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# Polygenic risk score of shorter telomere length and risk of depression and anxiety in women

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## Abstract

Prior studies have reported significant cross-sectional associations between depression or anxiety and shorter telomere lengths, but the temporality of associations is uncertain. Little is known regarding whether shorter telomere length is related to risk of developing depression or anxiety. In this study, using the genetic tool of polygenic risk score (PRS), we evaluated the association between genetic predisposition to shorter telomere length and the risks of lifetime clinically significant depression (defined by self-reported clinician/physician diagnosis, antidepressant use, and/or presence of severe depressive symptoms) and of clinically meaningful anxiety symptoms among 17,693 female participants of European ancestry. The weighted PRS of telomere lengths (TLs) combined the dosage of nine alleles that were significantly associated with inter-individual variation in TLs in published genome-wide association studies. Higher score of PRS, corresponding to *shorter* TL in the literature, was significantly associated with shorter relative TLs ($p$=0.008). However, higher PRS was not associated with the lifetime risk of either depression or anxiety. Furthermore, higher PRS was not associated with long-term patterns of depressive symptom trajectories or specifically with later-life onset of depression or anxiety. In summary, this study did not observe a significant association between genetic predisposition to shorter telomere length and risk of depression and anxiety in a large sample of mid-life and older white women.

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However, these genetic variants jointly account for a limited proportion of interpersonal variation in leukocyte telomere length. Future studies will need to incorporate more genetic variants to improve the accuracy of predicted power, as such data become available.

**Keywords**

telomere length; polygenic risk score; depression; anxiety; trajectory; women

## INTRODUCTION

Depression and anxiety are common psychiatric disorders in the U.S. and worldwide (Global Burden of Disease Study, 2015), and they are associated with higher risk of somatic conditions and mortality (Batelaan et al., 2016, Chodosh et al., 2007, Cuijpers et al., 2013, Gan et al., 2014, Gulpers et al., 2016, Luppino et al., 2011, Mezuk et al., 2008). Although the underlying etiology is still largely unknown, it has been noted that accelerated biological aging may be more prevalent among those with psychiatric disorders (Wolkowitz et al., 2010). Telomere shortening reflects damage accumulated over time and, therefore, may serve as an indicator of biological or cellular aging (Bojesen, 2013).

The association between telomere length (TL) and depression and anxiety risk has been observed in several studies (Darrow et al., 2016, Lin et al., 2016). However, most studies were conducted cross-sectionally; thus, temporality could not be addressed. Several prospective studies that examined the hypothesis that depression and/or anxiety precede telomere shortening have yielded inconsistent findings (Hoen et al., 2011, Hoen et al., 2013, Phillips et al., 2013, Ramin et al., 2015, Rius-Ottenheim et al., 2012, Shalev et al., 2014, Verhoeven et al., 2016, Wium-Andersen et al., 2017). A recent study indicated that healthy girls at familial risk for depression (i.e., whose mothers had recurrent episodes of depression during their daughter's lifetime) had shorter telomeres than did their non-risk peers (i.e., whose mothers with no current or past psychiatric disorders), suggesting that short TL predisposed to depression (Gotlib et al., 2015). Only two studies have prospectively examined whether shorter TL, which reflects cumulative exposure to inflammation and oxidative stress, was a risk factor for depression or anxiety; both studies had null findings (Ramin, Wang, 2015, Wium-Andersen, Orsted, 2017). It is noteworthy, however, that these observed associations could be impacted by whether or not the common causes (i.e., confounders) of shorter TLs and psychiatric disorders, such as cigarette smoking, physical activity, and medical comorbidities (Kiecolt-Glaser et al., 2011, Latifovic et al., 2016, Lin et al., 2012, O'Donovan et al., 2011, Tyrka et al., 2016) were adjusted in the analyses. Because TL has been shown to be strongly influenced by genetic factors, with a heritability estimate of 70% from a recent meta-analysis (with individual studies ranging from 34 to 82%) (Broer et al., 2013). genetic predisposition to shorter TL may be a useful way to investigate the association. Four recently published studies have examined the effect of TLs and risk of depression by investigating the genetic predisposition to TLs, which in principle would not be influenced by lifestyle behaviors and medical problems; to date, such studies have not reported positive associations (Collaboration et al., 2017, Hamad et al., 2016, Wei et al., 2016, Wium-Andersen, Orsted, 2017).

