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ORIGINAL RESEARCH

CARDIOVASCULAR DISEASE AND STROKE

Sex Differences in the Association Between Vascular Risk Factors and Cognitive Decline

A UK Biobank Study

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ABSTRACT

BACKGROUND Age-related cognitive decline is accelerated by vascular risk factors for cerebral small vessel disease. However, the association of vascular risk factors with cerebral small vessel disease contributing to the sex differences in cognitive decline remains unclear.

OBJECTIVES The purpose of this study was to evaluate sex differences in cognitive decline and the association between vascular risk factors and cognitive decline by sex.

METHODS We used data from the UK Biobank (>55 years of age; n = 19,067) to assess cognitive tests (executive function, processing speed, and memory) while adjusting for baseline measurements to examine how vascular risk factors affect cognition. A univariate regression analysis was used to assess sex differences at the first time point (2014). A repeated measure analysis with a mixed effect model was used to determine cognitive decline (between 2014 and 2019). Any significant interaction between vascular risk factors and sex was investigated.

RESULTS Females had lower scores in all 3 domains at the first cognitive tests (2014). We found a significant sex-by-time interaction over a 5-year period in matrix pattern completion ($P = 0.03$). After adjusting for vascular risk factors, this interaction was reduced ($P = 0.08$). High low-density lipoprotein, low education, and high blood pressure had a greater effect on the rate of cognitive decline in the executive function for females compared to males for the sex*vascular risk factor interaction ($P < 0.05$).

CONCLUSIONS The rate of cognitive decline did not differ significantly between males and females. However, the impact of several vascular risk factors on cognitive decline was greater in females than in males.

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CSVD = cerebral small vessel disease

HDL = high-density lipoprotein

LDL = low-density lipoprotein

WHR = waist-to-hip ratio

Cognitive decline is common in the aging population.[1,2] On average, older adults have lower episodic memory, lower executive function, and slower processing speed, compared to healthy young adults.[3] Interestingly, recent studies suggest that there are sex differences in the rate of age-related cognitive decline,[4] with females showing a faster decline in global cognition and executive function. However, little is known about the underlying mechanisms for this sex difference. One possible mechanism for the observed sex differences in the rate of cognitive decline with age is the presence of vascular risk factors associated with the incidence of cerebral small vessel disease (CSVD).

CSVD is a microvascular brain disease that is a leading cause of stroke and vascular dementia.[5-7] It frequently manifests as cognitive impairment prior to stroke and dementia.[8-10] CSVD-related cognitive impairment can exhibit a distinct pattern with early involvement in domains such as executive function, processing speed, and memory function.[11] Other than age, female sex and high blood pressure are important risk factors for the development of CSVD.[12] Vascular risk factors that are strong contributors to CSVD, such as diabetes, hypertension, and obesity in early adulthood can affect the rate of cognitive decline in older age,[8,9] may have a different magnitude of effect in males and females for cognitive outcomes. Thus, accounting for such vascular risk factors is important to studying sex differences in cognitive decline.[13]

Cognitive testing is the most common and widely accepted method of determining the degree of cognitive impairment.[14,15] Three cognitive domains: executive function, memory, and processing speed have been related to CSVD. Therefore, the present study aims to evaluate sex differences in these cognitive domains (in 2014) and compare the rate of cognitive decline during 5 years (2014 and 2019) using longitudinal data from the UK Biobank. Furthermore, we aim to determine the association between vascular risk factors involved in the pathogenesis of CSVD and cognitive decline in both sexes. We hypothesize that females will show a steeper decline in processing speed, memory, and executive functions and that vascular risk factors will be associated with cognitive decline in females more so than in males.

METHODOLOGY

Ethics approval and consent to participate: UK Biobank has obtained Research Tissue Bank approval from its governing Research Ethics Committee, as recommended by the National Research Ethics Service. This research has been conducted using the UK Biobank Resource (application 45551). Permission to use the UK Biobank Resource was approved by the access subcommittee of the UK Biobank Board. Written informed consent was obtained for all participants electronically.

PARTICIPANTS. We used data from the UK Biobank, a prospective cohort study with data from over 500,000 participants aged 40 to 69 years at baseline who were recruited between 2006 and 2010 in 22 centers across the United Kingdom.[16] The UK Biobank has extensive information on participants' lifestyle, environment, medical history, and physical measures, along with biological samples. In the current study, we focused on participants who completed web-based cognitive testing in both 2014 and at the 5-year follow-up (2019).[16] Of note, the follow-up for 2019 had a lower number of participants because of delays in follow-up due to COVID-19.

