Neuroticism as a Predictor of Frailty in Old Age: A Genetically Informative Approach

Hilda Björk Daníelsdóttir, MSc, Juulia Jylhävä, PhD, Sara Hägg, PhD, Yi Lu, PhD, Lucía Colodro-Conde, PhD, Nicholas G. Martin, PhD, Nancy L. Pedersen, PhD, Miriam A. Mosing, PhD, and Kelli Lehto, PhD

ABSTRACT

Objective: Neuroticism is associated with poor health outcomes, but its contribution to the accumulation of health deficits in old age, that is, the frailty index, is largely unknown. We aimed to explore associations between neuroticism and frailty cross-sectionally and longitudinally, and to investigate the contribution of shared genetic influences.

Methods: Data were derived from the UK Biobank (UKB; $n = 274,951$), the Australian Over 50's Study (AO50; $n = 2849$), and the Swedish Twin Registry (Screening Across the Lifespan of Twins Study [SALT], $n = 18,960$; The Swedish Adoption/Twin Study of Aging [SATSA], $n = 1365$). Associations between neuroticism and the frailty index were investigated using regression analysis cross-sectionally in UKB, AO50, and SATSA and longitudinally in SALT (25–29 years of follow-up) and SATSA (6 and 23 years of follow-up). The co-twin control method was applied to explore the contribution of underlying shared familial factors (SALT, SATSA, AO50). Genome-wide polygenic risk scores for neuroticism were used in all samples to further assess whether common genetic variants associated with neuroticism predict frailty.

Results: High neuroticism was consistently associated with greater frailty cross-sectionally (adjusted β [95% confidence intervals] in UKB = 0.32 [0.32–0.33]; AO50 = 0.35 [0.31–0.39]; SATSA = 0.33 [0.27–0.39]) and longitudinally up to 29 years (SALT = 0.24 [0.22–0.25]; SATSA 6 years = 0.31 [0.24–0.38]; SATSA 23 years = 0.16 [0.07–0.25]). When adjusting for underlying shared genetic and environmental factors, the neuroticism-frailty association remained significant, although decreased. Polygenic risk scores for neuroticism significantly predicted frailty in the two larger samples (meta-analyzed total β = 0.059 [0.055–0.062]).

Conclusions: Neuroticism in midlife predicts frailty in late life. Neuroticism may have a causal influence on frailty, whereas both environmental and genetic influences, including neuroticism-associated common genetic variants, contribute to this relationship.

Key words: negative affect, health decline, polygenic risk score, twins, cohort study.

INTRODUCTION

Although chronological age is a major determinant of health status, there is substantial diversity in health among older people of the same age (1). One indicator of such variation in health is frailty, a condition observed in older people reflecting cumulative decline in various physiological systems (2). A common method to assess frailty is the calculation of a frailty index (FI), where frailty is defined as the accumulation of health deficits expressed as the proportion of present deficits of the total health deficits considered (3). The health deficits can be symptoms, disabilities, signs of diseases, and diagnosed diseases covering multiple physiological systems, as well as psychological health and well-being, items often covered in health surveys and routine health assessments. FI is a strong predictor of mortality (4–6) and has been linked to numerous other negative health outcomes, such as disability, institutionalization, and hospitalization (7), even when varying number and types of health deficits are used for FI calculation (3).

The causes of frailty are multifactorial, and it is widely accepted that many biological, social, and psychological factors are likely involved (8). Although most research has focused on biological and physical factors associated with frailty (e.g., body weight) (8), as well as on sociodemographic factors (e.g., older age, female sex, and lower educational level) (9), less is known about how psychological factors could contribute to frailty. Neuroticism, a stable

AO50 = The Australian Over 50's Study, **BMI** = body mass index, **CI** = confidence interval, **DZ** = dizygotic, **EPQ** = Eysenck's Personality Questionnaire, **EPQ-R** = Eysenck's Personality Questionnaire – Revised, **FI** = frailty index, **GWAS** = genome-wide association study, **MZ** = monozygotic, **PRS** = polygenic risk score, **PRS_N** = polygenic risk score for neuroticism, **PC** = principal component, **SALT** = Screening Across the Lifespan of Twins Study, **SATSA** = The Swedish Adoption/Twin Study of Aging, **STR** = Swedish Twin Registry, **UKB** = UK Biobank

SDC Supplemental Content

From the Department of Medical Epidemiology and Biostatistics (Danielsdottir, Jylhävä, Hägg, Lu, Pedersen, Mosing, Lehto), Karolinska Institutet, Stockholm, Sweden; Department of Genetics and Computational Biology (Colodro-Conde, Martin), QIMR Berghofer Medical Research Institute, Brisbane, Australia; Department of Neuroscience (Mosing), Karolinska Institutet, Stockholm, Sweden; and Department of Chronic Diseases (Lehto), Institute for Health Development, Tallinn, Estonia.

Address correspondence to Kelli Lehto, PhD, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Nobels Väg 12a, 171 77, Sweden. E-mail: Kelli.lehto@ki.se

Received for publication December 30, 2018; revision received May 8, 2019.

DOI: 10.1097/PSY.0000000000000742

personality trait reflecting a tendency toward emotional instability and negative affect (e.g., depressed mood, worry, and fear), has been consistently associated with a wide range of physical and mental health problems such as cardiovascular disease, disrupted immune functioning, asthma, irritable bowel syndrome, atopic eczema, migraine, mood and anxiety disorders, and even increased risk of premature mortality (10–12), potentially also affecting frailty. To our knowledge, the association between neuroticism and FI has been investigated in only one previous study, suggesting that high neuroticism levels are associated with higher FI scores 2 years later (13). In addition, two previous studies have examined the association between neuroticism and a physical measure of frailty (i.e., the Fried frailty phenotype), indicating that high neuroticism is associated with physical frailty concurrently and longitudinally, over up to 8 years (14,15).

Twin and family studies show moderate heritability of neuroticism, with approximately 40% of individual differences in the trait attributable to genetic influences (16), potentially contributing to its persistent associations with health problems. Indeed, twin studies also show moderate heritability for many somatic and health-related measures (17), and genetic overlap between neuroticism and some somatic diseases have been detected (18), indicating that neuroticism and health problems could be associated in part because of shared genetic influences.

As a complex phenotype, recent genome-wide association studies (GWASs) have confirmed the complex genetic architecture of neuroticism where many genetic variants with small effects are involved (19). By using information from GWASs, polygenic risk scores (PRSs) allow for testing the contribution of thousands of neuroticism-related common genetic variants in frailty in old age, providing more insight into the potential sources underlying the association.

