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RESEARCH ARTICLE

Lifestyle and psychosocial associations with cognition at the cusp of midlife using twins and siblings

Anqing Zheng[1,2] | Naomi P. Friedman[1,3] | Daniel E. Gustavson[1,3] | Robin P. Corley[1] | Sally J. Wadsworth[1] | Chandra A. Reynolds[1,2,3]

[1]Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, Colorado, USA

[2]Department of Psychology, The University of California, Riverside, California, USA

[3]Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, Colorado, USA

Correspondence
Anqing Zheng, Institute for Behavioral Genetics, University of Colorado, Boulder, CO 80309, USA.
Email: anqing.zheng@colorado.edu

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Abstract

INTRODUCTION: This study investigates the relationship between cognitive functioning and 59 modifiable and intrinsic factors at the cusp of midlife.

METHODS: We analyzed data from 1221 participants in the Colorado Adoption/Twin Study of Lifespan behavioral development and cognitive aging (CATSLife; $M_{age} = 33.20$, %Female = 52.74). We assessed the impact of 59 factors on cognitive functioning using regularized regression and co-twin control models, controlling for earlier-life cognitive functioning and gray matter volume.

RESULTS: Eight robust factors were identified, including education attainment, cognitive complexity, purpose-in-life, and smoking status. Twins reporting higher levels of cognitive complexity and purpose-in-life showed better cognitive performance than their cotwin, while smoking was negatively associated. Using meta-analytically derived effect size threshold, we additionally identified that twins experiencing more financial difficulty tend to perform less well compared with their cotwin.

DISCUSSION: The findings highlight the early midlife link between cognitive functioning and lifestyle/psychological factors, beyond prior cognitive performance, brain status, genetic and familial confounders. Our results further highlight the potential of established adulthood as a crucial window for dementia prevention interventions targeting lifestyle and psychosocial factors.

KEYWORDS
cognitive function, established adulthood, life course, lifestyle, modifiable risk factors, psychosocial, twin

Highlights

- Cog complexity(+), purpose-in-life(+) were associated with cognition in early midlife.
- Smoking(−) was also associated with cognition in early midlife.
- Results were consistent controlling for genetic and environmental confounds.
- Association between EA and cognition might be mostly genetic and familial confounded.

1 | INTRODUCTION

The rising prevalence of cognitive impairment and dementia in the aging population has garnered considerable attention in recent years.[1] With demographic shifts, this number is projected to increase four-fold in the next 30 years.[2] While efficacious treatment for dementia remains elusive, mounting evidence indicates that protective mechanisms against neurodegenerative changes and cognitive decline may emerge early in life.[3,4] Such evidence has led public health authorities to advocate for life-course models that emphasize early detection and management, aiming for sustained and long-lasting impacts on preventing cognitive downturns (e.g., dementia prevention,[5] optimizing brain health[6]).

Current research in neurocognitive functioning has predominantly concentrated on specific life stages: early childhood, adolescence, and later life. There is a noticeable paucity of studies addressing the periods between these stages.[7] Notably, established adulthood, spanning from ages 30 to 45, represents a pivotal phase.[7,8] This period is often marked by intensified professional commitments, the cultivation of enduring personal relationships, and the intricate balancing act between career and familial responsibilities. Characterized as one of most demanding life stages, established adulthood has the potential to substantially influence the trajectory of one's later life.[5,9] With midlife being highlighted as a crossroads between growth and decline,[10] the years encompassing established adulthood, leading up to this critical midlife point, emerge as a vital demographic for early preventative and intervention strategies in the context of cognitive health.[3,11] Cognitive performance in this phase is a robust predictor of cognition maintenance in later life, underscoring the predictive value of studying this age group.[12] Furthermore, established adulthood is marked by biological, psychological, and sociocultural transitions that can have lasting ramifications for later life.[7] Navigating the complexities of an evolving sociocultural and environmental landscape, adults at the cusp of midlife encounter distinct challenges that warrant investigation into factors specifically related to neurocognitive functioning during this life stage.[10] Alarmingly, recent trends, especially in the United States, highlight an escalating mortality risk within this age bracket.[13] This alarming trajectory necessitates an in-depth understanding of the broader health metrics of this demographic, and studying neurocognitive functions that intersect with individuals' behaviors, lifestyles, and experiences[12–14] may also shed light on factors contributing to these trends.

When examining individual cognitive functioning, factors such as educational attainment (EA)[15] and physical activities[16] often emerge as focal areas. However, there is a growing recognition of the influence of broader lifestyle, psychosocial factors, as well as anthropometric, and sociodemographic factors.[5,17,18] For instance, a recent meta-analytical review illustrated how skills, like self-control, and emotional regulation, are linked to positive shifts in general cognitive functioning among adolescents[19] (effect size = 0.56 SD). Other studies have investigated the impact of lifestyle choices on cognition, highlighting factors like tobacco use[20,21] and social activity.[22] Anthropometric factors, such as body mass index,[23] along with sociodemographic factors such as family socioeconomic status,[24] have also been associated with cognitive performance.

While existing research has deepened our understanding of individual differences in cognitive functioning, a challenge lies in discerning whether observed associations arise due to causal pathways or are confounded by shared genetic and environmental influences.[25] This challenge is particularly relevant given the moderate heritability observed in many lifestyle and psychosocial factors, with genetic factors explaining 30%~50% of variance in these traits.[26] With cognitive functioning being well-established as a highly heritable trait[27] (~70% in adulthood), this raises the possibility that the observed association between lifestyle and psychosocial factors, with cognitive function, could stem from shared genetic factors rather than a direct causal relationship. It is crucial to emphasize that identifying a genetic influence does not necessarily imply these characteristics are fixed or predetermined, but rather suggestive of pervasive and complex effects of genetics on human behavior more broadly.[25] Nonetheless, distinguishing causal from confounding relationships between lifestyle and psychosocial factors with cognitive function is critical for informing effective regulation, interventions, and prevention strategies.

