered for this Study.* 

Test (Included tests in bold)	UKB links (C: center, O: Online)	Description	Number of participan ts	Included or Excluded
FI - Fluid intelligence	C <u>100027</u> O <u>118</u>	Under a time limit of 2 minutes, answer a set of 13 (center) or 14 (online) numerical and verbal reasoning questions.	C=205,333 O=123,613	Included
MAT - Matrix pattern completion	C <u>501</u>	Select the element that best completes matrix pattern blocks. 15 puzzles.	C=33,657	Included
TWR - Tower rearranging	C <u>503</u>	Looking at an illustration of three pegs (towers), on which three differently-colored hoops have been placed, find how many moves it would take to rearrange the hoops into another specific position.18 puzzles.	C=33,381	Included
MEMN - Numeric memory	C <u>100029</u> O <u>120</u>	memorize 2 digits displayed on the screen. After they disappear for 3 seconds, enter them. Every time a sequence is correctly remembered, the next sequence is made one digit longer, up to a maximum of 12 digits.	C=82,865 O=111,062	Included

MEMS - Pairs matching	C <u>100030</u> O <u>117</u>	memorize the position of matching pairs of cards. Once the cards are turned face down, find as many pairs as possible in the fewest tries. Up to 3 rounds, with an increasing number of pairs (3, 6, 8).	C=498,730 O=118,528	Included
MEMW - Paired associate learning	C <u>506</u>	memorize 12 pairs of words shown for 30 seconds in total. After an interval (different test), see the first word of 10 of these pairs and select the matching second word from 4 alternatives.	C=34,045	Excluded: ceiling effect
MEMP - Prospective memory	C <u>100031</u>	Early in the test session, the participant is shown "At the end of the games we will show you four colored shapes and ask you to touch the Blue Square. However, to test your memory, we want you to touch the Orange Circle instead."	C=211,952	Excluded: only 1 question
MEML - Lights pattern memory	C <u>100028</u>	See pictures of houses which have some windows lit. After a 10-second delay, indicate which windows were lit.	C=3,714 (pilot only)	Excluded: too few participan ts
RT - Reaction time	C <u>100032</u>	Watch two cards on the screen. If they are the same, press a button-box as quickly as possible.	C=496,829	Included
SDS - Symbol digit substitution	C <u>502</u> O <u>122</u>	Identify the digits attached to each symbol in a grid, by using another grid linking symbols to digits as a key.	C=33,679 O=118,466	Included
TMT - Trail making	C <u>505</u> O <u>121</u>	Click sequentially on a set of digits in circles scattered around the screen (numeric path), then on a set of digits/letters (alphanumeric path).	C=34,045 O=104,028	Included
VOC - Picture vocabulary	C <u>504</u>	Indicate which of 4 images is most closely related to a displayed word. Difficulty varies according to the correctness of the previous answers.	C=33,606	Excluded: data not available in February 2022

WRD - Word production	C <u>100077</u>	State as many words beginning with the letter 'S' as possible within one minute.	C=3,744 (pilot only)	
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*Note*. The numbers of participants are taken from UK Biobank's showcase, across all instances, and include uncompleted tests.

### 2.3.3. Obtaining Raw Scores

To obtain a raw score for each test, we had to select between variables when several measures were provided for a test and/or transform these measures. We excluded participants with abnormal results (e.g., too many errors in the Symbol digit substitution test, indicating non-compliance with the test instructions) or who did not finish the test. Retained measures, transformations, and exclusion criteria are described in Table 2.

**Table 2.** Raw scores Transformations for the Included Cognitive Tests

Test	Measures used	Raw score computation
FI - Fluid intelligence	Number of correct answers [0-14] Fields 20016 (center) & 20191 (online)	Measure unchanged
MAT - Matrix pattern completion	Number of correct answers [0-15] Field 6373 (center only)	Measure unchanged
TWR - Tower rearranging	Number of correct answers [0-18] Field 21004 (center only)	Measure unchanged
MEMN - Numeric memory	Maximum number of digits remembered correctly [0-12] Fields 4282 (center) & 20240 (online)	Measure unchanged
MEMS - Pairs matching	Numbers of correct and incorrect matches in each round. The test has up to 3 rounds, with increasing difficulty (more pairs to remember). Access to a round is subject to a high score in the previous round. Fields 10136/398 (center) & 20131 (online) Fields 10137/399 (center) & 20132 (online)	Score computed as follows: - Each correct pair earns 2 points in rounds 1 and 2, 1 point in round 3 - Each incorrect pair loses 1 point - Within each round, negative scores are brought back to zero

SDS - Symbol digit substitution	Number of correct matches and number of attempts Fields 23324 (center) & 20159 (online) Fields 23323 (center) & 20195 (online)	Score = the number of correct matches Exclusion criteria: scores with more than 35 attempts and less than 65% correct matches (participants likely did not follow test instructions, for example by repeatedly entering the same digit). These outlier limits were computed as ±3sd from the mean.
RT - Reaction time	Mean time to correctly identify matches Field 20023 (center only)	Score = -log(mean time to correctly identify matches) Higher scores represent better performance No exclusion criteria because response times out of the 50ms to 2000ms range were already excluded.
TMT - Trail making	Duration to complete alphanumeric path trail Fields 6350 (center) & 20157 (online)	Score = -log(duration to complete alphanumeric path trail) Higher scores represent better performance This measure had higher correlations with other tests than a measure based on a combination of the numeric and alphanumeric trails.