To date, little is known about the nature of the association between neuroticism and frailty because study designs used in previous studies do not allow for conclusions about the underlying genetic factors and whether neuroticism could be causally contributing to frailty. In the present study, we investigated the association between neuroticism and frailty in middle-aged and older adults using four large genetically informative samples. Specifically, we aimed to a) assess the phenotypic cross-sectional and longitudinal association between neuroticism and frailty, expanding the follow-up time to up to 29 years; b) assess whether the association between neuroticism and frailty remains after adjusting for shared familial influences (i.e., assess whether the association is in line with causality); and c) examine whether measured genetic risk for neuroticism contributes to frailty.

METHODS

Data Sources/Participants

Data were derived from four cohorts of middle-aged and older individuals of white descent, the UK Biobank (UKB) (20), the Australian Over 50's Study (AO50) (21), and two subsamples of the Swedish Twin Registry (STR) (22,23).

The UKB is a large resource of health, life-style and genetic data on currently approximately 500,000 individuals aged 39 to 73 years at recruitment (20). Genotype information was available for 244,070 individuals after exclusions (see details in the Supplemental Material, http://links.lww.com/PSYMED/A580).

The AO50 is a cross-sectional population-based study of Australian twins older than 50 years. The sample consisted of 3053 individuals aged between 50 and 94 years who answered a mailed-out questionnaire between 1993 and 1995, which included assessments on personality traits, physical and mental health, life-style factors, and demographic characteristics (21). Genotype information was available for 1037 individuals after exclusions.

Screening Across the Lifespan of Twins (SALT) is a cohort study of STR twins born in 1886 to 1958 (n = 44,919) (22). Health and life-style data were collected between 1998 and 2002 through a computer-assisted telephone interview. Personality information was available for all SALT participants born 1926 to 1958 who had completed a mailed-out questionnaire in 1973 (22), resulting in a 25- to 29-year follow-up between neuroticism and frailty assessments for 24,432 individuals. Genotype information was available for a subsample (n = 10,712) (23).

The Swedish Adoption/Twin Study of Aging (SATSA) is a longitudinal study of aging spanning more than 30 years and includes nine questionnaire-based study waves (24). In 1984, a questionnaire covering a wide range of health, life-style and personality factors was sent out to all STR twins who were reared apart and a matched sample of twins who were reared together (n = 3838) (24). In the present study, we used baseline information from wave 2 (Q2; 1987, n = 1637) and follow-up information from waves 4 (Q4; 1993, n = 1450) and 7 (Q7; 2010, n = 568), providing follow-up data over 6 (wave 4) and 23 years (wave 7). In total, there are 929 individuals with both baseline and 6-year follow-up information and 191 individuals with both baseline and 23-year follow-up information. Waves 2, 4, and 7 were selected based on data availability and to maximize sample size in longitudinal analyses. Sample overlap between SATSA and SALT was removed from all SALT analyses. Genotype information was available for 637 individuals.

Neuroticism Assessment

In the UKB and AO50, neuroticism was measured with a 12-item version of the neuroticism scale from the Eysenck Personality Questionnaire – Revised (EPQ-R) (25). In the STR, neuroticism was measured with a nine-item version from the EPQ (26). The EPQ itself is a reliable and valid tool to measure neuroticism (26). In addition, the 12-item version used in the UKB and AO50 has demonstrated good reliability and validity (25), and the 9-item version (27) used in the STR has previously been widely used in Scandinavian twin studies (28). Items were scored as "no" [0] or "yes" [1] and then summed with a higher score indicating higher levels of neuroticism (see Supplemental Figure 1 for the distribution of neuroticism scores in each sample, http://links.lww.com/PSYMED/A580).

Frailty Index

The Rockwood FI was used to assess frailty and created in each sample following the standard protocol (3). The minimum number of items considered is recommended to fall between 30 and 40, but the more deficits included, the more precise the measure. Here, the derived FIs were based on 49 health deficits in UKB, 44 in SALT, 42 in SATSA, and 40 in AO50, depending on the relevant measures available in each sample (see Supplemental Table 1 for a list of health deficits included in each FI, http://links.lww.com/PSYMED/A580). An individual's FI score constitutes of the number of deficits (for that individual) divided by the total number of deficits composing the FI. The FI ranges from 0 to 1, where higher values indicate greater frailty. Although the theoretical maximum of the FI is 1, >99% of individuals in all populations have an FI of <0.7, indicating that survival beyond this point is lethal (29). In addition, although FI captures age-related health decline into late life, it has been found useful in predicting disease end points also in middle-aged individuals (30). Detailed descriptions of the creation and validation of the FIs were reported elsewhere; see Refs. (31) for UKB, (5) for SATSA, and (32) for SALT. For a detailed description of the FI in AO50 study, see the Supplemental Materials, http://links.lww.com/PSYMED/A580. Because the FI in three samples included

some neuroticism items, and this could lead to overestimation of the effect sizes, items directly overlapping between FIs and the respective EPQ scales were excluded (three items in UKB, one item in AO50, and two items in SATSA; see Supplemental Table 1, http://links.lww.com/PSYMED/A580) and FIs were recalculated. The FIs excluding neuroticism items were used in the primary analyses.

Genotyping

For UKB, imputed genetic data released in 2018 were used. Two custom genotyping arrays were used to cover more than 800,000 markers and were further imputed to Haplotype Reference Consortium (HRC) and UK10K + 1000 Genomes phase 3 reference panels (33). In AO50, individuals were genotyped using Illumina single-nucleotide polymorphism (SNP) platforms—317, 370, 610, 660, Core-Exome, PsychChip, Omni2.5, and OmniExpress—and were imputed to HRC.1.1. In SALT, genotyping was carried out using the Illumina OmniExpress bead chip and further imputed to Hapmap 2 build 36 reference panel. In SATSA, genotyping was carried out using Illumina PsychArray-24 BeadChip and imputed to 1000 Genomes phase 3 reference panel. For both STR samples, only one twin from each monozygotic (MZ) pair was directly genotyped, and genotypes were later imputed to their co-twin.

PRSs for Neuroticism

PRSs for neuroticism (PRS_N) were created in the four independent target samples using the results (effect sizes and p values for each SNP) from a GWAS on neuroticism (34), by counting the numbers of risk alleles at independent loci, multiplying with the effect size, and summing the values across all investigated SNPs (performed in Plink 1.9 and Plink 2.0). The $PRSs_N$ were created under eight p value thresholds (p_T), from 5×10^{-8} to 1 in UKB, AO50, and SATSA and from 0.001 to 1 in SALT, and each PRS_N was standardized using z scores. The threshold that explains the highest percentage of variance in neuroticism in each sample was used in the main hypothesis testing.