For example, the phenotypic associations between cognitive functioning and variables like substance misuse or EA might be driven by underlying shared genetic factors.[21,28] Yet, genetic overlap alone does not automatically imply confounding or that the shared genetic underpinnings masked a direct causal relationship. Confounding arises when this genetic overlap is not accompanied by a corresponding

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional sources (e.g., PubMed, Google Scholar). Limited research has examined the relationships between lifestyle and psychosocial factors with cognitive functioning during established adulthood, especially by taking genetic confounding effect into consideration. We identified eight robust associations among 59 factors, and then exploring the potential mediating roles of genetics and early-life experience in these associations.
2. **Interpretation**: Our findings suggested that diverse factors (e.g., cognitive complexity, purpose-in-life), contributed to cognitive functioning beyond traditional assessments in established adulthood. Additionally, the potential confounding effects of genetics and early-life experiences needed to be considered in the relationship between traditional measures (i.e., EA) and cognition.
3. **Future directions**: Future research should evaluate the impact of prevention and screening strategies for the identified lifestyle and psychosocial factors, particularly their role in reducing dementia risk. Our results should be replicated in larger twin datasets.

environmental relationship. Co-twin control analyses offer a nuanced approach to help differentiate between genuine associations and potential confounding factors.[29] By examining differences within twin pairs, this method accounts for unmeasured shared family-level variables and genetic factors.[25,29] That is, if an association does not persist within pairs (e.g., if the twins with higher substance use do not show lower cognitive scores than their co-twins with lower substance use), it suggests the association may not be directly causal (i.e., that substance use causes cognitive decline). Conversely, associations persisting within twin pairs align with a causal interpretation, although they do not prove causation. For instance, a study by Caracciolo et al.[30] revealed a within-pair association between EA and subjective cognitive impairment. Other studies have connected within-pair differences in physical activity,[31] and smoking habits[21] to cognitive or brain-age outcomes. Yet, comparatively little attention has been paid to lifestyle and psychosocial factors using genetically-informed design, particularly in the established adult demographic.

The present study integrates a lifespan development perspective into the study of cognition by examining the potential contributions of psychological and lifestyle factors to cognitive functioning during the established adulthood phase at the cusp of midlife. Using cross-validated regularized regression, we identified robust associations across 59 lifestyle and psychosocial factors. We then employed a co-twin control analysis to assess if these relationships persisted when adjusting for adolescent cognitive functioning, brain status, and familial and genetic influences. Furthermore, we performed a meta-meta-analysis and derived effect size benchmark specified in the literature on modifiable factors related to cognition, and subsequently included candidate predictors based on the established threshold. The primary objective was to seek evidence of within-pair associations between these robust indicators and cognitive functioning.

2 | METHODS

2.1 | Participants

This study used data from the Colorado Adoption Project/Twin Study of Lifespan behavioral development and cognitive aging[11] (CATSLife). The CATSLife study initiated its data collection in 2015 and continued until 2021, recruiting 1327 participants from two parent longitudinal studies featuring comparable measures: the Colorado Longitudinal Twin Study[32] (LTS), encompassed same-sex twin pairs, and the Colorado Adoption Project[33] (CAP), encompassed adopted and biological sibling pairs across adoptive and non-adoptive families. To identify robust correlates across individual, we included 708 unrelated participants (M_{age} = 33.57; %Female = 51.41, %White = 89.55%, %Hispanic = 5.23%) from the CATSLife sample with cognitive performance (N = 1221)[a]. Our co-twin control design included data from a subset of LTS twins (N = 606; M_{age} = 29.28; %Female = 54.95%, %White = 87.13%, %Hispanic = 10.23%). The twins included 136 complete monozygotic (MZ) pairs, 122 complete dizygotic (DZ) pairs[b]. Sample descriptions are available in Table 1, with more detailed descriptions provided in supplementary material. Throughout this study, we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[34]

2.2 | Measures

2.2.1 | Cognitive functioning

Cognitive functioning was assessed using the third edition of the Wechsler Adult Intelligence Scale[35] (WAIS-III). We included both full-scale intelligence quotient (FSIQ) score and performance intelligence quotient (PIQ) in our analyses across the individuals (phenotypic analyses) and within twin pairs (co-twin control analyses)[c]. In our co-twin control analyses, we additionally adjusted for FSIQ and PIQ measured at around age 16 as covariates for corresponding analyses. Average FSIQ in our sample exceeded the expected population mean value of 100 (e.g., cross-sectional sample, M = 110.83, SD = 11.92, range 69–148), with relatively smaller variation than the expected population value (SD = 15).

2.2.2 | Cognitive correlates

From the CATSLife study phase, we included 59 variables from four domains as predictors of cognitive functioning. The four domains were lifestyle (13 measures; e.g., reading for fun; moderate activity metabolic equivalent (MET) minutes, current smoker), psychosocial (36 measures; e.g., cognitive complexity; family support), anthropometric (2 measures; i.e., body mass index; waist-to-hip ratio), and sociodemographic (8 measures; e.g., EA; financial strain). We imputed missing data based on all CATSLife subjects with eligible data (N = 1221), using K-nearest neighbor[37] and bagged tree algorithms[38] for continuous and ordinal variables, respectively. See Table 2 for the list of constructs by domains, and Table S1 for a full description of the cognitive correlates along with example items and descriptive statistics. To facilitate interpretation, we z-standardized all variables except for EA and ordinal variables (i.e., current smoking). We preserved the original scale for EA and dummy-coded the ordinal variables, as these scales hold meaningful metrics. All data pre-processing was conducted using tidymodels package[39] in R.[40]

2.2.3 | Covariates

In our co-twin control analyses, we accounted for gray matter volume (GMV) measured proximal to CATSLife at the LTS-EF (Executive Functioning) assessment[41] and cognitive scores measured at age 16, as both factors played an important role in brain health and are predictive of

[a] To circumvent non-independency challenges in the elastic net regression, one sibling was randomly selected from each family.

