Supplemental Online Content

Bell TR, Beck A, Gillespie NA, et al. A traitlike dimension of subjective memory concern over 30 years among adult male twins. *JAMA Psychiatry*. Published online May 10, 2023. doi:10.1001/jamapsychiatry.2023.1004

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

eMethods

Measures

Subjective Memory Concern (SMC)

The SMC questions and responses are shown in Table S2. Items asked about memory problems and concerns. Subjective memory concern was created as a latent factor score (M=0, SD=1) from structural equation modeling in MPlus v.8.4 that accounted for twin relatedness.[1] The structural equation model estimated ordinal thresholds for item responses. Changes in SMC over time are shown in Figure S2.

Objective Memory

In this study, objective memory refers to performance on episodic memory tasks. The assessment at age 38 did not have information on objective memory as it only included a survey of health. At in-person evaluations at average ages 56, 62, and 67, objective memory was measured using the total of the learning trials and short and long delay free recall conditions on the California Verbal Learning Test-II,[2] and the immediate and delayed recall conditions on Weschler Memory Scale-III Logical Memory and Visual Reproduction subtests.[3] Our previous confirmatory factor analysis showed that items on these tests can be best explained by a highly heritable common latent factor.[4] At follow-ups, each individual's factor score was adjusted for practice effects as previously described elsewhere.[5] Factor scores at average ages 62 and 67 were fitted in reference to objective memory at average age 56. As such, 0 represents performance similar to performance at average age 56, >0 indicates performance improvement from age 56, and <0 represents performance decline from average age 56. Objective memory at age 38 was not available.

Amnestic Mild Cognitive Impairment (MCI)

Amnestic MCI was diagnosed using the Jak-Bondi approach.[4,6-9] All test scores at waves 2 and 3 were adjusted for practice effects.[5] The impairment criterion was scoring >1.5 *SD*s below normative means on 2 or more episodic memory tasks. Prior to calculating those cutoffs, scores were adjusted for general cognitive ability measured at average age of 20 to ensure that they reflected a decline in performance rather than just longstanding low ability.[10-12]

Young Adult General Cognitive Ability

Young adult general cognitive ability was measured with the Armed Forces Qualification Test (AFQT) administered at average age 20 years.[11,12] The AFQT is a multiple-choice test comprising 4 dimensions: vocabulary, arithmetic, spatial processing, and knowledge and reasoning about mechanical relationships. This test is correlated ~.85 with Wechsler IQ, and had a test-retest reliability of .73 across more than 40 years in VETSA participants.[11,12] Inclusion of the AFQT as a covariate removes some confounding of overall cognitive ability from measures of objective memory performance and removes some variance related to longstanding cognitive ability that might otherwise be mistaken for aging effects.

Race and Ethnicity

Participants were asked to select the racial category with which they most identified, including American Indian or Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, Black or African-American, White, more than one race, or decline to answer. Participants were asked to select the group that best describes their ethnicity, including Hispanic or Latino, Not Hispanic or Latino, or decline to answer. Responses for the largest groups (non-Hispanic White and Black) are summarized in Table 1.

Affect-Related Measures

Depressive Symptoms. Depressive symptoms were measured using the 20-item Center for Epidemiological Studies-Depression scale (CES-D).[13] The survey asks participants to rate the frequency of 20 feelings from rarely or none of the time (1) to most or all of the time (4), including 16 negative statements (e.g., depressed, fearful, restless, lonely) and 4 positive statements (i.e., happy, enjoyed life). Responses to positive feelings are reverse-scored. Scores >1 are indicative of the presence of depressive symptoms and are summed to create a score for the number of depressive symptoms, ranking from 0 to 20.

Anxiety. Anxiety was measured at average ages 62 and 67 using the trait form of the State-Trait Anxiety Inventory (STAI).[14] The trait form asks participants to rate how they generally feel from 1 (Almost Never) to 4 (Almost Always) on 20 statements, including positive statements ("I feel pleasant") and negative statements ("I feel nervous and restless"). Responses to positive feelings are reverse scored and summed with responses to negative feelings to form the total anxiety score, ranging from 20 to 80. The STAI was not administered at age 56, however, anxiety was measured at age 56 using the Stress Reaction scale from the Multidimensional Personality Questionnaire (MPQ), which asks people about tendencies to be nervous, sensitive, and worried.[15]

Negative Emotionality. Negative emotionality was measured using the MPQ Negative Emotionality scale.[15] The MPQ negative emotionality scale includes 3 subscales: stress reaction (e.g., nervous, easily upset, troubled by guilt), alienation (e.g., victim of bad luck, feels mistreated), and aggression (e.g., physically aggressive, vindictive).[16] MPQ negative emotionality represents a reliable and valid measure of trait neuroticism.[15,17,18] VETSA used a shortened (211 item) version of the MPQ developed for less well-educated participants (New Zealand version: Form NZ).[19,20]