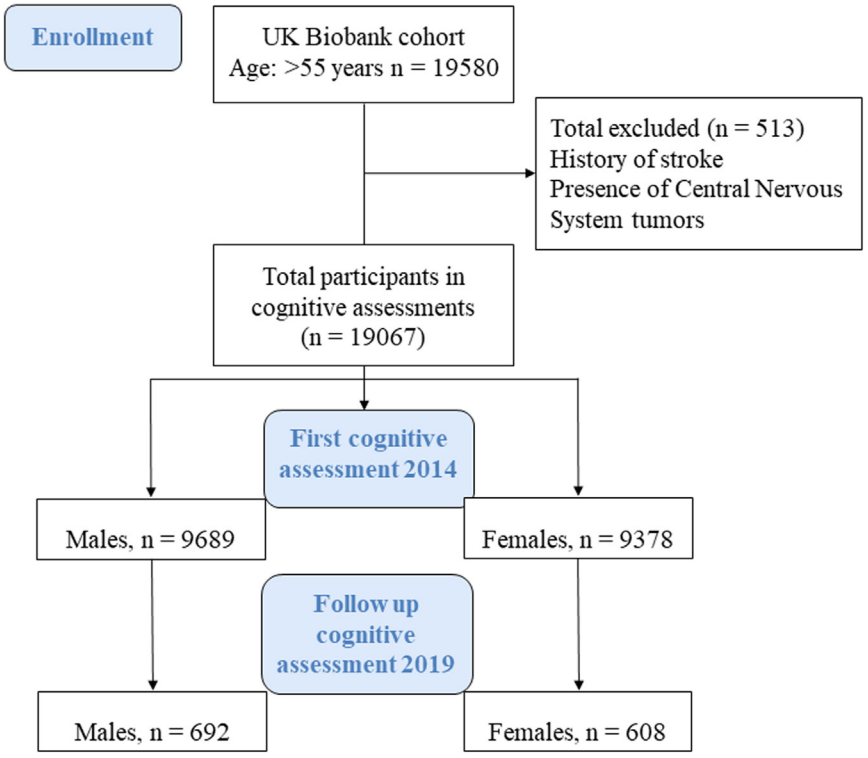
Inclusion criteria for the current study were the following: absence of a diagnosis of dementia and no history of neurological disease (ie, tumors, stroke). In addition, all participants included in our analyses were aged 55 years old or older to minimize the possible impact of menopause in females on performance in the first cognitive assessment (**Figure 1**).[17]

COGNITIVE FUNCTION ASSESSMENTS. We devised a three-step process for selecting cognitive assessments associated with CSVD. In the first step, we listed all the cognitive tests used in the UK Biobank cohort (Supplemental Table 1). Next, through a literature review, we identified cognitive function tests that have been reported to measure decline related to CSVD.[18] Finally, we selected tests that have been validated for CSVD based on the literature review and availability of cognitive in the UK Biobank. Decreases in processing speed, executive functioning, and aspects of working memory performance, which mainly affect retrieval and encoding rather than retention, are cognitive changes associated with CSVD.[19]

To evaluate executive function, we used the following tasks: trail making, fluid intelligence, matrix pattern completion, symbol digit substitution, and tower rearrangement picture. For memory, we assessed numeric and prospective memory, as well as pairs matching. For processing speed, we assessed reaction time (Supplemental Table 2).

VASCULAR RISK FACTORS. We considered the following vascular risk factors in our analyses as they are related to CSVD and available: age, blood pressure (systolic and diastolic), smoking status and intensity,

FIGURE 1 Flowchart of Study Participants



alcohol consumption, diabetes, adiposity (via body mass index [BMI]), waist-to-hip ratio (WHR), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and education level.

Blood pressure was measured using the Omron HEM-7015IT digital blood pressure monitor by taking the mean of 2 sitting measurements and was used as a continuous variable. Smoking was self-reported and was categorized into 3 groups: never smoked, smoked occasionally, and smoked on most/all days. Alcohol intake was also self-reported and was categorized based on consumption as: never consumed, previous consumer, and current consumer. Diabetes was both based on hospital admission data and self-reported. BMI was calculated as the weight of the individual in kilograms, measured using the Tania BC-418 MA body composition analyzer, divided by the square of the individual's height in meters. We used the waist and hip circumference ratio, with both measurements taken with the Wessex non-stretchable sprung tape measure. Both BMI and WHR were used a continuous variable. Education level was categorized into 4 levels, ranging from no secondary education to an American education equivalent (Supplemental Table 3).[20] Glycosylated hemoglobin measured using high-performance liquid chromatography, and blood lipids (HDL and LDL cholesterol) were obtained from biological samples.

