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BRIEF COMMUNICATION

Adults With Mild-to-Moderate Congenital Heart Disease Demonstrate Measurable Neurocognitive Deficits

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BACKGROUND: Neurocognitive impairment is a common complication of congenital heart disease (CHD) as well as acquired cardiovascular disease. Data are limited on neurocognitive function in adults with CHD (ACHD).

METHODS AND RESULTS: A total of 1020 individuals with mild-to-moderate ACHD and 497 987 individuals without ACHD from the volunteer-based UK Biobank study underwent neurocognitive tests for fluid intelligence, reaction time, numeric memory, symbol-digit substitution, and trail making at enrollment and follow-up. Performance scores were compared before and after exclusion of preexisting stroke or coronary artery disease as measures of cerebro- and cardiovascular disease. Individuals with ACHD had significantly poorer performance on alpha-numeric trail making, a measure of visual attention and cognitive flexibility, spending 6.4 seconds longer on alpha-numeric trail making (95% CI, 3.0–9.9 seconds, P=0.002) and 2.5 seconds longer on numeric trail making (95% CI, 0.5–4.6 seconds, P=0.034), a measure of visual attention and processing speed. The ACHD cohort had modestly lower performance on symbol-digit substitution, a measure of processing speed, with 0.9 fewer correct substitutions (95% CI, – 1.5 to – 0.2 substitutions, P=0.021). After excluding preexisting stroke or coronary artery disease, individuals with ACHD continued to show poorer performance in all 6 domains (P=NS).

CONCLUSIONS: Individuals with mild-to-moderate ACHD had poorer neurocognitive performance, most significantly in tests of cognitive flexibility, analogous to deficits in children with CHD. These differences appear to be driven by increased burden of cerebro- and cardiovascular disease among individuals with ACHD.

Key Words: adult congenital heart disease ■ cerebrovascular disease ■ cognitive deficits ■ cognitive dysfunction ■ cognitive impairment ■ coronary artery disease ■ neurocognitive

Neurocognitive differences and developmental delay are recognized complications of congenital heart disease (CHD), detectable in school-aged children with persistence into adolescence.[1-3] A diverse set of risk factors for neurocognitive deficits in children are well described, including perinatal risk factors, cyanosis, hypoperfusion, and perioperative complications that may manifest as impaired myelination and white-matter brain injury in up to 50% of neonates with repaired CHD.[4,5] The severity of neurological impairment is directly correlated with the complexity of CHD, with the most severe deficits observed in individuals with single ventricle defects.[6]

With increasing survivorship to adulthood, individuals with adult congenital heart disease (ACHD) have been observed to have an increased risk for depression, post-traumatic stress disorder, decreased quality of life, and neurodegenerative disease.[1,7] Previously, we have shown a substantially increased burden of cardiovascular risk and disease in a small subset of

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individuals with ACHD among a large British cohort study of volunteers.[8] While the deleterious effects of acquired cardiovascular disease on neurocognitive functioning in normal adults have previously been reported,[9,10] data on the neurocognitive effects in the ACHD population are minimal. Here we report the performance of individuals with mild-to-moderate ACHD on 6 neurocognitive tests and specifically examine the impact of acquired cardiovascular disease upon these outcomes.

METHODS

Study Population and Data Access

The study population was derived from the UK Biobank (UKB), which includes >502 000 middle- and older-aged volunteers from the general UK population who have undergone detailed phenotypic and functional assessments. All data from the UKB used in this study are available to qualified researchers from the UKB organization (https://www.ukbiobank.ac.uk/using-the-resource/) for a nominal application fee and all methods are available upon request from the authors. CHD was defined as any structural cardiac abnormality present in the heart or adjoining great vessels from birth in the absence of syndromic illness (ie, syndromes characterized by extracardiac or neurocognitive manifestations in addition to cardiac malformations). As previously described, we used a multistep classification algorithm derived from hospital encounter statistics and self-reported medical history at the time of enrollment in the UKB, to identify 1020 individuals with ACHD (excluding isolated aortic valve defects) and 497 983 non-ACHD comparison individuals.[8] A minority of individuals with ACHD (n = 96) were determined as having "complex" lesions associated with cyanosis (ie, single ventricle lesions). The remaining 924 individuals with ACHD represent mild-to-moderate lesions, most predominantly left-to-right shunt lesions.