Despite the above-mentioned prior work, there remain important knowledge gaps and limitations in the literature. First, in prior work depression outcome was typically measured in a binary form (yes/no) and did not address depression phenotypes that involve more variations in symptom patterns. Second, there have been not been comparable examinations of the genetic predisposition to shorter TLs and risk of anxiety. Thus, we aim to examine whether genetic predisposition to shorter TL is respectively associated with lifetime risk of depression and anxiety. Depression and anxiety were investigated separately because there is inconsistent evidence of whether the effect of TLs is similar for both disorders (Hoen, Rosmalen, 2013, Verhoeven, van Oppen, 2016). Furthermore, we extend prior work in which depression was examined only as a dichotomous outcome: we leverage the unusual resource of information on depressive symptoms repeatedly assessed over 20 years among nearly 18,000 participants with genetic data in order to examine whether genetic predisposition to shorter TL is associated with development of long-term trajectory patterns of depressive symptoms that may overlap with aging. Finally, we aim to investigate whether a genetic predisposition to shorter TL is related to higher risk of onset of depression or anxiety at later-life.

## MATERIALS AND METHODS

### Study population and description of datasets

The Nurses' Health Study (NHS) is a prospective cohort that includes 121,701 U.S. female registered nurses aged 30–55 years at cohort initiation in 1976. Participants have completed questionnaires biennially since then to update information on demographic characteristics, lifestyle behaviors, and newly diagnosed diseases, with ≥90% follow-up in each 2-year cycle (Colditz, 1995, Colditz et al., 1986). Since 2007, fourteen separate genome-wide association studies (GWAS) with specific disease endpoints (venous thromboembolism, breast cancer, mammographic density, ovarian cancer, gout, endometrial cancer, squamous cell carcinoma, colon cancer, pancreatic cancer, glaucoma, kidney stones, melanoma, type II diabetes, and coronary heart disease) have been conducted using a nested case-control design within the NHS (Li et al., 2016, Lindstrom et al., 2017). Extensive quality control procedures, including filters for single nucleotide polymorphisms (SNPs) and/or samples, removing duplicate and related individuals, dataset merging within each genotyping platform family, and marker imputation using the 1,000 genomes phase III release have been detailed elsewhere (Lindstrom, Loomis, 2017, Sinnott and Kraft, 2012). Markers with poor imputation quality score <0.3, determined by the RSQR_HAT value in MaCH software (Li et al., 2010), were excluded. These data sets comprise 18,471 participants of European ancestry genotyped on five different high-throughput platforms (various generation Illumina arrays including 317K, 550K, 610K, and the 660W arrays, the Illumina OmniExpress, the Affymetrix 6.0, the OncoArray, and the HumanCoreExome arrays). After excluding individuals without complete information on depression or anxiety, a total 17,693 women were included in the final analysis. The institutional review board at Brigham and Women's Hospital approved the study protocol.

### Assessment of depression and anxiety

Information on depression included self-reported depressive symptoms, antidepressant medication use, and physician/clinician diagnosis of depression. Depressive symptoms were assessed using: 1) the Mental Health Inventory-5 (MHI-5) subscale of the Short-Form 36 Health Status Survey in 1992, 1996, and 2000, 2) the 10-item Center for Epidemiologic Studies Depression (CESD-10) in 2004, 3) the 15-item Geriatric Depression Scale (GDS-15) in 2008 and 2012; all of these scales have validated cut-points for clinical depression or severe depressive symptoms (MHI-5≤52; CESD-10≥10; GDS-15≥6) (Andresen et al., 1994, Friedman et al., 2005, Yamazaki et al., 2005). Self-reported regular use of antidepressants has been ascertained biennially since 1996. Participants were first asked in 2000 if they ever in their lifetime had physician-diagnosed depression and were assessed for self-reported physician/clinician-diagnosed depression biennially thereafter. Lifetime clinically significant depression was defined by having ever reported physician/clinician diagnosis of depression, regular antidepressant use, or the presence of severe depressive symptoms above clinical cutoffs anytime up to and including 2012. Preliminary data from separate, ongoing validation work supported optimal sensitivity and specificity using this “Boolean OR” definition, and prior publications also illustrated the ability to use this definition to predict health outcomes or to relate individual factors to depression risk (Mekary et al., 2013, Pan et al., 2012),

