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Research Article

Age and Sex Differences in the Genetic Architecture of Measures of Subjective Health: Relationships With Physical Health, Depressive Symptoms, and Episodic Memory

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Abstract

Objectives: Subjective health (SH) is not just an indicator of physical health, but also reflects active cognitive processing of information about one's own health and has been associated with emotional health measures, such as neuroticism and depression. Behavior genetic approaches investigate the genetic architecture of SH, that is, genetic and environmental influences on individual differences in SH and associations with potential components such as physical, cognitive, and emotional health. Previous twin analyses have been limited by sex, sample size, age range, and focus on single covariates.

Methods: The current analysis used data from 24,173 adults ranging in age from 40 to 90 years from the international Interplay of Genes and Environment across Multiple Studies consortium to investigate the genetic architecture of 3 measures of SH: self-rated health, health compared to others, and impact of health on activities. Independent pathways model of SH included physical health, depressive symptoms, and episodic memory, with age, sex, and country included as covariates.

Results: Most or all of the genetic variance for SH measures were shared with physical health, depressive symptoms, and episodic memory. Genetic architecture of SH differed across measures, age groups (40–65, 66–90), and sexes. Age comparisons indicated stronger correlations with all 3 covariates in older adults, often resulting from greater shared genetic variance.

Discussion: The predictive value of SH has been amply demonstrated. The higher genetic contributions to associations between SH and its components in older adults support the increasing conceptualization with age of SH as an intuitive summation of one's vital reserve.

Keywords: CIRS, SRH, Twins, Word recall

Subjective health is typically measured with a single item. The fact that this item can predict mortality and other health outcomes independent of objective health measures (Idler & Benyamini, 1997; Latham & Peek, 2013; McFadden et al., 2009) suggests that it taps more than just perceptions of physical health. Subjective health likely also reflects active cognitive processing of explicit information about one's own health and intuitive knowledge of symptoms and physical sensations (Jylhä, 2009). Some researchers emphasize that culturally influenced concepts of health in general play a role in subjective health (Jylhä, 2009). Subjective health has also been associated with emotional health measures, such as neuroticism and depression, that may influence response tendencies or may correlate with objective physical health measures (Östberg & Nordin, 2022; Svedberg et al., 2006). In addition, individual differences in subjective health have been shown to be highly valid (predicting health outcomes) and reliable (Lundberg & Manderbacka, 1996). Therefore, it is of interest

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to investigate the mechanisms that drive these individual differences.

Behavior genetic methods are a powerful tool for understanding what shapes individual differences in subjective health. Previous studies suggest that between 20% and 46% of individual differences in subjective health are explained by genetic factors, and most, if not all, of the remaining variance is explained by unique environmental factors (Franz et al., 2017). Multivariate behavior genetic analyses can provide insight into genetic architecture of subjective health, that is, the genetic and environmental influences on individual differences in subjective health and its association with potential components such as physical health and emotional health. Because subjective health arises from a combination of component variables, it is likely that the genetic variance is not specific for subjective health but rather mediated through factors related to underlying perceptions of health. Shared genetic variance among subjective health and covariates would indicate that a common set of genes contributes to individual differences in these variables, affecting our understanding of subjective health and what it measures. In addition, common environmental variance among subjective health and the covariates may arise from the effects of environmental resources to support multiple components of health.

Myriad potential components of subjective health have been investigated, and they tend to fall into three major domains: physical health, cognitive functioning, and emotional health (Benyamini, 2016; Huisman & Deeg, 2010; Jylhä, 2009; Layes et al., 2012). Moreover, measures in all three domains have been shown to have significant genetic variance (Finkel et al., 2014; Pahlen et al., 2018; Petkus et al., 2017) and thus may contribute to the genetic architecture of subjective health. In Swedish twin data, the relationship between life satisfaction and subjective health arose from both genetic and unique environmental factors after age 65, whereas before age 65, the correlation resulted from shared and unique environmental factors (J. R. Harris, Pedersen, Stacey, et al., 1992). A co-twin control approach found genetic factors contributed to the relationship between subjective health and physical symptoms (Svedberg et al., 2006). Correlations between cognitive measures and subjective health were modest but significant ($rs \sim 0.10$), and they arose primarily from shared genetic variance (Svedberg et al., 2009). In a sample of Dutch twins, the correlation between subjective health and exercise participation was completely explained by shared genetic variance (De Moor et al., 2007). In Australian and Swedish samples, the relationship between optimism and subjective health resulted largely from shared genetic factors (Mosing, Pedersen, et al., 2010; Mosing et al., 2009). In one of the few investigations to examine the genetic architecture of subjective health incorporating multiple covariates, Leinonen and colleagues (2005) found that there was no genetic variance specific to subjective health in a sample of Danish female twins; instead, genetic variance associated with disease severity, walking speed, and depressive symptoms explained all of the genetic variance in subjective health.