Institutional Review Board Approval

The study of de-identified patient data was determined as exempt from oversight by the Stanford University Institutional Review Board. Informed consent was obtained at the time of enrollment by the UKB research organization. The study was performed using data from UKB applications 15860 and 13721.

Neurocognitive Domains

All UKB participants were invited to complete a set of novelly designed computer-based neurocognitive tests of fluid intelligence, reaction time, pairs matching, and numeric memory at enrollment. These tests have been previously described with demonstration of sufficient stability in all but pairs matching, which was excluded from this study.[11] Standardized tests of symbol-digit substitution (adapted from the Symbol Digit Modalities Test) and trail making (adapted from the Halstead-Reitan Trail Making Test [TMT]) were completed at a mean follow-up time of 5.82 years via an online platform.[12] The difference in scores between the numeric TMT (TMT-A) and alpha-numeric TMT (TMT-B) was computed to assess for cognitive flexibility.[13] Table 1 lists the definitions, names, and descriptions of domains tested, assessment instructions, scoring, and examples of real-life applications of neurocognitive deficits within each domain.

Demographics

Demographic information obtained through self-report and objective measurement at time of enrollment include age, sex, ethnicity (White, non-White), Townsend deprivation index (a validated measure of socioeconomic status in the United Kingdom),[14] smoking status (current, previous, never), alcohol consumption (seldom, daily, weekly), weight (obese, nonobese), systolic and diastolic blood pressure, family history of cognitive dysfunction, educational attainment, employment status, and whether the individual lives alone.

Clinical Definitions

Neurocognitive, cerebrovascular, and cardiovascular diseases were defined with the use of *International Classification of Diseases, Ninth Revision* (*ICD-9*), *International Classification of Diseases, Tenth Revision* (*ICD-10*), and Operating Procedure Codes-4 codes from hospital encounter statistics data, as well as self-reported survey responses (see Table S1 for details). Mood disorders include depression, anxiety, panic attacks, suicidality, and/or bipolar depression. Dementia and degenerative diseases include Alzheimer disease, vascular dementia, and neurodegenerative diseases other than Parkinson disease (defined separately). Intellectual delays include cognitive impairments from organic brain damage, developmental delays, and mental retardation. Seizure disorders include any history of epilepsy. Stroke was defined by both ischemic and hemorrhagic pathogenesis. Coronary artery disease was defined as history of initial or recurrent unstable angina, non–ST-segment–elevation myocardial infarction, ST-segment–elevation myocardial infarction, chronic ischemic heart disease, prior percutaneous coronary interventions, and/or prior coronary artery bypass graft procedures.

Table 1. Neurocognitive Assessment and Scoring

Test Name	Neurocognitive Domain Tested	Domain Characteristics	Test Description	Real-life Application	Scoring
Fluid Intelligence	Reasoning	Problem-solving using logic and reasoning ability, independent of acquired knowledge	Multiple choice questions	Problem-solving, reasoning, abstraction, decision making	Number answered correctly in 2 min (range 0-13)
Reaction Time	Simple Processing Speed	Processing speed, sustained attention, and inhibition	Match pairs of symbols	Attention, starting and stopping tasks, driving a car, inhibiting actions/ verbalizations	Time in ms
Numeric Memory	Working Memory	Attention, working memory (maintenance)	Recall strings of numbers of increasing lengths	Attention, remembering directions/to-do lists, efficient learning	Number recalled correctly (range 0-12)
Symbol-Digit Substitution	Complex Processing Speed	Processing speed, sustained attention, visual scanning, and incidental memory	Match symbols to numbers using a key	Attention, learning and applying information to memory in daily life (unconscious memory processes), efficiency in routine tasks	Number correct
Numeric Trail Making (TMT-A)	Visual Attention	Visual scanning, attention, processing speed	Touch 25 circles in ascending numerical order	Efficient searching, numeric sequencing, brief attention for tasks	Time in seconds
Alpha-Numeric Trail Making (TMT-B)	Visual Attention	Visual scanning and attention, processing speed, set-shifting, multitasking	Touch 25 circles in ascending alternating alpha-numeric order	Multitasking, prioritizing, maintenance of information in working memory, planning, organizing	Time in seconds
Trail Making Difference	Visual Attention	Cognitive flexibility, intelligence	Difference in TMT-A and TMT-B scores	NA	Time in seconds

NA indicates not applicable.