Physical Health Conditions

Physical health conditions were based on information collected during a medical interview at each study wave (range: 0-14). Health conditions included history of hypertension, heart attack, heart failure, stroke, peripheral vascular disease, thrombolysis, angina, diabetes, bronchitis, asthma, cancer, osteoarthritis, rheumatoid arthritis, and cirrhosis, These conditions were chosen as they are listed in the Charlson Index, a validated index of major medical conditions.[21]

Polygenic Risk Scores (PRSs)

Genome-wide assays using Illumina HumanOmniExpress-24 v1.0A beadchips were performed on VETSA DNA samples that were whole-genome amplified (for more details see Logue et al.[22]). Genotyping assays were performed for all individuals from dizygotic (DZ) twin pairs, and for one randomly selected individual from each monozygotic (MZ) twin pair, as well as all unpaired twins whose cotwin did not participate. Some additional MZ co-twins were genotyped as a check. Initial quality controls used Plink 1.9,[23] included removing single nucleotide polymorphism (SNPs) that exceeded >5% missingness or where Hardy-Weinberg equilibrium test p-values < 1e-06. Imputations were performed on the Michigan Imputation Server (Minimac)[24] using the 1000 genomes phase 3 EUR data as a haplotype reference panel.[25] SNPs were excluded if there was low imputation quality (INFO or $r^2 \leq .8$), strand ambiguity, minor allele frequencies (MAFs) less than 1%, or missing call rates exceeding 1%. Genotyping results for the randomly selected MZ twin were applied to their cotwin. PRSs were created using a clumping and thresholding approach (C+T) in Plink 1.9 and genome-wide association study (GWAS) summary statistics.[23,24] Clumping was done using an r^2 threshold of .1 in a 1,000 kb window.

Genetic ancestry can influence PRSs and was accounted for in two ways. First, individuals with self-reported European ancestry or European ancestry >50% according to SNPweights[26] were selected for further analysis. Next, PRSs were adjusted for principal components (PCs) representing cryptic population structure. PCs were calculated from 1000 Genomes reference data using 100,000 SNPs common to both datasets and these weights were applied to VETSA samples. VETSA participants >6 SD from the mean of the first 2 PCs in the 1000 Genomes European population were excluded. A PCA was applied to one individual from each twin pair in this putatively White non-Hispanic sample, and these weights were applied to the rest of the sample. Individuals that were >6 SDs from the mean of the first 10 PCs were excluded. For the current analyses, PRSs were pre-adjusted for the first 3 PCs but results did not change when adjusting PRSs for all 20 PCs (but avoided due to risk of over-adjustment).

Neuroticism-PRS

The neuroticism-PRS was calculated using the GWAS summary statistics from Luciano et al.[27] For the present study we used a threshold of $p<.05$ which has been shown to have the strongest correlation with trait negative emotionality (partial $r=.16$; $p<.001$) and stress reaction (partial $r=.20$; $p<.001$) in the VETSA sample.[28]

Depression-PRS

The depression PRS was calculated using the GWAS summary statistics from Okbay et al.[29] This study focused on the severity of depressive symptoms rather than major depressive disorder, which was more applicable

for this non-clinical sample. For the present study, we used a threshold of p<.30 which showed the strongest correlation with our phenotypic measure of depressive symptoms (CESD, r=.07, p=.022).

AD-PRS

The AD-PRS was computed using GWAS summary statistics from the Kunkle et al genetic meta-analysis of AD.[30,31] A threshold of p<5e-8 was used for analyses as it was most predictive of AD in the Kunkle et al. study.[31]

APOE Genotyping

APOE genotype was determined from blood samples using established methods.[32,33] All genotypes were independently determined twice by laboratory personnel at the VA Puget Sound Healthcare System. Of the 375 participants utilized for the present analyses, 2 (.5%) possessed a 2/2 genotype, 58 (15.5%) were 2/3, 16 (4.2%) were 2/4, 220 (58.7%) were 3/3, 70 (18.7%) were 3/4, and 9 (2.4%) were 4/4. These rates are roughly equivalent, those found in the general population.[34] Participants with at least 1 copy of the ε4 allele were classified as being ε4 positive (ε4+; 25.3%); all other participants were classified as ε4 negative (ε4−; 75.7%).

Descriptives of objective memory, MCI, neuroticism, depressive symptoms, anxiety, PRSs, and *APOE* genotype are provided in Table S1.

Statistical Analysis

Phenotypic Analyses

When examining phenotypic correlations of SMC with genetic risk indicators (neuroticism-PRS, depression-PRS, AD-PRS, *APOE* genotype, parental history of dementia), we used the OpenMx2.9.9.1 software package in R3.4.1.[35-37] to estimate threshold liabilities for ordinal and binary variables and to account for twin relatedness. These polychoric correlations were also adjusted for twin relatedness and zygosity (although the influence of zygosity is usually negligible). Analyses of PRSs were restricted to individuals of European ancestry due to insufficient representation of non-European ancestry. Phenotypic correlations of SMC with objective memory, depressive symptoms, and anxiety symptoms were simultaneously estimated by the biometric twin models that estimated genetic and environmental correlations, described below. Biometric models inherently model data by twin dependencies and zygosity.