The studies reviewed here are limited by at least one of several factors: utilized a single domain of subjective health covariate, limited sample size to detect age or sex differences (Mosing, Pedersen, et al., 2010; Mosing et al., 2009), reduced age range (De Moor et al., 2007; Leinonen et al., 2005), or samples that included only one sex (De Moor et al., 2007; Leinonen et al., 2005). The experience of aging differs at midlife and later, and for men and women (Sainio et al., 2006); thus, the role of individual components of subjective health, and the genetic and environmental contributions to their interrelationships, may vary across age and sex. The meaning of "good health" is unlikely to be the same for middle-aged and older adults; thus, genes associated with subjective health may vary between age groups. In fact, studies have suggested age differences in genetic influences on subjective health (Franz et al., 2017), as well as the genetic architecture of subjective health (J. R. Harris, Pedersen, Stacey, et al., 1992; Svedberg et al., 2009). Identification of age differences would highlight the developmental processes involved from mid- to late life in personal conceptions of health.

Sex differences in genetic influences on subjective health have also been identified (Franz et al., 2017), although attempts to identify sex differences in genetic architecture of subjective health were suggestive but limited by sample size (Mosing, Pedersen, et al., 2010; Mosing et al., 2009). Men tend to have earlier and more compressed histories of major illnesses and disability before death, whereas women live longer and have high prevalence of chronic but not fatal diseases in later life (Sainio et al., 2006). Identifying sex differences in the genetic contribution to the relationship between objective health measures and subjective health may contribute to our understanding of the differences in the experience of aging for men and women (Deeg et al., 2002). Most investigations of subjective health use a single item asking participants to rate their overall health. In previous investigations, we have found that the phrasing of the subjective health item influences the frame of reference used to respond to the item and can significantly affect results (Finkel et al., 2022; Franz et al., 2017). Both sex and age may affect frames of reference.

The goal of the current study is to investigate the genetic architecture of subjective health in a twin sample large enough to support examination of possible age and sex differences, incorporating a large age range, covariates in three domains (physical, cognitive, and emotional health), and multiple measures of subjective health. In these analyses we use data from 24,173 twins ranging in age from 40 to 90 from 10 studies from the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium (Pedersen et al., 2013, 2019). Our aims are to investigate the extent to which measures of physical health, episodic memory, and depressive symptoms contribute to the genetic architecture of subjective health, and whether the relationships among the variables differ across age, sex, or measure of subjective health.

Method

Participants

IGEMS is an international consortium of 18 twin studies covering the adult lifespan (Pedersen et al., 2013, 2019). The sample sizes and age ranges of the 10 IGEMS studies that collected the variables included in the current analyses are presented in Table 1. Data come from Australia, Denmark, Sweden, and the United States. Because sample sizes were quite small before age 40 and after age 90, only data from adults aged 40–90 were included in the current analyses (98.6% of the full sample). Mean age in the full sample was 62.58 (standard deviation [*SD*] = 11.37). Because two studies of veterans include only male twins (National Academy of Sciences–National Research Council [NAS/NRC] and Vietnam Era Twin Study of Aging [VETSA]), the sample was 44.67% female. Only three of the studies included people of color: Carolina African American

Table 1. Sample Description

Study	*N* individuals	MZ/DZ pairs	% Female	Age range	Mean age (*SD*)	Subjective health variables
Australia						
OATS	496	119/96	65.72	65–90	71.18 (5.40)	SRH, ACT, COMP
Denmark						
LSADT	4,091	410/604	57.88	70–90	76.35 (4.90)	SRH, ACT, COMP
MADT	4,256	666/1,195	48.87	45–68	56.38 (6.34)	SRH, ACT, COMP
MIDT	9,924	704/2,143	53.12	40–80	56.59 (9.40)	SRH, ACT, COMP
Sweden						
GENDER	425	0/211	48.47	69–79	72.89 (2.58)	SRH, ACT, COMP
SATSA	314	38/72	61.46	48–86	65.78 (8.27)	SRH, ACT, COMP
United States						
CAATSA	404	57/63	59.41	40–89	55.79 (11.18)	SRH, COMP
MIDUS	188	48/20	59.57	40–72	51.98 (8.84)	SRH, ACT, COMP
NAS/NRC	2,850	742/629	0.00	70–82	74.12 (2.76)	SRH, ACT
VETSA	1,225	340/260	0.00	51–61	55.89 (2.48)	SRH, ACT, COMP
Total	24,173	3,124/5,293	44.67	40–90	62.58 (11.37)	

Notes: ACT = health impacts activities; CAATSA = Carolina African American Twin Study of Aging; COMP = health compared to others; DZ = dizygotic twins; GENDER = Ageing in Men and Women; LSADT = Longitudinal Study of Aging Danish Twins; MADT = Middle-Aged Danish Twins; MIDT = Mid-aged Danish Twins; MIDUS = Midlife in the United States; MZ = monozygotic twins; NAS/NRC = National Academy of Sciences–National Research Council; OATS = Older Australian Twin Study; SATSA = Swedish Adoption/Twin Study of Aging; *SD* = standard deviation; SRH = self-rated health; VETSA = Vietnam Era Twin Study of Aging.