Information on clinically meaningful anxiety symptoms was assessed by the Crown Crisp Phobic Index (CCI) on the 1988 and 2004 questionnaires and the 7-item Generalized Anxiety Disorder (GAD-7) scale in 2012 (Crown and Crisp, 1966, Spitzer et al., 2006). The CCI contained 8 items assessing fear and/or desire for avoidance of crowds, heights, enclosed spaces, going out alone, as well as worrying (Crown and Crisp, 1966); the GAD-7 maps to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (Cooper, 1995) for GAD and also captures symptom severity. Both the CCI and GAD-7 have good discrimination for individuals with diagnosable anxiety disorders, and have been validated in psychiatric outpatient clinics (Burgess et al., 1987, Crown and Crisp, 1966, Wild et al., 2014). In this study, the presence of clinically meaningful anxiety was defined as CCI score ≥ 6 points or GAD-7 score ≥ 5 points, up to and including 2012. These cutoffs were selected based on prior studies among participants with similar age range or prior NHS findings (Ramin, Wang, 2015, Wild, Eckl, 2014). The last assessment was in year 2012 for both depression and anxiety.

### Formation of weighted polygenic risk score for shorter telomere length

We identified nine SNPs that showed independent association signals at the genome-wide significance level ($P < 5 \times 10^{-8}$) with shorter TL in previously published GWAS among individuals of European ancestry (Codd et al., 2013, Mangino et al., 2012, Pooley et al., 2013). These individual SNPs each explained the variance in measured average TL by 0.08 to 0.32% (Codd, Nelson, 2013), and the variance in TL explained by these nine SNPs jointly was 1.8% (Collaboration, Haycock, 2017). Each risk allele corresponded to 57–120 base pair decrease in TL. We used this information to create a weighted polygenic risk score (PRS), since prior research suggested that PRS analyses could be more successful in predicting disease risk than using single genetic markers (Dudbridge, 2013). Weights were

assigned for each SNP using the number of base-pair decrease in TL associated with each risk allele (Zhang et al., 2015), summarized in Supplemental Table 1. A higher value of the PRS means that an individual is genetically predisposed to *shorter* telomeres.

The actual measure of relative leukocyte TLs was also available in a subset of participants (N=2,615). The measurement of leukocyte TLs has been detailed elsewhere (Crous-Bou et al., 2014).

## Statistical analysis

Because the sample included both cases and controls from prior nested case-control GWAS, and shorter TL has been associated with diseases such as cardiovascular disease and cancer (Collaboration, Haycock, 2017, Haycock et al., 2014, Ma et al., 2011), we performed logistic regression analysis to examine the associations between PRS for shorter TL and risk of depression and anxiety using three analytic approaches: (1) utilizing the full sample that included both cases and controls of prior GWAS and adjusting for each disease endpoint ("conventional model"); (2) using only controls (free of major chronic diseases, including cancer and cardiovascular disease) from prior GWAS ("controls-only model"); and (3) using the full sample of prior GWAS but weighted by the inverse of the probability that each individual was selected from the original full NHS cohort into the genotyped samples ("inverse-probability-of-sampling-weighted (IPW) model") (Tchetgen Tchetgen et al., 2013). This IPW procedure reconstructed the original cohort from the nested case-control genetic samples to avoid the potential ascertainment bias of selective sampling, and the robust variance estimator was used to account for nested case and control sampling fractions in the IPW model. Because these three methods produced very similar results, we presented the results from "conventional model" as our primary findings because it is more efficient in the absence of ascertainment bias.