Statistical Analysis

Statistical analysis was performed using the "tableone," "stats," and "lsmeans" packages in R software for statistical computing version 3.4.3. In preliminary analyses of the data, many variable distributions appeared to be non-normal[8]; therefore, sociodemographic and comorbid illness variables were compared across groups using χ^2 tests for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Neurocognitive test performance scores were compared across ACHD and non-ACHD cohorts using multivariable linear regression adjusted for age at enrollment, sex (categorical), Townsend deprivation index, alcohol consumption (categorical), and systolic and diastolic blood pressure measured at time of enrollment. Neurocognitive function was then compared using the same models after exclusion of all individuals with history of prior ischemic or hemorrhagic stroke and/or coronary artery disease. The Benjamini-Hochberg method was used to correct *P* values for multiple hypothesis testing while preserving power with an alpha threshold of 0.05 after correction. For each model, we performed standard diagnostics for assumptions of linearity, equal variance, and normality.

RESULTS

Demographics and Clinical Characteristics

Of the 1020 participants with ACHD, the majority had mild-to-moderate ACHD (N = 924, 91%) while the remaining 96 individuals (9%) had a history of cyanotic ACHD. More than 50% of individuals with mild-to-moderate ACHD had left-to-right shunt type lesions (Table S2).

Demographic factors, quality of life measures, and prevalence of comorbid illnesses among ACHD and non-ACHD participants are displayed in Table 2. Compared with the non-ACHD group, the ACHD group was not significantly different in age, genetic sex, ethnicity, obesity, or smoking status from the non-ACHD group. The ACHD group had slightly more socioeconomic deprivation (median Townsend Deprivation Index –1.89 versus –2.14, $P<0.001$), decreased alcohol consumption (37.6% versus 30.8% reported "seldom" drinking, $P<0.001$), and lower blood pressure (median systolic blood pressure 134 mm Hg versus 137, $P<0.001$; median diastolic blood pressure 79 versus 82 mm Hg, $P<0.001$) than the non-ACHD group. The unemployment rate in the ACHD group was nearly twice that of the non-ACHD group (12.2%

Table 2. Demographic Characteristics of Participants in the UK Biobank

	No ACHD	ACHD	*P* Value
N	497 983	1020	
Demographic factors			
Age (y) at enrollment (median, [IQR])	58 [50, 63]	57 [49, 63]	0.032
Male sex (%)	226 574 (45.5)	482 (47.3)	0.274
Year of birth (median [IQR])	1950 [1945, 1958]	1951 [1945, 1959]	0.064
White ethnicity (%)	468 429 (94.2)	964 (94.5)	0.755
Townsend (median [IQR])	−2.14 [−3.65, 0.54]	−1.89 [−3.40, 1.28]	<0.001*
Smoking (%)			0.840
Current	52 473 (10.6)	102 (9.9)	
Previous	171 277 (34.6)	351 (34.7)	
Never	271 321 (54.8)	562 (55.3)	
Alcohol (%)			<0.001*
Daily	100 874 (20.3)	190 (18.7)	
Weekly	242 782 (48.9)	444 (43.7)	
Seldom	152 844 (30.8)	382 (37.6)	
Obese (%)	120 854 (24.4)	254 (25.2)	0.602
Systolic blood pressure (median, IQR])	137 [125, 150]	134 [121, 147]	<0.001*
Diastolic blood pressure (median [IQR])	82 [76, 89]	79 [72, 87]	<0.001*
Family history of cognitive disorder (%)	109 286 (22.6)	237 (24.0)	0.304
Quality of life measures			
Achieved college graduation (%)	161 115 (32.6)	308 (30.6)	0.173
Unemployed (%)	28 857 (5.8)	124 (12.2)	<0.001*
Hours worked per week (median [IQR])	37 [28, 42]	37 [25, 42]	0.155
Lives with a partner/ spouse (%)	359 958 (89.1)	726 (88.4)	0.555
Comorbid illness			
Dementia (%)	139 (0)	0 (0)	0.973
Parkinson (%)	821 (0.2)	1 (0.1)	0.604
Intellectual delay (%)	24 (0)	0 (0)	0.985
Mood disorder (%)	34 202 (6.9)	77 (7.7)	0.330
Seizure disorder (%)	4354 (0.9)	16 (1.6)	0.019
Ischemic or hemorrhagic stroke (%)	8304 (1.7)	89 (8.9)	<0.001*
Coronary artery disease (%)	24 047 (4.9)	185 (18.7)	<0.001*