Biometric Twin Analyses

The OpenMx2.9.9.1 software package[38] in R3.4.1[39] was used to fit univariate and multivariate biometric genetic twin models[36] estimating the relative contribution of genetic and environmental influences within and between the SMC measures.[37,40]

Univariate Biometric Models

In univariate biometric analyses, the total variation in each measure of SMC at ages 38, 56, 62, and 67 were decomposed into additive (A) genetic (heritability), shared or common environmental (C), and non-shared or unique (E) environmental variance components. Shown in Figure S1, this approach is referred to as the 'ACE' variance component model. The decomposition is achieved by exploiting the expected genetic and environmental correlations between monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ twin pairs are genetically identical, whereas DZ twin pairs share, on average, half of their genes. Therefore, the MZ and DZ twin pair correlations for the additive genetic effects are fixed at r_A=1.0 and r_A=.5, respectively. The model assumes that shared environmental effects (C) are equal in MZ and DZ twin pairs (r_C=1.0), while non-shared environmental effects (E) are by definition uncorrelated. Shared environmental effects are defined as those that make siblings similar. Non-shared environmental factors are defined as those that make siblings different; this term also includes measurement error.

Multivariate biometric models

We extended the univariate model to longitudinal multivariate models to explain changes in genetic and environmental influences in SMC over time, and determine phenotypic, genetic, and environmental correlations. For a reference model to determine best model fit, we first fitted a multivariate ACE correlated factors model. This is a

saturated model that reproduces perfectly all mean and variance-covariance information for the observed variables. The ACE correlated factors model makes no theoretical prediction regarding how genes and environments influence SMC change over time.

We also used the correlated factors model—which accounts for twin relatedness—to determine phenotypic, genetic, and environmental correlations of SMC with objective memory, depressive symptoms, and anxiety at ages 56, 62, and 67 (waves when all variables were assessed), and with negative emotionality at age 56. Modified correlated factors models that combined separate estimates for MZ and DZ twins were also used to examine correlations of SMC with PRSs for neuroticism, depression, and AD, and additional genetic risk indicators of ADRD (*APOE* genotype and parental history of dementia).

The independent pathways (IP) model predicts that genetic and environmental risk factors have separate pathways to the SMC scores. Factor loadings onto SMC scores from the total decomposed A, C, and E variances estimate the strength of unique A, C, and E influences for SMC scores at each occasion. Residual variances for each SMC score is decomposed into 'as', 'cs', 'es' specific to each occasion.

The common pathway (CP) model predicts a covariance structure between all 4 SMC measures can be explained by a common liability decomposed into A, C, and E influences. As with factor analysis, the CP is indicated by the strength of the factor loadings to each observed SMC score. Residual variances or risks unique to each SMC score are further decomposed into variable-specific 'as', 'cs', and 'es' effects. To further explore the multivariate space, we fitted a model with two common factors.

In contrast to the common pathway model, the autoregression model predicts that time-specific random genetic or environmental effects may persist over time (autoregressive effects).[41] As described elsewhere,[41-43] autoregression assumes that a trait measured at time t+1 is partly a function of the same trait measured at a prior timepoint t. New variation at each assessment reflects time-specific genetic or environmental influences. Such autoregression may occur between phenotypes, or in the latent genetic or environmental variables. Differences at each occasion are therefore a function of (i) new random effects that arise and (ii) a (linear) function of individual differences expressed at preceding times. All cross-temporal correlations within subjects arise because innovations are more or less persistent over time and may, under some circumstances, accumulate, potentially giving rise to developmental increases in genetic or environmental variance and increased correlations between adjacent measures. A feature of the autoregressive model is that cross-temporal correlations tend to decay as a function of increasing time differential. Depending on the magnitude of an innovation and its relative persistence, the observed variances and cross-temporal covariances may increase during development towards a stable asymptotic value. See Eaves et al.[41] for graphical examples of an application to longitudinal cognitive data.

Model fit

Model comparisons for best fit involved log-likelihood ratio tests to determine significant improvements or deteriorations in fit and the Akaike information criterion (AIC). Under certain regularity conditions, the change in the -2 Log Likelihood is asymptotically distributed as chi-squared with the degrees of freedom equal to the difference in the number of free parameters in the two models. AIC provides an estimation of the expected divergence in a candidate model from the true data—the optimal balance of goodness-of-fit and parsimony.[44] Lower AIC values indicate better model fit.

Statistical Code

All code is provided online (https://github.com/trbellucsd/SubjectiveMemory).

