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ORIGINAL RESEARCH

Gene–Environment Interplay in Physical, Psychological, and Cognitive Domains in Mid to Late Adulthood: Is *APOE* a Variability Gene?

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Abstract Despite emerging interest in gene–environment interaction (GxE) effects, there is a dearth of studies evaluating its potential relevance apart from specific hypothesized environments and biometrical variance trends. Using a monozygotic within-pair approach, we evaluated evidence of G×E for body mass index (BMI), depressive symptoms, and cognition (verbal, spatial, attention, working memory, perceptual speed) in twin studies from four countries. We also evaluated whether *APOE* is a 'variability gene' across these measures and whether it partly represents the 'G' in G×E effects. In all three domains, G×E effects were pervasive across country and gender, with small-to-moderate effects. Age-cohort trends were generally stable for BMI and depressive symptoms; however, they were variable—with both increasing and decreasing age-cohort trends—for different cognitive measures. Results also suggested that *APOE* may represent a 'variability gene' for depressive symptoms and spatial reasoning, but not for BMI or other cognitive measures. Hence, additional genes are salient beyond *APOE*.

Keywords Gene–environment interaction · Twins · BMI · Depression · Cognitive performance · *APOE* · Variability gene

Introduction

Emerging evidence suggests that gene–environment interplay, including gene–environment interactions (G×E), may contribute to multiple life domains. Here we focus on

Members of the consortium on Interplay of Genes and Environment across Multiple Studies (IGEMS) are listed in Appendix.

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measures sampled from three domains: physical [body mass index (BMI)]; psychological (depressive symptoms); and cognitive (verbal, spatial, attention/working memory, perceptual speed). The role of G×E among these domains has been variously studied by examining the interaction of a specific environmental exposure with a specific gene variant, how genetic variance may differ due to a specific exposure, or how environmental variance may differ as a function of a specific gene variant. For each of these domains, the current paper concerns establishing evidence of G×E, evaluating age-cohort differences in G×E effects, and testing whether *APOE* is a variability gene, i.e., in phenotypes where there is evidence of G×E, whether sensitivity to environmental influences varies with *APOE* gene variants.

As concerns obesity, a variety of twin studies have shown how genetic risk for obesity-related traits may be mitigated (or facilitated) by specific environmental factors. For example, in a Danish Twin Registry study, higher education levels corresponded with substantially reduced genetic variance, as well as shared and nonshared environmental variance, for BMI in women, with similar reductions in shared and nonshared environmental variance for BMI in men (Johnson et al. 2011). Vigorous exercise has also been associated with reduced genetic variance in BMI (McCaffery et al. 2009) in middle-aged men, and higher levels of physical activity have been associated with reduced genetic variance for BMI, waist-hip ratio, and percent body fat (Mustelin et al. 2009; Silventoinen et al. 2009) in young adult twins from Finland and adult twins from Denmark.

In the psychological domain, lower SES indexed by income level has been associated with magnified total variance for internalizing psychopathology in middle adulthood, indexed by major depression, generalized anxiety disorder, panic attacks, and neuroticism (South and Krueger 2011). However, the moderation of total variance for internalizing psychopathology was mainly due to magnification of unique environmental variance at the lowest SES levels. The finding of moderation of internalizing psychopathology via SES in middle adulthood builds on earlier work evaluating G×E for depression and indices of adversity (see Rutter 2012; Rutter and Silberg 2002). In particular, a greater risk of depression has been observed in the presence of a combination of prior stress, particularly childhood maltreatment, and a variant in the serotonin transporter gene promoter region (5-HTTLPR) (Caspi et al. 2003; Karg et al. 2011), although not all studies replicate this finding (see Duncan and Keller 2011).

A potential signal of the presence of G×E for adult cognitive performance has come from observations that unique environmental influences may accelerate in importance with age across multiple cognitive tests (Pahlen et al. under review; Reynolds et al. 2005, 2007), although others have reported stability of twin similarity on a cognitive composite score (McGue and Christensen 2013). Moreover, twin studies examining G×E for mid to late adult cognition are limited compared to childhood and early adulthood. There is some evidence that higher levels of childhood SES are associated with greater genetic influences on general cognitive ability (Turkheimer and Horn 2014), although this effect has not been observed when assessed in adulthood (Grant et al. 2010). In adult male twins, across greater years of parental education, total variance and particularly common environmental variance for word recognition was reduced; whereas genetic variance was relatively stable (Kremen et al. 2005). A personality trait, Experience Seeking (ES), a subscale of the Sensation Seeking Scale (Dutch translation) has been evaluated as a moderator of genetic and environmental variance in cognitive ability in an adult twin sample with results suggesting reduced genetic variance but increased nonshared environmental variance at the highest levels of ES (Vinkhuyzen et al. 2012).

'Agnostic' tests of G×E

Typically G×E is tested with a selected environmental feature or exposure, or a specific gene target in mind, or both. However, an agnostic test has been available, without identified genes or environments, as first proposed by Fisher (1925; see Martin et al. 1983 for correction). Specifically, Fisher delineated a test of heterogeneity that relies on evaluating monozygotic (MZ) within-pair differences (Fisher 1925; Martin et al. 1983), i.e., the test compares mean squared pair differences for a trait with the mean absolute pair differences squared. The extent to which these values differ supports a mixture of distributions of the within-pair differences rather than one distribution of differences and suggests there is possible G×E interaction. This indicates a differential sensitivity of genotypes to environments such that the MZ pair differences, which reflect nonshared environment, vary according to particular genotypes. MZ within-pair approaches are rarely used (Cornes et al. 2008; Martin 2000; Martin et al. 1983; Reynolds et al. 2007; Surakka et al. 2012), particularly since the advent of genome-wide genotyping, but such an approach may usefully quantify the extent of heterogeneity and identify the likely presence of G×E. Coupling an agnostic general test with potential genetic markers using MZ pairs can be more powerful than evaluating GxE in population-based samples of unrelated individuals (Visscher and Posthuma 2010).