*Indicates significance at $P<0.001$.

versus 5.8%, $P<0.001$). There was no significant difference between the ACHD and non-ACHD groups in the attainment of a college degree, median hours worked per week, or percentage of individuals living with a partner or spouse. The sociodemographics of individuals with mild-to-moderate ACHD were not significantly different from individuals with cyanotic ACHD with the exception of a higher prevalence of obesity among those with mild-to-moderate disease (26% versus 13%, $P=0.010$) (Table S3).

The overall prevalence of neurologic and neuropsychiatric disorders was low (Table 2). Less than 1% of UKB participants were found to have a history of dementia, Parkinson disease, or intellectual delay. There was no significant difference between the ACHD and non-ACHD groups in the prevalence of mood disorders (7.7% versus 6.9%, $P=0.330$) or seizure disorders (1.6% versus 0.9%, $P=0.019$, nonsignificant at $P>0.002$ with Bonferroni correction). The prevalence of cerebro- and cardiovascular disease was vastly greater among the ACHD participants compared with the non-ACHD group, as previously reported. The ACHD group had 5 times greater prevalence of stroke (8.9% versus 1.7%, $P<0.001$) and nearly 4 times greater incidence of coronary artery disease (18.7% versus 4.9%, $P<0.001$). There were no significant differences in the prevalence of aforementioned comorbid illnesses between individuals with mild-to-moderate and cyanotic ACHD (Table S3).

Neurocognitive Outcomes

The ACHD group showed worse performance than the non-ACHD group in all 6 neurocognitive assessments examined (Table 3), with performance differences meeting significance threshold for 3 of 6 tests. After adjusting for standard risk factors, the greatest difference was observed for TMT-B, a measure of visual attention and cognitive flexibility, in which the ACHD group spent 6.47 seconds longer on average (95% CI, 3.01–9.94 seconds, $P=0.002$) to complete the test than their non-ACHD peers (Table 3). On TMT-A, the simpler numbers-only trail-making task, the ACHD group spent 2.51 seconds longer on average (95% CI, 0.45–4.58 seconds, P 0.034) than the non-ACHD group for completion (Table 3). The score difference between TMT-A and TMT-B, a measure of cognitive flexibility that is highly correlated with intelligence and impairment severity,[15] was also greater in the ACHD group compared with non-ACHD (Table 3). In symbol-digit substitution, the ACHD group achieved 19 correct substitutions on average compared with 20 correct substitutions in the non-ACHD group (95% CI, −1.5 to −0.22 correct substitutions, $P=0.021$), representing a modestly lower performance another measure of cognitive flexibility (Table 3). In a sensitivity analysis, these differences did not appear to be driven by the subgroup of 96 individuals with complex CHD (Table S4). After exclusion of individuals with history of stroke and/or coronary artery disease, the ACHD group continued to show worse performance in all domains on average, though without statistically significant difference (Table 4).