Phenotypic Results

Table S6 shows the phenotypic correlations of SMC across assessments. Table S7 shows phenotypic correlations of SMC with genetic risk indicators (neuroticism-PRS, depression-PRS, AD-PRS, APOE genotype, parental history of dementia). Tables S5-S7 show phenotypic correlations of SMC with objective memory, anxiety, and depressive symptoms, respectively.

Univariate Biometric Model Results

Table S8 shows the results for univariate model fitting and variance component estimates. For SMC at age 38, there was insufficient power to choose between the competing AE and CE models; the ACE was therefore

retained as the best fitting. For SMC at ages 56 and 62, the AE model provided the best fit to the data. For SMC at age 67, the best-fitting ACE model included a negative variance estimate for the C influences. Negative variance estimates can indicate either stochastic variation or model misspecification.[45] We note also that the MZ correlation was more than 4 times the magnitude of the DZ correlation at age 67, which is consistent with non-additive genetic influences. We thus resolved this issue by substituting the shared environmental influences (C) with dominance/non-additive genetic influences (D) and an ADE model followed by AE, DE, and E submodel comparisons. Here, the AE model provided the best fit to the data with an estimated heritability of 37%.

Multivariate Biometric Model Results

Model fit results for multivariate analyses are provided in the main text as Table 2. Table S3 and S4 provide phenotypic, genetic, and environmental correlations of SMC across occasions. Table S9 provides variance component estimates from the best-fitting autoregressive model.

Tables S5-S7 show phenotypic, genetic, and environmental correlations of SMC with objective memory, anxiety, and depressive symptoms, respectively. Table S7 shows correlations of SMC with the PRSs, *APOE* genotype, and parental history of dementia.

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eTable 1. Descriptives of non-SMC study variables in the VETSA analytical sample across waves.

Variable		Age 38 Assessment	VETSA Wave 1	VETSA Wave 2	VETSA Wave 3
Sample size	n	1555	520	1199	1192
Objective memory[a]	M(SD)	----	.03 (1.04)	-.27 (1.02)	-.50 (1.08)
Amnestic MCI	n(%)		58 (11%)	129 (11%)	323 (27%)
Depressive Symptoms (CES-D)	M(SD)	----	8.25 (8.15)	7.41 (8.11)	7.11 (7.61)
Anxiety (STAI)	M(SD)	----	----	31.37 (9.67)	30.79 (9.29)
Anxiety (MPQ)	M(SD)	----	4.51 (3.75)		
Neuroticism (MPQ)	M(SD)	----	10.07 (7.73)		
Health Conditions		----			
0	n(%)	----	169 (32%)	256 (21%)	174 (15%)
1	n(%)	----	117 (23%)	232 (19%)	227 (19%)
2+	n(%)	----	234 (45%)	712 (59%)	792 (66%)
Parental History of Dementia	n(%)	141 (23.3%)	43 (8%)	146 (12%)	148 (12%)
APOE ε4+	n(%)	294 (19%)	92 (18%)	274 (23%)	299 (25%)
PRS Data Available[b]	n	1401	514	1180	1049

Note. VETSA = Vietnam Era Twin Study of Aging; MCI = mild cognitive impairment; CES-D = Center of Epidemiological Studies - Depression Scale; STAI = State-Trait Anxiety Index; MPQ = Multidimensional Personality Questionnaire; PRS = polygenic risk score. Memory ratings and memory concern were rated from 1 to 4, with higher scores indicating more subjective memory concern (poorer memory ratings, more memory concern).

[a] Objective memory was based on a factor score derived from the immediate and delayed portions of the California Verbal Learning Task-II and the Weschler Memory Scale-III Logical Memory Visual Reproductions subtests.

[b] PRS analyses were restricted to people of European ancestry and pre-adjusted for 3 principal components capturing cryptic population structure.

eTable 2. Measures of subjective memory concern

	Description	Response
SMC at Age 38	In the last 6 months have you had… Had trouble with your memory?	1 - Very Often 2 - Often 3 - Sometimes 4 - Almost Never 5 - Never
SMC at Ages 56, 62, and 67	In general, rate your memory in terms of the kinds of problems you have:	1 - No problems 2 - Minor problems 3 - Moderate problems 4 - Major problems
	In general, how concerned you about your memory are?”	1 - Not at all concerned 2 - A little concerned 3 - Somewhat concerned 4 - Very Concerned

Note. SMC = subjective memory concern. SMC at ages 56, 62, and 67 was measured by estimating a latent liability from a structural equation model (a sounder form of averaging that considers the ordinal nature of the items). The structural equation model also accounted for twin relatedness. The item at age 38 was recoded so that higher values indicated greater SMC.

eTable 3. Associations of subjective memory concern with objective memory.