### 2.3.4. Standardization of test scores

Standardization served two purposes: (1) to adjust for age effects (since intellectual performance varies with age), and (2) to provide a test score relative to the UK population (Figure 1). We created a common norming model for males and females. We simultaneously performed two adjustments:

- 1. An age adjustment by using the semiparametric continuous norming method proposed by Lenhard eand colleagues (2016). With this method, raw scores are modeled as a function of both standard scores and an explanatory variable, age when taking the test in this case.
- 2. A socio-demographic adjustment: by using standardization samples and computing weights to apply to participants, to compensate for the socio-demographic differences between the UK Biobank population and the complete UK population.

To do so, we first created standardization samples for each test and location (online/center), with about 32,000 to 497,000 participants. Details regarding the standardization sample creation and the number of participants in each sample are available in Supplemental Section 1.2.

We then used cell weighting to adjust measures from the standardization samples to reflect the UK population characteristics: For each standardization sample, we computed the proportion of participants for each possible combination of country, sex, age range at census, occupation status, and occupation SOC group. We compared the proportion of UK Biobank participants in each cell to the 2001 census and created weights for each cell by dividing the census proportion by the UK Biobank proportion. See Supplemental section 1.3. for details and an example.

We used the cNorm package (Lenhard et al., 2018) to compute norming models on the standardization samples with census weights, using the semiparametric continuous norming method. We modeled raw scores as a function of standard scores (percentiles) and age at test completion. Age at test completion is provided in <u>field 21003</u> for tests taken at the assessment center and in fields <u>20134</u> to <u>20138</u> for tests taken online. This age differs from the age used to compute census weighting factors, which is the participant's age on the day of the 2001 census.

We applied the norming models to the whole dataset and obtained standardized test scores for all participants on the tests they took (Figure 1).

### 256 2.4. *G* factor

We created a g factor score for all participants who completed at least one of the eight cognitive tests using confirmatory factor analysis (CFA). The g factor was standardized relative to the UK population. We also evaluated the impact of missing test scores on the quality of the g factor.

### 2.4.1. CFA Parameters

We performed a CFA with one-factor loading on the eight cognitive tests, using all pairwise complete cases (i.e., data from all participants who performed at least two tests). First, we checked whether the data was suitable for factor analysis by looking at the Kaiser, Meyer, Olkin measure of sampling adequacy and Bartlett's test of sphericity. We then estimated the CFA model with the *lavaan* R package (Rosseel, 2012). We used the full information maximum likelihood (FIML) estimator to make use of all data points even for cases with missing values, estimated the mean structure, and set the variance of the latent variable to 1 to

- estimate each observed variable loading. Model fit was assessed using commonly used model fit indices: the Tucker Lewis Index (TLI), the Comparative Fit Index (CFI), Standardized Root
- Mean Square Residual (SRMR), and the Root Mean Square Error of Approximation (RMSEA).
- Good fit was established with a CFI and TLI > 0.95, a RMSEA < 0.06 and a SRMR < 0.08 (Hu
- 273 & Bentler, 1999). See Supplemental Section 1.4. for a discussion on the choice of factor
- analysis.

### 2.4.2. G Factor Score Standardization

We created a standardization sample with 496,990 participants who had data for the census variables: sex, age on census day, and occupation on census day (countries were merged, see Supplement Section 1.3), to compute census weighting factors for these participants (Figure 1).

We computed factor scores using the regression estimation method, which maximizes validity (DiStefano et al., 2019). We then computed the weighted mean and weighted standard deviation of these scores, using the census weighting factors. We subtracted the weighted sample mean from the raw factor scores and divided the result by the weighted sample standard deviation, to obtain factor scores with a general population mean of 0 and a standard deviation of 1.

### 2.4.3. Evaluation of the g Factor Score Quality in the Presence of Missing Data

We examined how well a *g* factor score computed using a subset of tests (called partial factor score) correlates with the factor score that would have been obtained from the full set of eight tests (called full factor score) by looking at the correlation between the full and the partial factor scores for each the 80 subsets of tests present in the data, in the 30,471 participants who completed all the tests.

### 2.5. Analyses

In the following analyses, we included participants whose combination of cognitive tests allowed for a correlation with the complete g factor of 0.70 or higher (N=261,701). This threshold was chosen to maximize the robustness of the factor as well as the number of participants for which we would generate a g factor.

### 2.5.1. Correlations with Alternative estimates of g and Life outcomes

We examined the external validity of our g measure by examining correlations in complete cases between our g factor and FI, life and health outcomes expected to correlate with intelligence (e.g., educational attainment, income, deprivation indices, etc., life and health outcomes described in Supplemental Data S8). In brief, we selected well-being, household income before taxes, highest qualification as well as the Townsend deprivation score – a deprivation score of an individual's postal code from the census data - and the index of multiple deprivations that regroups several deprivation indices which vary by country. The latter include subindices such as health, income, education, employment, and housing. The index of multiple deprivations and its subindices come from a UK government qualitative study of deprived areas in British local councils and are calculated separately for England, Wales, and Scotland. Common multiple deprivation scores across countries were combined into a single variable for the correlation matrix (Supplemental Data S8). We adjusted each measure for sex and age at which the measure was reported.