Variability genes, i.e., the 'G' in G×E

A significant Fisher test of heterogeneity could indicate the presence of G×E interaction, i.e., differential sensitivity of

particular genotypes to particular environments, or could reflect a shared environment by nonshared environment interaction, C×E. To support that an observed significant heterogeneity test is due to G×E, it is useful to consider measured genes that may explain such heterogeneity (Berg et al. 1989; Martin 2000; Martin et al. 1983). The genes of interest may be regarded as 'variability genes' (Berg et al. 1989), i.e., genes that are associated with trait variation and not simply associated with trait mean (Martin 2000). *APOE* may be of particular interest in this regard. The *APOE* gene, coding for the major cholesterol transporter in the brain, and its ε4 haplotype in particular, has demonstrated associations with cognitive decline, Alzheimer's disease (AD) and dementia (e.g., Bennet et al. 2010; Davies et al. 2014; Reynolds et al. 2006; Schellenberg and Montine 2012). In addition, *APOE* has also shown some evidence of associations with, or moderation of, risk factors that are predictive of cognitive decline and dementia, including BMI (e.g., Besser et al. 2014; Keller et al. 2011) and depression (e.g., Karlsson et al. 2015; Skoog et al. 2015).

APOE has shown evidence that it may act as a variability gene; that is, the effects of environmental risk and protective factors have been shown to differ according to *APOE* genotype. For example, MZ twin pairs who were *APOE* ε4− were more variable in their semantic memory trajectories, whereas those who were ε4+ were less variable (Reynolds et al. 2007). Additionally, individuals with particular *APOE* haplotypes may be differentially sensitive to dietary and exercise interventions, albeit not consistently (Brown et al. 2013a Carvalho-Wells et al. 2012; Gomez-Pinilla and Hillman 2013; Hotting and Roder 2013). For example, in those who lead sedentary lives, amyloid burden is greater for those with ε4+ compared to other *APOE* haplotypes, whereas for those who engage in physical activity, amyloid burden does not vary across *APOE* haplotypes (Brown et al. 2013b; Head et al. 2012). Moreover, a recent experimental study in sedentary women suggested a particular benefit of acute exercise to ε4+ carriers on a cognitive inhibition task (Stroop) in comparison to a spatial attention task (Posner) that engages the prefrontal region to a lesser extent, but no benefit accrued for non-ε4 individuals across tasks (De Marco et al. 2015). MZ twin pair differences in semantic memory change have also been associated with twin-pair differences in depressive symptoms but in this case only among non-ε4 individuals (Reynolds et al. 2007). Thus, taken together, emerging evidence across multiple traits and domains supports the role of *APOE* as a variability gene and suggest that the associations of *APOE* may be complex and depend in part on environmental factors. Indeed, for BMI *APOE* may show differing patterns of evidence for sensitivity, as compared to cognition or depression traits.

The aims of the current study were to evaluate general evidence of G×E for BMI, depressive symptoms, and cognitive performance in twin studies participating in the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium (Pedersen et al. 2013). We further considered whether there were age-cohort trends in G×E. Once general evidence for G×E was evaluated, we considered specific genetic aspects further, by testing the extent to which *APOE* was a variability gene across these traits. That is, we evaluated whether different *APOE* haplotypes were more or less sensitive to environmental factors and thereby showed differences in the variance of pair differences in depressive symptoms, BMI and cognitive performance.

Methods

Samples

The current analysis sample includes individuals from up to nine twin studies representing four countries: the United States, Sweden, Denmark and Finland, from the IGEMS consortium (Pedersen et al. 2013). The primary analyses considered complete MZ twin pairs to evaluate heterogeneity of within-pair differences and homogeneity of within-pair variance by *APOE* haplotypes (see Table 1). Each of the respective studies described below obtained approvals by their Institutional Review Boards, or equivalent, to carry out the original data collection, obtaining informed consent from participants as required.

USA

Data were available from the Vietnam Era Twin Study of Aging (VETSA) (Kremen et al. 2013), Minnesota Twin Study of Adult Development and Aging (MTSADA) (Finkel et al. 1995), and the Midlife Development in the United States (MIDUS) twin study (Kendler et al. 2000; Radler 2014). The VETSA study included only male twin pairs (51–60 years), while from MTSADA (25–92 years) and MIDUS (34–82 years) we included same-sex male and female pairs.

Sweden

Data were available from three population-based samples of same-sex male and female twins that originated from the Swedish Twin Registry (Lichtenstein et al. 2006; Magnusson et al. 2013): the Swedish Adoption/Twin Study of Aging (SATSA) (Pedersen et al. 1991), the Origins of Variance in the Oldest-Old (OCTO-twin) (McClearn et al. 1997), and the Twin-Offspring Study in Sweden (TOSS) (Neiderhiser et al. 2007). Data for SATSA twins (39–88 years) came from the first available questionnaire or in-person testing wave, available during one of 6 respective assessment waves. Data on OCTO-twin participants (79–99 years) came from the first assessment.

Table 1 MZ pairs contributing to G×E Analyses

Study	Country	Sex	BMI				Depressive Sx				Cognitive (1+ test)			
			N	N_{APOE}	Mean age	SD	N	N_{APOE}	Mean age	SD	N	N_{APOE}	Mean age	SD
VETSA	USA	M	349	340	55.35	2.53	346	337	55.36	2.52	347	339	55.33	2.49
MTSADA	USA	M	69	–	56.70	12.26	117	–	58.98	9.93	66	–	56.19	12.12
		F	150	–	54.33	13.35	210	–	56.65	12.33	149	–	54.41	13.08
MIDUS	USA	M	132	–	45.56	11.46	33	–	54.70	11.70	83	–	55.19	11.12
		F	155	–	44.35	12.39	48	–	52.63	10.98	96	–	52.87	11.56
SATSA	SWE	M	112	52	55.69	13.87	102	53	57.00	13.40	59	52	62.69	7.45
		F	138	70	59.80	13.59	116	72	59.97	13.28	83	73	64.15	9.03
Octo-Twin	SWE	M	41	37	82.81	2.47	47	43	82.59	2.90	42	38	82.88	2.63
		F	66	62	83.48	2.95	67	63	83.19	3.27	55	50	82.83	2.31
TOSS	SWE	M	120	–	46.48	4.50	101	–	46.57	4.53	121	–	46.50	4.49
		F	104	–	43.40	5.27	213	–	43.69	4.64	259	–	43.68	4.66
MADT	DEN	M	335	191	56.57	6.41	333	191	56.54	6.40	330	189	56.45	6.40
		F	327	198	56.36	6.41	328	197	56.36	6.41	326	195	56.33	6.41
LSADT	DEN	M	171	52	75.05	4.57	172	51	74.92	4.54	132	37	74.31	3.73
		F	274	98	76.05	4.79	266	97	75.87	4.73	190	77	74.95	4.03
FTC	FIN	M	405	–	60.14	3.69	407	–	59.71	3.70	–	–	–	–
		F	602	–	59.85	3.69	602	–	59.38	3.69	–	–	–	–
Total pairs	–	–	3550	1100	–	–	3508	1104	–	–	2338	1050	–	–

Sx Symptoms, *USA* United States of America, *SWE* Sweden, *DEN* Denmark, *FIN* Finland

Twin data from the parent generation (32–60 years) of the TOSS study were used in the current study.