Covariates

Variables with a conceptual rationale for being associated both with neuroticism trait scores and FI scores were considered as potential confounders. These included age, sex, education, smoking status, physical activity, and body mass index (BMI). In the UKB and AO50, all covariates were measured concurrently with neuroticism and frailty. In SATSA and SALT, all covariates were measured at baseline, with the exception of education in SALT, which was concurrent. For more detailed description of covariate assessment, see the Supplemental Materials, http://links.lww.com/PSYMED/A580. In analyses including PRS_N, 4 to 20 principal components (PCs; depending on the target sample size) were included as covariates to account for population stratification.

Statistical Analysis

We included all white participants with available information on variables of interest for each respective analysis. In the UKB, nonwhite participants and those who had withdrawn their participation consent were excluded. Exclusion criteria for the PRS analyses are described in more detail in the Supplemental Materials, http://links.lww.com/PSYMED/A580.

Phenotypic Analyses

Multivariable linear regression analyses were used to determine whether neuroticism was phenotypically associated with FI scores cross-sectionally in UKB, AO50, and SATSA, and longitudinally in SALT and SATSA (over 25–29 years in SALT and over 6 and 23 years in SATSA; aim 1). In the cross-sectional analyses, we adjusted for age, sex, and educational level (model 1) and then additionally for smoking status, exercise, and BMI (model 2). In the longitudinal analyses, follow-up FI scores were predicted from baseline neuroticism while adjusting for all covariates (model 1). To reduce the possibility of reverse causation (i.e., higher baseline frailty influencing neuroticism level), baseline FI score/chronic illness (chronic illness in SALT as baseline frailty could not be derived) was additionally included as a covariate (model 2). Because the cohorts are composed of related individuals (twins in AO50, SALT, and SATSA), dependency between observations due to relatedness was adjusted for by using cluster-robust standard error estimator (i.e., the sandwich estimator) on family ID.

Co-twin Control Analyses

Co-twin control analysis was used to examine associations between neuroticism and frailty with regard to familial (genetic and environmental) factors shared within the twin pair (aim 2). Dizygotic (DZ) twins share on average 50% of their segregating genes and MZ twins share all their genes, whereas both MZ and DZ twins share their family environment. If neuroticism's effect on frailty is beyond familial influences (consistent with a causal hypothesis), we would expect that the twin with higher neuroticism would also be more frail; that is, the within-pair associations (MZ and DZ) between neuroticism and frailty would be similar in strength to the individual-level association in the whole sample (35). If the association is better explained by shared underlying factors (e.g., genetic factors), the strength of the association would be attenuated within DZ and especially MZ twins (see Ref. (35) for further details). Within-pair difference scores for neuroticism and FI were calculated. Linear regression analyses were used to test whether within-pair differences in neuroticism predicted within-pair differences in FI scores, both cross-sectionally (in AO50 and SATSA) and longitudinally (25–29 years in SALT and in SATSA only over 6 years as the number of full pairs was low after 23 years), adjusting for within-pair differences in education, smoking, exercise, and BMI. Because only same-sex twins were included, and twins are by default the same age, possible confounding influences of sex and age were intrinsically adjusted for by the co-twin design.

PRS Analyses

Multivariable linear regression with PRS_N as an independent variable adjusting for age, sex, and PCs was used. First, to validate PRS_N as a predictor for neuroticism and to determine which PRS_N p_T explained the highest proportion of variance in phenotypic neuroticism in each sample to be used for the main analyses, the differences in R^2 between the full (including PRS_N) and reduced (including only the covariates) models were compared. The selected $PRSs_N$ were then regressed on the respective frailty score in each sample to examine whether measured genetic risk for neuroticism predicts frailty (aim 3). The resulting coefficients from each cohort were then combined in a meta-analysis to get an estimate of the overall effect taking into account sample size. Dependency between observations was adjusted for by using the cluster-robust standard error estimator on family ID.

Standardized regression coefficients were reported for all regression analyses to enable comparison between models. Statistical analyses were carried out using Stata version 15.

Sensitivity Analyses

Because neuroticism shows correlations with mental health (11), we also created additional FIs in UKB, AO50, and SATSA cohorts, further removing any mental health items (i.e., four items in UKB, three items in AO50, and two items in SATSA; see Supplemental Table 1, http://links.lww.com/PSYMED/A580), and re-ran the cross-sectional analyses as sensitivity analysis, to assess whether the association between neuroticism and frailty held after excluding mental health items in addition to already excluded neuroticism items. Furthermore, item-level sensitivity analyses between frailty and neuroticism (i.e., neuroticism items predicting FI score and neuroticism sum score predicting frailty items) were conducted. A sensitivity analysis was also carried out to test the association between PRS_N created under all eight p_T values and FI scores.

RESULTS

Descriptive statistics of baseline characteristics and follow-up FI scores of the four samples are presented in Table 1. In all cohorts with cross-sectional data, higher neuroticism was associated with higher FI scores (Table 2) with approximately 0.3-SD increase in FI scores with each SD increase in neuroticism. The sensitivity analysis without any mental health items in the FI showed similar results, though attenuated in all cohorts (UKB, 28% attenuation; AO50, 19% attenuation; and SATSA, 12% attenuation; see Supplemental Table 2, http://links.lww.com/PSYMED/A580). The longitudinal analyses between neuroticism and frailty in SALT and SATSA showed that high baseline neuroticism was associated with higher frailty measured 6, 23, and 25 to 29 years later (Table 3, model 1). Furthermore, the association remained significant when adjusting for baseline chronic illness in SALT as well as baseline frailty in SATSA across 6 but not 23 years (Table 3, model 2).

Item-level sensitivity analysis showed that most neuroticism items were associated with frailty, with no single item standing out across the four samples (Supplemental Tables 3 and 4, http://links.lww.com/PSYMED/A580). In addition, neuroticism sum score was associated with most frailty items in all four samples, although relatively stronger associations were found for depressed mood and self-rated health (Supplemental Tables 5 and 6, http://links.lww.com/PSYMED/A580).

Within-pair differences in neuroticism significantly predicted within-pair differences in FI scores cross-sectionally, both in DZ and MZ twin pairs (Figure 1A). The association was lower in DZ pairs compared with the cross-sectional association observed in the full cohorts and even lower in MZ pairs, although the attenuation was not significant. Within-pair differences in baseline neuroticism also significantly predicted within-pair differences in follow-up FI scores. Again, there is a trend toward a weaker association between neuroticism and FI scores in MZ twins compared with DZ twins and compared with the association observed in the full cohort, especially evident in SALT (Figure 1B).