[b] We included 90 single twins as they could contribute to stabilize the between-pair estimates.
[c] We did not prioritize Verbal IQ in this analysis given its established representation in FSIQ.[36]

TABLE 1 Demographic characteristics

Parameter	Cross-sectional (*N* = 708)	Co-twin (*N* = 606)
Age, mean years (SD)		
Year 16	–	16.52 (0.75)
LTS-EF		28.77 (0.85)
CATSLife	33.57 (4.82)	29.28 (1.25)
Zygosity		
Adoptee	159 (22.46%)	–
Sibling	181 (25.56%)	–
MZ Twin	188 (26.55%)	312 (51.49%)
DZ Twin	180 (25.42%)	294 (48.51%)
Sex		
Female	364 (51.41%)	333 (54.95%)
Male	344 (48.59%)	273 (45.05%)
Race/ethnicity		
Non-Hispanic White	634 (89.55%)	528 (87.13%)
Non-Hispanic Black	0	0
Hispanic	37 (5.23%)	62 (10.23%)
Other	37 (5.23%)	16 (2.64%)
EA, mean years (SD)	15.55 (2.10)	15.41 (2.18)
Current smoker	120 (16.95%)	102 (16.83%)
Full scale IQ, mean (SD/range)		
Year 16	–	103.39 (11.26) 74 - 142
CATSLife	110.83 (11.92/69–148)	109.39 (11.14) 79–143
Performance IQ, mean (SD/range)		
Year 16	–	102.11 (10.88) 74 - 136
CATSLife	113.67 (13.66 / 68 - 155)	110.40 (12.40) 75 - 148
Raw total gray matter (L3)	–	666287.82 (60123.39)

Notes: MRI data were collected as part of a separate assessment *M* = 0.5 (SD = 0.9) years before the primary CATSLife assessment. Prior to enter into the co-twin control models, gray matter volume was adjusted on age as measured during LTS-EF assessment. Dashes indicate not applicable.
Abbreviations: CATSLife,Colorado Adoption Project/Twin Study of Lifespan behavioral development and cognitive aging; EA, educational attainment, DZ, dizygotic; IQ, intelligence quotient; LTS-EF, Colorado Longitudinal Twin Study-Executive Functioning; MZ, monozygotic; SD, standard deviation.

adult cognitive performance.[12,42] This approach allowed us to emphasize within-twin cognitive changes and mitigate potential confounds from prior cognitive disparities and brain structure variation. We incorporated measures from age 16 as the participants underwent the same cognitive assessment, WAIS-III, as they did during CATSLife. Details on structural MRI data processing are available in the supplementary material.

2.3 | Analytic approach

2.3.1 | Phenotypic associations

Our first goal was to elucidate associations between 59 factors and cognitive functioning among established adulthood. To achieve this, we utilized a five-fold cross-validated elastic net, incorporating all 59 predictors into the model simultaneously. This regularized approach efficiently addresses multicollinearity and refines predictor selection by setting some coefficients to zero.[43] Coefficient confidence intervals were established via five-step block-bootstrapping; see supplementary material for more methodological details. To control for confounders, such as cohort effects, we regressed age-normed intelligence scores on age at measurement, sex, race, and ethnicity. The resulting residuals from the regression were then used in the regularization regression. Only effects that are significant based on bootstrapped confidence intervals were followed up with co-twin control analyses. Analyses were conducted using the glmnet[44] and tidymodels package[39] in R.

2.3.2 | Effect size benchmark

One concern over the usage of regularization model in examining complex relationships among related predictors, is the potential for underestimating the importance of upstream determinants when all

TABLE 2 List of constructs from anthropometric, lifestyle, sociodemographic, and psychosocial domains, and robust association in regularized models

Domain	Variable	Robust correlates	Example item	Cognitive function (unstandardized ES, 95%CI)	
DV	FSIQ, PIQ, adjusted for age, sex, race, and ethnicity			FSIQ	PIQ
Anthro (2)	Body mass index, waist-to-hip ratio	–	–	–	–
Lifestyle (13)	Hour of sleep, sleep quality, sleep disturbance, reading engagement, screen-time engagement, social activity engagement, leisure activity engagement, family activity engagement, activity score, sitting time, moderate MET, vigorous MET, current smoking	Current smoking	Are you a current or former smoker?	–	−0.167 [−0.349, −0.048]
Socio (8)	Educational attainment, financial difficulties, perceived neighborhood safety, perceived neighborhood service, currently married, currently in romantic relationship, currently on job, hours work on job	Educational attainment	Seven categories of educational attainment based on educational qualification	0.292 [0.230, 0.346]	0.156 [0.092, 0.210]
Psycho (36)	BIS attention subscale, BIS motor subscale, BIS self-control subscale, BIS cognitively complexity subscale, MASQ general distress, MASQ anhedonia depression, PSWQ (worry) score, BFI Extraversion assertion facet, BFI Extraversion activity facet, BFI Agreeableness altruism facet, BFI Agreeableness compliance facet, BFI Conscientiousness order facet, BFI Conscientiousness self-displace facet, BFI Neuroticism depression facet, BFI Neuroticism anxiety facet, BFI Openness aesthetic facet, BFI Openness ideas facet, RRS brooding subscale, RRS self-reflection subscale, EASI sociality subscale, EASI activity subscale, EASI impulsivity subscale, EASI fearfulness subscale, EASI anger subscale, Satisfaction with life score, RPWB self-acceptance subscale, RPWB purpose in life subscale, RPWB environmental mastery subscale, RPWB positive relations subscale, RPWB personal growth subscale, RPWB autonomy subscale, CRQ family support, CRQ family strain, CRQ friend appraisal, CRQ friend belonging, CRQ friend tangible support,	BIS cognitive complexity	I like to think about complex problem	0.264 [0.203, 0.313]	0.223 [0.166, 0.294]
		BFI Openness aesthetic facet	I am someone who values artistic, aesthetic experiences	0.101 [0.043, 0.151]	0.040 [0.002, 0.121]
		RRS self-reflection	Go someplace alone to think about your feelings	0.066 [0.005, 0.112]	–
		RPWB purpose in life	Some people wander aimlessly through life but I am not one of them	0.078 [0.004, 0.151]	–
		BFI Extraversion activity facet	I am someone who is full of energy	−0.119 [−0.176, −0.025]	–
		PSWQ worry	Many situations make me worry.	−0.086 [−0.146, −0.010]	–