Denmark

The Longitudinal Study of Aging Danish Twins (LSADT) (70–100 years) and the Middle Aged Danish Twins (MADT) (45–68 years) included pairs drawn from the Danish Twin Register (McGue and Christensen 2013; Skytthe et al. 2013). Data from the first assessment wave were used in the present study.

Finland

The Finnish Adult Twin Cohort (FTC; Kaprio and Koskenvuo 2002) sample included data from the fourth assessment wave of twins born 1945–1957, done as a postal questionnaire survey in 2011 to 2012 (Kaprio 2013).

Measures

All studies had data from at least one of the following three domains.

BMI

BMI was computed in standard fashion as weight, measured in kilograms, divided by height squared, measured in meters (kg/m^2). BMI scores were adjusted for self-report versus measured assessments (Johnson et al. 2012) given that self-reports are biased towards over-reporting of height yet under-reporting of weight (Dahl et al. 2010), i.e., Adjusted BMI $= 0.35 + 1.038*(BMI_{self\text{-}rept})$. Studies in the current analysis with measured height and weight assessments included OCTO-Twin and VETSA, the remainder of the studies provided self-reported data. Prior to analysis, BMI scores were rank-normalized to reduce non-normality (c.f., Reynolds et al. 2007; Surakka et al. 2012).

Depression

Depressive symptoms were measured with either the Center for Epidemiologic Studies Depression (CESD) scale (Radloff 1977) or the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) as modified by McGue and Christensen (McGue and Christensen 1997). To create a common metric, both scales were collected from a separate crosswalk sample, and item response theory methods were applied in order to compare items from the two measures and create a conversion table between the scales (Gatz et al. in press). We retained those items from both CESD and CAMDEX that loaded on the respective affect and somatic subscales. The co-calibrated score is expressed in CAMDEX units, such that the total score can range from 16 for someone who endorses no symptoms of depression

to 46. After harmonization, scores were rank-normalized to reduce non-normality.

Cognitive performance

Five measures of cognitive ability spanning four cognitive domains were considered in the current study: verbal (Synonyms), spatial (Block Design), attention and working memory (Digit Span Forward and Backward), and perceptual speed (Symbol Digit). Each measure was available in at least two studies. Number of individuals available for each test was therefore variable, reflecting the differential availability of the tests across studies. Cognitive tests and harmonization procedures have been described previously (Pahlen et al. under review). In short, those in the analysis sample completed at least one of the cognitive tests and scored 24 or above on the Mini-Mental State Exam (MMSE; Folstein et al. 1975); a total of 7.3 % of the total sample were excluded based on the MMSE criteria. Scores were residualized for sex and transformed to T-score scaling ($M = 50.0$ and $SD = 10.0$) against the reference age group 50 to 59.99 years (Pahlen et al. under review) and subjected to winsorizing within age group for values falling outside of ±3 SDs. Prior to within-pair analyses, scores were rank-normalized to reduce non-normality.

Genotyping

APOE haplotypes were available for a subset of studies and were categorized as ε2+ (ε22, ε23, ε24), ε33, and ε4+ (ε34, ε44). Samples with MZ pairs and genotyping included: VETSA (US) SATSA and OCTO-Twin (Swedish), MADT and LSADT (Danish). Genotyping procedures for VETSA, SATSA and OCTO-Twin have been described elsewhere (Reynolds et al. 2013; Schultz et al. 2008). For the Danish samples, *APOE* haplotypes were formed from two genotyped SNPs, rs429358 and rs7412, that for MADT were based on TaqMan® SNP Genotyping Assays (Applied Biosystems, Foster City, CA, USA) and for LSADT were based on custom-designed assays.

APOE haplotype frequencies are reported in supplementary Table 1 (Table S1). Hardy–Weinberg Equilibrium based on computations for a three allele system were calculated for each study and met ($p \geq 0.121$). MZ twins who were not directly genotyped were assigned their cotwin's value.

Statistical analysis

We evaluated the presence of G×E by applying a test of mixture distributions of MZ within-pair differences overall, and separately by country, sex, and age group. Given that the data are cross-sectional such that age group and birth cohort are unable to be dissociated, we refer to age group as age-cohort. Specifically, we applied a test first proposed by Fisher (Fisher 1925; Martin et al. 1983). The test evaluates the difference between mean squared pair differences for a trait and the mean absolute pair differences squared as follows (Fisher 1925; Martin et al. 1983):

$$\Delta = \overline{d^2} - \frac{\pi}{2}\overline{d}^2 \tag{1.0}$$

and corresponding standard error as (Fisher 1925; Martin et al. 1983):

$$se = \frac{\overline{d^2}}{\sqrt{n}}(.5321) \tag{1.1}$$

A one-tailed t test was used to evaluate significance (Δ/se), given that the expected values were assumed to be positive (Martin et al. 1983), with df equal to the number of pairs minus 1.0. To address multiple testing, we conducted false-discovery rate (FDR) tests (Benjamini and Hochberg 1995; Weinkauf 2012) and provided Holm-Bonferroni adjusted p values as well for each set of tests by trait (Gaetano 2013; Holm 1979).

In addition, effect size rs were calculated from the t statistics (Rosenthal 1991) to consider the potential impact of G×E across country, sex, and age-cohort, apart from power considerations:

$$ESr = \sqrt{\frac{t^2}{(t^2 + df)}} \tag{2}$$

A measure of the heterogeneity of effect size rs (ESrs) were calculated according to the Chi square test outlined by Snedecor & Cochran (1989; as cited in Rosenthal 1991).