Table 3. Neurocognitive Performance in ACHD and Non-ACHD Participants

	n	Raw Mean (SD)		Least-Squares Mean (95% CI)			
	Non-ACHD/ACHD	Non-ACHD	ACHD	Non-ACHD	ACHD	Beta (95% CI)*	*P* Value*
Neurocognitive testing							
Completed at enrollment							
Reaction time, ms	492 245/1007	559 (118)	564 (123)	558 (558, 559)	561 (554, 568)	3.0 (–3.9, 10.0)	0.393
Fluid Intelligence, n correct	164 041/305	6.0 (2.1)	5.7 (2.1)	6.0 (6.0, 6.0)	5.9 (5.6, 6.1)	-0.2 (–0.4, 0.1)	0.233
Numeric memory, n digits remembered	51 324/93	6.5 (1.8)	6.1 (1.9)	6.5 (6.5, 6.5)	6.2 (5.9, 6.6)	-0.3 (–0.6, 0.1)	0.228
Completed at follow-up							
SymbolDigit Substitution, n correct	116 903/202	19.8 (5.1)	19.1 (5.4)	19.8 (19.7, 19.8)	18.9 (18.3, 19.5)	-0.9 (–1.5, –0.22)†	0.021†
TMT-A, seconds	103 270/188	39.17 (14.99)	41.23 (18.31)	39.04 (38.95, 39.13)	41.55 (39.49, 43.62)	2.51 (0.45, 4.58)†	0.034†
TMT-B, seconds	103 268/188	66.76 (25.73)	73.35 (30.35)	66.66 (66.50, 66.82)	73.14 (69.67, 76.60)	6.47 (3.01, 9.94)†	0.002†
Trail Making Difference, seconds	103 268/188	27.59 (20.49)	31.12 (21.54)	27.62 (27.49, 27.75)	31.58 (28.72, 34.44)	3.96 (1.10, 6.82)†	0.021†

ACHD indicates adult congenital heart disease; TMT-A, Numeric Halstead-Reitan Trail Making Test; and TMT-B, Alphanumeric Halstead-Reitan Trail Making Test.

*Linear model included age at enrollment, sex, Townsend deprivation index, alcohol consumption, and blood pressure.

†indicates significance at $P<0.05$. *P* values adjusted using Benjamini-Hochberg correction with significance threshold of 0.05.

DISCUSSION

Here we use a cross-sectional approach to show that older adults with mostly mild-to-moderate complexity ACHD have worse performance in tests of neurocognition compared with individuals without ACHD. The most significant deficits were found in symbol-digit substitution and numeric/alpha-numeric trail making, indicative of deficits in processing speed, attention, and cognitive flexibility, which fall under the broad category of executive functioning. The TMT has previously been shown to correlate strongly with overall severity of neurological impairment, with predictable age-related decline in performance.[15] Deficits in alpha-numeric trail making have been described in school-aged children and adolescents with CHD following cardiac surgery,[3,16] demonstrating that differences in cognitive flexibility among individuals with CHD can be observed much earlier than adulthood. While similar studies among ACHD are sparse, 2 recent studies of 48 adults with ACHD detected deficits in visuospatial skills, working memory, and processing speed.[1,17] Notably, both of these studies were of individuals with more severe ACHD and did not have sufficient power to detect differences in those with milder ACHD. Our study recapitulates neurocognitive differences in an older population of primarily low-to-moderate-complexity CHD.

The substantially increased burden of cerebro- and cardiovascular disease in the ACHD cohort may be a significant contributor to poor neurocognitive outcomes in this cohort, as demonstrated by the attenuation in neurocognitive differences between the ACHD and non-ACHD cohorts when excluding individuals with a history of stroke and coronary artery disease. Atherosclerosis of the carotid arteries has been shown to be a strong risk factor for vascular dementia and Alzheimer disease, likely mediated by thromboembolic events and hypoperfusion.[18] Thromboembolic cerebrovascular events are common sequelae of atrial fibrillation and coronary artery bypass grafting, indications of poor cardiovascular health, both of which have been strongly associated with cognitive decline in prospective studies.[19,20] Heart failure, 1 of several common long-term complications of cardiac dysfunction in ACHD, has also been widely associated with cognitive deficits in executive function attributable to hypoperfusion of the brain.[21] The strong connection of vascular disease with neurocognitive dysfunction combined with the substantial burden of vascular disease in the ACHD population highlights the importance of early preventive care and early intervention for this population.