Note: List of 59 constructs from four domains, and identified robust associates and their parameter estimates from the regularized model ($N = 708$). Dashes indicate not applicable.
Abbreviations: Anthro, anthropometric; BFI, Big Five Inventory; BIS, Barrat Impulsiveness Scale; CRQ, Close Relationship Quality Scale; DV, dependent variable; EASI, EASI Temperament Survey; FSIQ, full-scale intelligence score; MASQ, Mood and Anxiety Symptom Questionnaire; MET, metabolic equivalents; PIQ, performance intelligence score; Psycho, psychosocial; PSWQ, Penn State Worry Questionnaire; RPWB, Ryff's Scales of Psychological Well-Being; RRS, Ruminative Response Scale; Socio, sociodemographic.

variables are considered simultaneously in a mutually adjusted regression model (i.e., Table 2 Fallacy[45 (p2),46]). To address this concern, we employed an empirically derived effect size benchmark for the inclusion of additional variables in the co-twin control analyses, based on the magnitude of correlation presented in Table S2. Rather than relying on generic, one-size-fits-all thresholds for effect size benchmarks (i.e., Cohen's recommendation[47]), we followed the guidelines proposed by Gignac & Szodorai[48] and conducted a meta-meta-analytical review to derive empirical effect size quantiles from the literature focusing on modifiable factors of cognition to inform our decision-making process.

The most widely used thresholds for interpreting effect sizes as small, medium, or large (r = 0.1, 0.3, 0.5, respectively) were proposed by Cohen.[47] However, effect sizes should be evaluated in light of typical values from relevant literature,[49,50] and several empirical studies suggest that Cohen's effect size benchmarks may overestimate the boundaries, especially for medium and large effect sizes.[48,51] To obtain an empirically derived effect size distribution in research on cognitive functioning, we followed procedures provided by Lovakov and Agadullina[51] and Gignac and Szodorai,[48] and conducted a specialized meta-analysis of meta-analyses involving cognition and modifiable exposures. We searched ProQuest using the following Boolean operators: "(title((meta-analysis) OR (meta-analytic) OR (umbrella review)) AND title((cognition) OR (cognitive) OR (intelligen*)))". The search was limited to peer-reviewed papers published in English between 2014 and 2023, with 'cognitive ability' as a subject. All reported meta-analysis provided correlation coefficients as effect sizes. Figure 1 provides a schematic overview of the inclusion and exclusion criteria. More detailed meta-analysis procedures, coding of additional variables can be found in the supplementary material. Data, codebook, and script used to perform the analyses are available at https://osf.io/8rwdq/?view_only=c3fb2df9d2e840c892be85b0daf8f203.

2.3.3 | Co-twin control

In our co-twin control design, we evaluated the within-pair associations between each previously identified cognitive correlates and cognitive functioning, adjusting for GMV measured proximal to CATSLife and cognitive scores measured at age 16. Between-pair and within-pair predictors were composed of family-level means and twins' deviations from their family's mean. To examine whether the within-twin pair effect differs by zygosity status, we included zygosity as a covariate and an interaction term with the within-twin pair effect. At the within-pair level analysis, we integrated GMV, age, and cognitive scores at age 16 as covariates, while controlling for the sex effect at the between-pair level.

Our co-twin control analyses utilized Mplus 8.4.[52] We captured each within-pair effect using Bayesian multilevel modeling,[53] and obtained robust standard errors using the TYPE = COMPLEX option and the cluster option of Mplus. We used a uniform distribution as prior for our parameters, as the results are insensitive to prior when the sample size exceed 500.[54] All our analytical code and supplemental materials can be found on the project's page (https://osf.io/tep53/?view_only=5b78fdaa8d2849c8ad9a3b21ed467c0a).

3 | RESULTS

3.1 | Phenotypic associations

The associations among all cognitive correlates, cognitive functions, and demographic variables are summarized in Table S2.