In a subset of available samples, we considered measured genes to substantiate G×E and not C×E. Specifically, heterogeneity of variance by *APOE* haplotype was evaluated using SAS Proc Mixed (SAS Inc, Cary, NC) specifying between and within pair random effects. Analyses of within-pair variation were adjusted for average effects of *APOE* haplotype, country, sex and age. A series of model constraints were tested on within pair variances, considering *APOE* haplotype differences within and across country or sex. Given the potential differential regional and within-country impact of ε4 on health outcomes, such as mortality (Ewbank 2004) and Alzheimer's disease (Ward et al. 2012), as well as differential impact of *APOE* on cognitive outcomes for women versus men (Altmann et al. 2014; Damoiseaux et al. 2012; Farrer et al. 1997), we evaluated whether *APOE* effects could be generalized. Hence, we tested whether within-pair variances for each *APOE* haplotype could be constrained: (1) across men and

women within country (i.e., $\varepsilon 2+_m = \varepsilon 2+_f$, $\varepsilon 33_{m=}\varepsilon 33_f$, $\varepsilon 4+_{m=}\varepsilon 4+_f$), and (2) across country (i.e., $\varepsilon 2+_{US} = \varepsilon 2+_{SWE} = \varepsilon 2+_{DEN}$, etc.). Last, we tested whether within-pair variances could be constrained equal within country across the three *APOE* haplotype groups (i.e., $\varepsilon 2+=\varepsilon 33 = \varepsilon 4+$) to evaluate the significance of an *APOE* effect on variability. Sensitivity analyses considered adjustments when dropping individuals with the *APOE* ε24 haplotype. We did not evaluate age trends in within pair variances by *APOE* haplotype, primarily due to the reductions in sample sizes of those with both phenotypic data and genotyping and to resultant confounding of age-cohort and country.

Follow-up tests of association at the mean level based on *APOE* haplotype were undertaken in SAS Proc Mixed (SAS Inc, Cary, NC) allowing for within and between pair variances to differ by country; analyses adjusted for average effects of age, sex and country. Specifically, we tested whether entering the *APOE* haplotype (ε2+, ε33, ε4+) led to a significant improvement in fit based on a two-degree of freedom test.

Results

Fisher heterogeneity test

The full sample heterogeneity tests for BMI included 3550 complete MZ pairs and for depressive symptoms 3508 MZ pairs. For the cognitive measures, 2338 MZ pairs had at least one cognitive test where both members participated and met MMSE criterion; test availability across studies the analysis samples ranged from 390 to 1727 MZ pairs. The Fisher (1925) test suggested significant within-pair heterogeneity in the full sample for BMI, $p = 3.54E{-}34$, and depressive symptoms, $p = 1.99E{-}41$ (see Table 2), with significant within-pair heterogeneity for each age-cohort ($p \leq 6.87E{-}03$; see Table 2), as well as both sexes and all four countries ($p \leq 3.90E{-}04$; see supplement Table S2). Overall effect size *r*s (ESrs) were small for both BMI and depressive symptoms (median = .19, .21, respectively). Effect sizes were consistent across age-cohort groups for both BMI and depressive symptoms [χ^2 (4) ≤ 2.55, $p \geq 6.36E{-}01$] (see Table 2). BMI showed consistent small ESrs across country [χ^2 (3) = 3.68, $p = 3.68E{-}01$]. Although depressive symptoms showed small and signficant evidence for G×E for each country, the ESrs were significantly variable with lower effect sizes for Sweden and Finland and higher effects for US and Demark [χ^2 (3) = 18.77, $p = 3.06E{-}04$] (see supplement Table S2).

For cognitive performance, G×E was suggested in the full sample ($p \leq 2.16E{-}04$) (see Table 2). The ESrs were small, ranging from .12 to .23, and were not significantly heterogeneous from one another [χ^2 (4) = 7.71, $p = 1.03E{-}01$] (see Table 2, supplement Table S2). As depicted in Fig. 1, three prototypical age-cohort trends in ESRs were noticeable: (a) Block Design represented a linear pattern of increasingly stronger effect sizes across age groups: (b) Digits Backward represented a nonlinear u-shaped pattern with peaks before age of 50 (ESr = .27) and after age of 80 (ESr = .39) with a similar trend for Digits Forward (not shown), and (c) Symbol Digit displayed a pattern of decreasing effect sizes with age-cohort, with the peak at ages 50–59 (ESr = .22). The pattern for Synonyms was less consistent and is not shown in Fig. 1 (but see Table 2). The FDR tests and Holm-Bonferroni adjusted *p*-values generally supported the age-based patterns described in terms of significance (see Table 2); however, heterogeneity tests of ES*r*s among age-cohorts suggested that only Digits Backward reached significance [χ^2 (4) = 10.14, $p \leq 3.81E{-}02$], with a trend effect in Digits Forward ($p = 5.07E{-}02$).

G×E was indicated on all cognitive measures both for women ($p \leq 5.48E{-}03$) and for men ($p \leq 4.56E{-}05$), apart from Synonyms ($p = 6.26E{-}02$). For all five measures, there was evidence of significant heterogeneity of within pair differences across all countries, although for Symbol Digit, only Denmark showed a significant effect ($p = 8.62E{-}12$; ESr = .23), and for Synonyms, only Sweden ($p = 1.11E{-}03$; ESr = .13) (see supplemental Table S2).

Measured G×E: APOE

In the primary analyses of APOE as a variability gene, we focused on testing for heterogeneity in the variance of pair differences among *APOE* haplotypes evaluating whether variances could be constrained by country and sex, adjusting for average effects of age, sex and *APOE* haplotypes on the trait scores (see Table 3). We did not evaluate age trends in within pair variances by *APOE* haplotype for BMI, depression or for cognition, primarily due to the reductions in sample sizes of those with phenotypic data and genotyping and consequent confounding of age-cohort and country. Moreover, we note that the general age-cohort consistency of the evidence for G×E observed for BMI and depressive symptoms. Significant findings are described further below. Analyses of mean level associations (i.e., whether individuals score higher or lower on the trait on average) are reported (see Table 4), with no significant associations observed; description of mean trends is provided below for traits showing significant evidence for *APOE* x variance effects. Dropping *APOE* ε24 individuals from the analysis did not alter any of the conclusions.