### 2.5.1. Genetic Analyses

We conducted genetic analyses to (i) examine whether our measure of intelligence leads to the identification of novel SNPs and genomic loci that were not previously associated with cognitive performance (Lee et al., 2018) or intelligence (Savage et al., 2018) and to (ii) create polygenic scores (PGS) for individuals with neuroimaging data for future UK Biobank studies. A detailed overview of the genetic analyses is available in Supplemental Section 1.6.

### 2.5.1.1. Main Analyses

In brief, we conducted the first *g* factor GWAS on all 223,731 UK Biobank participants with good g factor quality (Full GWAS) to identify novel SNPs and a second *g* factor GWAS on 187,288 individuals without neuroanatomical data or twins/siblings with neuroanatomical data (No Neuroimaging GWAS) for the creation of PGSs. We removed participants with neuroanatomical data and their siblings to maintain the independence of predictions and prevent overfitting. GWASs were conducted with fastGWA (Jiang et al., 2021) on individuals of British ancestry and we controlled for relatedness, sex, center, genotyping chip, birth year,

and the first 40 PCs of the PCA on the genetic variation of a population to adjust for populationstratification.

We conducted functional mapping and annotation analyses on the GWAS summary statistics with FUMA to (i) report the genes associated with our *g* factor measure in the Full GWAS and No Neuroimaging GWAS (Supplemental Data S1-4 on OSF) and (ii) identify the genes associated with novel SNPs and genetic loci (Supplemental Data S6-7 on OSF). We report the SNP2GENE analysis on the summary statistics from the Full and No Neuroanatomy GWAS in the main text, the GENE2FUNC analysis of these summary statistics in Supplemental Data S3-4, and the GENE2FUNC analyses of the novel SNPs and genomic loci in text.

Using sBayesR (Lloyd-Jones et al., 2019), we created PGSs from the summary statistics of the No Neuroanatomy GWAS for individuals with either neuroimaging data or siblings with neuroimaging data to (i) assess the predictive power of genetic variance from the no neuroanatomy GWAS on the *g* factor and to (ii) be returned to the UK Biobank for use by future studies.

### 2.5.1.2. Additional Analyses

- We conducted additional analyses to answer the following questions.
  - 1. Does the g factor PGS explain more variance in g than the FI PGS? We ran a GWAS of the verbal-numerical reasoning test score (also known as Fluid Intelligence) on 180,722 individuals without neuroanatomical data or twins/siblings with neuroanatomical data (FI GWAS) and calculated FI PGS for individuals with neuroimaging data with the GWAS and PGS parameters described above. We then adjusted the FI PGS for sex, birth year, and the first 40 PCs and examined the percentage of variance explained in g and FI, separately.
  - 2. Once you control for environmental factors, what proportion of variance in g does the g PGS predict? To quantify to what extent the polygenic signal captures genetic effects that pass through the environment (indirect genetic effects or genetic nurture; Howe et al., 2021), we conducted family fixed-effects analyses. To do so, we first ran a g factor GWAS on the sample from the No Neuroimaging GWAS without siblings (No Family, No Neuroimaging GWAS). We used the summary statistics from this GWAS to create polygenic scores for individuals with siblings and then adjusted the PGS for sex, birth year, and the first 40 PCs. Finally, we ran the family fixed effects

- model with and without controlling for genetic relatedness and reported the change in explained variance of the PGS on the *g* factor when adjusting or not for sibling pairs.
  - 3. Do our g factor and FI measures have similar genetic correlations and heritabilities as the g factor and Educational Attainment (EA) measures from Lee and colleagues (2018)? We examined whether the genetic influences underlying our g factor and FI measure were similar to the genetic influences underlying the EA and the g factor (also known as Cognitive Performance) reported by Lee and colleagues (2018). To do so, we calculated the genetic correlations between our g-factor GWAS summary statistics, our FI GWAS summary statistics, and the publicly available Educational Attainment (EA) and g factor summary statistics. We additionally calculated the heritability estimates of each summary statistics file to examine whether our g factor was more heritable than our FI measure, previous g factor measures, and EA. These analyses were conducted with linkage disequilibrium score regression using the ldsc function from the GSEM package (Grotzinger et al., 2019).
  - 4. If had included participants with a poor g factor measure (r < .7), would the genetic correlation and heritabilities be the same? We conducted a GWAS on 307,009 individuals with a g factor measure and without neuroanatomical data or twins/siblings with neuroanatomical data (Low Quality No Neuroimaging g factor GWAS). If the genetic correlation and heritabilities were similar or better for this Low g Quality GWAS compared to the No Neuroimaging GWAS, we should be able to use this larger sample size to obtain more lead SNPs and better polygenic predictions.