3.1.1 | Full-scale IQ (FSIQ)

Table 2 displays the robust associations between various cognitive correlates and cognitive functioning. Using bootstrapped confidence intervals from the regularized model, we identified seven distinct effects associated with FSIQ. Specifically, we found positive associations of FSIQ with EA (b = 0.292, 95% confidence interval [CI] = [0.230, 0.346]), cognitive complexity (BIS_Cogcx; b = 0.264, 95%CI = [0.203, 0.313]), aesthetic appreciation (BFI_O_Aes; b = 0.101, 95%CI = [0.043, 0.151]), self-reflection (RRS_SelfReflect, b = 0.066, 95%CI = [0.005, 0.112]), and a sense of purpose-in-life (RPWB_PurInLife; b = 0.078, 95%CI = [0.004, 0.151]). Moreover, a higher FSIQ score was associated with lower activity, or inclination toward being energetic (BFI_E_Act, b = −0.119, 95%CI = [−0.176, −0.025]), and decreased endorsement of worry (PSWQ_Worry; b = −0.086, 95%CI = [−0.146, −0.010]). Some traditionally identified correlates of cognitive functioning, such as physical activity, were not retained by the model (see Figure S1 for more details). Notably, care should be exercised when interpreting the magnitude of elastic net parameter estimates, as regularized models tend to bias these estimates toward zero due to the bias-variance trade-off.[55]

3.1.2 | Performance IQ (PIQ)

For PIQ, our regularized model identified four significant associations. Notably, cognitive complexity, EA, and aesthetic appreciation mirrored the correlates of FSIQ, with effect sizes ranging from b = 0.040 to 0.223 (detailed in Table 2 and Figure S2). Current smoking status emerged as a unique associate of PIQ, such that people who identified as a current smoker tended to have lower PIQ in our sample (Current_Smoke; b = −0.167, 95%CI = [−0.349, −0.048]).

To explore the robustness of the regularization approach, we included height as our negative control. None of the 59 included variables turned out to be robustly associated with height, and the results can be found in supplementary material and Table S3.

3.2 | Effect size benchmark relevant to modifiable predictors of cognition

A total of 62,285 correlation coefficients were extracted from 2726 studies or samples covered by 13 meta-analyses (see Table S4 for all included meta-analysis). To ensure a balanced contribution from each meta-analysis, we conducted 1000 weighted permutations with

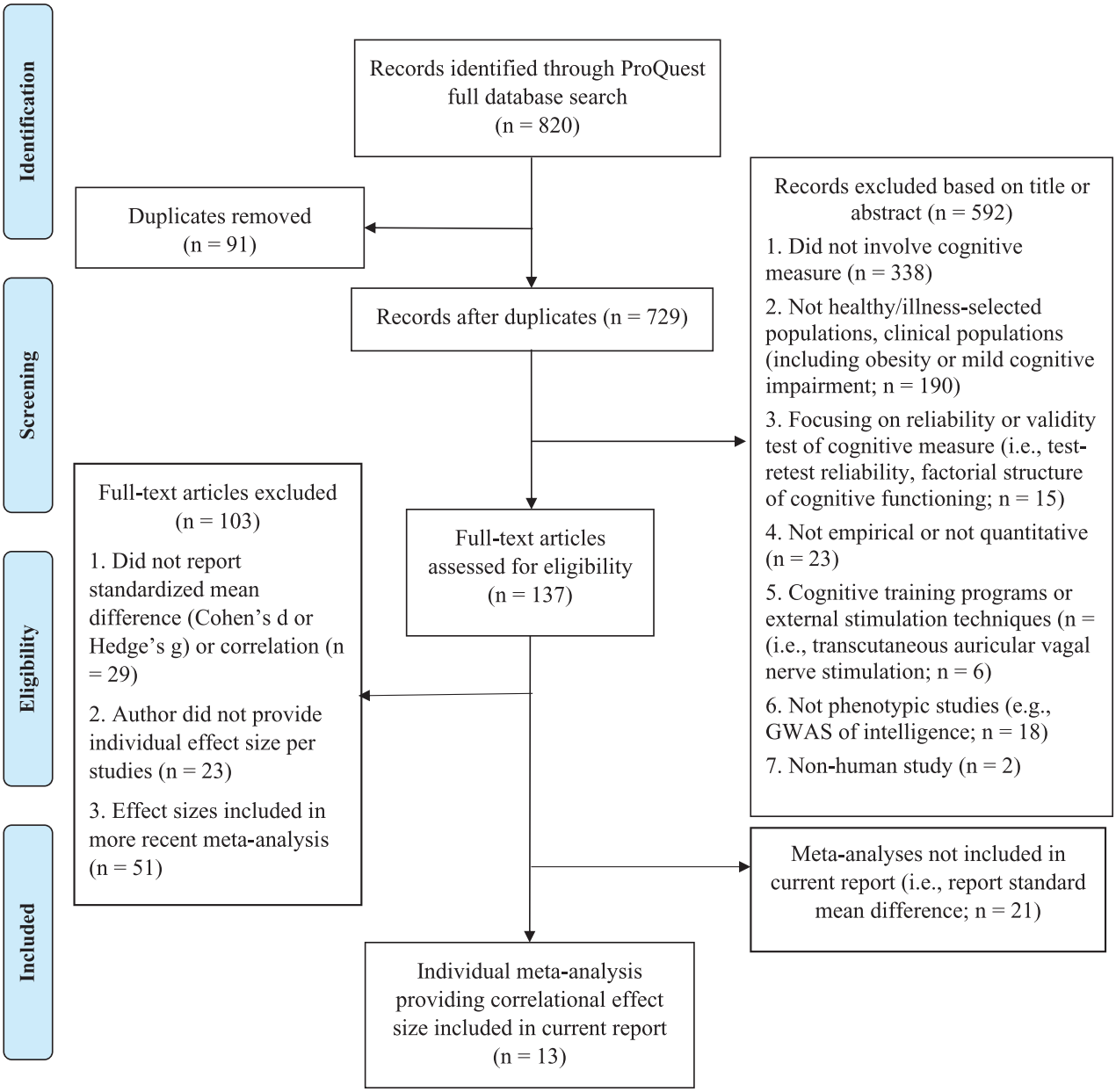

FIGURE 1 PRISMA flow diagram for literature search and study inclusion process. A total of 13 records reported in current study. The search term is "(title((meta-analysis) OR (meta-analytic) OR (umbrella review)) AND title((cognition) OR (cognitive) OR (intelligen*)))"