Twin Study of Aging (CAATSA; 100% Black), Midlife in the United States (MIDUS; 10.74% non-White), and VETSA (9.2% non-White). As a result, people of color made up 3.3% of the total sample for the current analyses.

Measures

Subjective health

Three self-reported variables are used to measure subjective health, based on which items were included in the 10 IGEMS studies. All 10 studies included the most common question used to assess subjective health: "How would you rate your overall health?" (SRH). Nine of the studies asked participants to compare their health to others (COMP). Seven of the studies included a single question about how their health affected their daily activities (ACT): "Is your health condition preventing you from doing things you like to do?" As part of the Short Form Health Survey (Ware & Sherbourne, 1992) administered by VETSA and MIDUS, individuals indicated whether their health affected their participation in a list of activities: responses were averaged to create a single ACT score. Across studies, response scales varied from dichotomous options to 7-point Likert scales. Previous analysis of harmonization methods (Gatz, Reynolds, et al., 2015) indicated that the most parsimonious approach was standardizing the variables within study, transforming to a *T*-score, and then combining data across studies. Higher scores indicated worse subjective health.

Physical health

The Cumulative Illness Rating Scale (CIRS) was developed to provide a brief assessment of physical impairment (Linn et al., 1968). Harmonization of an IGEMS version of the CIRS is derived from the Parmelee et al. (1995) modification geared toward geriatric patients. The IGEMS CIRS reflects self-reported illnesses and medical conditions in 13 domains: cardiac, hypertension, vascular, respiratory, otolaryngological, gastrointestinal, hepatic, renal, musculoskeletal, neurological, endocrine–metabolic, cancer, and stroke (Gatz, Petkus, et al., 2015). The total score is prorated for up to three missing domains. Higher scores indicated illnesses in more domains.

Depressive symptoms

IGEMS studies administered various inventories to assess depressive symptoms (DEPR), including the Center for Epidemiological Studies—Depression scale (Radloff, 1977), the Cambridge Mental Disorders of the Elderly Examination (CAMDEX; Roth et al., 1986), General Health Questionnaire (Goldberg, 1972), and the Geriatric Depression Scale (Yesavage & Sheikh, 1986). A crosswalk between all measures of depression was developed utilizing an independent sample administered each of the scales of interest (Gatz, Reynolds, et al., 2015). Rasch item response theory modeling was used to obtain latent trait score estimates representing an underlying depressive symptoms continuum. Each scale was transformed to CAMDEX units. Higher scores indicated more depressive symptoms.

Episodic memory

The harmonized Word List variable (WORD) is a test of verbal recall that asked participants to listen to or read aloud 10–16 words (number varied across study), and then immediately repeat back as many words as possible. From the raw score, a percent correct score was created and then translated to a *T*-score within study, based on mean and *SD* in the 65–70 age range (Luczak et al., 2023). Higher scores indicated better memory performance; however, for the current analyses WORD scores were reversed so that higher scores indicated worse functioning on all variables.

Statistical Methods

The standard twin method incorporates monozygotic (MZ) twins and dizygotic (DZ) twins to decompose the variance of any trait into the proportion attributed to additive genetic

influences (A), shared environmental influences that contribute to similarity within families (C), and unique environmental influences that contribute to differences within families (E). MZ twins share all their genetic material (A) and DZ twins share on average half of their segregating genes. In standard analysis of twin data, effects attributable to measurement error are included with E. Data from both complete and incomplete pairs can be included, with incomplete pairs contributing to estimation of means.

The independent pathways model (Martin & Eaves, 1977) was used to estimate the extent of shared genetic and environmental variance among subjective health measures and physical health, depressive symptoms, and word recall, as shown in Figure 1. Variance shared among the variables is decomposed into three latent common factors: Ag, Cg, and Eg. The residual variance that is not shared among the four variables but specific to an individual variable is also decomposed into specific factors for each variable: As, Cs, and Es. Reduced versions of the model were tested to identify the most parsimonious model to fit the data and, especially, to examine whether genetic and environment variance specific to subjective health (gray circles in Figure 1) remained significant when physical health, depressive symptoms, and word recall were included in the model. All statistical models were tested using the structural equation modeling package OpenMx 2.20.6 (Boker et al., 2021). Analyses were cross-sectional, using first wave at which study variables were collected for each study. Evaluation of relative fit of statistical models was performed using the likelihood ratio test (LRT). Given the number of models compared, significance level was set at $p < .01$.