# 2.5.3. Correlations with Alternative estimates of g, Life outcomes, Neuroimaging, and Genetic Measures

We conducted additional correlational analyses on a subset of participants that had neuroimaging data and PGSs. We examined correlations on complete cases between our *g* factor and alternative measures of intelligence for the UK Biobank (FI alone, *g* factor with 4 tests...), life and health outcomes expected to correlate with intelligence (e.g., educational attainment, income, deprivation indices, etc., life and health outcomes in Supplemental Data S8 on OSF), Total Brain Volume (TBV; Williams et al., 2021), and the FI and *g* factor PGS in individuals with neuroimaging data.

We compared our g factor score to alternate measures of intelligence by transforming the cognitive variables and extracting the g factor as done by Cox and colleagues (2019b) and

de Nooij and colleagues (2020), which used a different combination of cognitive tests and factoring methods with a similar sample to the one we used to calculate PGSs. The authors used cognitive tests completed at the center during the neuroimaging visit (Instance 2) and included tests that were not initially available at the first center visit. Cox and colleagues (2019) created a latent factor using CFA from the MAT, the SDS, the FI, and the TMT-B cognitive tests, and de Nooij and colleagues (2020) extracted the first principal component of the numerical memory, the FI, the SDS, the TMTB, the MAT, and the TWR cognitive tests.

Since our *g* factor is adjusted for age, we created alternative *g* factors that are adjusted for age in the CFA or after extracting the first PC. We additionally similarly controlled for sex to examine whether differences between our *g* factor and the *g* alternatives could be explained by sex differences.

### 403 2. Results

### 3.1. Cognitive Tests

We compared the distribution of the standard test scores before and after adjusting for the difference between the UK Biobank population and the general UK population (Figure 2). After adjusting for age and census weights, the distribution of the scores shifted to the right, indicating a relatively higher score in the UK Biobank relative to the UK norm (Supplemental Section 2.1.1). In some cases, the distribution was not normal because of its categorical nature (e.g., MEMN) or because of threshold effects (e.g., MEMS). Correlations between standard scores ranged from 0.07 (MEMN and RT) to 0.50 (TMT and SDS). TMT and FI had the highest correlation coefficients with other cognitive tests (Supplemental Section 2.1.2).

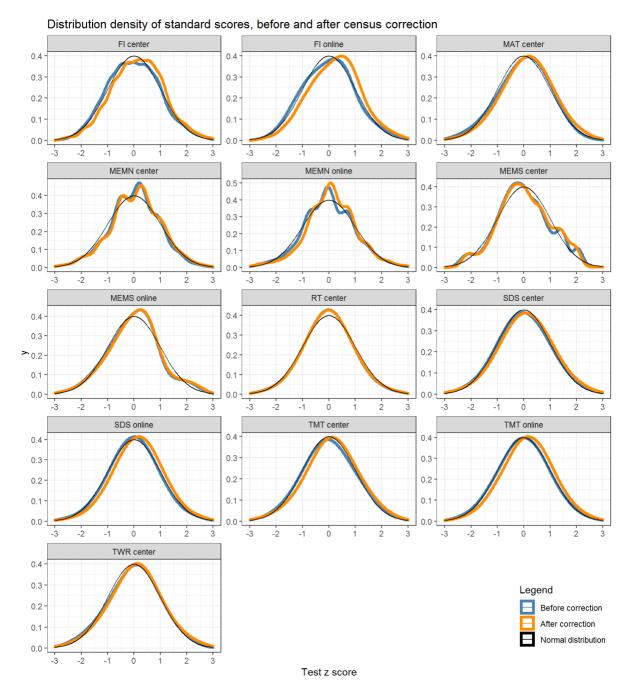


Figure 2. The Distribution of Cognitive Tests Before (blue) and After (orange) correcting for Sociodemographic Differences between the UK Biobank Population and the UK Population (2001 Census). FI: Fluid Intelligence. RT: Reaction Time. MAT: Matrix Pattern Completion. TWR: Tower Rearranging. MEMN: Numeric Memory. MEMS: Pair Matching. SDS: Symbol Digit Substitution. TMT: Trail Making.

### 3.2. CFA results

### **3.2.1.** Model Fit

The CFA model fit on 501,650 participants (30,307 with complete data; N Women = 272,955; N Men = 228,695) was good (CFI = 0.955, TLI = 0.938, RMSEA = 0.024, SRMR = 0.028). The g factor accounted for 29% of the variance across cognitive tests and the loadings ranged from 0.77 (TMT) to 0.277 (RT) (Figure 3; Supplemental Section 2.1.3). Sex differences in cognitive and g factor scores are available in Supplemental Section 2.1.4.

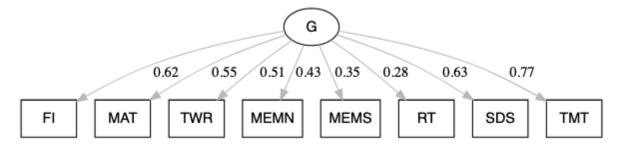


Figure 3. Confirmatory Factor Analysis of UK Biobank Cognitive Tests. Analyses were conducted with full information maximum likelihood with the lavaan package (Rosseel et al., 2021). Explained variance: 29%. FI: Fluid Intelligence. MAT: Matrix Pattern Completion. TWR: Tower Rearranging. MEMN: Numeric Memory. MEMS: Pair Matching. SDS: Symbol Digit Substitution. TMT: Trail Making. Loadings from completely standardized solutions (i.e., standardized observed and latent variables).