Table 2 Test of mixture distributions of MZ within pair differences in full sample and by age-cohort

	$\bar{d}$	$\overline{d^2}$	delta	se	t	p	p'	ESr
BMI (Npair)								
Full sample (3550)	0.61	0.65	0.07	0.01	12.26	**3.54E−34**	**4.25E−33**	0.20
<50 years (643)	0.51	0.45	0.04	0.01	4.65	**2.05E−06**	**8.21E−06**	0.18
50–59 (1351)	0.60	0.64	0.07	0.01	7.93	**2.36E−15**	**2.12E−14**	0.21
60–69 (929)	0.61	0.63	0.05	0.01	4.49	**3.97E−06**	**1.19E−05**	0.15
70–79 (429)	0.69	0.84	0.09	0.02	4.09	**2.60E−05**	**5.21E−05**	0.19
80+ (198)	0.76	1.01	0.10	0.04	2.49	**6.87E−03**	**6.87E−03**	0.17
Depressive Sx (Npair)								
Full sample (3508)	0.81	1.19	0.14	0.01	13.61	**1.99E−41**	**2.39E−40**	0.22
<50 years (550)	0.80	1.12	0.13	0.03	4.99	**4.06E−07**	**2.03E−06**	0.21
50–59 (1326)	0.81	1.16	0.14	0.02	7.98	**1.57E−15**	**1.25E−14**	0.21
60–69 (995)	0.77	1.08	0.14	0.02	7.88	**4.37E−15**	**3.06E−14**	0.24
70–79 (436)	0.92	1.51	0.17	0.04	4.52	**3.91E−06**	**1.57E−05**	0.21
80+ (201)	0.86	1.30	0.14	0.05	2.80	**2.81E−03**	**2.81E−03**	0.19
Synonyms (Npair)								
Full sample (912)	0.64	0.68	0.04	0.01	3.53	**2.16E−04**	**2.16E−03**	0.12
<50 years (318)	0.56	0.50	0.01	0.01	0.92	1.79E−01	3.59E−01	0.05
50–59 years (463)	0.69	0.79	0.03	0.02	1.74	4.13E−02	2.39E−01	0.08
60–69 years (48)	0.57	0.64	0.13	0.05	2.71	**4.64E−03**	**3.25E−02**	0.37
70–79 years (32)	0.64	0.62	−0.01	0.06	−0.19	5.75E−01	5.75E−01	0.03
80+ years (51)	0.72	0.94	0.13	0.07	1.79	3.98E−02	2.39E−01	0.25
Block design (Npair)								
Full sample (393)	0.56	0.57	0.07	0.02	4.61	**2.75E−06**	**2.75E−05**	0.23
<50 years (60)	0.46	0.37	0.04	0.03	1.43	7.85E−02	1.57E−01	0.18
50–59 years (85)	0.47	0.37	0.03	0.02	1.36	8.94E−02	1.57E−01	0.15
60–69 years (124)	0.59	0.60	0.06	0.03	1.98	**2.47E−02**	1.23E−01	0.18
70–79 years (37)	0.59	0.66	0.11	0.06	1.84	**3.69E−02**	1.23E−01	0.29
80+ years (87)	0.68	0.82	0.09	0.05	1.89	**3.08E−02**	1.23E−01	0.20
Digits forward (Npair)								
Full Sample (1551)	0.83	1.21	0.12	0.02	7.28	**2.60E−13**	**2.86E−12**	0.18
<50 years (124)	0.91	1.39	0.07	0.07	1.13	1.31E−01	1.94E−01	0.10
50–59 years (695)	0.80	1.13	0.12	0.02	5.31	**7.54E−08**	**6.78E−07**	0.20
60–69 years (285)	0.79	1.01	0.04	0.03	1.30	9.69E−02	1.94E−01	0.08
70–79 years (313)	0.94	1.51	0.12	0.05	2.56	**5.52E−03**	**1.66E−02**	0.14
80+ years (134)	0.80	1.26	0.26	0.06	4.46	**8.67E−06**	**5.20E−05**	0.36
Digits backward (Npair)								
Full sample (1722)	0.83	1.21	0.14	0.02	8.81	**1.51E−18**	**1.66E−17**	**0.21**
<50 years (194)	0.82	1.25	0.18	0.05	3.84	**8.23E−05**	**3.20E−04**	0.27
50–59 years (745)	0.82	1.18	0.12	0.02	5.38	**4.87E−08**	**3.41E−07**	0.19
60–69 years (323)	0.82	1.11	0.06	0.03	1.83	**3.42E−02**	**3.42E−02**	0.10
70–79 years (327)	0.88	1.39	0.16	0.04	3.82	**8.01E−05**	**3.20E−04**	0.21
80+ years (133)	0.74	1.10	0.25	0.05	4.92	**1.28E−06**	**7.70E−06**	0.39
Symbol digit (Npair)								
Full sample (1256)	0.58	0.57	0.04	0.01	5.17	**1.39E−07**	**1.39E−06**	**0.14**
<50 years (190)	0.54	0.51	0.04	0.02	2.26	**1.26E−02**	7.56E−02	0.16
50–59 years (360)	0.59	0.61	0.07	0.02	4.20	**1.66E−05**	**1.49E−04**	0.22
60–69 years (371)	0.59	0.58	0.03	0.02	1.86	**3.18E−02**	1.59E−01	0.10

Table 2 continued

	$\bar{d}$	$\overline{d^2}$	delta	se	t	p	p'	ESr
70–79 years (256)	0.57	0.54	0.03	0.02	1.85	**3.25E−02**	1.59E−01	0.12
80+ years (79)	0.63	0.63	0.01	0.04	0.33	3.70E−01	8.92E−01	0.04

D absolute pair difference, *delta* $\overline{d^2} - \frac{\pi}{2}\overline{d}^2$; *se* $= \frac{\overline{d^2}}{\sqrt{n}}(.5321)$, ES$r$ *effect size* $r = \sqrt{\frac{t^2}{(t^2+df)}}$, where $df =$ Npair-1. p-values are based on one-tailed t-tests; bolded p values are signficant according to FDR tests. $p' =$ Holm-Bonferroni sequentially adjusted p values, where bolded are signficant

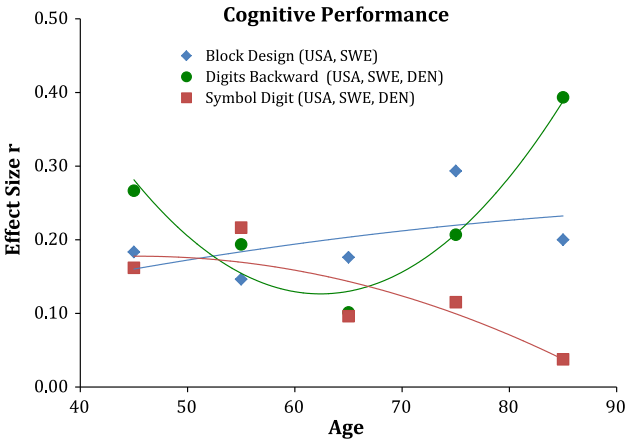

Fig. 1 Effect size r (ESr) for evidence for mixture distribution suggesting possible G×E: representative cognitive tests