STATISTICAL ANALYSES. To compare baseline demographics and covariates, descriptive analyses were performed. Continuous variables are presented as the mean ± SD or median (IQR), as appropriate. Dichotomous variables are presented as percentages and were compared by using chi-square (or Fisher exact) testing. The covariates included sex, age, BMI, smoking, alcohol, WHR, diabetes, blood pressure, LDL, HDL, and education level measured at baseline. The risk factors were specifically chosen because they are strongly associated with cognitive decline.[21-25]

To assess sex differences in executive function, memory, and processing speed domains at first time point (2014), we performed univariate regression analysis. To evaluate any difference in cognitive function across the 2 cognitive assessment time points (2014 and 2019), we repeated the measure analysis using a mixed effect model which accounts for the repeated nature of the continuous measurements which models time categorically rather than continuously.[26] Moreover, regardless of whether an

TABLE 1 Measurements of Vascular Risk Factors Relating to Cerebral Small Vessel Disease at Baseline

	Males (n = 9,689)	Females (n = 9,378)	*P* Value
Age (y)	61.5 ± 3.6	60.9 ± 3.5	<0.0001
Systolic BP, mm Hg	146.8 ± 18.8	143.8 ± 20.8	<0.0001
Diastolic BP, mm Hg	79.6 ± 10.4	77.1 ± 10.7	<0.0001
Diabetes	432 (4.5%)	187 (2.0%)	<0.0001
Glycated Hb (HbA1c), mmoL/mol	35.9 ± 5.6	35.9 ± 4.4	0.92
HDL cholesterol, mg/dL	1.3 ± 0.3	1.7 ± 0.4	<0.0001
LDL cholesterol, mg/dL	3.5 ± 0.8	3.8 ± 0.8	<0.0001
Ever smoked	6,249 (64.5%)	5,239 (56.0%)	<0.0001
Alcohol intake status			<0.0001
Never	147 (1.5%)	331 (3.5%)	
Previous	205 (2.1%)	203 (2.2%)	
Current	9,333 (96.4%)	8,843 (94.3%)	
Waist-to-hip ratio	0.9 ± 0.1	0.8 ± 0.1	<0.0001
BMI, kg/m^2	27.1 ± 3.6	26.2 ± 4.3	<0.0001
Education			<0.0001
Category 0[a]	1,948 (20.4%)	1,520 (16.5%)	
Category 1[b]	1,557 (16.3%)	2,111 (22.8%)	
Category 2[c]	947 (10.2%)	1,127 (12.2%)	
Category 3[d]	5,055 (53.0%)	4,479 (48.5%)	

Values are mean ± SD or n (%). [a]Education 0 = None of the above| NVQ (National Vocational Qualification) or HND (Higher National Diploma) or HNC (Higher National Certificates) or equivalent |CSEs (Certificate of Secondary Education) or equivalent. [b]1 = O levels/GCSEs (General Certificate of Secondary Education) or equivalent. [c]2 = A levels/AS levels or equivalent. [d]3 = College or university degree |Other professional qualifications, for example: nursing, teaching.

BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

individual has complete data or not, all outcome data are used.

To determine whether the impact of vascular risk factors differed by sex, we also conducted 2-way individual vascular risk factors-by-sex interactions. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute, Inc), with 2-tailed tests for statistical significance at an $\alpha = 0.05$. Bonferroni correction was applied for multiple comparisons where applicable.

RESULTS

After applying the baseline exclusion criteria, we had 9,378 females who completed the first cognitive assessment (2014) and 608 who returned for follow-up (2019), while there were 9,689 males who completed the first cognitive assessment (2014) and 692 who returned for follow-up (2019) (Figure 1). Comparing the demographics and covariates at baseline (2006-2010), the mean age of females and males was similar (60.9 and 61.5 years, respectively). Males had a higher prevalence of vascular risk factors (Table 1). For instance, diabetes was almost twice as prevalent in males. Results for comparison of demographics and covariates between males and females at 2014 and 2019 follow-up provided in Supplemental Table 4.

COGNITIVE FUNCTION AT FIRST ASSESSMENT. To examine sex differences at first cognitive assessment for executive function, memory, and processing speed domains, univariate analyses demonstrated that females (n = 9,378) had lower scores in all 3 domains, that is, executive function, memory, and processing speed, than males (Table 2). For example, females had a lower number of puzzles correctly

TABLE 2 Sex Differences in Cognitive Function Tests First Time Point (2014)