Individual SNP variants were coded for risk allele dosage associated with shorter TL, with values ranging from zero (no risk alleles) to two (two risk alleles). The PRS of shorter TL was defined as the sum across SNPs of the number of risk allele dosage at that SNP multiplied by the weight for that SNP. PRS was modeled in two ways: quintiles (to test for a possible nonlinear relationship) and per standard deviation increase. We first conducted analyses separately for each NHS platform-specific dataset and then performed meta-analysis using random-effects models to obtain combined estimates across 5 platforms. No effect heterogeneity was found across platform-specific datasets, so we only presented the meta-analyzed results. All models adjusted for age at baseline in 1988 (which was in proximity to the first phenotype measurement) and the first three principal components-derived eigenvectors to account for residual population stratification. Additional models were conducted that further adjusted for body mass index, pack-years of cigarette smoking, and physical activity. As results were similar after including these variables, they were omitted from the final models.

We first examined the association between PRS of shorter TL and actual measures of relative leukocyte telomere lengths among a subset of participants (N=2,615) who had both PRS and measured leukocyte TLs data available and were healthy controls using linear regression models. These models included age in 1988, paternal age at participant's birth,

and first three genetic principal components-derived eigenvectors; both PRS and relative leukocyte TL measures were standardized using z-scores.

Then, we examined the associations between PRS for shorter TLs and lifetime risk of depression and the presence of clinically meaningful anxiety symptoms separately up to and including 2012. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of the associations were calculated using logistic regression models. Next, we examined the association between PRS for shorter TL and different patterns of long-term depressive symptoms from 1992 to 2012. Multinomial logistic regression models were used to relate PRS for shorter TL to likelihood of long-term depression symptom trajectory class. To characterize the long-term symptom trajectory, a single scale (the MHI-5) was used after CESD-10 and GDS-15 scores were converted to the MHI-5 scale using a method detailed elsewhere (Kolen and Brennan, 2005). Group-based trajectory modeling was used to determine distinct classes of trajectories of depressive symptoms through a polynomial relationship estimated via a latent variable (Chang et al., 2016b). For the robustness of group membership assignment, the procedure was done in the full NHS cohort who had depressive symptoms data available in at least 3 out of 6 questionnaire cycles (N=81,382). Trajectory was modeled as a function of age (age was scaled to improve the numerical property for the minimizer search).

We further conducted two separate analyses to assess the association between PRS for shorter TL and the emergence of depression and anxiety in later-life among those with no prior history of the depression or anxiety indicators. For the risk of later-life onset of depression, participants with prior history of depression before 2000 and aged below 60 years in 2000 were excluded (Chang, Wang, 2016b). For the risk of later-life emergence of anxiety, participants with CCI score ≥ 4 points in 1988 and aged below 50 years in 1988 were excluded (Chou, 2009, Le Roux et al., 2005). The identification of new cases of depression any time after 2000 up to and including 2012 and cases of anxiety after 1988 until 2012 was as described above.

Several secondary analyses were performed. First, we considered mechanism-specific pathways by calculating PRS for SNPs involving in telomere length (rs2736100 and rs10936599), SNPs involving in telomere stability (rs755017, rs3027234, rs9420907, and rs7675998), and SNPs involving in other pathways (rs8105767, rs6772228, and rs1112552). Second, we examined the association between PRS for shorter TL and risk of lifetime depression using alternative depression definitions: (1) self-reported physician/clinician diagnosis only, (2) self-reported regular antidepressant use only, and (3) presence of severe depressive symptoms only. Lastly, depressive symptom trajectory was modeled additionally adjusting for risk factors of depression that may influence the probability of belonging to a group membership (Chang et al., 2016a). Statistical analyses were conducted using Unix SAS v. 9.4 (SAS Institute Inc., Cary, NC). All nominal $p$-values were 2-sided ($p < 0.05$).

## RESULTS

The mean age of the study sample was 55.5 years (standard deviation: 6.8 years) at baseline in 1988. 42.0% and 30.9% of participants reported lifetime depression (based on doctor

diagnosis, antidepressant use and/or symptoms) and clinically meaningful anxiety symptoms up to 2012, respectively. 52.8% of the study sample was GWAS controls from their original nested case-control studies (Table 1). Increasing value of 9-SNP PRS for shorter TL was significantly associated with shorter relative leukocyte TLs (β (95% CI)= −0.05 (−0.09, −0.01); *P*=0.008).