	SMC Age 38			SMC Age 56			SMC Age 62			SMC Age 67		
		95% CI			95% CI			95% CI			95% CI	
	r	LL	UL	r	LL	UL	r	LL	UL	r	LL	UL
Objective Memory Age 56												
Phenotypic r	.001	-.11	.11	**-.24**	**-.33**	**-.13**	**-.10**	**-.16**	**-.03**	**-.08**	**-.14**	**-.01**
Genetic r*	-.03	-.15	.06	**-.22**	**-.30**	**-.14**	-.05	-.11	.01	**-.17**	**-.32**	**-.02**
Unique environmental r*	.02	-.03	.07	**-.18**	**-.23**	**-.13**	**-.09**	**-.14**	**-.04**	.04	-.01	.09
Objective Memory Age 62												
Phenotypic r	-.03	-.13	.08	**-.23**	**-.33**	**-.13**	**-.13**	**-.19**	**-.05**	**-.13**	**-.19**	**-.06**
Genetic r*	-.28	-.38	.99	**-.31**	**-.38**	**-.28**	**-.19**	**-.24**	**-.14**	**-.29**	**-.34**	**-.24**
Unique environmental r*	.10	-.02	.21	**-.07**	**-.12**	**-.02**	**-.12**	**-.17**	**-.07**	-.004	-.05	.05
Objective Memory Age 67												
Phenotypic r	-.01	-.12	.10	**-.26**	**-.36**	**-.15**	**-.15**	**-.22**	**-.08**	**-.14**	**-.21**	**-.07**
Genetic r*	**-.09**	**-.14**	**-.04**	**-.23**	**-.48**	**-.13**	**-.08**	**-.14**	**-.02**	**-.26**	**-.31**	**-.21**
Unique environmental r*	.06	-.04	.16	**-.17**	**-.22**	**-.12**	**-.20**	**-.25**	**-.15**	**-.06**	**-.11**	**-.01**

Notes. r = correlation coefficient; 95% CI = 95% confidence interval; LL = lower limit of 95% confidence interval; UL = upper limit of 95% confidence interval; SMC = subjective memory concern. Correlated factor models were used to estimate phenotypic, genetic, and unique environmental correlations. Such models inherently account for being nested within monozygotic and dizygotic twin pairs.
Correlations with significant p-values are bolded (p<.05).
*Estimates were derived from an AE correlated factors model (A = additive genetic influences; E = unique environmental influences), which was able to drop the C component (shared environmental influences) without significant deterioration in model fit indicated by lower AIC and no significant deterioration in -2 loglikelihood compared to ACE correlated factors model.

eTable 4. Associations of subjective memory concern with depressive symptoms.

	SMC Age 38			SMC Age 56			SMC Age 62			SMC Age 67		
		95% CI			95% CI			95% CI			95% CI	
	r	LL	UL	r	LL	UL	r	LL	UL	r	LL	UL
Depressive Symptoms Age 56												
Phenotypic r	**.17**	**.06**	**.29**	**.32**	**.21**	**.42**	**.26**	**.19**	**.33**	**.27**	**.20**	**.33**
Genetic r*	**.19**	**.12**	**.26**	**.20**	**.10**	**.29**	**.15**	**.05**	**.25**	**.19**	**.11**	**.27**
Unique environmental r*	**.12**	**.07**	**.17**	**.35**	**.31**	**.39**	**.32**	**.28**	**.36**	**.28**	**.23**	**.33**
Depressive Symptoms Age 62												
Phenotypic r	**.22**	**.09**	**.32**	**.37**	**.27**	**.47**	**.37**	**.31**	**.43**	**.34**	**.27**	**.40**
Genetic r*	**.14**	**.07**	**.21**	**.23**	**.12**	**.33**	**.17**	**.10**	**.25**	**.21**	**.14**	**.29**
Unique environmental r*	**.21**	**.16**	**.26**	**.28**	**.23**	**.33**	**.39**	**.35**	**.43**	**.18**	**.13**	**.23**
Depressive Symptoms Age 67												
Phenotypic r	**.30**	**.19**	**.40**	**.23**	**.12**	**.34**	**.28**	**.22**	**.35**	**.35**	**.29**	**.41**
Genetic r*	**.63**	**.59**	**.66**	**.15**	**.09**	**.21**	**.14**	**.06**	**.22**	**.17**	**.10**	**.25**
Unique environmental r*	**.20**	**.15**	**.25**	**.24**	**.19**	**.29**	**.32**	**.28**	**.36**	**.33**	**.29**	**.37**

Notes. r = correlation coefficient; 95% CI = 95% confidence interval; LL = lower limit of 95% confidence interval; UL = upper limit of 95% confidence interval; SMC = subjective memory concern. Correlated factor models were used to estimate phenotypic, genetic, and unique environmental correlations. Such models inherently account for data being nested within monozygotic and dizygotic twin pairs.
Correlations with significant p-values are bolded (p<.05).
*Estimates were derived from an AE correlated factors model (A = additive genetic influences; E = unique environmental influences), which was able to drop the C component (shared environmental influences) without significant deterioration in model fit indicated by lower AIC and no significant deterioration in -2 loglikelihood compared to ACE correlated factors model.

eTable 5. Associations of subjective memory concern with anxiety and negative emotionality.