Cognitive Domain	Cognitive Test Type	Cognitive Test Definition (Units)	Males (n = 9,689)	Females (n = 9,378)	*P* Value[a]
Executive function	Fluid intelligence	Fluid intelligence score (out of 13)	6.7 (2.1)	6.4 (2.0)	<0.0001
	Trail making	Duration to complete numeric path, trail #1 (deciseconds)	250.8 (90.8)	245.5 (101.9)	0.07
		Duration to complete alphanumeric path, trail #2 (deciseconds)	648.0 (289.2)	646.9 (294.9)	1.00
		Total errors traversing numeric path, trail #1 (out of 8)	1.3 (3.9)	1.7 (4.1)	<0.0001
		Total errors traversing alphanumeric path, trail #2 (out of 10)	2.0 (5.0)	2.4 (5.4)	<0.0001
	Matrix pattern completion	Number of puzzles correctly solved (out of 15)	7.7 (2.0)	7.4 (2.1)	<0.0001
	Tower rearranging	Number of puzzles correct (out of 18)	9.6 (3.2)	9.0 (3.1)	<0.0001
	Symbol digit substitution	Number of symbol digit matches made correctly (out of 37)	17.0 (4.8)	16.9 (5.0)	1.00
	Pairs matching	Number of correct matches in round test 1 (out of 8)	5.9 (0.9)	5.9 (0.9)	1.00
		Number of correct matches in round test 2 (out of 8)	4.0 (4.0)	4.0 (4.0)	1.00
		Time to complete round test 1 (deciseconds)	322.2 (138.4)	318.7 (133.5)	1.00
		Time to complete round test 2 (deciseconds)	468.5 (174.9)	464.2 (164.8)	1.00
Memory	Numeric memory	Maximum digits remembered correctly (out of 11)	6.8 (1.3)	6.5 (1.2)	<0.0001
		Time to complete the test (deciseconds)	1,369.5 (403.5)	1,348.5 (398.4)	0.09
	Prospective memory	Prospective memory result n (%)	7,226 (80.38)	6,848 (80.26)	<0.0001
		Duration screen displayed (deciseconds)	119.2 (179.0)	114.3 (182.4)	1.00
Processing Speed	Reaction time	Mean time to correctly identify matches (milliseconds)	608.8 (112.5)	631.9 (112.2)	<0.0001

Values are n (%). [a]*P* values corrected for multiple comparisons (Bonferroni correction).

TABLE 3 Univariate Analysis of Sex Differences in Cognitive Decline Over a Period of 5 Years (2014-2019)

Cognitive Domain	Cognitive Test Type	Cognitive Test Definition (Units)	Estimate Difference (95% CI) Males (n = 9,689)	Females (n = 9,378)	*P* Value
Executive function	Fluid intelligence	Fluid intelligence score (out of 13)	−0.12 (−0.24 to 0.001)	0.014 (−0.12 to 0.14)	0.14
	Trail making	Duration to complete numeric path (deciseconds)	0.63 (−6.97 to 8.2)	5.49 (−2.59 to 13.57)	0.39
		Duration to complete alphanumeric path (deciseconds)	9.62 (−9.89 to 29.13)	2.70 (−18.11 to 23.52)	0.63
		Total errors traversing numeric path (out of 8)	0.06 (−0.07 to 0.18)	0.03 (−0.11 to 0.16)	0.72
		Total errors traversing alphanumeric path (out of 10)	−0.06 (−0.22 to 0.11)	−0.02 (−0.19 to 0.16)	0.74
	Matrix pattern completion	Number of puzzles correctly solved (out of 15)	0.2 (0.06-0.35)	−0.02 (−0.16 to 0.12)	0.03
	Tower rearranging	Number of puzzles correct (out of 18)	0.05 (−0.17 to 0.26)	0.31 (0.08-0.53)	0.10
	Symbol digit substitution	Number of symbol digit matches made correctly (out of 37)	0.02 (−0.30 to 0.33)	0.26 (−0.08 to 0.60)	0.31
Memory	Pairs matching	Number of correct matches in round test 1 (out of 8)	−0.13 (−0.21 to 0.06)	−0.04 (−0.11 to 0.04)	0.06
		Number of correct matches in round test 2 (out of 8)	0.54 (0.16-0.93)	0.44 (0.03-0.85)	0.71
		Time to complete round test 1 (deciseconds)	−9.61 (−19.53 to 0.31)	−3.02 (−13.51 to 7.47)	0.37
		Time to complete round test 2 (deciseconds)	−5.32 (−26.65 to 16.00)	27.78 (4.65-50.92)	0.04
	Numeric memory	Maximum digits remembered correctly (out of 11)	−0.05 (−0.13 to 0.04)	0.005 (−0.08 to 0.09)	0.47
		Time to complete the test (deciseconds)	−65.64 (−96.23 to −35.06)	−43.94 (−76.50 to −11.38)	0.34
	Prospective memory	Duration screen displayed (deciseconds)	4.37 (−8.79 to 17.53)	−6.49 (−20.52 to 7.54)	0.27
Processing speed	Reaction time	Mean time to correctly identify matches (milliseconds)	2.09 (−5.53 to 9.71)	12.13 (4.05-20.21)	0.07

Difference here is between the decline in females from 2014 to 2019 compared to males from 2014 to 2019 on cognitive test performances; *P* values for sex*time interaction.

solved for the matrix pattern completion test (executive function domain) at 7.4 ± 2.1 as compared to males 7.7 ± 2.0 ($P < 0.0001$), as well as a lower score for the maximum number of digits remembered for the numeric memory test (memory domain) 6.5 ± 1.2, compared to males 6.8 ± 1.3 ($P < 0.0001$). Similarly, for processing speed, females reported a higher reaction time 631.9 ± 112.2 deciseconds than males (608.8 ± 112.5 deciseconds; $P < 0.0001$). Even after controlling for vascular risk factors, sex differences in executive function, memory, and processing speed persisted, with females performing worse than males (Supplemental Table 5).