The best PRS_N explained 1.3% of the variance in neuroticism in UKB ($p_T < .1$), 0.5% in AO50 ($p_T < 1 \times 10^{-5}$), 0.3% in SALT ($p_T < .3$), and 1.8% in SATSA ($p_T < 1$; Supplemental Figure 2, http://links.lww.com/PSYMED/A580). Furthermore, PRS_N explained 0.36% of the FI variance in UKB and 0.26% in SALT but was nonsignificant in AO50 and SATSA (Figure 2). When meta-analyzed, overall higher polygenic risk of neuroticism significantly predicted FI scores (Figure 3). See Supplemental Table 7 for sensitivity analysis including all eight p_T values, http://links.lww.com/PSYMED/A580.

DISCUSSION

By using cross-sectional and longitudinal data from large genetically informative samples of middle-aged and older adults, we

TABLE 1. Descriptive Characteristics of the Samples

					STR			
	UKB		AO50		SALT		SATSA	
	Mean (SD)/%	Total *n*	Mean (SD)/%	Total *n*	Mean (SD)/%	Total *n*	Mean (SD)/%	Total *n*
Baseline age, y	56.89 (8.01)	423,960	61.35 (8.60)	3011	29.14 (8.82)	23,744	62.42 (13.72)	1637
Age <10 y follow-up	na		na		na		65.06 (12.98)	1450
Age >20 y follow-up	na		na		55.88 (8.00)	23,744	73.56 (9.89)	568
Sex (female)	54%	423,960	70%	3011	53%	23,744	59%	1637
Zygosity (MZ)	na		49%	3011	40%	18,444	34%	1563
Neuroticism[a]	4.12 (3.26)	343,744	4.00 (3.17)	2946	2.78 (2.33)	21,175	2.43 (2.22)	1575
Smoking status		422,078		2960		21,081		1460
Nonsmoker	55%		51%		45%		71%	
Ex-smoker	35%		36%		42%		6%	
Current smoker	10%		13%		13%		23%	
Exercise (yes)	85%	423,960	89%	2847	89%	21,123	88%	1609
Educational level (high)	78.70%	341,812	74.25%	2901	26.95%	22,100	13.37%	1518
BMI, kg/m^2	27.40 (4.81)	421,520	25.86 (4.02)	2973	21.74 (2.85)	20,951	24.56 (3.50)	1444
Chronic illness (yes)	na		na		14.10%		na	
FI score baseline[b]	0.11 (0.07)	422,931	0.14 (0.09)	3011	na		0.10 (0.09)	1479
FI score <10 y follow-up[c]	na		na		na		0.09 (0.08)	1407
FI score >20 y follow-up[d]	na		na		0.12 (0.085)	23,085	0.12 (0.10)	522

STR = Swedish Twin Registry; UKB = UK Biobank; AO50 = The Australian Over 50's Study; SALT = Screening Across the Lifespan of Twins Study; SATSA = The Swedish Adoption/Twin Study of Aging; MZ = monozygotic; na = not applicable; BMI = body mass index; FI = frailty index.

[a] Neuroticism was assessed using different scales.

[b] Range of baseline FI scores in UKB (min = 0, max = 0.57), AO50 (min = 0, max = 0.71), and SATSA (min = 0, max = 0.60).

[c] Range of <10-y follow-up FI scores in SATSA (min = 0, max = 0.51).

[d] Range of >20-y follow-up FI scores in SALT (min = 0, max = 0.70) and SATSA (min = 0 to max = 0.61).

TABLE 2. The Cross-Sectional Association Between Neuroticism and FI Scores in UKB, AO50, and SATSA Cohorts (β and 95% CI)

	UKB		AO50		SATSA	
	Model 1[a] (*n* = 274,951)	Model 2[b] (*n* = 273,769)	Model 1 (*n* = 2849)	Model 2 (*n* = 2650)	Model 1 (*n* = 1365)	Model 2 (*n* = 1318)
Neuroticism	0.33 (0.32 to 0.33)	0.32 (0.31 to 0.32)	0.35 (0.31 to 0.38)	0.35 (0.31 to 0.39)	0.34 (0.28 to 0.39)	0.33 (0.27 to 0.39)
Age	0.18 (0.18 to 0.19)	0.17 (0.17 to 0.18)	0.23 (0.19 to 0.27)	0.27 (0.23 to 0.31)	0.49 (0.44 to 0.55)	0.48 (0.43 to 0.54)
Sex	0.02 (0.02 to 0.03)	−0.01 (−0.01 to −0.01)	0.05 (0.01 to 0.08)	0.08 (0.05 to 0.12)	0.00 (−0.04 to 0.04)	0.00 (−0.04 to 0.05)
Education	−0.01 (−0.02 to −0.01)	0.00 (0.00 to 0.01)	0.02 (−0.01 to 0.06)	0.04 (0.00 to 0.08)	−0.03 (−0.06 to 0.00)	−0.02 (−0.05 to 0.02)
Smoking		0.08 (0.08 to 0.09)		0.09 (0.05 to 0.13)		0.03 (−0.01 to 0.08)
Exercise		−0.06 (−0.07 to −0.06)		−0.03 (−0.07 to 0.01)		−0.12 (−0.18 to −0.06)
BMI		0.25 (0.24 to 0.25)		0.17 (0.13 to 0.21)		0.06 (−0.00 to 0.11)

FI = frailty index; UKB = UK Biobank; AO50 = The Australian Over 50's Study; BMI = body mass index; SATSA = The Swedish Adoption/Twin Study of Aging; CI = confidence interval.

Ninety-five percent CIs including zero indicate a nonsignificant association. Coefficients are standardized; effects of an SD change in neuroticism scores on an SD change in FI scores.

[a] Adjusted for age, sex, and educational level.

[b] Additionally adjusted for smoking status, exercise, and BMI.

