The association between telomere length (TL) dynamics on cognitive performance over the life-course is not well understood. This study meta-analyses observational and causal associations between TL and six cognitive traits, with stratifications on APOE genotype, in a Mendelian Randomization (MR) framework. Twelve European cohorts (N = 17 052; mean age = 59.2 ± 8.8 years) provided results for associations between qPCR-measured TL (T/S-ratio scale) and general cognitive function, mini-mental state exam (MMSE), processing speed by digit symbol substitution test (DSST), visuospatial functioning, memory and executive functioning (STROOP). In addition, a genetic risk score (GRS) for TL including seven known genetic variants for TL was calculated, and used in associations with cognitive traits as outcomes in all cohorts. Observational analyses showed that longer telomeres were associated with better scores on DSST (β = 0.051 per s.d.-increase of TL; 95% confidence interval (CI): 0.024, 0.077; P = 0.0002), and MMSE (β = 0.025; 95% CI: 0.002, 0.047; P = 0.03), and faster STROOP (β = −0.053; 95% CI: −0.087, −0.018; P = 0.003). Effects for DSST were stronger in APOE ε4 non-carriers (β = 0.081; 95% CI: 0.045, 0.117; P = 1.0 × 10⁻⁵), whereas carriers performed better in STROOP (β = −0.074; 95% CI: −0.140, −0.009; P = 0.03). Causal associations were found for STROOP only (β = −0.598 per s.d.-increase of TL; 95% CI: −1.125, −0.072; P = 0.026), with a larger effect in ε4-carriers (β = −0.699; 95% CI: −1.330, −0.069; P = 0.03). Two-sample replication analyses using CHARGE summary statistics showed causal effects between TL and general cognitive function and DSST, but not with STROOP. In conclusion, we suggest causal effects from longer TL on better cognitive performance, where APOE ε4-carriers might be at differential risk.

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INTRODUCTION
Telomeres, short DNA sequences at the end of chromosomes, are considered markers of biological age. Cell replication and oxidative stressors contribute to the loss of telomere nucleotides over time; below critical length, cellular senescence will follow.1 An increasing number of studies have shown the importance of telomere length (TL) in ageing, specifically in the development of dementia and cognitive impairment.2-8 Using a relatively large group of non-demented older individuals, Yaffe et al.3 demonstrated an association between longer telomeres and higher score in the digit symbol substitution test (DSST)—a measure of processing speed—at baseline. After seven years, the individuals with longer telomeres at baseline performed better in the modified mini-mental state exam (MMSE) but not in DSST.
### Table 1. Study samples

| Cohort | Full name of cohort | N | Age (yr) mean (s.d.) | Women (%) | GRS mean (s.d.) | MMSE | DSST | BLOCK | MEMORY | STROOP | General | APOE | genotype |
|--------|--------------------|---|---------------------|-----------|----------------|-------|------|-------|--------|--------|---------|-------|-----------|
| BETULA1 | The Betula Study a | 163 | 50.9 (7.8) | 54.8 | 8.5 (1.57) | 58.3 | 8.87 (1.55) | x | x | x | x | x | Yes |
| BETULA2 | The Betula Study a | 396 | 62.4 (14.5) | 54.0 | 8.6 (1.51) | 54.8 | 8.87 (1.56) | x | x | x | x | x | Yes |
| ERF | Erasmus Rucphen Family (EUROSPAN) | 2502 | 51.6 (15.8) | 58.3 | 1.76 (0.36) | 55.6 | 8.65 (1.57) | x | x | x | Yes |
| FITSA | The Finnish Twin Study on Ageing | 1280 | 14.1 (2.4) | 54.8 | 3.7 (0.6) | 52.6 | 8.5 (1.5) | x | x | x | Yes |
| LBC1936 | Lothian Birth Cohort 999 | 69.6 (0.8) | 58.0 | 1.3 (0.5) | 49.0 | 8.36 (1.52) | x | x | x | x | Yes |
| LLS1 | Leiden Longevity Study 1 | 2305 | 59.2 (6.8) | 61.6 | 1.46 (0.26) | 54.8 | 8.47 (1.53) | x | x | x | Yes |
| LLS2 | Leiden Longevity Study 2 | 868 | 93.3 (2.6) | 58.0 | 1.28 (0.22) | 61.6 | 8.41 (1.47) | x | x | x | x | Yes |
| NSHD | National Survey of Health and Development | 2425 | 53 (0) | 58.0 | 1.54 (0.3) | 52.6 | 8.65 (1.45) | x | x | x | x | Yes |
| NTR | Netherlands Twin Register | 200 | 40.3 (16.4) | 58.0 | 2.72 (0.56) | 66.5 | 5.26 (1.5) | x | x | x | x | x | Yes |
| QIMR | Twin studies at the Queensland Institute of Medical Research | 1280 | 14.1 (2.4) | 37.6 | 0.76 (0.27) | 3.7 (0.6) | 587 | 6.68 (1.96) | x | x | x | x | Yes |

Abbreviations: BLOCK, block design test; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium; DSST, digit symbol substitution test; ENGAGE, European Network for Genetic and Genomic Epidemiology; GRS, genetic risk score; MEMORY, verbal memory or picture learning test; MMSE, mini-mental state exam; STROOP, Stroop color word task interference score; TL, telomere length; Yr, year.