replacement, using the inverse of the number of effect sizes provided per study as the weight. The resulting 25th (small effect), 50th (medium effect), and 75th (large effect) percentiles corresponded to Pearson's *r* values of 0.07, 0.15, and 0.29, respectively (see Table 3 and Figure S3). These estimates are lower than the median estimate of 0.19 observed in individual differences research[48] and the median estimate for social psychology ($r = 0.24$).[51] Additionally, we examined the effect sizes descriptively by five domains. The results revealed differential patterns, with early life ($r = 0.11$) and psychosocial ($r = 0.12$) domains exhibiting the lowest median effect sizes, and the environmental domain ($r = 0.24$) showing the largest median effect size (see Figure S4 for distribution of effect sizes across domain). However, due to the substantial variation in the number of effect sizes available for percentile estimates across domains (ranging from 4896.1 to 231,193.0[d]), these differences in median effect sizes should be interpreted with caution. As a result, we employed the pooled median effect size ($r = 0.15$) as our criterion for the additional inclusion of cognitive predictors derived from phenotypic associations.

The analysis of age information in the meta-meta-analysis sample further illuminates the underrepresentation of established and middle adulthood. Among the 60.2% of the studies that provided age information, low percentages focused exclusively on the age ranges of 30–45 (6.3%) and 45–65 (5.5%). In contrast, childhood to adolescent (age 0–18), young adulthood (age 18–30), and older adulthood

[d] Averaged number of effect sizes across permutation

TABLE 3 Effect size benchmark with observed correlations from meta-meta-analyses

	Domain					
Percentile	Overall mean (SD)	EarlyLife	Environment	Lifestyle	Psychosocial	Socioeconomic
0%	0 (0.000)	0 (0.000)	0.003 (0)	0 (0)	0 (0)	0 (0)
25%	0.07 (0.000)	0.04 (0.001)	0.119 (0.002)	0.07 (0.001)	0.07 (0)	0.083 (0.003)
50%	0.15 (0.001)	0.11 (0.000)	0.24 (0.001)	0.189 (0.003)	0.12 (0)	0.19 (0.002)
75%	0.29 (0.000)	0.195 (0.012)	0.44 (0.001)	0.388 (0.008)	0.201 (0.003)	0.297 (0.004)
100%	0.982 (0.023)	0.66 (0.001)	0.69 (0)	0.877 (0)	0.976 (0.036)	0.74 (0)
Neffect Mean (SD)	62285	5791.7 (70.6)	4896.1 (67.2)	11004.8 (97.7)	23193 (119.3)	17335 (110.9)
Median N	164.8 (3.5)	118.6 (1.4)	302.9 (1.5)	37.1 (1.3)	188.4 (2.2)	448.8 (13)

Notes: Mean and SD stands for average and standard deviation of percentile estimates across 1000 permutations. Neffect = number of effect sizes. Median *N* = median sample sizes. We divided the modifiable variables into five categories: (1) early life factors (e.g., breastfed as a baby; two meta-analyses), (2) local environment (e.g., lead exposure; two meta-analyses), (3) lifestyle (e.g., exercise; four meta-analyses), (4) psychosocial factors (e.g., well-being; six meta-analyses), and (5) socioeconomic status (e.g., household income; four meta-analyses).
Abbreviation: SD, standard deviation.

(age 65+) received larger shares of attention, accounting for 13.5%, 19.8%, and 15.3% of the studies, respectively[e]. These findings underscore the notable paucity of research addressing the periods between the extensively studied life stages, specifically established and middle adulthood. The empirical evidence presented here reinforces the urgent need for increased scholarly attention to these critical yet understudied periods of human development within the field of cognitive research. More descriptions on the meta-meta-analysis can be found in the supplementary material and Figures S3–S5.

3.3 | Co-twin control

Co-twin control analyses were conducted on a total of 606 individual twins, with results detailed in Table 4 and Table S5. Each identified correlate was evaluated independently for FISQ and PIQ, respectively. To enhance interpretability, we reported the standardized coefficients for each model.[56] It is important to note that that in multilevel modeling, the total variance is partitioned into multiple sources of variation (i.e., within- and between-twin part[54]), allowing for interpretation of the predictor's effect on the outcome at both between- and within- person level (i.e., how much differences in EA within twin pairs explained the differences in FSIQ within pair[57]).

After adjusting for GMV and cognitive scores at age 16, EA, cognitive complexity, and purpose-in-life displayed small, positive associations with FSIQ scores at the between-pair level (βs = 0.061~0.112). Energetic tendency was negatively associated with FSIQ (β = −0.068, 95%CI = [−0.121, −0.013]). At the within-pair level, we detected no significant interactions across zygosity, indicating consistent effects across MZ and DZ twins. Within-twin pair effects of cognitive complexity significantly associated with FSIQ (β = 0.061, 95%CI = [0.014, 0.104]), corresponding to 0.061 SD increase in FSIQ per one standard unit increase in cognitive complexity. Moreover, those with a higher purpose-in-life also tended to have higher FSIQ scores (β = 0.069, 95%CI = [0.023, 0.112])[f]. It is worth noting that zygosity[g] had a moderate effect on moderating the association between cognitive complexity and FSIQ between pair (β = −0.288); however, the estimate is highly uncertain (95% credible interval = [−0.917, 0.111]).

Regarding PIQ, twins with higher family-level cognitive complexity and EA tended to show higher PIQ scores (βs = 0.141, 0.135, respectively). Specifically, we found significant within-twin pair effect for cognitive complexity (β = 0.065, 95%CI = [0.020, 0.109]) but not for EA (β = 0.026, 95%CI = [−0.015, 0.063]). Current smokers tend to perform less well on PIQ, such that, for twin pairs where both members quit smoking, we projected the PIQ to increase by 0.578 SD (95%CI = [−0.907, −0.255]). Furthermore, when considering the within-pair effect, a smoking sibling would score 0.489 SD (95%CI = [−0.949, −0.058]) lower than a non-smoking co-twin.