	SMC Age 38			SMC Age 56			SMC Age 62			SMC Age 67		
		95% CI			95% CI			95% CI			95% CI	
	r	LL	UL	r	LL	UL	r	LL	UL	r	LL	UL
Anxiety (MPQ) Age 56												
Phenotypic r	**.23**	**.17**	**.30**	**.39**	**.29**	**.48**	**.33**	**.27**	**.40**	**.30**	**.24**	**.37**
Genetic r*	**.67**	**.62**	**.71**	**.36**	**.18**	**.51**	**.30**	**.19**	**.41**	**.34**	**.24**	**.43**
Unique environmental r*	-.08	-.21	.24	**.65**	**.49**	**.82**	**.70**	**.59**	**.80**	**.66**	**.57**	**.76**
Anxiety (STAI) Age 62												
Phenotypic r	**.21**	**.14**	**.28**	**.23**	**.12**	**.34**	**.37**	**.31**	**.43**	**.32**	**.25**	**.38**
Genetic r*	**.65**	**.62**	**.68**	**.70**	**.65**	**.74**	**.57**	**.43**	**.70**	**.64**	**.46**	**.82**
Unique environmental r*	**.35**	**.30**	**.40**	**.30**	**.01**	**.35**	**.43**	**.29**	**.57**	**.36**	**.18**	**.54**
Anxiety (STAI) Age 67												
Phenotypic r	**.23**	**.16**	**.29**	**.26**	**.16**	**.36**	**.34**	**.28**	**.40**	**.40**	**.35**	**.45**
Genetic r*	**.73**	**.70**	**.76**	.59	-.01	.89	**.60**	**.44**	**.75**	**.57**	**.44**	**.67**
Unique environmental r*	**.27**	**-.03**	**.56**	**.41**	**.10**	**.84**	**.40**	**.25**	**.57**	**.43**	**.31**	**.56**
Negative Emotionality (MPQ) Age 56												
Phenotypic r	**.26**	**.21**	**.31**	**.34**	**.26**	**.41**	**.30**	**.25**	**.35**	**.30**	**.25**	**.30**
Genetic r*	**.63**	**.58**	**.68**	**.51**	**.44**	**.57**	**.54**	**.50**	**.58**	**.51**	**.47**	**55**
Unique environmental r*	**.08**	**.03**	**.13**	**.20**	**.12**	**.28**	**.16**	**.10**	**.22**	**.13**	**.07**	**.19**

Notes. r = correlation coefficient; 95% CI = 95% confidence interval; LL = lower limit of 95% confidence interval; UL = upper limit of 95% confidence interval; SMC = subjective memory concern; MPQ = Multidimensional Personality Questionnaire; STAI = State-Trait Anxiety Index. Correlated factor models were used to estimate phenotypic, genetic, and unique environmental correlations. Such models inherently account for data being nested within monozygotic and dizygotic twin pairs. Correlations with significant p-values are bolded (p<.05).

eTable 6. Phenotypic correlations between SMC at age 38, 56, 62, and 67.

	1	2	3	4
	r (95%CI)	r (95%CI)	r (95%CI)	r (95%CI)
1. SMC Age 38	-			
2. SMC Age 56	**.27 (.14, .38)**	-		
3. SMC Age 62	**.19 (.08, .30)**	**.52 (.42, .61)**	-	
4. SMC Age 67	**.25 (.14, .36)**	**.47 (.37, .56)**	**.59 (.54, .64)**	-

Notes. r = correlation coefficient; 95%CI=95% confidence interval; SMC = subjective memory concern. Bolded values are statistically significant at p<.05. Estimates were derived from an AE correlated factors model (A = additive genetic influences; E = unique environmental influences), which was able to drop the C component (shared environmental influences) without significant deterioration in model fit indicated by lower AIC and no significant deterioration in -2 loglikelihood compared to ACE correlated factors model.

eTable 7. Associations of subjective memory concern with genetic risk indicators for neuroticism, depression, and Alzheimer's disease.

	SMC Age 38	SMC Age 56	SMC Age 62	SMC Age 67
	r (95% CI)	**r (95% CI)**	**r (95% CI)**	**r (95% CI)**
Neuroticism-PRS	**.10 (.03, .18)**	.07 (-.05, .19)	.05 (-.03, .13)	**.09 (.01, .16)**
Depression-PRS	.02 (-.05, .10)	.06 (-.05, .17)	.02 (-.05, .09)	.04 (-.03, .11)
APOE-ε4 allele status	.04 (-.06, .13)	-.05 (-.19, .10)	.001 (-.10, .09)	.01 (-.08, .10)
Alzheimer's disease-PRS	.001 (-.08, .07)	-.02 (-.14, .10)	.02 (-.06, .10)	.01 (-.06, .09)
Parental History of Dementia	-.02 (-.19, .13)	-.001 (-.19, .19)	.04 (-.06, .15)	.08 (-.01, .18)