BMI

Variances of absolute pair differences by *APOE* haplotype could not be constrained across sex within country [$\chi^2(6) = 19.64$, $p = 3.21\text{E}{-03}$] (see Table 3 for within pair variance estimates and test statistics); hence, further analyses were conducted separately for men and women. Non-significant country differences in within pair variances within *APOE* haplotype were observed for men and women ($p = 9.31\text{E}{-02}$). In addition, within pair variances could be constrained across *APOE* haplotype within country ($p = 7.22\text{E}{-01}$). In sum, within pair variances for the *APOE* haplotypes differed between men and women, but across country the *APOE* haplotype effects were not statistically different from each other. Hence, there was no support for an *APOE* effect on within pair variability, but there was heterogeneity of within pair variances across men and women suggesting that female pairs are more variable than male pairs in terms of the degree to which twins differ from their cotwin in BMI.

Depressive symptoms

Variances of absolute pair differences by APOE haplotype could be constrained across sex within country [$\chi^2(6) = 2.05$, $p = 9.15\text{E}{-01}$]; hence analyses were conducted collapsing men and women together (see Table 3). Haplotype-based within pair variances could not be constrained across country [$\chi^2(6) = 44.99$, $p = 4.70\text{E}{-08}$]. Thus, haplotype-based within pair variances were allowed to vary within country and significant differences by *APOE* haplotype were observed [$\chi^2(6) = 19.78$, $p = 3.04\text{E}{-03}$]. Figure 2a indicates that *APOE* effects could be observed in the US and in the Swedish samples, with smaller variances of pair differences for *APOE* ε4+ compared to larger variances for *APOE* ε33 and ε2+ . This pattern suggests that those with *APOE* ε4 + may be less affected by environmental factors compared to the other haplotypes. Last, we followed up these variance tests of within-pair differences to consider whether *APOE* effects were evident for average depressive symptom scores, with no significant differences observed ($p = 2.83\text{E}{-01}$).

Cognitive performance

Among the five cognitive measures considered, only Block Design showed evidence of significant haplotype differences in within pair variances (see Table 3). Variances by *APOE* haplotype could be constrained across sex [$\chi^2(3) = 5.76$, $p = 1.24\text{E}{-01}$]; hence, analyses were conducted collapsing men and women together. As Block Design and APOE genotyping were only available in two Swedish samples, no country comparisons could be conducted. Significant differences in within pair variances by *APOE* haplotype were observed [$\chi^2(2) = 11.91$, $p = 2.60\text{E}{-03}$]. Smaller within pair variances of pair differences for *APOE* ε4 + versus larger variances for *APOE* ε2 + were observed (see Fig. 2b). This pattern indicates that those with *APOE* ε4 + may be less affected by environmental factors compared to those with *APOE* ε33 and *APOE* ε2 + , and is consistent with the overall pattern observed for depressive symptoms above. Last, we followed up these within-pair variance tests to consider whether *APOE* effects were evident for average Block Design performance scores, and no significant differences were observed ($p = 2.49\text{E}{-01}$).

Table 3 Homogeneity of within pair variance by *APOE*

Measure	Country	Within pair σ^2			Likelihood ratio tests									Total Npair
		APOE			Equate males & females			Equate countries			Equate ε2+, ε33, ε4+			
		ε2+	ε33	ε4+	$\Delta\chi^2$	df	*p*	$\Delta\chi^2$	df	*p*	$\Delta\chi^2$	df	*p*	
BMI	USA (m)	0.39	0.30	0.31	**19.64**	6	**3.21E−03**	10.85	6	9.31E−02	3.67	6	7.22E−01	672
	SWE (m)	0.32	0.26	0.32	–	–	–	–	–	–	–	–	–	–
	DEN (m)	0.24	0.19	0.24	–	–	–	–	–	–	–	–	–	–
	SWE (f)	0.26	0.45	0.52	–	–	–	4.50	3	2.12E−01	6.53	4	1.63E−01	428
	DEN (f)	0.30	0.31	0.40	–	–	–	–	–	–	–	–	–	–
Depressive Sx	USA	0.91	0.44	0.39	2.05	6	9.15E−01	**44.99**	**6**	**4.70E−08**	**19.78**	**6**	**3.04E−03**	1104
	SWE	0.55	0.47	0.41	–	–	–	–	–	–	–	–	–	–
	DEN	0.76	0.71	0.91	–	–	–	–	–	–	–	–	–	–
Synonyms	USA	0.45	0.43	0.38	1.91	3	5.92E−01	1.62	3	6.54E−01	1.77	4	7.79E−01	506
	SWE	0.32	0.40	0.32	–	–	–	–	–	–	–	–	–	–
Block design	SWE	0.40	0.33	0.15	5.76	3	1.24E−01	–	–	–	**11.91**	**2**	**2.60E−03**	203
Digits forward	USA	0.51	0.46	0.50	3.32	6	7.68E−01	9.24	6	1.60E−01	4.58	6	5.98E−01	1038
	SWE	0.53	0.66	0.63	–	–	–	–	–	–	–	–	–	–
	DEN	0.66	0.64	0.49	–	–	–	–	–	–	–	–	–	–
Digits back	USA	0.43	0.63	0.52	6.73	6	3.46E−01	10.04	6	1.23E−01	6.71	6	3.48E−01	1031
	SWE	0.32	0.47	0.44	–	–	–	–	–	–	–	–	–	–
	DEN	0.57	0.51	0.58	–	–	–	–	–	–	–	–	–	–
Symbol digit	SWE	0.24	0.30	0.31	6.03	6	4.20E−01	0.08	3	9.94E−01	1.71	4	7.88E−01	618
	DEN	0.26	0.31	0.31	–	–	–	–	–	–	–	–	–	–

USA United States of America, *SWE* Sweden, *DEN* Denmark, *m* male, *f* female, *Sx* symptoms. Random effects model adjusted for average effect of *APOE* haplotype, country, sex and age