Based on our empirically derived effect size benchmark (r = 0.15), we additionally included three predictors for both PIQ and FSIQ (i.e., waist-to-hip ratio, personal growth, and financial difficulty), and three predictors uniquely for FSIQ (i.e., reading-for-fun, moderate MET minutes, and openness-idea) in the co-twin control analyses (see Table S6 for details). At the between-pair level, we observed null associations except for waist-to-hip ratio and FSIQ (β = −0.092, 95%CI = [−0.153, −0.031]), indicating that those with a lower waist-to-hip ratio also tend to have higher FSIQ scores, but this was not confirmed within-pairs comparing each sibling to another, suggesting familial confounding may underlie the association. At the within-pair level, a small and significant within-twin pair effect for financial difficulties on PIQ was observed (β = −0.051, 95%CI = [−0.090, −0.007], unstandardized β = −2.688 [−4.076, −1.138]), suggesting the twin with higher financial difficulties performed worse on the PIQ test. Furthermore, significant differences were found in the within-pair effect of financial difficulty between MZ and DZ twins (β = 0.451, 95%CI = [0.119, 0.870], unstandardized β = 3.111[0.816, 5.432]). This finding indicates the presence of

[e] Studies that focused on an exclusive life stage accounted for 60.4% of studies that reported age information.

[f] Standardized coefficients were standardized relative to within- or between- level variance. Within-level estimate was within-person standardized effect.

[g] Zygosity was coded with DZ twin as reference group (1 = MZ, 0 = DZ).

TABLE 4 Within- and between-twin pair effect on cognitive functioning (controlling for age 16 cognitive functioning)

	Standardized β [95% credible interval], $N = 606$		
Parameter	**Between-pair**	**Within-pair**	**Zyg x within-pair**
FSIQ			
Activity[a]	**−0.068 [−0.121, −0.013]**	0.018 [−0.027, 0.059]	0.046 [−0.207, 0.314]
Aesthetic[a]	0.035 [−0.019, 0.091]	0.033 [−0.013, 0.076]	−0.062 [−0.638, 0.321]
Cogcx[a]	**0.108 [0.049, 0.167]**	**0.061 [0.014, 0.104]**	−0.288 [−0.917, 0.111]
EA[a]	**0.112 [0.044, 0.180]**	0.037 [−0.003, 0.072]	−0.207 [−0.878, 0.217]
Purpose[a]	**0.061 [0.005, 0.116]**	**0.069 [0.023, 0.112]**	−0.159 [−0.830, 0.273]
Reflection[a]	0.047 [−0.009, 0.102]	0.026 [−0.018, 0.068]	0.128 [−0.162, 0.528]
Worry[a]	0.005 [−0.055, 0.064]	−0.035 [−0.081, 0.010]	0.15 [−0.248, 0.661]
PIQ			
Aesthetic[a]	0.028 [−0.041, 0.100]	0.025 [−0.021, 0.069]	−0.151 [−0.526, 0.133]
Cogcx[a]	**0.141 [0.065, 0.219]**	**0.065 [0.020, 0.109]**	−0.14 [−0.768, 0.232]
EA[a]	**0.135 [0.052, 0.219]**	0.026 [−0.015, 0.063]	−0.202 [−0.874, 0.237]
Smoke[b]	**−0.578 [−0.907, −0.255]**	**−0.489 [−0.949, −0.058]**	0.141 [−1.670, 1.656]

Notes: Results from Bayesian multilevel models. The between-pair component reflects the effects that are common to a twin pair. The within-twin component reflects the estimates of each key variable on cognitive function within each twin pair. A zygosity by within-twin (MZ = 1) pair random effect was included to examine whether the effects differed significantly across MZ and DZ twins. A significant negative within-twin pair zygosity interaction term reflects that the within-pair effect was stronger within DZ twins compared with MZ twins, consistent with some influence of genetic confounding. Bolding indicates significance.

Abbreviations: Cogcx, cognitive complexity; DZ, dizygotic; EA, educational attainment; FSIQ, full-scale IQ; GMV, gray matter volume; MZ, monozygotic; PIQ, performance IQ.

[a]Standardized using the variances of the predictor and outcome variables.

[b]Standardized using the variances of the continuous outcome variables, since a standard deviation change of a binary variable is not meaningful.

genetic influences on the association between financial difficulty and PIQ, which could also imply a gene-environment interaction, where the shared environment interacts with genetic factors to influence PIQ. The between-pair effect was similar in direction to the within-pair main effect but was not statistically significant. However, given the wide confidence interval, the overall findings regarding the relationship between financial difficulty and PIQ remain somewhat ambiguous and warrant further investigation.

4 | DISCUSSION

The present study investigated the relationship between diverse factors and cognitive functioning in a large, genetically informative sample of established adults at the cusp of midlife. Using cross-validated regularization models, we identified eight robust cognitive correlates from 59 indicators: EA, cognitive complexity, aesthetic appreciation, self-reflection, purpose-in-life, energetic tendency, worry, and smoking status. Additionally, using an empirically derived effect size benchmark, we included six more candidates: waist-to-hip ratio, personal growth, financial difficulty, reading-for-fun, moderate MET minutes, and openness-idea facet. We observed within-pair effect across both FSIQ (e.g., cognitive complexity, purpose-in-life) and PIQ (e.g., cognitive complexity, smoking status, financial difficulty). These effects did not differ significantly between MZs and DZs, with the exception of financial difficulty, suggesting genetic mediation of the association between financial difficulty and cognition. Conversely, while EA showed between-pair associations with both PIQ and FSIQ, limited evidence of within-pair effects across MZ and DZs is suggestive of genetic and familial confounding.