We did not observe any significant associations between genetic predispositions to shorter TL measured by 9-SNP PRS and lifetime risk of either depression or clinically meaningful anxiety symptoms in middle-aged to older-aged women (Table 2). Compared to the lowest group of PRS score (quintile 1; Q1), the OR (95% CI) of lifetime depression and anxiety was 0.98 (0.96–1.02) and 1.00 (0.89–1.11), respectively, for the highest group of PRS value (Q5). Consistently, no association was observed when PRS was defined by per standard deviation increase. The similar findings in the "control-only" and "IPW regression" models were shown in Supplemental Table 2.

Six distinct 20-year trajectory types were identified (Supplemental Figure 1): minimal depressive symptoms-stable (52.3%); mild symptoms-not improving (14.0%); sub-threshold symptoms-worsening (4.0%); sub-threshold symptoms-improving (20.6%); clinical range of depressive symptoms-improving (7.5%); and clinical range of depressive symptoms-persistent (1.7%) (percentages do not add to 100% due to rounding). Compared to participants with minimal depressive symptoms-stable, PRS for shorter TL was not significantly associated with other trajectory patterns of longitudinal depression symptoms (Table 3). The results were similar when trajectories were modeled with inclusion of depression risk factor variables previously identified in this cohort and elsewhere in the literature (data not shown) (Chang, Pan, 2016a, Chang, Wang, 2016b).

Genetic predisposition to shorter TL was not associated with higher risk of later-life onset of depression or anxiety (Table 4). There was also no association between PRS based on mechanism-specific pathways and risk of depression or anxiety (Supplemental Table 3). Finally, no significant associations were observed when depression was defined alternatively based on diagnosis only, antidepressant medication only, or the presence of severe symptoms only (data not shown).

## DISCUSSION

In this study of 17,693 mid-age and older women of European ancestry, we observed no evidence of associations between genetic predisposition to shorter TL, measured by a weighted polygenic risk score of nine SNPs, and the lifetime risk of depression or anxiety, long-term patterns of depressive symptom trajectories, or the risk of later-life onset of depression or anxiety.

The directionality between TL and psychiatric disorders is uncertain in the literature. Most studies that reported positive associations came from cross-sectional designs. Several prospective studies have investigated the impact of depression and/or anxiety on telomere changes, but these have yielded mixed findings (Hoen, de Jonge, 2011, Hoen, Rosmalen, 2013, Phillips, Robertson, 2013, Rius-Ottenheim, Houben, 2012, Shalev, Moffitt, 2014,

Verhoeven, van Oppen, 2016). Fewer studies examined the opposite direction – namely, whether shorter TL is prospectively associated with risk of depression or anxiety; however, no evidence of such an association has been reported to date (Ramin, Wang, 2015, Wium-Andersen, Orsted, 2017). Overall, there are important methodologic considerations that may explain the mixed findings in the extant literature regarding telomere-mental health associations. Specifically, reverse causation or unmeasured or residual confounding may influence estimates, and there are a wide range of endogenous and exogenous factors that may impact participants' inflammation/oxidative stress status as well as psychological distress levels (Kiecolt-Glaser, Gouin, 2011, Latifovic, Peacock, 2016, Lin, Epel, 2012, O'Donovan, Epel, 2011, Tyrka, Parade, 2016).

Using genetic variation in predisposition to TL as an exposure is an alternative method to examine the prospective relationship between TL and risk of psychiatric disorders. Because germline genetic variants were fixed before birth, they would not be influenced by lifestyle or other environmental factors after birth; thus, results should be less susceptible to confounding and reverse causation. The first study that examined genetic variation of TL and risk of depression was published in early 2016: the minor allele of hTERT polymorphism rs2736100, which was associated with shorter leukocyte TLs (Codd, Nelson, 2013), was significantly associated with DSM-IV-based diagnosis of depression, but only among participants with no childhood adversity (Wei, Martinsson, 2016). Since then, three additional studies that utilized the Mendelian Randomization approach have been published. Hamad et al. (Hamad, Walter, 2016) and Haycock et al. (Collaboration, Haycock, 2017) reported that shorter TL was not causally associated with lifetime DSM-IV-defined major depressive disorder in Psychiatric Genomics Consortium samples when using 7–8 SNPs significantly associated with TL jointly as the instrumental variable. In a large sample of 67,306 individuals from a general population, Wium-Andersen et al (Wium-Andersen, Orsted, 2017) similarly found that shorter TL was not causally associated with depression, which was defined respectively by registry-based diagnosis and purchase of antidepressant medication. However, the genetic instrument only combined three SNPs significantly associated with TL from a recent GWAS (Pooley, Bojesen, 2013). The validity of the Mendelian Randomization approach requires assumptions, including a sufficiently strong association between the genetic instrument and exposure (Burgess and Thompson, 2011), as well as the absence of pleiotropy, which cannot be ruled out in these studies. In contrast with these prior studies, the current study included community-dwelling participants without reliance on clinical samples, and more SNPs (e.g., nine instead of three) were selected to generate the PRS.