Table 4 Average effects of *APOE*: adjusted for age, sex and country

Measure	*APOE* haplotype			Test of *APOE* effect			Npair
	ε2+	ε33	ε4+	$\Delta\chi^2$	df	*p*	
BMI	−0.19	−0.12	−0.13	1.04	2	5.94E−01	1100
Depressive Sx	−0.62	−0.53	−0.50	2.53	2	2.83E−01	1104
Synonyms	−0.06	0.09	0.03	2.33	2	3.12E−01	506
Block design	0.04	0.29	0.26	2.78	2	2.49E−01	364
Digits forward	−0.04	−0.02	0.09	3.98	2	1.37E−01	1038
Digits backward	0.12	0.08	0.18	2.81	2	2.45E−01	1031
Symbol digit	0.17	0.06	0.18	3.78	2	1.51E−01	618

Sx symptoms. Random effects models adjusted for average effects of age (centered at 65 years), sex (males = −0.5, females = +0.05), and country (reference = Denmark)

Discussion

We evaluated general evidence of G×E for BMI, depressive symptoms, and cognitive performance in twin studies from four countries, i.e., US, Sweden, Denmark, and Finland. We further evaluated whether *APOE* is a variability gene across these traits and represents, in part, the G in the G×E effects. We observed that across physical, psychological, and cognitive domains, G×E was pervasive across country and sex showing small to moderate effect sizes. While modest, the presence of these effects across domains argues for the importance of more routinely considering gene–environment interaction in biometric models. Generally stable age-cohort trends were observed for BMI and depressive symptoms. However, age-cohort trends varied by cognitive trait domains with some showing decreasing G×E effects and some showing increasing G×E effects. Last, *APOE* may represent one variability gene for

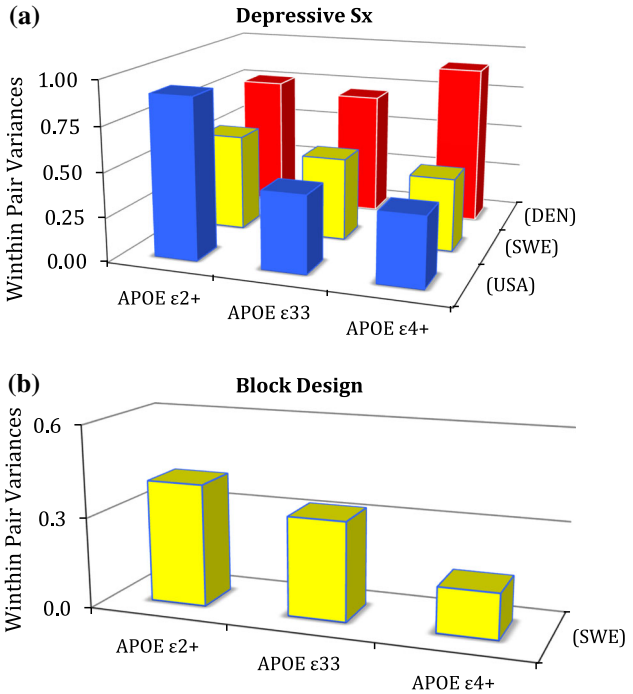

Fig. 2 Variance of absolute MZ within pair differences adjusted for age by *APOE*: **a** depressive symptoms, **b** block design

depressive symptoms and spatial reasoning, but not for BMI or other cognitive tests. Hence additional variability genes are salient beyond *APOE*.

BMI

BMI evidenced small G×E effects, and these effects were consistent across country, sex, and age-cohort. This is perhaps not surprising in that the candidate G×E studies evaluating education or exercise on genetic variations in BMI have reported G×E in samples from various countries represented in our study (US, Denmark, Finland; Johnson et al. 2011; Lajunen et al. 2012; McCaffery et al. 2009; Mustelin et al. 2009; Silventoinen et al. 2009; Silventoinen et al. 2004). Others have suggested that the genetic variance for BMI may be increasing in later born Swedish cohorts (Rokholm et al. 2011), perhaps suggesting a complex cohort/generational G×E given changing dietary and activity patterns amongst others. Further examinations of longitudinal data across multiple cohorts would be informative as to the extent to which G×E for BMI is dynamic across age versus birth cohort.

Despite agnostic evidence of G×E, no *APOE* associations were observed with within-pair variability for BMI. Prior studies have noted interactions of *APOE* with BMI, obesity, or of BMI variants (e.g., *FTO*) with outcomes such as metabolic traits (Elosua et al. 2003), dementia risk (Keller et al. 2011) or dementia progression (Besser et al. 2014). However, GWAS have not observed direct genetic association of *APOE* with mean BMI (Locke et al. 2015). Nonetheless, our lack of findings of *APOE* in the current analysis suggests that other variability genes, e.g., perhaps based on a polygenic risk score of 97 BMI loci (Locke et al. 2015), are relevant to pursue given evidence of G×E we observed in the agnostic Fisher analysis.

Depressive symptoms

Depressive symptoms showed consistently small but significant G×E effect sizes for sex and age-cohort, with lower effect sizes for Sweden and Finland and higher for US and Demark. Our findings of ubiquitous small G×E effects furthers earlier evidence there is not simply an effect of the environment (E) on depressive symptom levels but that there is genetically influenced sensitivity to environmental factors that may foster (or mitigate) depression (c.f., Kendler et al. 1995).

We observed associations of *APOE* with within-pair variability in depression symptoms but no effect on mean depression scores. Results varied across country; evidence for *APOE* as the 'G' in G×E was found for the U.S. and Sweden, but not the Danish sample. Indeed, *APOE* associations with average depression symptoms and risk for a diagnosis of depression have been mixed across studies, perhaps due to differential population effects or study designs (Skoog et al. 2015). *APOE* has been associated with depressive symptomatology and depression diagnosis in late adulthood in a prospective study of Swedish individuals even when excluding prevalent or incident dementia cases (Skoog et al.). Other comparably sized (or larger) cross-sectional and longitudinal studies have not found such effects (e.g., Locke et al. 2013; Schultz et al. 2008; Surtees et al. 2009); however, the average sample age tended to be between ages 55 and 61, suggesting that the association of *APOE* and depressive symptoms may tend towards older adults.

Our results suggest that the effect of *APOE* on depression would appear to lie, not in main effects, but in the role of *APOE* in magnifying or reducing the effects of environmental risk factors for depressive symptoms. Specifically, MZ pairs carrying the ε4 haplotypes showed the smallest within-pair differences while those carrying the ε2 haplotypes the largest within-pair differences in depression scores. Hence, the depressive symptoms experienced by those with *APOE* ε4 + may be less driven by environmental factors, and more by familial or endogenous factors, compared to depressive symptoms experienced by those with other *APOE* haplotypes. Together with the observed age-cohort trends, such an interpretation would be consistent with the role of vascular factors and white matter changes in late onset depression (Nebes et al. 2001; Taylor et al. 2013).