Growing evidence suggests that dementia and Alzheimer's Disease processes begin decades before clinical onset,[3,4] with modifiable lifestyle and psychosocial factors potentially acting as early antecedents.[5,19,22] Furthermore, these factors exert their influence at different times in the life course,[3,6] highlighting the importance of early intervention strategies. Established adulthood, with its unique challenges regarding work-life balance, identity maintenance, and value systems, presents a crucial window for dementia prevention. Additionally, this period post challenge on maintaining protective lifestyles and taking on risky behaviors,[22] and this period coincides with the peak stability of psychosocial traits,[17,18] facilitating their role in early identification and treatment planning.[18]

Our findings align with previous research on the links between cognitive functioning and EA,[15] smoking,[21] and psychosocial factors such as negative affect[18] (worry). However, we also identified novel correlates, including self-report cognitive complexity, aesthetic appreciation, purpose in life, self-reflection, and energetic tendency, which also emerged as significant independent correlates. Notably, the robust association between cognitive complexity and cognitive functioning, potentially representing the relationship between cognitive flexibil-

ity and engagement with aspects of cognition and dementia,[18,58] represents a novel contribution to the literature.

Recognizing the potential limitations of the elastic net method in handling causal relationships and the possibility of underestimating the importance of more distal variables, we employed an empirically derived effect size benchmark to guide the inclusion of additional variables. Among the additionally included candidates, we observed a small within-pair effect of financial difficulties on FSIQ, which differs significantly across zygosity. These differences between zygosity suggest the presence of genetic influences on the association between financial difficulty and PIQ, which could also imply a gene-(shared) environment interaction. More genetically related individuals respond to the environment in a similar manner, but less genetically related individuals respond differently such that individuals with certain genetically influenced traits are more susceptible to exposure to experiencing financial difficulties. These findings align with past literature, suggesting that genetic influences mediate the association between financial outcomes and cognitive functioning, and the potential existence of gene-environment interaction as the underlying process.[59]

We additionally included moderate MET minutes as a candidate predictor of cognition, and our analysis did not find significant between- or within- pair association between moderate MET minutes and cognition. A recent umbrella review on the effect of physical exercise on cognition found that, after controlling for moderators and correcting for publication bias, the association between physical exercise and cognition was negligible.[16] However, it is important to note that this finding does not necessarily imply an absence of cognitive and brain benefits associated with regular physical exercise. Instead, the effect may be inconclusive due to the heterogeneity observed across individuals, suggesting that the relationship between physical exercise and cognitive function may vary depending on individual characteristics and circumstances.

The use of co-twin control design in our study offers a robust approach to account for shared genetic and early-life environmental factors known to influence variability in cognitive functioning, lifestyle factors, and psychosocial factors.[26,27] The within-pair associations observed for smoking, cognitive complexity, and purpose-in-life with cognitive function, even after controlling for brain status, age, sex, and earlier cognitive functioning, support recommendations to incorporate these measures into clinical screening or diagnosis.[17] These significant within-pair effects suggested that part of the association is accounted for by individual factors varied across members of a twin pair, partially consistent with a causal process. Additionally, although we observed a significant phenotypic association between aesthetic appreciation, self-reflection, worry and cognitive functioning, we did not observe these effects at between-pair level. This finding may be the result of reduced precision in the twin subsamples.

In summary, our findings suggest that diverse factors beyond traditional assessments contribute to cognitive functioning at the cusp of midlife. Our findings additionally underscore the potential of established adulthood as a crucial window for dementia prevention interventions targeting modifiable lifestyle and psychosocial factors. Future research should explore the underlying mechanisms of these associations and develop targeted interventions tailored to these factors and provide further insights into dementia prevention strategies.

4.1 | Limitations

Our study has several limitations. First, our sample predominantly comprises White, non-Hispanic participants from the United States, which could limit the generalizability of our findings beyond this demographic and cultural context. Follow-up studies should replicate these findings across diverse population and cultural settings. Second, our co-twin control design reduced confounding from shared familial and genetic factors, but it does not warrant causal interpretation as unmeasured non-shared environmental factors can still represent confounding factors capable of creating spurious correlations.[29,60] Third, we did not include certain relevant variables like occupational complexity[12,24] and childhood socioeconomic status,[24] nor did we incorporate more fine-grained assessments of relevant constructs, such as social support and resources.[5] Relatedly, while this study provided insights into the changes in cognitive performance from age 16 to cusp of midlife, earlier factors (e.g., neonatal factors) could play a role in shaping some of the measures we studied, which could, in turn, impact the cognitive functioning we observed during established adulthood. Future study might benefit from incorporating earlier developmental measures to offer a more comprehensive understanding of cognitive functioning during established adulthood. Nevertheless, our study did explore an extensive range of variables from different domains to deepen understanding of cognitive functioning during established adulthood. Future replication with larger, diverse samples is crucial for validating and expanding upon our findings.

5 | CONCLUSION

Our findings suggest significant unique associations of cognitive complexity, purpose-in-life, and smoking status with cognitive functioning during established adulthood. Leveraging the strength of co-twin control analyses, these associations persist after accounting for environmental and partial genetic predispositions common to families. Nonetheless, we note the potential for genetic confounding when extrapolating these findings to the broader population. Given the dynamic challenges and distinct experiences that established adults endure, it is of pivotal importance to continue identifying factors that contribute to cognitive functioning during this period.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

Written informed consent was obtained from all participants.

ORCID

Anqing Zheng https://orcid.org/0000-0003-0238-8275

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Additional supporting information can be found online in the Supporting Information section at the end of this article.

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