Notes. r = correlation coefficient; 95%CI = 95% confidence interval; SMC = subjective memory concern; PRS = polygenic risk score. Correlations were calculated using a modified biometric model that accounted for data dependencies due to twin relatedness and zygosity. Modified biometric models also accounted for the continuous or categorical nature of the variables. Models accounted for data dependencies due to twin relatedness and zygosity. Statistically significant correlations are bolded ($p<.05$).

eTable 8. Subjective memory concern univariate model fitting results and comparisons

	Model Fit Statistics							Model Estimates		
Variables & Models	**ep**	**-2LL**	**df**	**AIC**	**□-2LL**	**□ df**	**p**	**A (95% CI)**	**C (95% CI)**	**E (95% CI)**
SMC Age 38										
ACE	4	4329.74	1533	4337.74				.09 (-.19,.38)	.13 (-.12,.36)	**.78 (.70,.87)**
AE*	3	433.81	1534	4336.81	1.06	1	.303	**.24 (.15,.32)**		**.77 (.69,.85)**
CE	3	433.15	1534	4336.15	.40	1	.526		**.20 (.12,.28)**	**.80 (.72,.88)**
E	2	4358.99	1535	4362.99	29.24	2	<.001			**.99 (.91, 1.02)**
SMC Age 56										
ACE	4	1455.84	516	1463.84				**.35 (.12,.82)**	-.03 (-.03,.38)	**.68 (.52,.84)**
AE*	3	1455.87	517	1461.87	.03	1	.869	**.31 (.17,.44)**		**.69 (.56,.83)**
CE	3	1457.99	517	1463.99	2.15	1	.142		**.25 (.13,.37)**	**.75 (.61,.89)**
E	2	1473.70	518	1477.69	17.85	2	.000			**.99 (.87,1.11)**
SMC Age 62										
ACE	4	3371.06	1195	3379.06				**.36 (.05,.68)**	-.07 (-.34,.19)	**.71 (.61,.81)**
AE*	3	3371.34	1196	3377.34	.28	1	.599	**.30 (.19, .41)**		**.70 (.59,.81)**
CE	3	3376.24	1196	3382.24	5.18	1	.023		**.21 (.13,.29)**	**.79 (.69,.89)**
E	2	3401.61	1197	3405.61	3.55	2	<.001			**.99 (.91,1.07)**
SMC Age 67										
ACE*	4	3332.21	1188	334.21				**.68 (.35,.99)**	**-.60 (-.31,-.02)**	**.62 (.53,.72)**
AE	3	3336.54	1189	3342.54	4.34	1	.037	**.35 (.25,.44)**		**.65 (.57,.75)**
CE	3	3348.95	1189	3354.95	16.74	1	<.001		.25 (.15,.35)	**.75 (.65,.85)**
E	2	3381.36	1190	3385.36	49.16	2	<.001			**.99 (.91,1.07)**

Note. SMC = subjective memory concern; A = additive genetic; C = common or shared environment; E = non-shared environment, ep = number of estimated parameters; -2LL = -2 x log-likelihood; Δ-2LL = change in -2 x log-likelihood, Δdf = change in degrees of freedom, AIC = Akaike Information Criteria. Bolded model estimate values are statistically significant at p<.05.
*Best fitting models.

eTable 9. Variance components from best-fitting autoregressive biometric model describing genetic and unique environmental influences for SMC at each age.

SMC	Variance Component Estimate (95% CI)
SMC Age 38	
A1	**.26 (.19, .28)**
E1	**.76 (.74, .78)**
SMC Age 56	
A2	**.31 (.23, .39)**
E2	**.69 (.64, .73)**
SMC Age 62	
A3	**.33 (.26, .36)**
E3	**.68 (.65, .71)**
SMC Age 67	
A4	**.34 (.29, .39)**
E4	**.67 (.64, .70)**

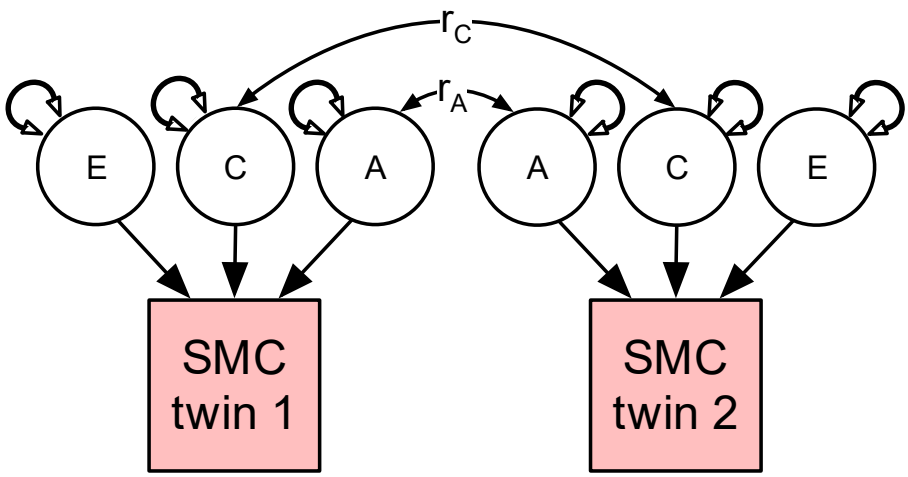
Note. SMC = subjective memory concern. A1-A4 represent the cumulative magnitude of additive influences on SMC. E1-E4 represent the cumulative magnitude of unique environmental influences on SMC. Results were derived from the best-fitting autoregressive model which was able to drop contributions from shared environmental influences (C) from the model without a significant loss in model fit ($p>.05$).