TABLE 3. The Longitudinal Association Between Baseline Neuroticism and Follow-up FI scores in SALT and SATSA Cohorts (β and 95% CI)

	SALT		SATSA			
	FI Score 25- to 29-y Follow-up		FI Score 6-y Follow-up		FI Score 23-y Follow-up	
	Model 1[a] (*n* = 18,960)	Model 2[b] (*n* = 18,773)	Model 1 (*n* = 1031)	Model 2 (*n* = 1031)	Model 1 (*n* = 418)	Model 2 (*n* = 418)
Neuroticism	0.24 (0.22 to 0.25)	0.22 (0.21 to 0.24)	0.31 (0.24 to 0.38)	0.06 (0.02 to 0.11)	0.16 (0.07 to 0.25)	0.04 (−0.05 to 0.12)
Age	0.12 (0.10 to 0.13)	0.10 (0.09 to 0.12)	0.49 (0.41 to 0.57)	0.19 (0.13 to 0.26)	0.60 (0.44 to 0.76)	0.53 (0.37 to 0.68)
Sex	0.12 (0.11 to 0.14)	0.13 (0.11 to 0.14)	0.08 (0.03 to 0.14)	0.07 (0.03 to 0.11)	0.08 (−0.01 to 0.16)	0.08 (0.01 to 0.16)
Education	−0.04 (−0.06 to −0.03)	−0.05 (−0.06 to −0.04)	0.02 (−0.03 to 0.06)	0.02 (−0.02 to 0.05)	−0.00 (−0.07 to 0.06)	0.00 (−0.06 to 0.06)
Smoking	0.03 (0.02 to 0.04)	0.03 (0.01 to 0.04)	0.04 (−0.01 to 0.10)	0.01 (−0.03 to 0.06)	0.08 (0.00 to 0.16)	0.07 (0.00 to 0.14)
Exercise	−0.04 (−0.05 to 0.02)	−0.04 (−0.05 to −0.02)	−0.05 (−0.12 to 0.01)	0.00 (−0.04 to 0.04)	0.05 (−0.02 to 0.13)	0.02 (−0.05 to 0.09)
BMI	0.13 (0.11 to 0.15)	0.13 (0.11 to 0.15)	0.11 (0.04 to 0.19)	0.03 (−0.02 to 0.08)	0.08 (−0.01 to 0.17)	0.06 (−0.02 to 0.14)
Baseline FI/chronic illness		0.13 (0.12 to 0.15)		0.78 (0.71 to 0.85)		0.56 (0.42 to 0.70)

FI = frailty index; SALT = Screening Across the Lifespan of Twins Study; SATSA = The Swedish Adoption/Twin Study of Aging; BMI = body mass index.

Ninety-five percent CIs including zero indicate a nonsignificant association. Coefficients are standardized; effects of an SD change in neuroticism scores on an SD change in FI scores.

[a] Adjusted for age, sex, educational level, smoking status, exercise, and BMI.

[b] Additionally adjusted for baseline FI/chronic illness.

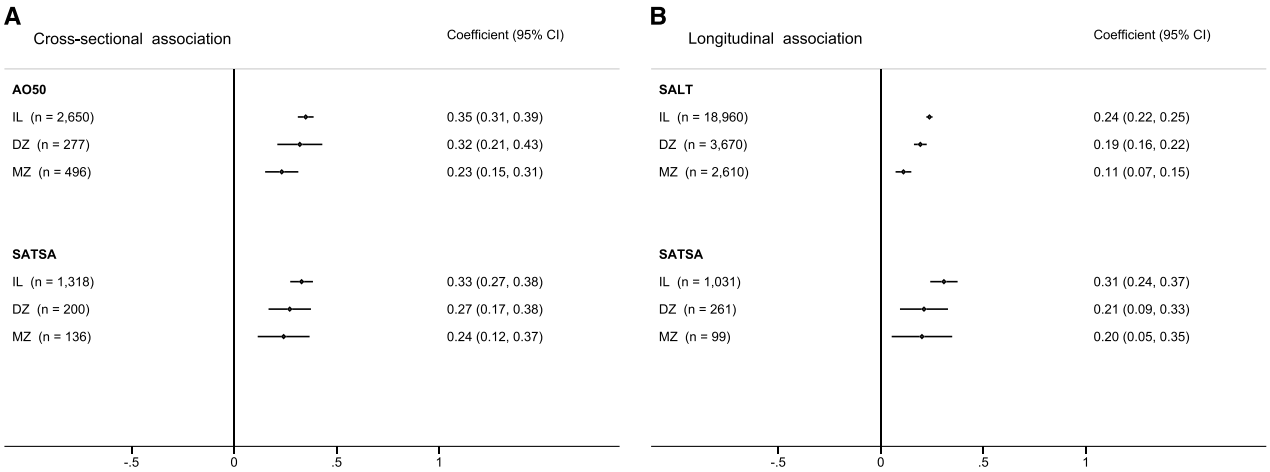

FIGURE 1. The cross-sectional (A) and longitudinal (B) associations between neuroticism and FI scores in AO50, SATSA, and SALT for the individual level association observed in the full cohort as well as for same-sex DZ and MZ twins (β, 95% CI). Models were corrected for relatedness and covariates: education, smoking, exercise, and BMI. Longitudinal association in SALT over 25 to 29 years and in SATSA over 6 years. FI = frailty index; AO50 = The Australian Over 50's Study; SATSA = The Swedish Adoption/Twin Study of Aging; SALT = Screening Across the Lifespan of Twins Study; IL = individual level; DZ = dizygotic twins; MZ = monozygotic twins; CI = confidence interval; BMI = body mass index.

found that higher neuroticism was consistently associated with greater frailty cross-sectionally and over more than two decades. After adjusting for underlying genetic and shared environmental factors using a co-twin control design, the association between neuroticism and frailty remained evident, although attenuated to some extent, suggesting a causal relationship and potentially indicating some shared underlying liability. Results from PRS analyses suggested the contribution of neuroticism-related genetic risk variants in frailty.

Overall, the results of the phenotypic analyses are in line with previous studies examining the association between neuroticism and frailty, based on two widely used measures of frailty: the Fried frailty phenotype (based on grip strength, weight loss, walking speed, exhaustion, and activity level) and the FI (13–15). This demonstrates the robustness of the neuroticism-frailty association, regardless of whether frailty is based on objective indicators (i.e., Fried frailty phenotype) or self-reported health deficits (FI). Our study expanded the follow-up time up to 29 years, elucidating the stability of neuroticism in midlife as a predictor of late-life frailty. The associations between neuroticism and frailty were independent of age, sex, education, and three life-style factors—smoking status, exercise, and BMI—suggesting that neuroticism influences frailty over and above these potential confounding or mediating variables. To reduce the possibility of reverse causation by which poorer health at baseline may have influenced responses to items on the neuroticism scale, we additionally adjusted for baseline chronic illness/frailty. Although the effect size diminished, the