### 3.2.2. Distribution of the g factor before and after census correction

We compared the distribution of the g factor scores before (M = -0.004, sd = 0.993) and after (M = 0.086, sd = 1.001) adjusting for the difference between the UK Biobank population and the general UK population (d = 0.09). After adjusting, the factor score distribution shifted to the right, indicating a relatively higher score in the UK Biobank relative to the UK norm (Figure 4; g distribution by job category in Supplemental Section 2.1.5).

### Distributions of G, before and after census correction

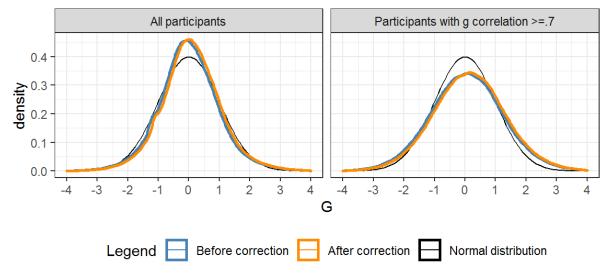


Figure 4. The Distribution of the g Factor Scores Before and After Census Correction for All Participants (left) and a Subset of Participants (right). The subset of participants had a g factor score from a combination of subtests that allowed for a minimum correlation of 0.70 between the partial g factor score and the full g factor score.

### 3.2.4. G Factor Quality

The quality of the g factor and the number of individuals for each possible combination of completed tests are available in Supplemental Section 2.1.6. For example, if we select participants with any of the first 73 cognitive test combinations observed in the UK Biobank, the worst factor scores of these participants would have a correlation of 0.70 with the ideal, 8-tests factor scores, and the number of available participants will be over 261,701.

### 3.3. Analysis of Individuals with a g Factor Quality over 0.70

### 3.3.1. Correlations: Alternative *g factors* and Life outcomes

We examined the external validity of our g measure by examining the association in complete cases between our g factor measure, FI (which is often used as a proxy of g in most studies), and life outcomes collected at the first center visit or online to estimate correlation coefficients on a larger number of participants (Figure 5). We removed well-being to include more participants because it was poorly correlated to our g factor (Figure S9).

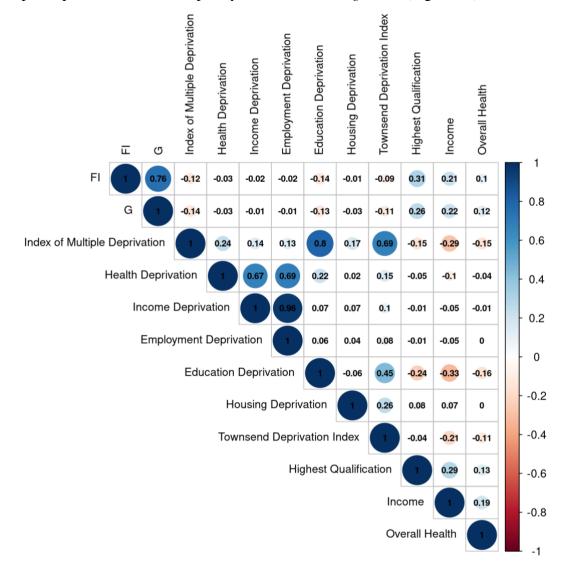


Figure 5. Correlation between age and sex-adjusted g factor Scores and Health and Life Outcomes. Pearson correlation coefficients were estimated on 181,327 individuals without missing data. All measures are adjusted for age at which the measure was taken and sex. G corresponds to the g factor of individuals with a combination of cognitive tests that allowed for a correlation of 0.70 or higher between their actual g factor and what their g factor would have been if they had completed all tests. FI: Fluid Intelligence.

### 3.3.2. Genetic Analyses

### **3.3.2.1. Main Results**

We identified 150 approximately independent SNPs attaining genome-wide significance in the full sample GWAS and 100 in the No Neuroanatomy Sample GWAS (Table 3). There were 127 genomic risk loci associated with the g factor in the Full GWAS and 84 genomic risk loci with the g factor in the No Neuroanatomy GWAS ( $P < 5 \times 10^{-8}$ ; Supplemental Data S1-S2 on OSF). See Figure S3 for the Manhattan and QQ-plots.

We found 37 novel SNPs and 36 novel genetic loci (rs10182628 and rs7595241 mapped to the same loci; Supplemental Data S5 on OSF) that were not within +-250kb of the genomewide significant SNPs associated with Lee's g factor (Cognitive Performance in Lee et al., 2018) and Savage's g factor (Intelligence in Savage et al., 2018) and SNPs previously associated with cognitive ability or educational attainment based on the GWAS catalog.