To examine possible sex differences in the genetic architecture of subjective health, equality of model parameters across sex was tested by setting parameters equal across sexes and using LRT to examine reduction in model fit. The models were corrected for age and country. The same method was used to examine possible age differences in the genetic architecture of subjective health, with the sample divided at the median age of 66 to create middle-aged and older groups. The models were corrected for age (within groups), sex, and country.

Results

Descriptive Statistics

Mean and *SD*s for all measures within each of the 10 studies are reported in Supplementary Table 1. Overall, the sample reported illnesses in 1.77 domains on average (*SD* = 1.63) and the mean ranged from 0.86 in MIDUS (the youngest sample) to 3.34 in Older Australian Twin Study (OATS; one of the oldest samples). Overall mean on depressive symptoms was 20.60 (*SD* = 4.24), with study means ranging from 19.26 (Middle-Aged Danish Twins) to 23.74 (Swedish Adoption/Twin Study of Aging [SATSA]). Mean word recall was lowest in Longitudinal Study of Aging Danish Twins, the oldest sample, and highest in Mid-aged Danish Twins (MIDT), one of the youngest samples. Means of the three subjective health variables did not vary greatly across studies.

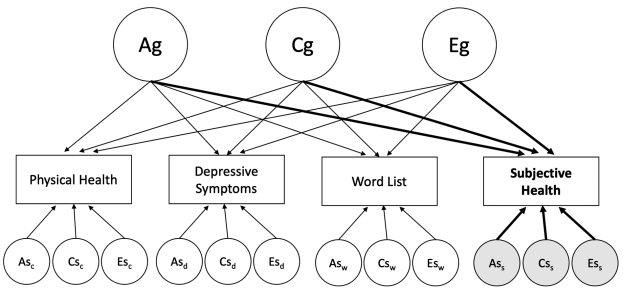

Figure 1. Independent pathways model. Ag, Cg, and Eg indicate additive genetic, shared environmental, and unique environmental variance common to the four variables. As, Cs, and Es indicate additive genetic, shared environmental, and unique environmental variance specific to the individual variables. Subscripts indicate individual variables (c = physical health, d = depressive symptoms, w = word list, s = subjective health).

Phenotypic correlations between the three subjective health variables and the covariates (physical health, depressive symptoms, and word recall) in the total sample and separately for men and women, middle-aged and older, are reported in Supplementary Table 2. All correlations were significant at $p < .01$; however, correlations with SRH and ACT tended to be higher than correlations with COMP. Correlations between the three subjective health variables and word recall (ranging from 0.06 to 0.13) were lower than between the subjective health variables and physical health or depressive symptoms (ranging from 0.21 to 0.42). The correlations between the three subjective health and depressive symptoms were weaker for middle-aged participants (ranging from 0.21 to 0.34) than for older participants (ranging from 0.29 to 0.42).

Components of Variance

Independent pathways models support two approaches to understanding the genetic architecture of subjective health: components of variance and bivariate relationships. Examining components of variance provides a test of the presence of any variance unique to subjective health (As_s, Cs_s, and Es_s) in the context of variance associated with all three covariates combined (Ag, Cg, and Eg; see bold paths in Figure 1). Supplementary Table 3 provides the model fit statistics for the full and reduced models, indicating which parameters were dropped without significantly reducing model fit. The full list of parameter estimates (and standard errors) from best-fitting models is provided in Supplementary Tables 4–6. These parameter estimates were used to calculate the A, C, and E variance for each subjective health variable shared with depressive symptoms, physical health, and memory (general variance) and specific to the subjective health variable (specific variance) reported in Table 2. Heritability estimates for the three subjective health measures were 38% (SRH), 33% (ACT), and 24% (COMP). Little or no C variance was identified in the models. However, for all three subjective health variables, all or nearly all the genetic variance (A) was shared with the covariates and there was little or no genetic variance specific to a subjective health variable. The only real source of variance specific to subjective health was nonshared environmental variance (E): estimates were 0.07 (SRH), 0.11 (ACT), and 0.25 (COMP). Overall, 92% of total variance in SRH was shared with depressive symptoms, physical health, and memory, 84% of ACT, and 62% of COMP.

Models were then tested for sex and age differences; Supplementary Table 3 provides the model fit statistics for the full and reduced models, indicating which parameters were dropped and which parameters were equated across groups without significantly reducing model fit. The full list of parameter estimates (and standard errors) from best-fitting models are provided in Supplementary Tables 4–6. These parameter estimates were used to calculate the general and specific A, C,

and E reported in Table 3, separately for men and women and middle-aged and older adults. Variances specific to COMP were either dropped (As_s and Cs_s) or identical across both sex and age groups (Es_s) in best-fitting models; therefore, the results for COMP are not included in Table 3. Again, no genetic variance specific to SRH and ACT was indicated, and little or no shared environmental variance. Total variances in SRH and ACT was greater for older than middle-aged adults, but the impact on heritability estimates was modest.