The current study complements the existing literature and breaks new ground in other areas. First, information on depression was measured in multiple ways, including physician/clinician diagnosis, antidepressant use, and depressive symptoms, which also allow us to compare results across separate definitions with different sensitivity and specificity. Furthermore, repeated measurement of depressive symptoms over time allows us to utilize the longitudinal information of depressive symptoms and contrast inter-individual variations. Second, this study examines the association between genetic variants of shorter TL and risk of clinically meaningful anxiety, which has not yet been studied. Third, this study specifically assessed the important question of whether shorter telomeres may predispose

individuals to the outcome of later-life emergence of depression or anxiety; this is a relatively unexplored question and may enrich biological understanding of later-life depression and anxiety. The findings in the present study of no significant association between genetic predisposition to shorter TL and risk of depression or clinically meaningful anxiety appears more consistent with the concept that depression or anxiety may lead to telomere attrition; alternatively, there may be some common causes that lead to both depression/anxiety and telomere shortening and that would warrant further investigations.

Strengths of the study design include the prospective nature, large sample size, repeated measures of severe depressive and anxiety symptoms, the ability to explore potential discrepancies and biases using different subset of participants ("conventional", "controls only", and "IPW" analyses), and greater number of genetic variants of shorter TL used to create the PRS compared to prior studies (Collaboration, Haycock, 2017, Hamad, Walter, 2016, Wei, Martinsson, 2016, Wium-Andersen, Orsted, 2017). Limitations should also be noted. First, the results from the "controls-only" approach may be biased due to selection bias and/or confounding if there was strong relationship between depression, telomere length, and comorbidities including cardiovascular disease and cancer; however, the controls-only results did not differ from the other two approaches when everyone was included. Second, although we included more SNPs in the PRS calculation than previous studies, based on the most recent GWAS of TL, the nine selected SNPs in this study only explained approximately 2% of TL variance. Inclusion of more genetic susceptibility loci when available may improve the prediction accuracy (Mavaddat et al., 2015, Pashayan et al., 2015). Nonetheless, the study was well-powered. For example, $r^2$ of 1.8% implied Pearson correlation coefficient of 0.134; thus, the power is estimated at 100% to detect such a correlation with a sample of 2,615. In addition, when predicting risk of depression, if we assumed that PRS explained 10% and 5% as much variation in depression as it did in telomere length, the estimated power was 100% and 98%, respectively, with a sample of 17,693. Third, depression was not classified by DSM-based diagnostic interviews in this study, and outcome misclassification is possible. However, in our prior work (Chang, Pan, 2016a), depression incidence in this cohort was consistent with age- and sex-specific estimates from studies featuring clinical evaluations to define depression and prior NHS publications have also illustrated the ability to use these depression and anxiety definitions to predict other outcomes (Albert et al., 2005, Farvid et al., 2014, Pan et al., 2011) or to relate individual factors to depression risk (Mekary et al., 2013). The outcome misclassification in this study is likely to be non-differential, which would attenuate the association magnitudes. Finally, our study was conducted in mid- to older-aged women with European ancestry; thus, our results may not be generalizable to males, other racial/ethnic groups, or younger persons. Specifically, it is noteworthy that the proportion of women having "persistent depressive symptoms" over 20 years in this study (1.7%) was lower than that reported by Byers et al. (2012) (3.4%); therefore, it is possible that NHS participants may be more resilient with regard to mood symptoms and may differ in this respect from similarly aged women in the general population. This point, along with other potential generalizability issues in NHS, informs the need for caution in interpretation..