**Table 3.** No Neuroimaging and Full Sample GWAS Results.

GWAS Sample	N	Mean χ2	LD Score Intercept	Ratio (SE)	# Lead SNPs	# Loci	h2 (SE)
Full	223,731	1.93	1.046 (0.017)	0.049 (0.018)	150	127	0.201 (0.008)
No Neuroanatom y	187,288	1.76	1.032 (0.015)	0.0412 (0.0191)	100	84	0.197 (0.009)

*N.B.* N, GWAS sample size; mean  $\chi$ 2, mean GWAS  $\chi$ 2 statistics across HapMap3 SNPs with MAF greater than 0.01; LD score intercept, the estimate of the intercept from an LD score

regression using HapMap3 SNPs with MAF greater than 0.01; no. lead SNPs, number of

approximately independent (pairwise r2 < 0.1) FUMA lead SNPs; no. loci, number of

associated loci. H2, heritability estimated from the ldsc function in the Genomic SEM package.

The positional annotation of candidate SNPs indicated that the majority of independent lead SNPs were located in the intronic, mRNA intronic, and intergenic regions in the Full and No Neuroanatomy GWAS (Supplemental Data S1-S2 on OSF).

From the 37 novel lead SNPs, we pinpointed 90 genes (44 protein-coding genes) by positional, eQTL, and chromatin interaction mapping in the *g* factor Full GWAS. MAGMA Tissue expression in the SNP2GENE analyses revealed that associated genes were highly expressed in several brain regions (Figure S4). The heatmap of gene expression showed that RIMS4, SEZ6, and SLC24A2 were highly expressed in the brain, whereas PLEKHB1 was highly expressed in the brain amongst other tissues (Figure S5). Several of these genes were previously associated with the cognitive dimension dimensional psychopathology among other traits (Figure S6).

We created PGS for 40,871 individuals with either neuroimaging data or siblings with neuroimaging data and g factor quality greater than r >= 0.70. Of the 39,131 individuals with neuroimaging data, 24,229 had a g factor quality of r = 1 (Table S5).

We adjusted the g and FI values for sex, year of birth, and the first 40 genetic PCs. The g factor PGS created from the No Neuroanatomy GWAS explained 7.7% of the variance in the g factor, whereas the FI created from the No Neuroanatomy GWAS explained 6.6% of the variance in FI.

### 3.3.2.2. Additional Analyses

- 1. Does the g factor PGS explain more variance in g than the FI PGS? The g factor PGS created from the No Neuroanatomy GWAS explained 1.7% more variance in g than the FI PGS created from the No Neuroanatomy GWAS, which explained 6.0% of the variance in the g factor. The g factor PGS created from the No Neuroanatomy GWAS explained 5.8% of the variance in FI.
- 2. Once you control for environmental factors, what proportion of variance in g does the g PGS predict? The family fixed-effect analysis on the PGS from the No Family, No Neuroimaging GWAS summary statistics when adjusting for sex, year of birth, and the first 40 genetic principal components, showed a decrease in explained variance from 6.6% to 3.2% and a reduction of 17% in the beta. See Supplemental Section 2.2.4. for additional PGS analyses.
- 3. Do our g factor and FI measures have similar genetic correlations and heritabilities as the g factor and Educational Attainment (EA) measures from Lee and colleagues (2018)? The SNP heritability of the present g factor was similar to the heritability of Lee's g factor (h2 = 0.199, SE = 0.008) and greater than Lee's EA (h2 = 0.151, SE = 0.004; Table 3 and S10). Lee's g factor was highly correlated to our various estimates

- of the g factor 0.92-0.93, suggesting that they capture common genetic influences (Figure S8).
- 4. Do participants with a low-quality g factor estimate (r < .7) impact the results? We found that the heritability of the Low-Quality No Neuroimaging GWAS (h2 = 0.127, SE = 0.005) was much lower than the heritability of the No Neuroimaging GWAS (h2 = 0.197, SE = 0.008; Table S10) and that the genetic correlation between the Low-Quality No Neuroimaging GWAS and the No Neuroimaging GWAS was of 0.98 (Figure S8), suggesting that although both GWASs are measuring overlapping genetic effects, the Low-Quality No Neuroimaging GWAS has more measurement error. The genetic correlations of the Low-Quality No Neuroimaging GWAS were lower with Lee's g factor (0.87 vs. 0.93) and EA (0.5 vs. 0.55), suggesting that doubling the sample size by including g factor estimates of lower quality is counterproductive for the GWAS.

## 3.3.3. Correlations: Alternative *g factors*, Life outcomes, Neuroimaging, and Genetic

### Measures

We conducted separate correlation analyses on our g factor with the alternative g factors, neuroimaging, and PGSs because these data were only available for participants who visited the center for the neuroimaging visit.

The alternative g factors were created from cognitive tests scores from their neuroimaging visit and cognitive tests that were only available at the second visit. The correlation between our study's g factor (adjusted for age, not sex) and the cognitive tests ranged from 0.25 (RT) to 0.84 (TMT), whereas the age-adjusted g factors from previous studies ranged from about 0.16 (RT) to 0.71 (MAT; Figure S11).