Table 2. Variance Components for Three Measures of Subjective Health

Component	SRH	ACT	COMP
A variance			
General	0.30	0.23	0.16
Specific	0.00	0.00	0.01
Total	0.30	0.23	0.17
C variance			
General	0.00	0.00	0.00
Specific	0.00	0.01	0.00
Total	0.00	0.01	0.00
E variance			
General	0.42	0.35	0.27
Specific	0.07	0.11	0.25
Total	0.49	0.46	0.52
Total variance			
General	0.72	0.58	0.43
Specific	0.07	0.12	0.26
Total	0.79	0.70	0.69

Notes: A = additive genetic effects; ACT = health impacts activities; C = shared environment; COMP = health compared to others; E = unique environment; SRH = self-rated health.

Two primary sex differences were identified in variance components. For SRH, higher total variance in men was explained by greater nonshared environment specific to SRH in men than women (0.14 vs 0.03). As a result, both heritability (43% vs 37%) and proportion of total variance in SRH shared with the covariates (95% vs 84%) were higher for women than men. For ACT, the genetic variance was greater in women than men, again resulting in higher heritability for women than men (46% vs 37%) and greater proportion of total variance in ACT shared with the covariates for women than men (84% vs 80%).

Bivariate Relationships

The second approach to understanding genetic architecture supported by the independent pathways model focuses on the nature of the bivariate relationships between subjective health and each covariate, individually. Using the Ag, Cg, and Eg pathways in the model, it is possible to calculate the A, C, and E contributions to the phenotypic correlations between measures of subjective health and the three covariates (see Figure 2). Physical health has the highest correlation with SRH and similar correlations with ACT and COMP. Contributions to all three correlations were equally divided between A and E. Correlations with depressive symptoms were similar for both SRH and ACT and lower for COMP, and correlations were equally divided between A and E. Although correlations with word list were modest and similar across measures of subjective health, in this case they arose primarily or entirely from shared genetic variance.

Comparisons of correlations across age and sex are also presented in Figure 2. With one exception (COMP × CIRS), correlations are stronger in older adults than middle-aged adults. For SRH and ACT, the age differences in correlations are primarily driven by higher E contributions. For ACT × CIRS, all three components of the correlation are higher in older adults. The decomposition of the correlation with subjective health measures is markedly different for word list. In this case, the

Table 3. Age and Sex Differences in Variance Components for SRH and ACT

Variance component	SRH		SRH		ACT		ACT	
	Middle-aged	Older	Men	Women	Middle-aged	Older	Men	Women
A variance								
General	0.27	0.27	0.32	0.32	0.21	0.34	0.28	0.40
Specific	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
Total	0.27	0.27	0.32	0.32	0.21	0.34	0.29	0.40
C variance								
General	0.03	0.00	0.01	0.00	0.03	0.03	0.00	0.00
Specific	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total	0.03	0.00	0.01	0.00	0.03	0.03	0.00	0.00
E variance								
General	0.40	0.48	0.40	0.40	0.19	0.45	0.33	0.33
Specific	0.06	0.06	0.14	0.03	0.10	0.14	0.14	0.14
Total	0.46	0.54	0.54	0.43	0.29	0.59	0.47	0.47
Total variance								
General	0.70	0.75	0.73	0.73	0.42	0.83	0.61	0.73
Specific	0.06	0.06	0.14	0.03	0.10	0.14	0.15	0.14
Total	0.76	0.81	0.87	0.76	0.52	0.97	0.76	0.87

Notes: A = additive genetic effects; ACT = health impacts activities; C = shared environment; E = unique environment; SRH = self-rated health.

