SHORT TELOMERE LENGTH IS ASSOCIATED WITH IMPAIRED COGNITIVE PERFORMANCE IN EUROPEAN ANCESTRY COHORTS

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Supplementary Data

GENOTYPE DATA

Genotyping was done on the Illumina Human610-Quad BeadChip (ERF, QIMR, LBC1936), the HumanOmniExpress BeadChip (BETULA1-3, LLS1, LLS2, HRS), HumanCoreExome (FITSA), HumanExome-12v1-1_A (BETULA2,3), the Metabochip (NSHD, Gender, SATSA) (Illumina Inc, San Diego, California), and on the Affymetrix 6.0 (NTR). Quality control for genotyping in each cohort was done for 1) samples: those samples with genotyping call rate <95% (or similar cohort specific cut-off) or with extreme heterozygosity were removed; and 2) SNPs: those SNPs with call rate <95% (or similar cohort specific cut-off), minor allele frequency <1% or Hardy Weinberg equilibrium p-value $<10^{-4}$ were excluded. Imputation was performed either using a hidden Markov model algorithm implemented in MACH ([Center for Statistical Genetics, University of Michigan, Ann Arbor]) or IMPUTE 2.0 with exclusion of poorly imputed SNPs (MACH: r2hat<0.3; IMPUTE: proper_info<0.4).

DATA OVERLAP

In the current ENGAGE effort we include data from several cohorts of European ancestry populations from around the world. Moreover, we also include data from the CHARGE consortium as well as rely on earlier telomere length GWAS data. Hence, it is inevitable that some data overlap exist between different studies and data sets. Here we try to disentangle what the implications are; essentially we have three types of overlap:

ENGAGE COHORTS AND TELOMERE LENGTH GWAS

About 40% of the ENGAGE samples in this study (ERF, LLS, NTR, QIMR) were already used to identify the seven SNPs in the TL GWAS by Codd et al[1]. This corresponds to the overlap between discovery sample and MR sample discussed by Lawlor[2]; this is not an issue for a true two-sample MR, and in our study, which is somewhere between a two-sample and a one-sample study, it would likely bias the causal estimation towards the null. This may affect the power of our study somewhat, but no impact on the validity of the results.

CHARGE DATA AND TELOMERE LENGTH GWAS

In short, the same situation applies as described above which is sometimes referred to as “Winners curse”. Hence, the sample overlap was found for ERF only and would here only push our results towards the null where the validity of the results would not be questioned.

ENGAGE COHORTS AND CHARGE DATA

Some ENGAGE studies contributed to the CHARGE cognition GWAS efforts as well. For general cognitive function BETULA1, ERF, HRS, and LBC1936 contributed with data, where LBC1936 also contributed to the DSST GWAS. The effect is moderate for both general cognitive function and DSST, where about 10-15% of the CHARGE samples have already been used in ENGAGE MR analysis. The situation is different for STROOP, where about 45% of the CHARGE data (ERF) have already been used in ENGAGE MR study.

GENETIC RISK SCORE CALCULATION

An individual *non-weighted* genetic risk score (GRS) using the 7 SNPs reported by Codd *et al*[1] was used as an instrumental variable (IV) in the Mendelian Randomization analysis. All cohorts with genotype information (direct or imputed for lead SNP or proxies) on *at least 4 of the 7 SNPs* listed in Table S2 performed these analyses. In short, the calculation was done using information from (in prioritized order): 1) directly genotyped lead SNPs counting 0, 1 or 2 alleles of the TL-decreasing allele; 2) imputed lead SNPs calculating the probability of the TL-decreasing allele on a scale from 0-2; 3) a directly genotyped proxy (in high linkage disequilibrium, r^2 >0.8 in HapMap II CEU with the lead SNP) counting 0, 1 or 2 alleles of the TL-decreasing allele; or, if data was missing, 4) the average allele frequency in European populations as reported by Codd et al[1]. In reality, most cohorts contribute with the same SNPs, either directly genotyped or imputed. Only for two SNPs, there was a proxy used for analysis.

DIRECTLY GENOTYPED SNPS

Each directly genotyped SNP was transformed to be a count of 0/1/2 alleles of the TL-decreasing allele from **Table S2**.