COGNITIVE DECLINE. When comparing the cognitive decline for executive function, memory, and

TABLE 4 Multivariable Analysis of Sex Differences in Cognitive Function Decline Over 5 Years (2014-2019)

Cognitive Domain	Cognitive Test Type	Cognitive Test Definition (Units)	Estimate Difference (95% CI) Males (n = 9,689)	Females (n = 9,378)	*P* Value
Executive function	Fluid intelligence	Fluid intelligence score (out of 13)	−0.09 (−0.23 to 0.05)	−0.03 (−0.18 to 0.12)	0.53
	Trail making	Duration to complete numeric path (deciseconds)	2.55 (−6.22 to 11.33)	1.36 (−7.89 to 10.61)	0.85
		Duration to complete alphanumeric path (deciseconds)	8.1 (−14.16 to 30.36)	−0.10 (−23.58 to 23.38)	0.62
		Total errors traversing numeric path (out of 8)	0.09 (−0.06 to 0.23)	−0.02 (−0.17 to 0.13)	0.33
		Total errors traversing alphanumeric path (out of 10)	0.04 (−0.16 to −0.23)	0.08 (−0.12 to 0.29)	0.74
	Matrix pattern completion	Number of puzzles correctly solved (out of 15)	0.6 (−0.09 to 0.22)	0.3 (0.10-0.43)	0.08
	Tower rearranging	Number of puzzles correct (out of 18)	0.12 (−0.12 to 0.37)	0.33 (0.07-0.59)	0.25
	Symbol digit substitution	Number of symbol digit matches made correctly (out of 37)	−0.16 (−0.52 to 0.21)	0.41 (0.02-0.79)	0.04
Memory	Pairs matching	Number of correct matches in round test 1 (out of 8)	−0.16 (−0.25 to 0.08)	−0.07 (−0.16 to 0.01)	0.13
		Number of correct matches in round test 2 (out of 8)	0.39 (−0.06 to 0.84)	0.52 (0.05-0.98)	0.70
		Time to complete round test 1 (deciseconds)	−7.04 (−18.55 to 4.47)	−6.94 (−19.04 to 5.16)	0.99
		Time to complete round test 2 (deciseconds)	−6.5 (−31.40 to 18.25)	10.68 (−14.93 to 36.29)	0.34
	Numeric memory	Maximum digits remembered correctly (out of 11)	−0.07 (−0.16 to 0.03)	0.02 (−0.08 to 0.12)	0.23
		Time to complete the test (deciseconds)	−68.73 (−103.73 to −33.72)	−60.19 (−97.21 to −23.17)	0.74
	Prospective memory	Duration screen displayed (deciseconds)	10.35 (−4.11 to 24.80)	−3.5 (−18.81 to 11.82)	0.20
Processing speed	Reaction time	Mean time to correctly identify matches (milliseconds)	7.55 (−1.17 to 16.27)	13.6 (4.41-22.80)	0.35

Difference here is between the decline in females from 2014 to 2019 compared to males from 2014 to 2019 on cognitive test performances; *P* values for sex*time interaction. Adjusted for age, blood pressure (systolic and diastolic), smoking status and intensity, alcohol consumption, diabetes, adiposity (via BMI), waist-to-hip ratio (WHR), LDL, HDL, and education level.

Abbreviation as in Table 3.

TABLE 5 Analysis of Interactions Between Sex and Each Individual Vascular Risk Factor From the First Cognitive Assessment (2014) to Follow-Up Cognitive Assessment (2019) (N = 19,067; Males [n = 9,689]; Females [n = 9,378])