### MATERIALS AND METHODS

#### Study samples

Twelve cohorts with a total of 17 052 individuals (Table 1), all with European ancestry populations, participated in the ENGAGE effort. The sample-size weighted mean of age was 59.2 years with s.d. = 8.8. Most cohorts contributed data measured at mid-life or older. The Leiden Longevity Study 2 (LLS2) was the oldest cohort (mean age = 93.3 years). The Netherlands Twin Register (NTR) included middle-aged adults (mean age = 40.3 years, s.d. = 16.4) and QIMR (Twin studies at the Queensland Institute of Medical Research) included adolescents only (mean age = 14.1 years, s.d. = 2.4). All but one study showed a fairly even proportion of sexes (range: 49–67% women); FITSA (The Finnish Twin Study on Ageing) included women only. Additional study-specific details are found in Supplementary Table 1.

#### Cognitive traits

Six different cognitive traits were tested in a combined meta-analysis of the ENGAGE cohorts: (1) general cognitive function; (2) MMSE; (3) processing speed with DSST or the variant symbol digit substitution task; (4) visuospatial functioning with block design test (BLOCK); (5) episodic memory by either verbal learning or picture learning tests (MEMORY); and (6) executive functioning using Stroop interference score (STROOP). Detailed descriptions of the different cognitive traits are found in the supplement (Supplementary Table 3). All cohorts participated with at least one cognitive trait; no single cohort had all of them (Table 1).
Telomere length measurements
Telomere length was measured in leukocytes in whole blood/buffy coat except for the HRS study, which used measurements from saliva. DNA from saliva derives for the most part (~74%) from leukocytes, and TL measurements from blood and saliva have been reported to have good correlations (R = 0.72). Standard qPCR techniques for TL measurement were applied as described by Cawthon with minor modifications in the Lothian Birth Cohort (LBC) and BETULA. In brief, telomere (T) and single copy gene (S) quantity were measured and a T/S-ratio was calculated. One or several reference samples were included in all runs and a relative telomere length was calculated for each sample.

Genotyping
Information on genotyping platform, quality control and single-nucleotide polymorphisms (SNPs) used in each cohort is available in the supplement (Supplementary Data and Supplementary Table 2). An additive un-weighted GRS was calculated for each individual by summarizing the number of risk alleles from seven different loci (TFRC, TERT, NAFI, OBFC1, ZNF208, RTE1 and ACYP2) where SNPs (rs10936599, rs2736100, rs7675998, rs9420067, rs8105767, rs755017 and rs11125529) have been found to be associated with TL. Investigations of possible pleiotropic effects from the different genetic variants used in the GRS are discussed in the supplement (Supplementary Data). Four cohorts (ERF (Erasmus Rucphen Family), LLS, NTR and QIMR) from the current effort contributed to CHARGE analyses (Supplementary Data). Four cohorts (ERF (Erasmus Rucphen Family), LLS, NTR and QIMR) from the current effort contributed to CHARGE analyses (Supplementary Data). Four cohorts (ERF (Erasmus Rucphen Family), LLS, NTR and QIMR) from the current effort contributed to CHARGE analyses (Supplementary Data).

Replication data
Summarized results from the CHARGE Consortium’s meta-analyses of genome-wide association studies between genotypes and general cognitive function (N = 53 949) were presented in Table 2. Four tests of processing speed including the DSST (Supplementary Data) were applied as described by Cawthon with minor modifications in the Lothian Birth Cohort (LBC) and BETULA. In brief, telomere (T) and single copy gene (S) quantity were measured and a T/S-ratio was calculated. One or several reference samples were included in all runs and a relative telomere length was calculated for each sample.

Results
RESULTS
Observational analyses of telomere length and cognitive traits
Significant associations, supporting the relationship between longer telomeres and better cognitive ability, were seen between TL and MMSE, DSST and STROOP using fixed-effects meta-analysis (Table 2, Figure 2). Positive associations were observed for MMSE (0.025 per s.d.-increase in TL; 95% confidence interval (CI) 0.002, 0.047) and DSST (0.051; 95% CI 0.024, 0.077). For STROOP, a negative beta (-0.053 per s.d.-increase in TL; 95% CI -0.087, -0.018) was seen, which was in accordance with the hypothesis that longer telomeres are associated with shorter time for completion of the Stroop interference test. However, after corrections for multiple comparisons, the association with MMSE was not significant.