MISSING AND IMPUTED GENOTYPES

For SNPs that were not directly genotyped and/or had missing information (either for one individual or for the full cohort) there were three different options to complete the dataset.

ALTERNATIVE 1. For imputed SNP data with good imputation quality (IMPUTE proper_info>=0.4 MACH r2hat>=0.3) the imputed lead SNP was used. The output from the imputation was different depending on which software used (posterior probabilities range 0-1 [IMPUTE] or range 0-2 [MACH]). The dosage for the TL-decreasing allele was used for calculating the score. For MACH users, the dosage information reported was used directly for calculation of the genotype score if minor allele= TL-decreasing allele. Otherwise the formula: dosage [TL-decreasing allele]=2 - dosage [non-TL-decreasing allele] was used. For IMPUTE users, the dosage was calculated as: dosage[TL-decreasing allele]= 1 * *p*(AB) + 2 * *p*(BB) where *p*(AB) and *p*(BB) were the posterior probabilities of the heterozygote (AB) and minor homozygote(BB) respectively and B was the TL-decreasing allele.

ALTERNATIVE 2. A proxy with r^2 >0.8 was used with the same effect allele as the TL-decreasing allele of the lead SNP assigned 0/1/2.

ALTERNATIVE 3. The imputed SNP genotype score from the *Codd et al*[1] paper was used.

CALCULATION OF INDIVIDUAL GENETIC RISK SCORE

The individual score was then calculated by adding the number of TL-decreasing alleles for each individual. The sum was within the range of 0-14 (**Table S1**).

PLEIOTROPY TEST

To assess the potential pleiotropic effects of selected SNPs, we used a method that utilized summarized statistics for this purpose. This test was conducted for each SNP set under the null hypothesis that each SNP used for the genetic risk score has an association with cognitive performance that is proportional to its association with telomere length. The rejection of the null hypothesis indicated heterogeneity of the associations between the SNPs and cognitive performance. In such cases where the null hypothesis was rejected,

stepwise removal of SNPs from the SNP set was performed until there was no significant heterogeneity[3, 4]. However, our analyses showed that there was no significant evidence supporting the pleiotropic effects in any of these SNPs (All P values > 0.1, Supplementary Figure 3). Similarly, additional sensitivity analyses using MR Egger regression and median weighted MR methods for general cognitive performance using CHARGE data did not indicate pleiotropic effects.

FUNCTIONS OF SELECTED SNPS AND GENES

The rs10936599 is within ***TERC*** (Telomerase RNA component) and the rs2736100 is within ***TERT*** (Telomerase reverse transcriptase). Telomerase is a ribonucleoprotein polymerase that maintains telomere ends by addition of the telomere repeat TTAGGG. The enzyme consists of a protein component with reverse transcriptase activity, and an RNA component, encoded by this gene, that serves as a template for the telomere repeat. Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres. Studies in mouse suggest that telomerase also participates in chromosomal repair, since de novo synthesis of telomere repeats may occur at double-stranded breaks. The gene ***RTEL1*** (Regulator of telomere elongation helicase 1), rs755017 is located within, encodes a DNA helicase which functions in the stability, protection and elongation of telomeres and interacts with proteins in the shelterin complex known to protect telomeres during DNA replication. The ***NAF1*** (Nuclear assembly factor 1 ribonucleoprotein) gene, rs7675998 is located in is involved in TERC biogenesis. The proteins coded by ***OBFC1*** (Oligonucleotide/oligosaccharide-binding fold containing 1), are subunits of an alpha accessory factor that stimulates the activity of DNA polymerase-alpha-primase, the enzyme that initiates DNA replication. OBFC1 also appears to function in a telomere associated complex with C17ORF68 and TEN1. The exact roles of ***ZNF208*** (rs8105767) and ***ACYP2*** (rs11125529) in telomere regulation are yet not clear.

MODEL DEFINITIONS

The following models were used to assess the relationship between (I) TL and cognitive trait, (II) genetic risk score (GRS) and TL, and (III) between GRS and cognitive trait. Study specific covariates below include study centres, sub-cohorts, family relatedness adjustments and other study specific covariates. All models were further adjusted for sex and age group defined as:

1. Age group 1 -> 0 – 29 years
2. Age group 2 -> 30 – 59 years
3. Age group 3 -> 60 – 79 years
4. Age group 4 -> 80+ years

Both TL and cognitive traits were Z-transformed before analyses.