Correlation coefficients between our study's g factor and alternative g factors were high (0.85 to 0.89; Figure S12). The alternative g factor measures were more correlated to the highest qualification achieved (r = 0.26-0.29 vs. r = 0.24) and income (r = 0.18-0.19 vs. r = 0.16) than the present g factor because the cognitive tests included in the alternative g factors were the cognitive tests with the highest correlations with highest qualification and income (Figure S13).

The g factor from the present study and the g factors calculated as done by previous studies were highly correlated after adjusting for the age of test completion and sex. The g factors positively correlated with the PGS, highest qualifications, income before tax, overall

health, and total brain volume, and negatively with the deprivation indices (Figure 6). We also
looked at the correlation coefficients of the $g$ factors with well-being and additional deprivation
indices, which reflect the degree of housing, employment, education, etc. deprivation in an
area. However, these correlations were small and therefore reported in Figure S14.

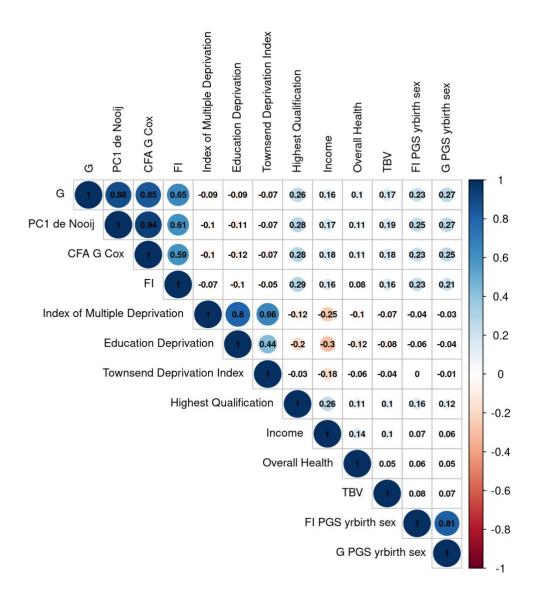


Figure 6. Correlation between age and sex-adjusted G Factor Scores, selected Life and Health Outcomes, Total Brain Volume (TBV), and sex and year of birth adjusted Polygenic Scores (PGS). Pearson correlation coefficients were estimated on 18,976 individuals without missing data. We included all life and health variables with an r > or = 0.1 with g except for the Townsend Deprivation Index. CFA: Confirmatory Factor Analysis. PC1: 1st Principal Component. G: General Factor for intelligence. G corresponds to the g factor of individuals with a combination of cognitive tests that allowed for a correlation of 0.70 or higher between their actual g factor and what their g factor would have been if they had completed all tests. FI: Fluid Intelligence. Income: Income before tax. PGS were adjusted for sex and birth year (yr birth).

### Discussion

We aimed to create a robust measure of general intelligence for all UK Biobank participants. We created an age-standardized *g* factor measure relative to the UK population for about 500,000 UK Biobank participants, with an estimation of the *g* factor's quality for each participant, allowing researchers to select their sample based on their quality requirements. We examined correlations between the present study's *g* factor, alternative measures of intelligence, and life outcomes. Our *g* factor was highly correlated with alternative *g* factor measures of intelligence in the UK Biobank and their correlations with life and health outcomes were similar. The GWASs and functional analyses on our new measure of general intelligence revealed novel SNPs that were either associated with genes related to the cognitive dimension of psychopathology or genes that were not previously associated with intelligence, cognitive ability, or educational attainment. Finally, our study provides a PGS for about 38,000 UK Biobank individuals with neuroimaging data that explained 7.7% of the variance in the intelligence score.

There was a high correlation between our g factor and the alternative g factor measures derived using methods from previous UK Biobank studies. Although g factors differed in terms of the included cognitive tests, and in some cases, in terms of the captured variance, they were highly similar (r = 0.85-0.94). This is consistent with the high level of common measurement reported across different cognitive tests, providing further support for a common underlying component of intelligence (Johnson et al., 2004; Kaufman, 2012).

The *g* factor from the present study and alternative *g* factor measures were similarly correlated to life outcomes, such as household income before tax or highest qualification (i.e., level of education) when adjusting for age and sex. The slightly higher correlations between the alternative *g* factor measures and the highest qualification achieved compared to our *g* factor could be explained by the tests used to create the alternative *g* factors, which correlated the most with the highest qualification. Therefore, some outcomes, such as the highest qualification, may not be as highly correlated to general intelligence as previously thought and may be more correlated with specific cognitive tests. However, the main advantage of our *g* factor is that it was calculated on all of the 500 000 UK Biobank participants with a measure of its quality.

Consistent with a previous meta-analysis (Veenhoven & Choi, 2012), we did not find a correlation between our *g* measure and well-being. Although the studies in this meta-analysis have been criticized for their limited measure of well-being, as they solely focused on life

satisfaction, another study with a larger range of well-being measures found that the positive association between IQ and well-being disappeared after controlling for socioeconomic status (SES; Altaras Dimitrijević et al., 2018).