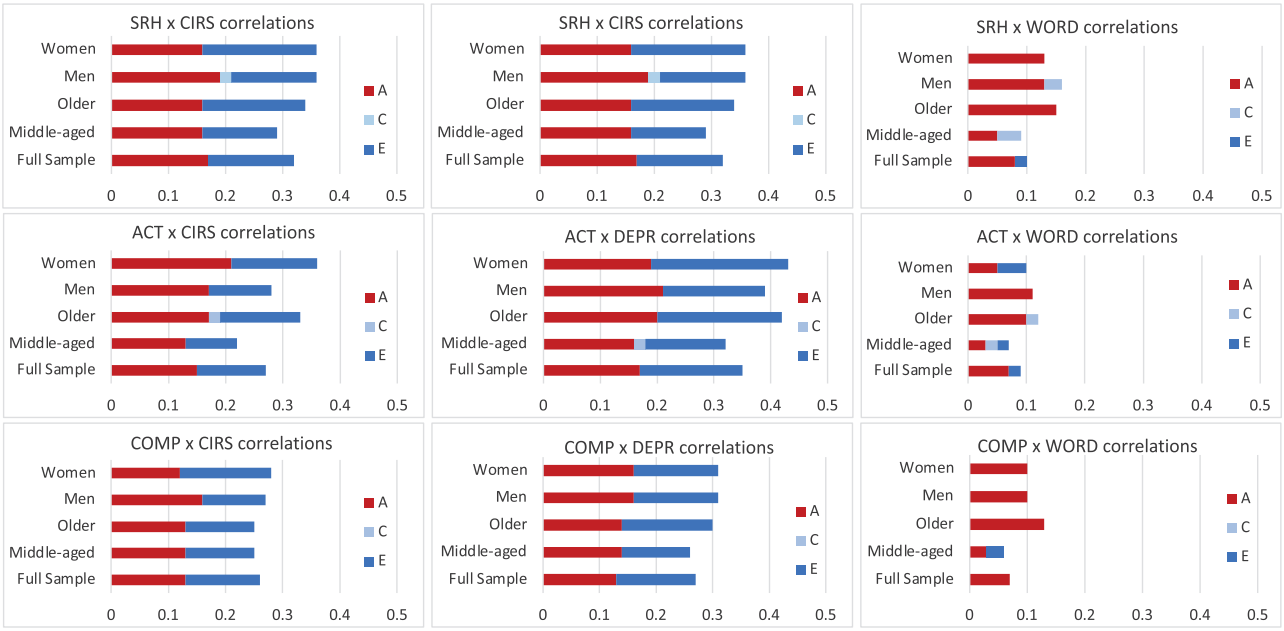

Figure 2. Decomposition of bivariate correlations between subjective health measures and covariates. A, C, and E indicate additive genetic, shared environmental, and unique environmental components of the correlations. ACT = health impacts activities; CIRS = physical health; COMP = health compared to others; DEPR = depressive symptoms; SRH = self-rated health; WORD = word list.

correlation is primarily or entirely driven by shared genetic variance in older adults, while in middle-aged adults the correlation is divided between genetic variance and shared and/or nonshared environmental variance. Sex differences in correlations are more mixed. In three instances, the total correlation and the genetic and environmental contributions to the correlations are identical for men and women (SRH × DEPR, COMP × DEPR, and COMP × WORD). In three instances (SRH × CIRS, COMP × CIRS, ACT × WORD), the total correlation is the same for men and women, but the A contribution is greater in men than women. In two instances, a greater correlation in women arises from more nonshared environmental variance common to the two variables (ACT × CIRS and ACT × DEPR). Finally, the A contribution for SRH × WORD is the same for men and women, but a contribution of C in men results in a higher total correlation in men than women.

Additional Analyses

Combining across three U.S. studies (CAATSA, VETSA, and MIDUS) resulted in a sample of 612 Black twins from 89 complete MZ pairs, 141 complete DZ, and individuals from incomplete pairs. Analyses were repeated in this sample to examine possible racial/ethnic differences in the genetic architecture of SRH and COMP (CAATSA did not include ACT). Power to detect small effects was reduced in the smaller sample; however, the best-fitting models for SRH and COMP in the full sample also resulted in sufficient fit to the data in the Black twin sample. Comparison of results between the full sample and the Black sample (Supplementary Figures S1 and S2) indicated modest differences in parameter estimates but no differences in overall pattern of results.

Discussion

The current analyses represent the largest twin sample, by far, used to investigate the genetic architecture of different subjective health measures and possible age, sex, and measure differences in that architecture. Generally, results indicated that most or all of the genetic influences on measures of subjective health were mediated through genetic influences on physical health, depressive symptoms, and episodic memory, leaving little or no genetic variance unaccounted for, or specific to subjective health. Overall, 92% of total variance in SRH was shared with depressive symptoms, physical health, and memory, 84% of ACT, and 62% of COMP. That associations among physical health, depressive symptoms, and subjective health measures are explained by genetic influences in common makes intuitive sense because these measures all involve observations and experiences of one's physical and mental health as well as similar methodology (self-report). The primarily genetic nature of the relationship between episodic memory and, in particular, SRH and ACT also suggests a set of genes influencing both cognitive processing of information about one's own health and perceptions of health (Bailis et al., 2003; Benyamini, 2011; Jylhä, 2009). This is of particular interest because the episodic memory measure is not self-report, unlike the depressive symptoms and physical health measures. It is also possible that subtle changes in episodic memory are detected by aging adults and incorporated into perceptions of health (Svedberg et al., 2009). Measures of subjective health are very commonly used in large epidemiological surveys, clinical trials, and in clinical practice, yet few studies examine multiple measures of subjective health, in particular their genetic architecture and/or relationship with other outcomes. In addition, most twin studies have been underpowered to examine the influence of sex and wide age ranges. Finally, little attention is paid to sources of differences in associations with outcomes, for instance, due to different forms of the subjective health questions or the effects of age and sex.