## CONCLUSION

In summary, our data did not provide evidence of an association between genetic predisposition to shorter TL, based on nine SNPS, and risk of either depression or anxiety among mid- and older-aged women of European ancestry. Our findings are consistent with recent work that similarly did not identify associations between genetic instrument variables for shorter telomere length and risk of depression. However, the amount of genetic variation in TL explained by known SNPs is low; an updated PRS-based analysis with more genetic susceptibility loci of shorter TL may be warranted, once such additional SNPs are identified.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Characteristics of Nurses' Health Study participants at baseline [a]

| Characteristics | Mean (SD) or % |
|---|---|
| N | 17,693 |
| Age (years) | 55.5 (6.8) |
| Follow-up time (years) | 22.6 (3.8) |
| Polygenic risk score of telomere length [b] | 76.2 (16.2) |
| Paternal age at birth (years) | 29.7 (9.7) |
| Body mass index (kg/m$^2$, BMI) | 25.3 (5.4) |
| physical activity (Mets) | 15.1 (21.2) |
| Alcohol (grams) | 5.3 (9.5) |
| Pack-years of cigarette smoking | 12.0 (18.0) |
| History of cancer | 3.8 |
| History of hypertension | 28.4 |
| History of hypercholesterolemia | 26.7 |
| History of diabetes | 5.0 |
| History of heart disease | 5.3 |
| Lifetime depression up to 2012 [c] | 42.0 |
| Based on self-reported physician-diagnosed depression only | 20.2 |
| Based on self-reported regular antidepressant use only | 24.5 |
| Based on the presence of severe depressive symptoms only | 27.6 |
| Lifetime clinically-meaningful anxiety up to 2012 [d] | 30.9 |
| GWAS controls | 52.8 |

[a] Baseline was defined as the questionnaire cycle (1988 questionnaire) prior to blood draw in 1989–90

[b] Weighted sum of the number of risk allele dosage with its published effect estimate for all 9 single nucleotide polymorphisms (SNPs) that were significantly associated with shorter telomere length published previously. The unit of polygenic risk score corresponds to decreases in base pairs of telomere length.

[c] Depression was defined by either self-reported physician-diagnosed depression, regular use of antidepressant medications, or the presence of severe depressive symptoms using published cutpoints (≥10 on the 10-item Center for Epidemiologic Studies Depression and ≥6 on the 15-item Geriatric Depression Scale) during follow-up until 2012. 872 (4.9%) had missing information on depression.

[d] Anxiety was defined by either Crown-Crisp Index score of 6 or more or Generalized Anxiety Disorder 7 score of 5 or more during follow-up until 2012. 2131 (12.0%) had missing information on anxiety.

Abbreviations: NHS: Nurses' Health Study; GWAS: genome-wide association study

## Table 2

Association between polygenic risk score of shorter telomere length and lifetime risk of depression and anxiety [a,b]

| | Depression [c] | | Anxiety [d] | |
|---|---|---|---|---|
| | N (yes/no) | OR (95% CI) | N (yes/no) | OR (95% CI) |
| Quintile 1 | 1407/1965 | 1.00 (ref) | 960/2150 | 1.00 (ref) |
| Quintile 2 | 1427/1941 | 1.04 (0.94–1.14) | 925/2208 | 0.94 (0.84–1.05) |
| Quintile 3 | 1429/1882 | 1.06 (0.94–1.19) | 971/2115 | 1.03 (0.92–1.15) |
| Quintile 4 | 1396/1971 | 1.00 (0.91–1.10) | 999/2110 | 1.07 (0.96–1.19) |
| Quintile 5 | 1398/2005 | 0.98 (0.89–1.08) | 953/2171 | 1.00 (0.89–1.11) |
| Per 1 SD increase | 7057/9764 | 0.99 (0.96–1.02) | 4808/10754 | 1.01 (0.98–1.05) |

[a]All models adjust for age at baseline, first three genetic principal components-derived eigenvectors, and disease endpoints in original nested case-control studies.

[b]Analyses were first conducted within each of the platform-specific genetic datasets and then a combined estimate was obtained using a random-effect meta-analysis. There was no effect heterogeneity between platforms. The estimates and p-values shown in the table were meta-analyzed results.