MODEL I

Cognitive trait = TL + sex + age group + study specific covariates

MODEL II

TL = GRS+ sex + age group + study specific covariates

MODEL III

Cognitive trait = GRS + sex + age group + study specific covariates

META-ANALYSES

Before meta-analysis, quality control was done in R, where risk score distributions were visually inspected. Inverse standard errors of the regression coefficient for each cognitive trait were plotted over the square-root of corresponding sample size and inspected for deviations from linearity that would indicate transformation- or processing errors. We assessed between-cohort heterogeneity via Cochrane's Q-statistic and I^2-statistics[5-7]. Additional sensitivity analyses were conducted for observational associations in STROOP with adjustments for smoking and alcohol in ERF and LLS1 cohorts.

META-REGRESSION ANALYSES FOR AGE

In order to make a deeper investigation whether age was important for the TL analyses, we conducted a meta-regression analysis treating mean age as a mediator in the GRS~TL association. There seemed to be a trend with increasing effect sizes with increasing age in the cohorts as seen in **Figure S4**, but considering sample size (circles proportional to sample size) the analysis gave a non-significant result even after removing the young QIMR and the old LLS2 cohorts.

INSTRUMENTAL VARIABLE ANALYSES

The GRS was used as instrumental variable (IV) in the Mendelian Randomization analysis, and the Wald ratio estimator was used to calculate IV-adjusted effect estimate for TL. Briefly, for each outcome, the corresponding beta from the meta-analysis of associations of GRS with the cognitive trait was divided by the beta from the meta-analysis of the association of GRS with TL: $\beta_{IV-trait} = \frac{\beta_{GRS-trait}}{\beta_{GRS-TL}}$. The standard errors (SE) for the IV estimators were estimated using the delta method[8]:

$$SE_{IV-trait} = \text{abs}(\beta_{IV-trait}) \cdot \sqrt{(SE_{GRS-TL}/\beta_{GRS-TL})^2 + (SE_{GRS-trait}/\beta_{GRS-trait})^2} \ .$$

The 95% confidence intervals (CI) were calculated as: $\beta_{IV-trait} \pm 1.96 \cdot SE_{IV-trait}$. P-values were attained using the Z-statistic: $Z_{IV-trait} = \beta_{IV-trait}/SE_{IV-trait}$.

To further investigate if the effect size estimates were divergent, the IV estimators β_{IV} and the observational associations $\beta_{TL-trait}$, were compared: $\beta_{Diff} = \beta_{IV-trait} - \beta_{TL-trait}$. The corresponding standard error was approximated by assuming zero covariance between the estimates:

$$SE_{Diff} = \sqrt{(SE_{IV-trait})^2 + (SE_{TL-trait})^2} \ .$$

Subsequently, we used standard normal asymptotics for the difference: $Z_{Diff} = \frac{\beta_{Diff}}{SE_{Diff}}$ with 95% CI as: $CI_{Diff} = \beta_{Diff} \pm 1.96\, SE_{Diff}$. The p-value for the hypothesis H_0: $\beta_{Diff} = 0$ was derived from the standard normal distribution.

STRATIFICATIONS

As a second step, we stratified the analysis based on *APOE* genotype as the ε4 allele is known to interact with cognitive performance. The definition of groups was as follows:

1. ε2/ε4 -> Exclude

2. ε4/ε4, ε4/ε3 -> Carriers
3. ε3/ε3, ε2/ε3, ε2/ε2 -> Non-carriers

Additional models were run to assess influence of *APOE* genotype and subsequently used in the IV analysis:

MODEL I
In APO ε4 carriers:
Cognitive trait = TL + sex + age group + study specific covariates
In APO ε4 non-carriers:
Cognitive trait = TL + sex + age group + study specific covariates
MODEL III
In APO ε4 carriers:
Cognitive trait = GRS + sex + age group + study specific covariates
In APO ε4 non-carriers:
Cognitive trait = GRS + sex + age group + study specific covariates