Cognitive Domain	Cognitive Test Type	Vascular Risk Factor	Estimate Difference From 2014 to 2019 (95% CI)	*P* Value
Executive function	Fluid intelligence score	BMI	0.021 (0.006-0.04)	0.007
		Waist-to-hip ratio	1.53 (0.57-2.49)	0.002
		SBP	−0.002 (−0.006 to 0.001)	0.21
		DBP	−0.006 (−0.02 to 0.0007)	0.08
		LDL	−0.09 (−0.17 to −0.02)	0.02
		HDL	−0.02 (−0.21 to 0.17)	0.85
		Age	−0.004 (−0.02 to 0.01)	0.67
		HbA1c	0.005 (−0.007 to 0.02)	0.40
		Education	−0.17 (−0.29 to −005)	0.004
	Matrix pattern completion	BMI	0.01 (−0.006 to 0.03)	0.18
		Waist-to-hip ratio	1.26 (0.08-2.44)	0.04
		SBP	−0.003 (−0.007 to 0.002)	0.21
		DBP	−0.003 (−0.01 to 0.005)	0.44
		LDL	−0.12 (−0.21 to −0.03)	0.009
		HDL	0.03 (−0.20 to 0.26)	0.79
		Age	0.003 (−0.02 to 0.02)	0.77
		HbA1c	0.005 (−0.01 to 0.02)	0.56
		Education	−0.02 (−0.16 to −0.13)	0.82
	Symbol digit substitution	BMI	0.03 (−0.01 to 0.08)	0.17
		Waist-to-hip ratio	3.81 (0.99-6.63)	0.008
		SBP	−0.0072 (−0.02 to 0.003)	0.16
		DBP	−0.02 (−0.04 to −0.002)	0.03
		LDL	−0.32 (−54 to −0.10)	0.004
		HDL	−0.10 (−0.65 to 0.45)	0.72
		Age	0.85 (−0.05 to 0.05)	0.06
		HbA1c	−0.003 (−0.04 to 0.04)	0.88
		Education	0.82 (−1.17 to −0.47)	<0.001
	Trail making (numeric)	BMI	0.01 (−0.004 to 0.02)	0.15
		Waist-to-hip ratio	0.58 (−0.30 to 1.45)	0.20
		SBP	0.003 (−0.0006 to 0.006)	0.11
		DBP	0.004 (−0.002 to 0.01)	0.21
		LDL	0.04 (−0.03 to 0.10)	0.27
		HDL	−0.07 (−0.24 to 0.10)	0.41
		Age	0.003 (−0.01 to 0.02)	0.73
		HbA1c	−0.0003 (−0.01 to 0.01)	0.96
		Education	−0.14 (−0.25 to −0.03)	0.01
	Trail making (alphanumeric)	BMI	−0.0006 (−0.02 to 0.02)	0.95
		Waist-to-hip ratio	−0.59 (−1.83 to 0.65)	0.35
		SBP	0.002 (−0.002 to 0.007)	0.35
		DBP	0.0009 (−0.007 to 0.009)	0.83
		LDL	0.02 (−0.08 to 0.11)	0.71
		HDL	−0.03 (−0.27 to 0.21)	0.82
		Age	0.003 (−0.02 to 0.02)	0.79
		HbA1c	−0.01 (−0.03 to 00.4)	0.14
		Education	0.07 (−0.08 to 0.23)	0.35
	Tower rearranging	BMI	−0.01 (−0.04 to 0.02)	0.37
		Waist-to-hip ratio	0.55 (−1.26 to 2.36)	0.56
		SBP	−0.007 (−0.01 to −0.0001)	0.05
		DBP	−0.01 (−0.03 to −0.001)	0.03
		LDL	−0.17 (−0.31 to −0.03)	0.01
		HDL	0.007 (−0.35 to 0.36)	0.97
		Age	−0.03 (−0.06 to 0.0007)	0.05
		HbA1c	−0.02 (−0.05 to −0.0004)	0.05
		Education	−0.002 (−0.23 to 0.22)	0.99

Continued on the next page

processing speed domains between 2014 and 2019, there was only 1 test for the executive function domain: matrix pattern completion for females had a significantly steeper decline than males for female sex*time interaction ($P_{interaction}$ = 0.03) (Table 3). However, when adjusted for vascular risk factors, this difference was reduced (P = 0.08) (Table 4). There was no significant difference in cognitive decline between males and females in the memory and processing speed domains (Table 3).

SEX AND VASCULAR RISK FACTORS INTERACTIONS. The interaction of each vascular risk factor with sex showed that high LDL, low education, and high blood pressure levels (systolic and diastolic) were associated with worse cognitive outcomes over time (2014-2019) in females than in males ($P_{female\ sex*vascular\ risk\ interactions}$ for cognitive test outcomes <0.05) in executive function domain. Females had poorer score in fluid intelligence, symbol digit substitution, and trail making tests. However, there was no significance of individual risk factors in the memory and processing speed domains (Table 5, Central Illustration).

DISCUSSION

In the present study, we explored sex differences in the rate of cognitive decline for functions that have been associated with CSVD. Furthermore, we investigated the differences in the magnitude of the association between vascular risk factors and cognitive decline in males and females. We measured 3 major cognitive domains that are recognized as critical for daily, social, and occupational functioning and are associated with CSVD: executive function, memory, and processing speed.

Among the 19,067 individuals pooled from the UK Biobank cohort, at time 1 (2014), females (>55 years of age) had lower scores in all 3 domains (executive function, memory, and processing speed); however, we did not find any differences in the rate of decline over the 5-year period (2014-2019). Upon isolating each vascular risk factor by sex, we observed that higher BMI, education, and high blood pressure levels (systolic and diastolic) had a greater impact on executive function tasks in females compared to males over time.

Our findings are consistent with other studies that show sex differences in processing speed and short-term memory but not in the rate of decline over time.[27,28] For example, a 2016 study of older adults in Baltimore (average age: 64-70 years) found no sex differences in cognitive declines on 8 of 12 cognitive tests, including verbal learning and memory, object recognition and semantic retrieval, fluent language

production, processing speed, working memory and set-shifting, perceptuomotor speed, and executive function.[29] However, 1 limitation of the Baltimore study is that the analysis did not entirely account for age. Indeed, they performed their analyses using age averages within an age interval. In our study, we had similar aged males and females.