eTable 10. Genetic correlations (below diagonal) and unique environmental correlations (above diagonal) of SMC between ages 38, 56, 62, and 67.

	1	2	3	4
	r (95%CI)	r (95%CI)	r (95%CI)	r (95%CI)
1. SMC Age 38	-	**.18 (.13, .22)**	**.07 (.05, .09)**	**.11 (.09, .13)**
2. SMC Age 56	**0.63 (.61, .99)**	-	**.47 (.43, .51)**	**.40 (.36, .44)**
3. SMC Age 62	**0.56 (.55, .57)**	**0.90 (.74, .99)**	-	**.43 (.39, .47)**
4. SMC Age 67	**0.49 (.45, .59)**	**0.78 (.01, .85)**	**0.87 (.73, .90)**	-

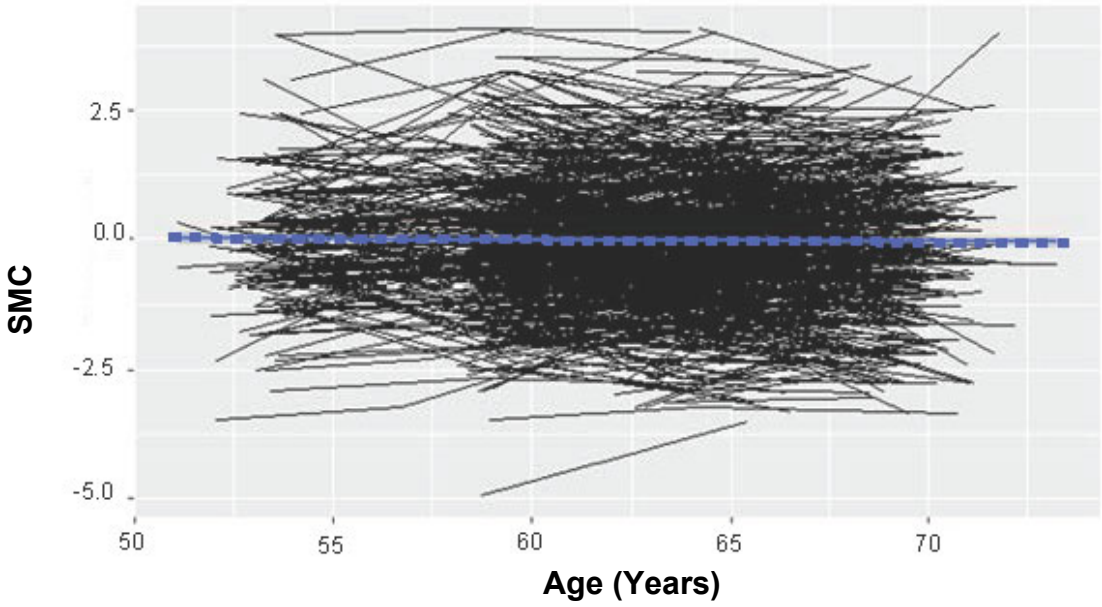
Notes. r = correlation coefficient; 95%CI=95% confidence interval; SMC = subjective memory concern. Bolded values are statistically significant at p<.05. Estimates were derived from an AE correlated factors model (A = additive genetic influences; E = unique environmental influences), which was able to drop the C component (shared environmental influences) without significant deterioration in model fit indicated by lower AIC and no significant deterioration in -2 loglikelihood compared to ACE correlated factors model.

eFigure 1. Univariate variance decomposition of relative contribution of genetic and environmental influences on subjective memory concern.



Note. SMC = subjective memory concern; A = additive genetic influences; C = shared environmental influences; E = unique environmental influences, r_C = correlation of 1 for MZ and DZ pairs, r_A = correlations of 1 for MZ and 0.5 for DZ pairs.

eFigure 2. Spaghetti plot showing the change in subjective memory concern (SMC) across age.



Note. Mean change in subjective memory concerns (SMC) is shown in the dashed line. Solid lines represent the individual trajectories. SMC was measured as the latent factor score of two items measured at each age. As suggested from the visualization here, a linear mixed model showed that age was unrelated to changes in subjective memory in a linear mixed model (p=.629). Linear mixed models were adjusted for twin relatedness.