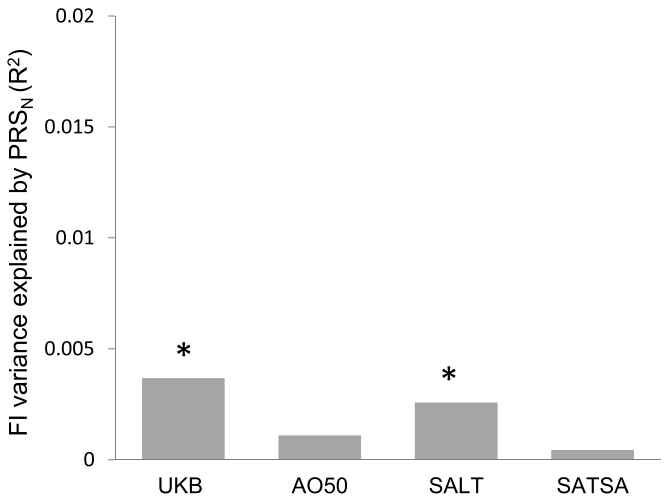

FIGURE 2. Variance in FI explained by polygenic risk scores for neuroticism in UKB (n = 243,734), AO50 (n = 1037), SALT (n = 6221), and SATSA (n = 548) cohorts. Variance refers to the difference in R^2 between full and reduced regression models. FI = frailty index; UKB = UK Biobank; AO50 = The Australian Over 50's Study; SALT = Screening Across the Lifespan of Twins Study; SATSA = The Swedish Adoption/Twin Study of Aging; CI = confidence interval; PRS_N = polygenic risk score for neuroticism. * $p < .001$.

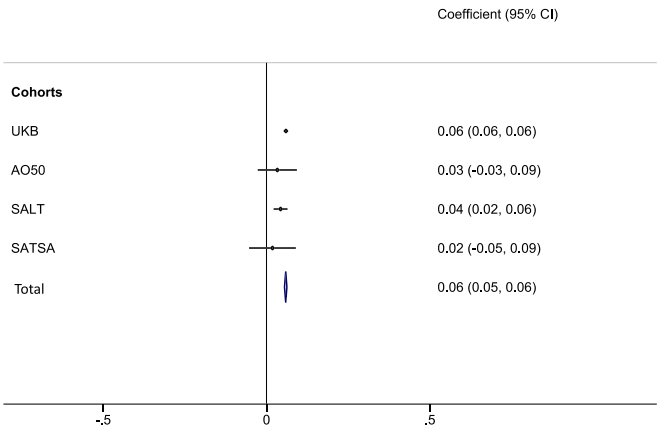

FIGURE 3. Effect sizes of polygenic risk scores for neuroticism on FI scores in UKB (n = 243,734), AO50 (n = 1037), SALT (n = 6221), and SATSA (n = 548) cohorts and meta-analytical effect size combining the observed effect in the four cohorts and taking into account sample size (β and 95% CI). Models were adjusted for age, sex, and PCs. FI = frailty index; UKB = UK Biobank; AO50 = The Australian Over 50's Study; SALT = Screening Across the Lifespan of Twins Study; SATSA = The Swedish Adoption/Twin Study of Aging; CI = confidence interval; PC = principal component. Color image is available only in the online version (www.psychosomaticmedicine.org).

association remained significant in SALT and in SATSA across 6 years but not 23 years where attrition likely affected the power as indicated by the vastly reduced sample size.

Our second aim was to assess how familial influences, that is, shared childhood environmental factors (e.g., socioeconomic factors and parental education) or common genetic factors, could potentially contribute to the relationship between neuroticism and frailty. Using the co-twin control design, we found that the neuroticism-frailty association remained evident even when adjusting for all underlying genetic and shared environmental factors (i.e., in MZ twins). This finding is in line with a causal hypothesis, indicating that higher neuroticism increases the risk of frailty (35). However, comparison of effect size attenuation (though not significant) in DZ and even further in MZ twins also suggests that part of the association between neuroticism and frailty is likely due to underlying shared factors, such as genetic risk.

Genetic risk for neuroticism was found to significantly predict frailty in the UKB and SALT, but not in AO50 and SATSA, which is likely due to the much smaller sample sizes and consequently low power. These results provide evidence that neuroticism and frailty are partly influenced by overlapping genetic factors. However, in all four cohorts, the amount of variance in FI scores explained by the PRS_N was small, yet not surprising considering the low predictive power of genetic risk scores in general (36). With increasing power of the discovery GWAS, estimation of effects sizes of common SNPs becomes more precise and PRS prediction will gain predictive power.

Together, our results demonstrate the involvement of both environmental and genetic factors in the relationship between neuroticism and health in late life. One possible mechanism through which neuroticism influences frailty is engagement in risky health behaviors. Previous research has shown that individuals with high neuroticism are more likely to smoke and have low physical activity (11,37), both factors that have previously been associated with frailty (38,39). Here, the neuroticism-frailty association only attenuated slightly when adjusting for life-style factors. However, our measures were crude (binary) and there may be other unmeasured health-related behaviors that could influence frailty.

Another possible explanation is that some mental health related aspects such as mood, feelings of loneliness, or nervousness are reflected in both measures of neuroticism and frailty. However, results of the sensitivity analysis with recalculated FI excluding all mental health items remained similar in all cohorts, emphasizing the robustness of neuroticism-frailty associations even without mental health items. The item-level sensitivity analyses revealed that neuroticism was significantly associated with most FI items, although with varying effects. The strongest associations were found with depressed mood and self-rated health, which are both independently associated with mortality and morbidity (40–46). However, pain items, fatigue, insomnia, hearing problems, and allergy also showed consistent associations across cohorts. Our results further highlight that psychological factors may influence the way older individuals perceive their health status and well-being, which emphasizes the importance of considering such factors when assessing the overall health status later in life.

Also, genetic overlap between neuroticism and frailty may contribute to the association, and this should be further investigated in the future when GWAS results on frailty become available, enabling investigations on potential genetic correlations. The pathophysiology of frailty is likely a complex combination of many physiological systems, including the aging brain, endocrine system, and immune system (2). Neuroticism may influence frailty through a number of such biologically relevant mechanisms. For example, neuroticism has been previously linked to biomarkers of the immune system (47) potentially associated with higher vulnerability to stressors and adverse disease outcomes. Another possible biological mechanism through which neuroticism could potentially influence frailty is the hypothalamic-pituitary-adrenal axis activity in the endocrine system. Physiological reserve is a prominent feature of frailty (2), and high neuroticism has been associated with dysregulation of the hypothalamic-pituitary-adrenal axis (48) and psychological stress (49). Future basic science research will need to examine the extent to which specific potential biological mechanisms may explain the neuroticism-frailty association.

This study has some limitations. First, FI was not available from SALT baseline measurement (Q73). The sample was

relatively young at the time, and because prevalence of frailty is low in young people (2), there would be little variance in frailty. However, we used information on chronic or serious illness collected in 1973 to adjust for baseline health status. Second, an insufficient sample size may have been a limitation for some analyses, such as in the longitudinal analysis in SATSA with the largest time interval and the polygenic prediction in SATSA and AO50. However, with the use of several cohorts, we could derive relatively consistent findings, highlighting the importance of well-powered samples, replication, and meta-analytic methods, especially when using the PRS approach. Finally, these results are based only on white populations; therefore, future studies should explore whether the neuroticism-frailty association holds also in other than Western societies and whether cultural differences in attitudes toward health and well-being could play a role.