Correlations between the subjective health measures and the covariates were fairly equally divided between genetic and

unique environmental sources, with the exception of episodic memory where the correlations between subjective health measures and word list were primarily mediated genetically. Previous investigations of genetic architecture of subjective health measures have reported similar findings for individual covariates of subjective health (J. R. Harris, Pedersen, Stacey, et al., 1992; Leinonen et al., 2005; Mosing, Pedersen, et al., 2010; Svedberg et al., 2006, 2009). Moreover, Genome-wide association study (genome-wide association study (GWAS)) analyses have identified a variety of single nucleotide polymorphisms (SNPs) that may contribute to subjective health, including SNPs associated with various health conditions, major depression, and measures of intelligence (S. E. Harris et al., 2017; Mosing, Verweij, et al., 2010). Although modest (*r*s ~ 0.10), correlations between subjective health and memory were consistent with the literature (e.g., Svedberg et al., 2009) and mediated primarily by genetic factors, particularly in late adulthood. Several studies indicate that subjective health can predict subsequent cognitive decline (Bendayan et al., 2017; Bond et al., 2006; Carmelli et al., 1997; Sargent-Cox et al., 2011), suggesting the possibility that genetic variance contributes to important facets of cognition that underly perceptions of (physical and cognitive) health and are vulnerable to changes with age.

The variance component specific to subjective health measures identified in these analyses was unique environmental variance. Unique environmental variance specific to subjective health could arise from measurement error, which is included in the estimate of E. Although studies suggest high reliability for the most common measure of subjective health (SRH; Lundberg & Manderbacka, 1996), ACT and COMP are less frequently measured, and reliability data are not as available. These measures may be more subject to measurement error, or they may be more sensitive than SRH to true environmental differences within families.

Different subjective health items tap different frames of reference for "good health," which can change the weighting of the factors that constitute self-perception of health (Franz et al., 2017; Sargent-Cox et al., 2008, 2010). Changing the frame of reference of a subjective health item from self (SRH) to activities (ACT) or "others" (COMP) appears to affect the genetic architecture of subjective health, such that more unique environmental variance specific to the measure is tapped by ACT and COMP than by SRH. Unique environmental sources of variance could include changes in physical health not captured by CIRS (e.g., changes in walking pace, balance, or sleep) or changes in the environment including loss of friends, widowhood, reduced social activity, lifestyle changes, living situations, or changes in health or abilities of members of one's social circle (J. R. Harris, Pedersen, Stacey, et al., 1992; Svedberg et al., 2009). The change in frame of reference could even tap different individual conceptions of the meaning of "good health" for self versus peers versus abilities (Jylhä, 2009). Studies that rely on a single subjective health item (e.g., SRH) may obscure interesting distinctions in the etiology and implications of diverse subjective health measures.

Age Differences

In addition to differences between subjective health measures, age differences in genetic architecture of subjective health were also identified for SRH and ACT, but not for COMP, with greater total variance for older than for middle-aged. Other analyses have also found that results for SRH and ACT tend to be more similar than results for COMP (Finkel et al., 2022; Franz et al., 2017). Increasing total variance for SRH and ACT is not surprising. People age at different rates, so individual differences in physical health increase with age, as well as individual differences in perceptions of health (Finkel et al., 2014; J. R. Harris, Pedersen, McClearn, et al., 1992). The genetic architecture underlying these increases in variance indicated increases in unique environmental variance for both SRH and ACT and increases in genetic variance for ACT. Correlations between all three measures of subjective health and the three covariates were higher in older than in middle-aged adults, especially correlations with word list. Previous studies have reported similar age differences (J. R. Harris, Pedersen, Stacey, et al., 1992).

These differences in genetic architecture suggest that subjective health measures may not be equivalent for middle-aged and older adults and may reflect different subjective conceptions of health. In particular, the role of memory in shaping subjective health is greater in older than in middle-aged adults. Evidence suggests that the discordance between objective health measures and subjective health increases in late adulthood (French et al., 2012; Zikic et al., 2009), possibly as a result of greater emphasis on psychological components of subjective health assessments by older adults (Araújo et al., 2018; Pinquart, 2001). Older adults may normalize their current health status by shifting their expectations of health (Puvill et al., 2016). Increased attention with age to perceived memory difficulties, in particular, may play a larger role in judgments of one's own health in later adulthood (Svedberg et al., 2009). In fact, awareness of cognitive change is associated with measures of subjective health (Sabatini et al., 2021). The higher genetic contributions to associations between subjective health and its components found in older adults in the current analyses may reflect an increasingly holistic self-assessment of health across domains in later ages that relies on a common set of genes associated with self-evaluation of functioning. Healthy aging is typically easier with sufficient resources, so the increasing genetic covariance may also arise from an underlying ability to amass and leverage resources in support of health (Mirowsky & Ross, 2003; Ross & Wu, 1996).