CHARGE DATA ANALYSES

Replication analyses were done using data from the CHARGE meta-analyses[9, 10] to investigate TL as a causal factor for general cognitive function, processing speed and executive functioning. First, 7 TL-associated SNPs used for the GRS were extracted from the CHARGE summary statistics. The individual effect of each SNP on cognitive function was plotted in the **Figure S2** with corresponding data in **Table S7**. The GRS was associated with cognitive function (β = -0.007 SD-decrease of TL per allele, 95% CI, -0.012, -0.002; p=0.006; **Figure S2; Table S7**) and was calculated as $X = \sum \beta_i s_i^{-2} / \sum s_i^{-2}$ where β_i is the effect of the TL-decreasing risk alleles and s_i its corresponding standard error[11]. The IV-estimator (**Figure S2; Table S8**) was calculated as $\beta_{GRS\_IV} = \beta_{GRS\_CHARGE\_cognition} / \beta_{GRS\_Codd\_TL}$.

MENDELIAN RANDOMIZATION TESTING USING Z-SCORE

Z-SCORE BASED WALD METHOD FOR A SINGLE SNP

Here, we denote β_1 as the effect of a SNP on the outcome with standard error being σ_1 and β_0 as the effect of a SNP on the exposure with standard error being σ_0, β_{iv} and σ_{iv} as the final Mendelian randomization estimate and standard error of the exposure on the outcome. Z_1, Z_0, Z_{iv} are the corresponding Z-scores. Thus, we have

$$\beta_{iv} = \frac{\beta_1}{\beta_0}$$

with standard error approximated via the Delta-method as

$$\sigma_{\beta_{iv}} = \sqrt{\beta_{iv}^2} \sqrt{(\frac{\sigma_1}{\beta_1})^2 + (\frac{\sigma_0}{\beta_0})^2}$$

Thus, the Z-score is

$$Z = \frac{\beta_{iv}}{\sigma_{\beta_{iv}}} = \frac{a}{\sqrt{(\frac{\sigma_1}{\beta_1})^2 + (\frac{\sigma_0}{\beta_0})^2}} = \frac{a}{\sqrt{(\frac{1}{Z_1})^2 + (\frac{1}{Z_0})^2}}$$

with a = 1 if Z_1 and Z_0 are in the same direction, otherwise a = -1.

TESTING THE ASSOCIATION BETWEEN GENETIC RISK SCORE AND THE OUTCOME BASED ON Z-SCORE

The association between GRS and the outcome is the averaged effect of each SNP on the outcome, which means the final estimate is a weighted summary of each individual SNP. Thus, we can use the same method as the authors used in the summary GWAS studies when pooling Z-scores across studies using sample sizes as the weights.

Here, we are pooling Z-scores across SNPs. The Z-score for GRS on the outcome with p SNPs and sample sizes N is thus as follows:

$$Z = \frac{\sum_{i=1}^{p} N_i Z_i}{\sum_{i=1}^{p} N_i}$$

TESTING THE ASSOCIATION BETWEEN THE EXPOSURE AND THE OUTCOME BASED ON Z-SCORE

We can obtain the Z-score for the association between GRS on the exposure and the outcome, separately. Then, we use the equation below to obtain the final Z-score for the Wald method of the Mendelian randomization estimate test.

$$Z = \frac{a}{\sqrt{(\frac{1}{Z_{GRS.outcome}})^2 + (\frac{1}{Z_{GRS.exposure}})^2}}$$

with a = 1 if $Z_{GRS\text{-}exposure}$ and $Z_{GRS\text{-}outcome}$ are in the same direction, otherwise a = -1.

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The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE) cognitive working group banner includes the authors of the following publications (in alphabetical order):

1. Davies G. et al. Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53949). Molecular Psychiatry 20:183-192, 2015

2. Ibrahim-Verbaas CA et al. GWAS for executive function and processing speed suggests involvement of the CADM2 gene. Molecular Psychiatry 21:189-197, 2016

Hieab Adams[1,2], David Ames[3,4], Helene Amieva[5], Najaf Amin[2,6], Philippe Amouyel[7], Nicola J Armstrong[8,9,10,11], Amelia A Assareh[8], John R Attia[12], Rhoda Au[13,14], Stefania Bandinelli[15],

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REFERENCES

1. Codd V, Nelson CP, Albrecht E, Mangino M, Deelen J, Buxton JL *et al.* Identification of seven loci affecting mean telomere length and their association with disease. *Nat Genet* 2013; **45**(4)**:** 422-427.