We report a negative correlation between our *g* factor and the Townsend Index, an SES measure that reflects a person's material deprivation based on unemployment rates, non–car ownership, non–homeownership, and household overcrowding in their postal code. This negative correlation coincides with the negative correlation between neighborhood deprivation and educational attainment (Garner & Raudenbush, 1991), as well as previous findings that childhood IQ remains stable across old age (Deary et al., 2000), predicts later SES outcomes (Deary et al., 2005). We additionally found a negative correlation between our *g* factor and the index of multiple deprivation of the area where a person resides, which was largely explained by the negative correlation between the *g* factor and the education deprivation index of the area where a person resides. The education deprivation index was measured by a score reflecting child and adolescent school performance (e.g., English, math, and science exams Stage 3 exams) and adult skills (e.g., the proportion of adults with no or low qualifications) in a given geographical area.

The GWASs led to the identification of novel SNPs that were not previously associated with cognitive performance or intelligence. These SNPs were not associated with genes related to educational attainment, or cognitive ability, although some were associated with genes involved in the cognitive domain of psychopathology (McCoy et al., 2018). For instance, the PLEKHB1 (Pleckstrin Homology Domain Containing B1) protein-coding gene was prioritized by eQTL and positional mapping. This gene is associated with neurological diseases and the cognitive dimension of psychopathology (McCoy et al., 2018).

The *g* PGS created from the No Neuro GWAS summary statistics explained 7.7% of the variance in the *g* factor of individuals with neuroimaging data and siblings with neuroimaging data. Lee and colleagues (2018) similarly found that their CP PGS created from their GWAS summary statistics explained 7% of the variance in CP for individuals in the Wisconsin Longitudinal Study, a study that used cognitive tests with similar properties to their discovery GWAS. However, they found that the CP PGS from the summary statistics of their multi-trait analysis GWAS (MTAG) of CP, which yielded more significant SNPs, explained 9.7% of the variance in CP for individuals in the Wisconsin Longitudinal Study.

The FI PGS explained 1.7% less variance in g than the PGS of the g factor, suggesting that the g PGS is a better genetic predictor of g. The genetic correlations between FI and the g factor were high, suggesting that FI and g have very similar genetic influences. The g factor and FI PGSs also similarly correlated with total brain volume, the most correlated brain measure to intelligence (Deary et al., 2021). Taken together, our findings suggest that a common genetic component to FI and the g factor may explain the genetic association between intelligence and TBV. Although the FI PGS may be sufficient when investigating global brain size associations with intelligence, the g factor PGS still explains a larger range of variance in general intelligence than FI and its use should be favored when controlling for the genetic components of intelligence.

The present study has several limitations. First, the selection of cognitive tests currently available in the UK Biobank severely underrepresents verbal ability. Indeed, of the 8 tests that could be considered in the present study, only 2 were verbal: the FI test (verbal-numerical reasoning) and the numeric memory test (digit span). These imbalances are currently being corrected by the addition of new tests (picture vocabulary and word production), which will become available later, and which would justify a new calculation of the g factor once they are taken by a sufficient number of participants.

The underrepresentation of verbal skills may partly explain why men were found to have a slightly higher g factor than women (d= -0.13). Another non-exclusive explanation may be that male and female UK populations are unequally sampled in the UK Biobank, with women representing 54.4% of the entire sample. Thus women with lower general intelligence may have been oversampled compared to men with lower intelligence. Finally, participants were born between 1934 and 1971 (median: 1950), a period when UK women may still have had inferior higher education opportunities, and therefore fewer opportunities to fully develop their intellectual potential. These three considerations suggest that the UK Biobank is not a suitable database to reliably estimate sex differences in cognitive abilities, and potentially in other phenotypes associated with cognitive ability.

We were limited when correcting for the socio-demographic imbalance in the UK Biobank. Due to occupation coding constraints, we had to use the 2001 census data, instead of the 2011 census data, and we only determine the occupation on census day of 71.5% of participants. Moreover, we were limited by the number of variables on which we adjusted the UK Biobank sample. Adjusting additional variables, such as years of education would have improved the adjustment.

Finally, the *g* factor score was calculated from different subsets of tests and although we took the first instance of a test, some tests were taken at different ages. Therefore, although we attempted to provide a *g* factor measure of pre-aging adult intelligence, some test scores may already be influenced by cognitive decline. One study reported that most UK Biobank cognitive tests show reasonable stability over time except for the visual memory task (pairsmatching; Lyall et al., 2016), while another study found declines in cognitive abilities before 65 years of age were small (Cornelis et al., 2019). Considering that the majority of participants were 64 years or younger and that the median age was 60, our g factor measure likely reflects pre-cognitive-decline intelligence scores.

The present study provides cognitive tests scores and a *g* factor score for UK Biobank participants that are adjusted for age and relative to the UK population, as well as a *g* PGS for UK Biobank individuals with neuroimaging data that explained 7.7% of the variance in the *g* factor. The behavioral and genetic scores from this study will enable the simultaneous investigation of the associations between the brain, genes, and intelligence, which are currently rare in the present literature (Deary et al., 2021). Taken together, the present study offers robust measures of intelligence that will foster homogeneity in intelligence research within the UK Biobank and provides summary statistics and PGSs for future studies interested in examining the genetic associations of intelligence with neuroimaging, behavioral, and environmental measures.

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