Genetic risk score for telomere length
The combined effect of the GRS on TL was −0.048 s.d.-change of TL per allele (95% CI: −0.064, −0.032, P-value = 4.0*10^-6) calculated using random-effects meta-analysis (Supplementary Data: Supplementary Figure S1). The corresponding R-statistic was 36, indicating that the GRS-TL estimate provided a sufficiently strong instrument for further use in IV analyses. Although heterogeneity was detected, all cohorts showed negative effect sizes ranging from −0.01 to −0.13 (Supplementary Table S1). Additional tests investigating possible pleiotropic effects for SNP-trait associations were done and found no evidence of such (Supplementary Data).

Instrumental variable analyses of telomere length and cognitive traits
Instrumental variable analyses for causal associations of TL on cognitive performance were conducted for all cognitive traits. Only the association between TL and STROOP was found to be causal (Table 2), and for each s.d.-decrease in TL an effect change of −0.60 in Stroop score was detected (95% CI: −1.12, −0.07, P-value = 0.026). However, the association would not be significant
after multiple testing adjustments. The difference in effect sizes between observational and causal betas for STROOP was statistically significant (Table 2).

**Stratified analyses**

Stratified meta-analyses were performed for *APOE* ε4-carriers (*n* = 2380) and ε4 non-carriers (*n* = 5669) separately (Supplementary Data). Observational associations were seen between TL and DSST in non-carriers (**β** = 0.081, 95% CI: 0.045, 0.117, *P*-value = 1 x 10^-5) and with better performance for STROOP in carriers (**β** = -0.074, 95% CI: -0.140, -0.009, *P*-value = 0.027) (Supplementary Table S4). A causal association between long telomeres and better performance for STROOP was detected amongst *APOE* ε4-carriers (**β** = -0.70, 95% CI: -1.33, -0.07, *P*-value = 0.030), although the finding would not hold after multiple testing adjustments. No other causal effects for TL on cognitive traits were seen in either carriers or non-carriers (Supplementary Table S6).

**Replication analyses**

In replication efforts, two-sample MR analyses were carried out using summary statistics from CHARGE GWAS on general cognitive function, DSST and STROOP. Data from the TL GWAS were used for the genetic instrument (Supplementary Data). Results provided evidence for a causal association between longer leukocyte TL and better general cognitive function (**β** = 0.086 per s.d.-increase of TL, 95% CI: 0.016–0.156, *P*-value = 0.016, Table 2) and better DSST
scoring (Z-score = 2.02, P-value = 0.043, Table 2). No evidence for a causal effect by TL on STROOP was found (Table 2).

**DISCUSSION**

In the present study, we provide evidence for observational and causal associations between longer telomeres and better cognitive performance. By conducting a large meta-analysis of 12 cohorts from European ancestry populations with measured telomeres and assessments of cognitive function, we were able to observe associations between TL and better scoring on MMSE, DSST and STROOP. Moreover, APOE ε4-carriers seemed to have different effects for the observed association with worse performance in DSST but better in STROOP. The association between longer telomeres and faster completion of the Stroop interference test was also found to be significant in causal analysis for all individuals and in APOE ε4-carriers only. However, none of the significant causal associations detected for STROOP passed multiple testing corrections. Hence, in line with this, using summary data from CHARGE, we found support for a causal association from TL on general cognitive function and DSST, but not on STROOP.

In the biology of aging, telomere length has long been considered as a biomarker reflecting the underlying cellular state. Recently, however, several research papers have presented evidence of telomeres being involved in the process of cellular senescence causing increased risk of disease.\(^5\),\(^6\),\(^16\),\(^27\) Moreover, other studies suggest telomeres might even elongate in somatic cells to maintain cellular stability.\(^7\),\(^12\),\(^26\),\(^29\) although this phenomenon could be partly explained by leukocyte turnover or imprecise measurements. Nevertheless, telomere biology has implications for the aging processes and studies are warranted to elucidate the full complexity.