2. Lawlor DA. Commentary: Two-sample Mendelian randomization: opportunities and challenges. *Int J Epidemiol* 2016; **45**(3)**:** 908-915.

3. Johnson T. Efficient Calculation for Multi-SNP Genetic Risk Scores. *ASHG poster, San Francisco* 2012.

4. gtx: Genetics ToolboX (R-package). https://cran.r-project.org/web/packages/gtx/, 2012, Accessed Date Accessed 2012 Accessed.

5. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**(11)**:** 1539-1558.

6. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj* 2003; **327**(7414)**:** 557-560.

7. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *Bmj* 2007; **335**(7626)**:** 914-916.

8. Oehlert GW. A note on the delta method. *American Statistician* 1992; **46:** 27-29.

9. Davies G, Armstrong N, Bis JC, Bressler J, Chouraki V, Giddaluru S *et al.* Genetic contributions to variation in general cognitive function: a meta-analysis of genome-wide association studies in the CHARGE consortium (N=53949). *Mol Psychiatry* 2015; **20**(2)**:** 183-192.

10. Ibrahim-Verbaas CA, Bressler J, Debette S, Schuur M, Smith AV, Bis JC *et al.* GWAS for executive function and processing speed suggests involvement of the CADM2 gene. *Mol Psychiatry* 2016; **21**(2)**:** 189-197.

11. Dastani Z, Johnson T, Kronenberg F, Nelson CP, Assimes TL, Marz W *et al.* The shared allelic architecture of adiponectin levels and coronary artery disease. *Atherosclerosis* 2013; **229**(1)**:** 145-148.

FIGURE LEGENDS

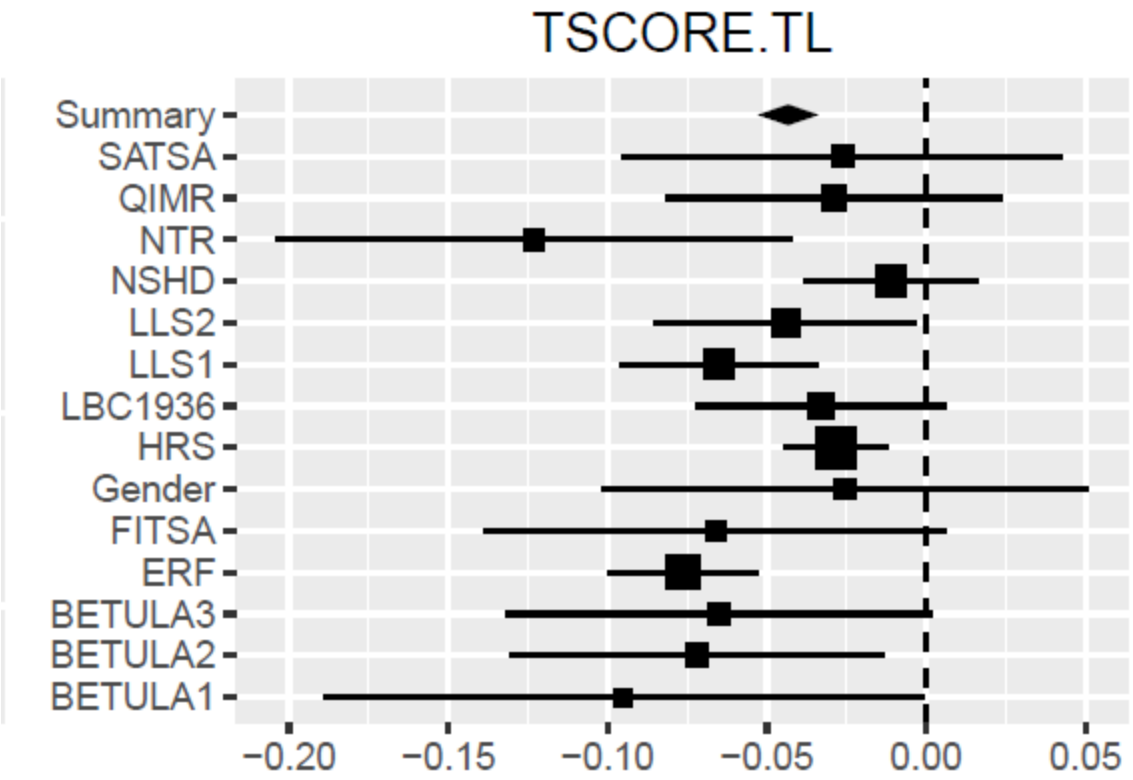
Supplementary Figure 1. Meta-analysis of genetic risk score association with telomere length across all European ancestry cohorts (N=17 052). The seven SNPs included in the risk score were all identified in the largest telomere length genome-wide association study to date (Codd et al, 2013).