Moreover, our results replicate those by Levine et al (2021),[4] demonstrating that males and females were not significantly different in the rate of memory and processing speed decline. This study, however, found that females had a faster rate of decline in executive function than males, which is not in line with the results of the present study. This finding might be attributed to the authors not studying an age interval associated with the greatest risk of sex-related cognitive decline.[30] The faster cognitive decline observed in females could be ascribed to their greater risk of CSVD compared to males, which relates to biological factors like cardiac health, pulmonary hypertension, endothelial dysfunction, and age (females living longer than males), all of which could affect cognitive trajectories.[11,13,31] A study conducted on memory clinic patients with vascular brain damage demonstrated that small vessel damage was more prevalent in the female subgroup as opposed to large vessel damage, which was more present in the male subgroup.[32] Moreover, it is known that CSVD is the most important cause of vascular dementia, and it leads to a decline in cognitive functions.[7] Many studies have examined the relationship between CSVD and cognitive domains. For instance, it has been shown that CSVD was significantly associated with a decline in global cognition and executive function over 4 years in individuals with hypertension.[33]

In terms of vascular risk factors, both blood pressure and serum cholesterol have been reported to have been related to steeper cognitive decline with increasing age.[34] Moreover, some studies have suggested that females may be more vulnerable to the effects of vascular risk factors on cognition than males, especially in older age. For example, multiple studies have found that higher BMI and lower education are associated with global cognitive function to a greater extent in females relative to males.[13,35,36] In addition, females with higher blood pressure may have a higher risk of developing dementia and brain structural damage than their male counterparts with similar levels of blood pressure.[37]

Similarly, a study using data from the UK Biobank reported that high blood pressure had a stronger association with dementia in females than in males.[38] Another study using data from a population-based cohort found that females had a steeper cognitive decline than males in tests of memory and word fluency, but not in tests of psychomotor speed and mental set shifting.[39] These studies imply that there may be sex-specific mechanisms that mediate the influence of vascular risk factors on cognition. Therefore, the role of vascular risk factors in the association between sex and cognitive decline may depend on various factors such as age, type of cognitive test, and type of vascular risk factor. Our findings support the existing literature demonstrating that hypertension may have a greater impact on cognitive impairment in females than in males; at the very least, it worsens cognitive performance on standardized tasks.

In this study, we demonstrate that vascular risk factors can influence the trajectory of cognitive decline differently in males and females. The impact of various vascular risk factors, namely, WHR, BMI, blood pressure, LDL, and education, differed between males and females, with females having worse outcomes for most of the risk factors.

STUDY LIMITATIONS. While we were able to adjust for several vascular risk factors (age, blood pressure,