Sex Differences

Current analyses generally supported the sex differences in subjective health reported by previous studies (Mosing, Pedersen, et al., 2010; Mosing et al., 2009). Heritability of both SRH and ACT was higher for women than men, although the underlying genetic architecture differed. Sex differences in the etiology of the correlations between subjective health and the covariates differed across measures of subjective health. Sex differences in genetic influences on measures of physical health tend to be mixed (Finkel et al., 2014), although any sex differences in heritabilities may reflect the higher prevalence of genetically influenced chronic disabling diseases in women compared to men's more compressed history of disability prior to death (Sainio et al., 2006). In the current analyses, overlapping genetic factors contributed more to the associations between physical health and SRH and COMP in men, but to the associations between physical health and ACT in women, where in women ACT seems to be a key component of subjective health. It is possible, then, that higher rates of chronic disabling conditions in women are captured more by

the perceived impact of health on one's activities than by general ratings of health and comparison to peers.

Research suggests that mean levels of depressive symptoms tend to be higher in women than men, as does heritability for depression (Petkus et al., 2017). Investigation of the genetic architecture of depressive symptoms indicated that the association between depressive symptoms and physical health resulted more from common genetic factors in men than in women (Petkus et al., 2017). In contrast, little or no sex differences in the genetic architecture of the association between subjective health and depression were identified in the current analyses, again highlighting the differences between physical health and subjective health.

Limitations

Pooling data across samples provided the sample size and thus statistical power to detect subtle age, sex, and measure differences in the genetic architecture of subjective health. However, pooling relies on harmonization of measures across multiple studies, which can be a source of measurement error. The measures of subjective health and depressive symptoms used in the current analyses were included in crosswalk samples to identify the optimal methods for harmonization (Gatz, Reynolds, et al., 2015). Harmonization of the measures of physical health and episodic memory were the result of extensive work by members of the IGEMS team (Gatz, Petkus, et al., 2015; Luczak et al., 2023). Pooling variables across countries could introduce error if there are significant country effects on measurement or recruiting procedures. For example, culturally influenced concepts of health may differ across countries (Jylhä, 2009). To address this possibility, the models were corrected for country effects. Finally, whereas the sample drawn from twin studies in four countries (Australia, Denmark, Sweden, and United States) was large and diverse in the variables of interest for this analysis, ethnic and racial compositions of the IGEMS samples were fairly homogenous.

Conclusion

In the largest investigation of the genetic architecture of subjective health to date, results indicate that, although these subjective measures all showed significant genetic influences, there was little or no genetic variance *specific* to measures of subjective health. Instead, genes contributing to perceptions of health are completely explained by genes associated with physical health, depressive symptoms, and episodic memory combined. All three covariates were necessary to explain the genetic variance in subjective health. The etiology of the relationship between subjective health and episodic memory was largely genetic while both genetic and environmental factors contributed to the associations between physical health and depressive symptoms and subjective health. The genetic architecture of subjective health differed across measures of subjective health (self-rated, compared to others, impact on activities) and between age group and sexes.

The predictive value of subjective health has been amply demonstrated; the current analyses identified significant nuances in the etiology of subjective health that contribute to understanding the value of subjective health for maintaining and improving quality of life of older adults. The higher genetic contributions to associations between subjective health and the three covariates (depressive symptoms, illnesses, memory) in older adults reported here support the conceptualization that, with increasing age, perceptions of health constitute intuitive summations of one's vital reserve in multiple domains (Jylhä, 2009). GWAS analyses of subjective health (S. E. Harris et al., 2017; Mosing, Verweij, et al., 2010) also support a multidimensional approach. Like any analysis, however, GWAS may be susceptible to age-specific effects, either through changes in relative weight of the multidimensional components of subjective health or changes in probability of "risk" alleles through population mortality (Escott-Price & Schmidt, 2023). For optimal utility, investigations of subjective health should take into account age, sex, and the multidimensionality of the construct of subjective health.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None.

Data Availability

This study was not preregistered. IGEMS data are not publicly available given the variety of data agreements and regulations governing the different studies and countries. However, many of the individual studies participating in IGEMS do have ways to access their data, some by direct request to the participating study, and many of the data sets may be accessed through National Archive of Computerized Data on Aging (NACDA). See https://doi.org/10.3886/ICPSR03843.v2 (SATSA), https://doi.org/10.3886/ICPSR25963.v2 (Study of Dementia in Swedish Twins), https://doi.org/10.3886/ICPSR02760.v19 (MIDUS), and https://www.icpsr.umich.edu/web/NACDA/studies/36234/versions/V6 (National Academy of Sciences–National Research Council Twin Registry). Two studies may be requested through Maelstrom: OCTO-Twin https://www.maelstrom-research.org/study/octo-twin and GENDER https://www.maelstrom-research.org/study/gender. For access to data from the Danish Twin Registry, see https://www.sdu.dk/en/om_sdu/institutter_centre/ist_sundhedstjenesteforsk/centre/dtr/researcher. To request OATS data please contact the CHeBA Research Bank via e-mail on CHeBAData@unsw.edu.au for a current application form. For VETSA data, see instructions to researchers: https://medschool.ucsd.edu/som/psychiatry/research/VETSA/Researchers/Pages/default.aspx

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