Supplementary Figure 2. Associations of the seven SNPs and the combined risk score with telomere length from Codd et al, 2013, (left panel) and with general cognitive performance in CHARGE data with N=53 949 from Davies et al, 2015, (middle panel). Right panel includes the full instrumental variable analysis providing a causal estimate for telomere length on general cognitive performance.

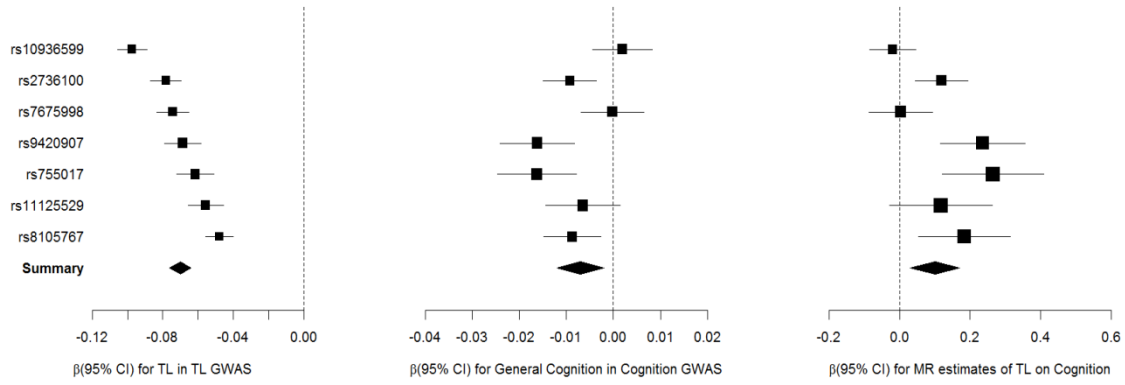
Supplementary Figure 3. Scatter plots showing the per-allele association from CHARGE summary data with cognitive performance traits (general cognitive performance, animal naming, LF, trails A, and trails B) plotted against the per-allele association with telomere length (with vertical lines showing 95% confidence interval for each SNP). Because the effect sizes of SNPs on DSST and Stroop are unavailable, we could not perform such pleiotropy test using the same method as for general cognitive performance.

Supplementary Figure 4. Scatter plot showing the regression coefficient for GRS~TL over mean age in cohorts. Area of circle is proportional to number of subjects in study, line is a loess smoothing curve.