Cognition

Different cognitive performance domains showed different patterns of results with respect to the agnostic Fisher G×E tests, with the pattern possibly reflecting the difference between age-sensitive cognitive tests versus more age-robust tests. The most age-sensitive test, perceptual speed indexed by Symbol Digit task performance, showed peak G×E effects in the younger age-cohorts compared to later age cohorts; whereas tests of attention, working memory, and spatial performance showed higher G×E in later age-cohorts. These latter tests tend to show later declines, accelerating across the adult lifespan (Salthouse 2009; Schaie 1994). We note that the complexity of findings underscores the need to consider specific cognitive abilities beyond general measures of ability.

In the *APOE* analyses, where we adjusted for age given the restricted sample size, we observed an effect for the spatial task, Block Design, but no other tasks. For Block Design, as for depressive symptoms, those with *APOE* ε4 + may be less affected by environmental factors compared to the other *APOE* haplotypes. It is worth noting that Block Design performance may be a salient predictor of subsequent cognitive dysfunction (e.g., Andel et al. 2001; Bozoki et al. 2001; Hamilton et al. 2008; Tabert et al. 2006). Hence those at risk for dysfunction or decline may show relatively less sensitivity to environmental factors compared to those without this risk allele, whose performance does reflect environmental influences.

The lack of association of *APOE* with variability for other cognitive measures could be viewed as puzzling. *APOE* associations with cognitive performance levels in non-demented adults have been mixed overall. However, we note that age-related change may be more salient than cross-sectional differences in performance level in terms of gene associations (e.g., Davies et al. 2014; Finkel et al. 2011; Salmon et al. 2013) as well as observing G×E effects (Reynolds et al. 2007). For example, in longitudinal work in SATSA using the within MZ pair methods, we observed significant G×E effects on semantic, episodic, and working memory trajectory features (e.g., linear and nonlinear change) but negligible effects on overall performance level (Reynolds et al. 2007). Hence, longitudinal examinations may reveal unique effects not apparent in baseline performance data. Another interpretation, given the longitudinal findings, might suggest that effects may not show up strongly until later ages. If age is adjusted for, then age periods where *APOE* or another gene or genes have a particular effect may be missed.

The smaller within-pair differences for those with *APOE* ε4 may seem to be counter-intuitive given that in some instances ε4 individuals may show greater rather than lesser sensitivity to particular environments that are relevant to brain reserve, not only dietary and exercise factors as mentioned above (Brown et al. 2013a, b; Carvalho-Wells et al. 2012; De Marco et al. 2015; Head et al. 2012), but also head injury and neuropsychological functioning and dementia (e.g., Sundstrom et al. 2004; Sundstrom et al. 2007; Tang et al. 1996) and combat exposure and PTSD (Kimbrel et al. 2015; Lyons et al. 2013). While a diathesis-stress model would expect ε4 always to act in the same direction, others have proposed the concept of a plasticity gene (Belsky et al. 2009; Belsky and Pluess 2009). Such an interpretation would be consistent with smaller within-pair differences for ε4 and greater sensitivity to some exposures or contexts but lessened sensitivity to other exposures or contexts.

Strengths, limitations, and future directions

The strengths of the current study include the relatively large samples of MZ pairs and the ability to evaluate (and replicate) G×E trends in physical, psychological, and cognitive domains across up to four countries, by sex, and age cohorts. Moreover, in a subset of studies we were able to evaluate a well-characterized gene, *APOE*, as a potential variability gene. The primary limitation was that a single-occasion was available for evaluation of G×E for BMI, depressive symptoms and cognition. Moreover, not all studies had available *APOE* genotyping, hampering age-cohort investigations. Moreover, we had a limited set of cognitive measures and, hence, future studies would benefit from inclusion of measures of executive function and episodic memory.

Overall, future research directions should consider the possible measured environmental factors, i.e., the 'E' in G×E, given that G×E was ubiquitously observed albeit with generally small impact. Indeed, particularly for depression and spatial reasoning, the impact of any measured environmental factors may be modified by the *APOE* gene.

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Compliance with Ethical Standards

Conflict of interest Dr. Korhonen has served as a consultant on nicotine dependence for Pfizer (Finland) in 2011-2015.

Research involving Human Participants and/or Animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the respective institutional and/or national research committees for each participating study providing archival data, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants from their respective parent study.

Appendix

Members of the consortium on Interplay of Genes and Environment across Multiple Studies (IGEMS) include: Nancy L. Pedersen (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, and Department of Psychology, University of Southern California, Los Angeles, CA), Kaare Christensen (Department of Epidemiology, University of Southern Denmark, Odense, Denmark), Anna K. Dahl Aslan (Institute of Gerontology, School of Health Sciences, Jönköping University, Jönköping, Sweden), Deborah Finkel (Department of Psychology, Indiana University Southeast, New Albany, IN), Carol E. Franz (Department of Psychiatry, University of California, San Diego, La Jolla, CA), Margaret Gatz (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, and Department of Psychology, University of Southern California, Los Angeles, CA), Briana N. Horwitz (Department of Psychology, California State University, Fullerton, CA), Boo Johansson (Department of Psychology, University of Gothenburg, Gothenburg, Sweden), Wendy Johnson (Department of Psychology and Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK), Jaakko Kaprio, Department of Public Health, University of Helsinki, Helsinki, Finland), William S. Kremen (Department of Psychiatry, University of California, San Diego, and VA Center of Excellence for Stress and Mental Health, La Jolla, CA), Robert Krueger (Department of Psychology, University of Minnesota, Minneapolis, MN), Michael J. Lyons (Department of Psychological and Brain Sciences, Boston University, Boston, MA), Matt McGue (Department of Psychology, University of Minnesota, Minneapolis, MN), Jenae M. Neiderhiser (Department of Psychology, ThePennsylvania State University, University Park, PA), Matthew S. Panizzon (Department of Psychiatry, University of California, San Diego, La Jolla, CA), Inge Petersen (Department of Epidemiology, University of Southern Denmark, Odense, Denmark), and Chandra A. Reynolds (Department of Psychology, University of California-Riverside, Riverside, CA).

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