With this effort we demonstrate several observational associations between TL and cognitive traits, both confirming earlier studies and presenting new links. General cognitive function is usually operationalized as a composite score across a number of diverse cognitive domains capturing most of the cognitive variation.\(^3\),\(^5\) As an overall measure of cognition it also predicts mortality;\(^30\) likewise, the length of telomeres can be used to predict mortality.\(^21\),\(^31\),\(^32\) Thus, if both general cognitive function and TL serve as valid biomarkers of aging, associations between these markers are expected, although causality needs to be further investigated. In the ENGAGE data (N = 12 283), we were not able to detect any association between general cognitive function and TL, but using the CHARGE summary data (N = 53 949) we provided evidence for a causal association. It is likely that the ENGAGE analysis was low in power; effect sizes had overlapping CIs. A possible biological mechanism for a causal association could be explained by overall body frailty; the lengths of telomeres are important for maintaining cellular stability at old age and hence also important for biological aging processes such as decline in cognitive performance.\(^1\) Causal links have also been demonstrated using animal models. A mouse with telomerase deficiency, expressing accelerated aging with malfunctioning tissue repair and impaired neurologic function, had restored functions again upon telomerase reactivation.\(^33\)

The DSST test assesses processing speed required to translate a code of symbols and digits as fast as possible in a given time frame. Processing speed has been demonstrated to have a steady, almost linear decline with advancing age, and its decline leads other forms of cognitive decline.\(^34\),\(^35\) Hence, in light of this it is not surprising that we, and others,\(^3\) detect a fairly stable observational association of longer telomeres and better DSST scoring. The MR analysis did not indicate a causal association in our samples (N = 4419); on the other hand, when increasing power using CHARGE data (N = 32 088) we were able to find support for a positive causal relationship from longer TL on DSST scoring.

Moreover, APOE ε4 non-carriers scored better on the test with a larger effect size seen in observational analysis from TL on DSST. Thus, as APOE genotype is important for elucidating different risk groups for many age-related phenotypes, it is possible that it applies to TL dynamics and cognitive performance as well.

Yaffe et al.\(^5\) showed that longer TL at baseline gave less longitudinal decline in MMSE, and we presented cross-sectional evidence from observational associations in line with these findings; longer TL is consistent with better MMSE scoring. However, while causal estimates support these associations, the CIs were wide and results did not reach statistical significance. Unfortunately, CHARGE data on MMSE were not available for replication analysis.

The STROOP variable taps the executive functioning by a combined color and word test to be completed as quickly as possible. To the best of our knowledge, there has been only one earlier small study investigating baseline and attrition TL associations with executive functioning, with inconclusive results.\(^3\) Our ENGAGE analysis included 2940 individuals where we found both an observational and causal association between longer telomeres and faster completion of the Stroop test. The large effect size difference was however disturbing and not explained by additional adjustments for smoking and alcohol (Supplementary Data). Further, causal associations did not hold after multiple testing corrections and when using the two-sample approach including the larger CHARGE data (N = 7726) we could not replicate the association, although the effects were in the same direction. Hence, it is possible that the STROOP finding observed in the ENGAGE data is a false discovery. In addition, the stratified analyses by APOE ε4 genotype found ε4-carriers to perform better, which is contradictory to what would be expected.

The strength of this study is the effort of combining multiple European cohorts with TL, cognitive and genetic data available as well as APOE genotype. By doing so, we were able to detect patterns of associations for different cognitive traits that would not be possible to find in single study analyses. Moreover, we included large-scale CHARGE GWAS data sets to perform two-sample MR analyses as replication. The weaknesses of the study include generalizability, as the analyses were performed solely in European ancestry populations, and some of the cohorts were included in both ENGAGE and CHARGE analyses as described in the supplement. Moreover, heterogeneity due to different tissues used (blood and saliva) and lab-specific technical variances (TL estimates from all 12 cohorts were done in five different labs) may have driven the results toward null. Another limitation relates to the three assumptions for conducting MR studies, which have been considered as follows: (1) a strong genetic instrument should be demonstrated between the GRS and TL (GRS-TL) which we have (F-statistic = 36); (2) the genetic instrument should not be confounded by e.g., age and sex (unlikely considering the randomization of alleles at conception); and (3) pleiotropic effects (when other pathways exist from the TL SNPs to the outcome (cognitive trait) without going through the intermediate phenotype (TL)) from the SNPs included in the GRS should be ruled out as much as possible. We did not find evidence for pleiotropic effects (Supplementary Data). Finally, also worth mentioning are the relatively weak P-values for some of the associations. The observational association for MMSE would not hold after Bonferroni correction of the P-value for the six cognitive traits tested, likewise for the causal associations found for STROOP.

To conclude, this study demonstrates an overall picture of the importance of biological aging processes such as TL dynamics for maintaining cognitive function throughout life. More specifically, we were able to show observational as well as causal associations between TL and different cognitive traits that have never been elucidated before. Hence, the current effort presents new important pieces of evidence for the continued search for a
better understanding of the biology behind aging and the factors explaining healthy aging.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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