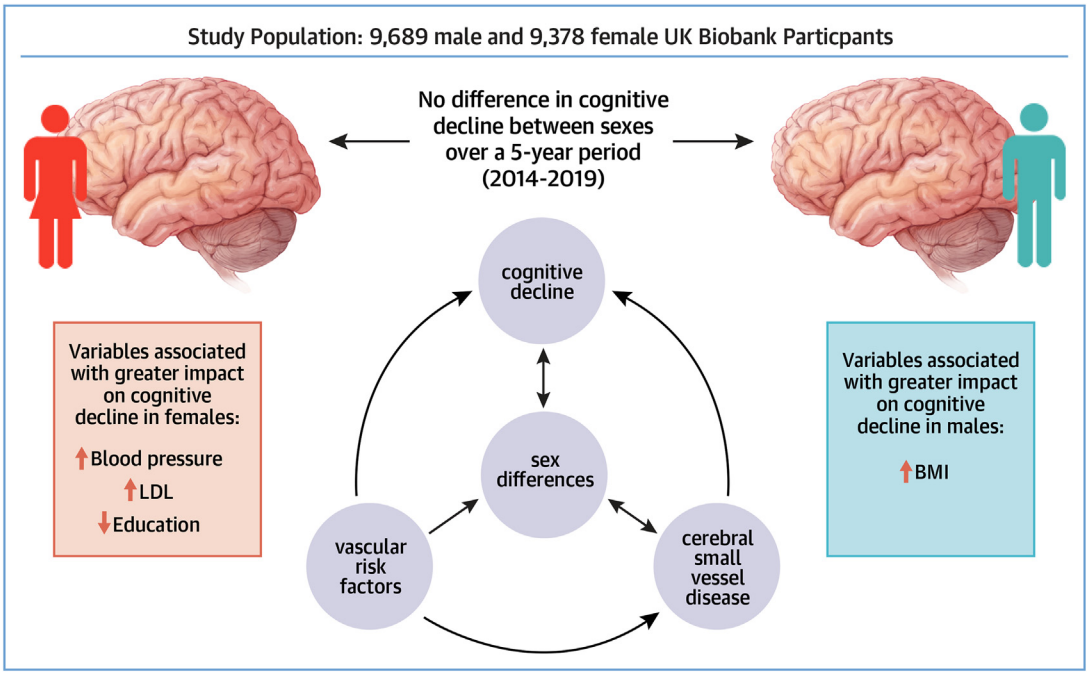
TABLE 5 Continued

Cognitive Domain	Cognitive Test Type	Vascular Risk Factor	Estimate Difference From 2014 to 2019 (95% CI)	*P* Value
Memory	Numeric memory	BMI	−0.003 (−0.01 to 0.009)	0.66
		Waist-to-hip ratio	0.45 (−0.26 to 1.16)	0.21
		SBP	−0.002 (−0.005 to 0.00005)	0.06
		DBP	−0.003 (−0.008 to 0.001)	0.15
		LDL	−0.05 (−0.10 to 0.009)	0.10
		HDL	−0.02 (−0.16 to 0.12)	0.80
		Age	−0.004 (−0.02 to 0.008)	0.51
		HbA1c	−0.002 (−0.01 to 0.007)	0.67
		Education	−0.07 (−0.16 to 0.01)	0.10
Processing speed	Reaction time	BMI	−0.21 (−1.03 to 0.61)	0.62
		Waist-to-hip ratio	−20.71 (−73.24 to 31.82)	0.44
		SBP	0.18 (0.0002-0.37)	0.05
		DBP	0.28 (−0.06 to 0.62)	0.11
		LDL	1.99 (−2.06 to 6.04)	0.34
		HDL	−2.88 (−13.36 to 7.6)	0.59
		Age	0.85 (−0.05 to 1.76)	0.07
		HbA1c	0.035 (−0.67 to 0.74)	0.92
		Education	3.91 (−2.67 to 10.50)	0.24

Difference here is between the decline in females from 2014 to 2019 compared to males from 2014 to 2019 on cognitive test performances; *P* values for sex*vascular risk factor interaction.

BMI = body mass index; BP = blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SBP = systolic blood pressure.

CENTRAL ILLUSTRATION **Sex Differences in the Impact of Vascular Risk Factors on Cognitive Decline**



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education, WHR, BMI, smoking, alcohol, and diabetes), we were unable to adjust for social determinants of health, except for education. Social determinants of health factors such as income, physical activity, and diet are well-known risk contributors to cognitive health. Moreover, we were only able to use risk factors reported at baseline (2006-2010) and not at the time of cognitive tests. Future studies could potentially perform sensitivity analyses while controlling for risk factors identified during the cognitive function test. Additionally, vascular risk factors that are self-reported, such as smoking, diabetes, and a history of stroke, may be subject to reporting bias. We were also unable to adjust for treatment of vascular risk factors. Although being important confounders, exploring the treatment of vascular risk factors is beyond the scope of this study. The population in our data set is relatively healthy, and college educated, whereas the data may not necessarily be representative of the general population. Nevertheless, we can observe sex differences in the relationship between vascular risk factors and cognitive decline even in this select healthy population. Another limitation is the loss of follow-up, with around 10% completing follow-up assessments in 2019. This could either reduce the precision of the estimate or distort the true association between sex and vascular risk factors for cognitive decline. Since the data collection for the UK Biobank is still ongoing,[40] future studies should be performed on a larger follow-up sample size. Lastly, the memory tasks in the UK Biobank assessed short-term memory. Therefore, in this study, we were unable to account for long-term memory, which is an important measure of cognitive health in the elderly population.[41] Finally, the average age of the cohort was 61 years at the time of the initial cognitive measurement. As a result, detection of cognitive decline might have been limited.

CONCLUSIONS

Overall, our study demonstrates that the rate of cognitive decline did not significantly differ between

males and females after controlling for vascular risk factors in all 3 cognitive domains: executive function, memory, and processing speed, over a period of 5 years. However, certain vascular risk factors, namely high blood pressure and LDL, as well as education, had stronger associations with cognitive decline in females relative to males. Understanding the biology and risk of sex differences in cognitive decline is critical not only for prevention but also for the development of personalized, sex-specific medicine.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The impact of several vascular risk factors such as blood pressure, LDL, and education was greater in females than in males.

COMPETENCY IN PATIENT CARE: Controlling vascular risk factors is critical for slowing cognitive decline, especially in females.

TRANSLATIONAL OUTLOOK 1: At the time of the initial cognitive assessment, the cohort's average age was 61 years. As a result, detection of cognitive decline may have been limited and would therefore benefit from a follow-up in an older population.

TRANSLATIONAL OUTLOOK 2: The rate of cognitive decline did not differ significantly between males and females over a 5-year period (2014-2019); however, we were limited by the number of participants during the 2019 follow-up as well as the cognitive function tests for long-term memory, an important measure of cognitive health in the elderly population. As a result, future studies might gain a better insight from a larger follow-up cohort and measures of long-term memory.

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KEY WORDS sex differences, cerebral small vessel disease, cognitive decline, vascular risk factors

APPENDIX For supplemental tables, please see the online version of this paper.