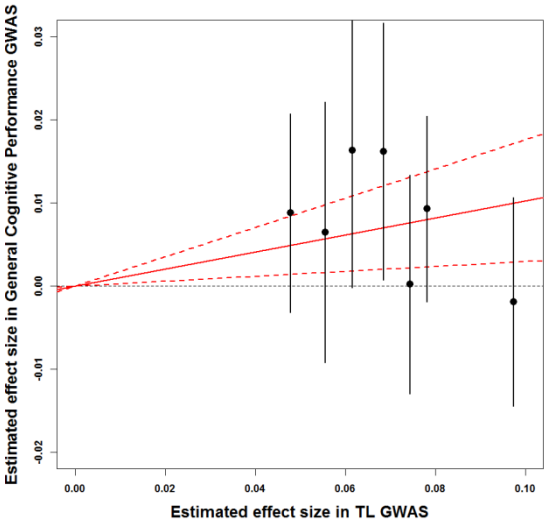
Supplementary Figure 1

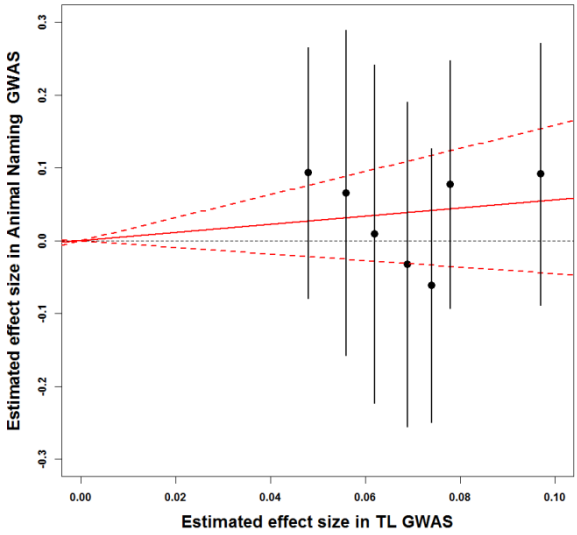


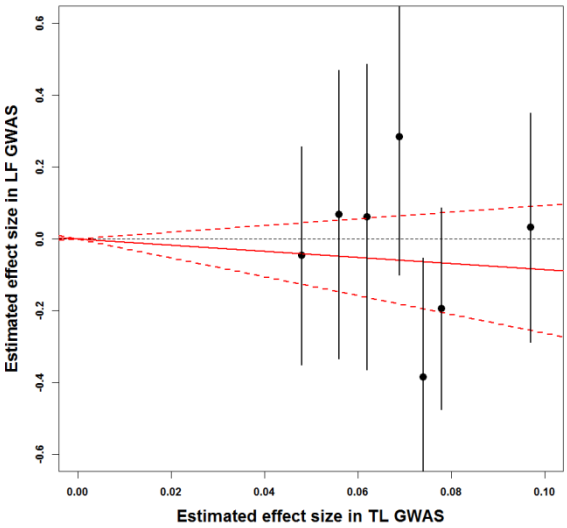
Supplementary Figure 2

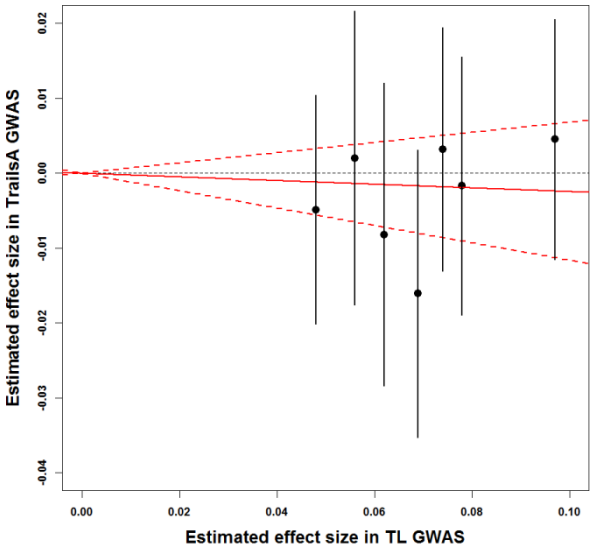


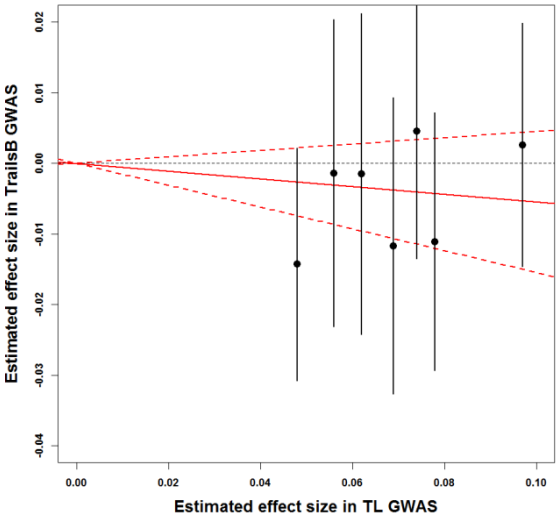
Supplementary Figure 3











Supplementary Figure 4.