In conclusion, this study indicates that in addition to physical and biological determinants of frailty, psychological predictors of frailty should also be acknowledged. The results provide evidence that neuroticism at midlife predicts frailty in late life and that, although the association may in part reflect shared underlying genetic liability, neuroticism may increase the risk of frailty.

We thank Xia Li for deriving the FI in SALT and Emma Raymond for her advice on FI methodology, and Dr. Robert Karlsson for bioinformatics support. We thank the Swedish and Australian twins for their participation and UKB participants. We also gratefully acknowledge the support and funding for the Over 50's twin study from Mr. George Landers of Chania, Crete. We acknowledge The Swedish Twin Registry for access to data. The Swedish Twin Registry is managed by Karolinska Institutet and receives funding through the Swedish Research Council under the grant no. 2017-00641. In addition, UKB data were used under application number 22224.

Sources of Funding and Conflicts of Interest: This work was supported by research grants from Swedish FORTE (grant number 2013-2292 to N.L.P.), the Swedish Research Council (grant numbers 521-2013-8689 and 2015-03255 to N.L.P.), Loo and Hans Osterman Foundation for Medical Research (grant number 2017-00103 to K.L., grant number 2018-0004 to M.A.M., grant number 2017-00108 to J.J.), and the Strategic Research Program in Epidemiology at Karolinska Institutet (to J.J., S.H.). K.L. is supported by European Regional Development Fund and the programme Mobilitas Pluss (grant number MOBTP142). L.C.-C. is supported by a QIMR Berghofer fellowship. The authors have no conflict of interests to declare.

Ethical Approvals: All participants have given informed consent. Ethical permits have been granted for UKB by North West–Haydock Research Ethics Committee (16/NW/0274) and Stockholm's Regional Ethical Committee (2016/1888-31/1), AO50 by the QIMR Berghofer Human Research Ethics Committee (P1204), and SALT and SATSA studies by Stockholm's Regional Ethical Committee (00-132; 98-319).

REFERENCES

1. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal 2001;1:323–36.
2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet 2013;381:752–62.
3. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr 2008;8:24.
4. Shamliyan T, Talley KM, Ramakrishnan R, Kane RL. Association of frailty with survival: a systematic literature review. Ageing Res Rev 2013;12:719–36.
5. Jiang M, Foebel AD, Kuja-Halkola R, Karlsson I, Pedersen NL, Hagg S, Jylhava J. Frailty index as a predictor of all-cause and cause-specific mortality in a Swedish population–based cohort. Aging (Albany NY) 2017;9:2629–46.
6. Kojima G, Iliffe S, Walters K. Frailty index as a predictor of mortality: a systematic review and meta-analysis. Age Ageing 2018;47:193–200.
7. Vermeiren S, Vella-Azzopardi R, Beckwée D, Habbig AK, Scafoglieri A, Jansen B, Bautmans I, Bautmans I, Verté D, Beyer I, Petrovic M, De Donder L, Kardol T, Rossi G, Clarys P, Scafoglieri A, Cattrysse E, de Hert P, Jansen B. Frailty and the prediction of negative health outcomes: a meta-analysis. J Am Med Dir Assoc 2016;17:1163.e1–1163.e17.
8. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, Ershler WB, Harris T, Fried LP. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc 2006;54:991–1001.
9. Mello Ade C, Engstrom EM, Alves LC. Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review. Cad Saude Publica 2014;30:1143–68.
10. Charles ST, Gatz M, Kato K, Pedersen NL. Physical health 25 years later: the predictive ability of neuroticism. Health Psychol 2008;27:369–78.
11. Lahey BB. Public health significance of neuroticism. Am Psychol 2009;64:241–56.
12. Widiger TA, Oltmanns JR. Neuroticism is a fundamental domain of personality with enormous public health implications. World Psychiatry 2017;16:144–5.
13. Gale CR, Mottus R, Deary IJ, Cooper C, Sayer AA. Personality and risk of frailty: the English longitudinal study of ageing. Ann Behav Med 2017;51:128–36.
14. Stephan Y, Sutin AR, Canada B, Terracciano A. Personality and frailty: evidence from four samples. J Res Pers 2017;66:46–53.
15. McHugh JE, Dowling M, Butler A, Lawlor BA. Psychological distress and frailty transitions over time in community-dwelling older adults. Ir J Psychol Med 2016;33:111–9.
16. Vukasovic T, Bratko D. Heritability of personality: a meta-analysis of behavior genetic studies. Psychol Bull 2015;141:769–85.
17. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, Posthuma D. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat Genet 2015;47:702–9.
18. Nagel M, Watanabe K, Stringer S, Posthuma D, van der Sluis S. Item-level analyses reveal genetic heterogeneity in neuroticism. Nat Commun 2018;9:905.
19. Nagel M, Jansen PR, Stringer S, Watanabe K, de Leeuw CA, Bryois J, Savage JE, Hammerschlag AR, Skene NG, Muñoz-Manchado AB. Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. Nat Genet 2018;50:920.
20. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, Downey P, Elliott P, Green J, Landray M, Liu B, Matthews P, Ong G, Pell J, Silman A, Young A, Sprosen T, Peakman T, Collins R. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
21. Mosing MA, Zietsch BP, Shekar SN, Wright MJ, Martin NG. Genetic and environmental influences on optimism and its relationship to mental and self-rated health: a study of aging twins. Behav Genet 2009;39:597–604.
22. Lichtenstein P, De Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. J Intern Med 2002;252:184–205.
23. Magnusson PK, Almqvist C, Rahman I, Ganna A, Viktorin A, Walum H, Halldner L, Lundstrom S, Ullen F, Langstrom N, Larsson H, Nyman A, Gumpert CH, Rastam M, Anckarsater H, Cnattingius S, Johannesson M, Ingelsson E, Klareskog L, de Faire U, Pedersen NL, Lichtenstein P. The Swedish Twin Registry: establishment of a biobank and other recent developments. Twin Res Hum Genet 2013;16:317–29.
24. Pedersen NL, McClearn GE, Plomin R, Nesselroade JR, Berg S, DeFaire U. The Swedish Adoption Twin Study of Aging: an update. Acta Genet Med Gemellol (Roma) 1991;40:7–20.
25. Eysenck SBG, Eysenck HJ, Barrett P. A revised version of the psychoticism scale. Pers Individ Dif 1985;6:21–9.
26. Eysenck HJ, Eysenck SBG. Manual of the Eysenck Personality Questionnaire. London: Hodder & Stoughton; 1975.
27. Floderus B. Psycho-social factors in relation to coronary heart disease and associated risk factors. Nord Hyg Tidskr 1974;(Suppl 6):7–148.
28. Pedersen NL, Plomin R, McClearn GE, Friberg L. Neuroticism, extraversion, and related traits in adult twins reared apart and reared together. J Pers Soc Psychol 1988;55:950–7.
29. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mech Ageing Dev 2006;127:494–6.
30. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health 2018;3:e323–32.
31. Williams DM, Jylhävä J, Pedersen NL, Hägg S. A frailty index for UK Biobank participants. J Gerontol A Biol Sci Med Sci 2018.
32. Li X, Ploner A, Karlsson IK, Liu X, Magnusson PKE, Pedersen NL, Hägg S, Jylhävä J. The frailty index is a predictor of cause-specific mortality independent of familial effects from midlife onwards: a large cohort study. BMC Med 2019;17:94.

33. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J, Cortes A, Welsh S, Young A, Effingham M, McVean G, Leslie S, Allen N, Donnelly P, Marchini J. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203–9.
34. Okbay A, Baselmans BM, De Neve JE, Turley P, Nivard MG, Fontana MA, Meddens SF, Linner RK, Rietveld CA, Derringer J, Gratten J, Lee JJ, Liu JZ, de Vlaming R, Ahluwalia TS, Buchwald J, Cavadino A, Frazier-Wood AC, Furlotte NA, Garfield V, Geisel MH, Gonzalez JR, Haitjema S, Karlsson R, van der Laan SW, Ladwig KH, Lahti J, van der Lee SJ, Lind PA, Liu T, Matteson L, Mihailov E, Miller MB, Minica CC, Nolte IM, Mook-Kanamori D, van der Most PJ, Oldmeadow C, Qian Y, Raitakari O, Rawal R, Realo A, Rueedi R, Schmidt B, Smith AV, Stergiakouli E, Tanaka T, Taylor K, Thorleifsson G, Wedenoja J, Wellmann J, Westra HJ, Willems SM, Zhao W, Amin N, Bakshi A, Bergmann S, Bjornsdottir G, Boyle PA, Cherney S, Cox SR, Davies G, Davis OS, Ding J, Direk N, Eibich P, Emeny RT, Fatemifar G, Faul JD, Ferrucci L, Forstner AJ, Gieger C, Gupta R, Harris TB, Harris JM, Holliday EG, Hottenga JJ, De Jager PL, Kaakinen MA, Kajantie E, Karhunen V, Kolcic I, Kumari M, Launer LJ, Franke L, Li-Gao R, Liewald DC, Koini M, Loukola A, Marques-Vidal P, Montgomery GW, Mosing MA, Paternoster L, Pattie A, Petrovic KE, Pulkki-Raback L, Quaye L, Raikkonen K, Rudan I, Scott RJ, Smith JA, Sutin AR, Trzaskowski M, Vinkhuyzen AE, Yu L, Zabaneh D, Attia JR, Bennett DA, Berger K, Bertram L, Boomsma DI, Snieder H, Chang SC, Cucca F, Deary IJ, van Duijn CM, Eriksson JG, Bultmann U, de Geus EJ, Groenen PJ, Gudnason V, Hansen T, Hartman CA, Haworth CM, Hayward C, Heath AC, Hinds DA, Hypponen E, Iacono WG, Jarvelin MR, Jockel KH, Kaprio J, Kardia SL, Keltikangas-Jarvinen L, Kraft P, Kubzansky LD, Lehtimaki T, Magnusson PK, Martin NG, McGue M, Metspalu A, Mills M, de Mutsert R, Oldehinkel AJ, Pasterkamp G, Pedersen NL, Plomin R, Polasek O, Power C, Rich SS, Rosendaal FR, den Ruijter HM, Schlessinger D, Schmidt H, Svento R, Schmidt R, Alizadeh BZ, Sorensen TI, Spector TD, Starr JM, Stefansson K, Steptoe A, Terracciano A, Thorsteinsdottir U, Thurik AR, Timpson NJ, Tiemeier H, Uitterlinden AG, Vollenweider P, Wagner GG, Weir DR, Yang J, Conley DC, Smith GD, Hofman A, Johannesson M, Laibson DI, Medland SE, Meyer MN, Pickrell JK, Esko T, Krueger RF, Beauchamp JP, Koellinger PD, Benjamin DJ, Bartels M, Cesarini D. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. Nat Genet 2016;48:624–33.
35. McGue M, Osler M, Christensen K. Causal inference and observational research: the utility of twins. Perspect Psychol Sci 2010;5:546–56.
36. Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA, Yang J. 10 Years of GWAS discovery: biology, function, and translation. Am J Hum Genet 2017;101:5–22.
37. Rhodes RE, Smith NE. Personality correlates of physical activity: a review and meta-analysis. Br J Sports Med 2006;40:958–65.
38. Kojima G, Iliffe S, Walters K. Smoking as a predictor of frailty: a systematic review. BMC Geriatr 2015;15:131.
39. Tribess S, Virtuoso Junior JS, Oliveira RJ. Physical activity as a predictor of absence of frailty in the elderly. Rev Assoc Med Bras (1992) 2012;58:341–7.
40. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA 2011;306:1241–9.
41. Fawcett J. The morbidity and mortality of clinical depression. Int Clin Psychopharmacol 1993;8:217–20.
42. Spijker J, Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand 2004;110:208–14.
43. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav 1997;38:21–37.
44. Wu S, Wang R, Zhao Y, Ma X, Wu M, Yan X, He J. The relationship between self-rated health and objective health status: a population-based study. BMC Public Health 2013;13:320.
45. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66:802–13.
46. DeSalvo KB, Bloser N, Reynolds K, He J, Muntner P. Mortality prediction with a single general self-rated health question. A meta-analysis. J Gen Intern Med 2006;21:267–75.
47. Sutin AR, Terracciano A, Deiana B, Naitza S, Ferrucci L, Uda M, Schlessinger D, Costa PT Jr. High neuroticism and low conscientiousness are associated with interleukin-6. Psychol Med 2010;40:1485–93.
48. Mangold DL, Wand GS. Cortisol and adrenocorticotropic hormone responses to naloxone in subjects with high and low neuroticism. Biol Psychiatry 2006;60:850–5.
49. Chida Y, Hamer M. Chronic psychosocial factors and acute physiological responses to laboratory-induced stress in healthy populations: a quantitative review of 30 years of investigations. Psychol Bull 2008;134:829–85.