[c]Depression was defined as self-reported doctor-diagnosed depression, regular antidepressant use, or the presence of severe depressive symptoms above clinical cutoff (Mental Health Index-5 ≤52 measured on the 1992Mental Health Index-5 ≤52 measured on the 1996, and 2000 questionnaires, 10-item Center for Epidemiologic Studies Depression ≥ 10 measured on the 2004 questionnaire, and/or 15-item Geriatric Depression Scale ≥ 6 measured on the 2012 questionnaire) anytime between 1992 and 2012 in the NHS cohort follow-up.

[d]The presence of severe anxiety symptom was defined by Crown-Crisp Index ≥ 6 measured in 1988 and 2004 and/or Generalized Anxiety Disorder Questionnaire (GAD-7) ≥ 5 measured in 2012

## Table 3

Association between polygenic risk score of shorter telomere length and long-term pattern of mid- to late-life depressive symptoms [a,b]

| Trajectory of 20-year depressive symptoms | N | OR (95% CI) |
|---|---|---|
| Clinical range depressive symptoms, persistent | 231 | 1.03 (0.91–1.18) |
| Clinical range depressive symptoms, improving | 1097 | 1.00 (0.94–1.07) |
| Sub-threshold depressive symptoms, not improving | 663 | 1.03 (0.95–1.12) |
| Mild depressive symptoms, not improving | 2522 | 0.98 (0.92–1.05) |
| Minimal depressive symptoms | 8699 | 1.00 (reference) |
| Sub-threshold depressive symptoms, improving | 3188 | 1.01 (0.96–1.07) |

[a] Genetically-predicted telomere length was assessed by per 1 standard deviation increase in polygenic risk score of telomere length corresponding to risk alleles associated with shorter telomere length. All models adjust for age at baseline, first three genetic principal components-derived eigenvectors, and disease status of original nested case-control studies.

[b] Analyses were first conducted within each of the platform-specific genetic datasets and then a combined estimate was obtained using a random-effect meta-analysis. There was no effect heterogeneity between platforms. The estimates and p-values shown in the table were meta-analyzed results.

## Table 4

Association between polygenic risk score of shorter telomere length and the risk of later-life onset of depression and anxiety [a,b]

| | Depression [c] | | Anxiety [d] | |
|---|---|---|---|---|
| | N (yes/no) | OR (95% CI) | N (yes/no) | OR (95% CI) |
| Quintile 1 | 432/1342 | 1.00 (ref) | 356/1583 | 1.00 (ref) |
| Quintile 2 | 440/1356 | 1.03 (0.88–1.20) | 357/1682 | 0.91 (0.71–1.16) |
| Quintile 3 | 466/1308 | 1.10 (0.94–1.28) | 336/1603 | 0.93 (0.79–1.10) |
| Quintile 4 | 455/1375 | 1.06 (0.91–1.23) | 344/1565 | 0.98 (0.83–1.15) |
| Quintile 5 | 461/1353 | 1.07 (0.91–1.24) | 351/1628 | 0.95 (0.82–1.11) |
| Per 1 SD increase | 2254/6734 | 1.02 (0.97–1.07) | 1744/8061 | 1.00 (0.95–1.06) |

[a]All models adjust for age at baseline, first three genetic principal components-derived eigenvectors, and disease status of original nested case-control studies.

[b]Analyses were first conducted within each of the platform-specific genetic datasets and then a combined estimate was obtained using a random-effect meta-analysis. There was no effect heterogeneity between platforms. The estimates and p-values shown in the table were meta-analyzed results.

[c]Only participants with age 60 years or above and with no prior history of depression in 2000 were included. New cases of depression was defined as self-reported doctor diagnosed depression, regular use of antidepressants, or depressive symptoms above the clinical cutoff (10-item Center for Epidemiologic Studies Depression ≥ 10 measured on the 2004 questionnaire and/or 15-item Geriatric Depression Scale ≥ 6 measured on the 2012 questionnaire) anytime after 2000 to 2012 in the NHS follow-up.

[d]Only participants with age of 50 or above and with Crown-Crisp Index score of 3 points or below in 1988 were included. New cases of severe anxiety symptoms was defined by Crown-Crisp Index ≥ 6 measured in 2004 and/or Generalized Anxiety Disorder Questionnaire (GAD-7) ≥ 5 measured in 2012