Important outcomes in congenital heart disease extend beyond just survival alone, with heightened focus on outcomes related to quality of life and neuropsychological functional status. Employment and social connectedness remain challenging for many individuals with ACHD.[22] Similar to the study by Ilardi et al, we found that while there was no perceivable difference in educational attainment, unemployment was more common among individuals with ACHD.[17,22] In adults

Table 4. Neurocognitive Performance in ACHD and Non-ACHD Participants After Exclusion of Preexisting Stroke or Acquired Cardiovascular Disease

	n	Raw Mean (SD)		Least-Squares Mean (95% CI)			
	Non-ACHD/ACHD	Non-ACHD	ACHD	Non-ACHD	ACHD	Beta (95% CI)*	*P* Value*
Neurocognitive testing							
Completed at enrollment							
Reaction time, ms	456 607/720	557 (116)	555 (113)	555 (555, 556)	555 (547, 563)	−0.3 (−8.4, 7.8)	0.943
Fluid Intelligence, n correct	152 804/219	6.0 (2.2)	5.8 (2.1)	6.1 (6.1, 6.1)	5.9 (5.6, 6.2)	−0.2 (−0.4, 0.1)	0.397
Numeric memory, n digits remembered	47 672/68	6.5 (1.8)	6.3 (1.7)	6.5 (6.5, 6.6)	6.4 (5.9, 6.8)	−0.2 (−0.6, 0.3)	0.558
Completed at follow-up							
Symbol Digit Substitution, n correct	111 124/154	19.9 (5.1)	19.3 (5.4)	19.9 (19.9, 19.9)	19.0 (18.3, 19.7)	−0.9 (−1.6, −0.1)	0.072
TMT-A, seconds	98 281/140	38.99 (14.87)	40.45 (18.87)	38.84 (38.74, 38.93)	40.97 (38.60, 43.34)	2.14 (−0.23, 4.51)	0.206
TMT-B, seconds	98 279/140	66.30 (25.39)	69.69 (29.86)	66.16 (66.00, 66.32)	70.93 (66.98, 74.88)	4.47 (0.82, 8.73)	0.072
Trail Making Difference, seconds	98 279/140	27.31 (20.21)	29.24 (20.78)	27.32 (27.19, 27.45)	29.96 (26.69, 33.22)	2.64 (−0.63, 5.90)	0.228

ACHD indicates adult congenital heart disease; TMT-A, Numeric Halstead-Reitan Trail Making Test; and TMT-B, Alphanumeric Halstead-Reitan Trail Making Test.

*Linear model included age at enrollment, sex, Townsend deprivation index, alcohol consumption, and blood pressure. *P* values adjusted using Benjamini-Hochberg correction with significance threshold of 0.05.

with multiple sclerosis, an example of chronic disease, differences in cognitive flexibility measured by the symbol-digit substitution and trail making tests display a negative impact upon employment and ability to perform activities of daily living.[23] While the differences in neurocognitive function observed in the ACHD group may be of nominal clinical significance (eg, 0.9 fewer correct answers in symbol-digit substitution), these findings could suggest the persistence of neurocognitive differences observable in childhood survivors of CHD into adult life. Furthermore, differences in education-matched employment rates may be explained by subtle neurocognitive differences such as the ones described in this study that cannot be distinguished by gross measures of cognitive function such as intelligence quotient scores.

These findings are not without limitations. The conclusions are derived from observational data of middle-aged and older volunteers from the UKB, which are different than the general population of Great Britain.[24] There is likely a strong survivorship bias in this ACHD population, which predates the modern era of pediatric CHD care by several decades.[25] Furthermore, there is likely a strong healthy volunteer bias affecting the rate of completed neurocognitive tests. This is evidenced by the substantially lower than expected prevalence of dementia and other neurocognitive dysfunction and lower rate of test completion among the ACHD cohort. Another limitation lies in the fact that neurocognitive tests were asynchronous, with half the tests being done at enrollment and the other half at follow-up separated by several years. The observed differences in symbol-digit substitution and trail making test performance between the experimental groups at follow-up may be accentuated by this time lapse between enrollment and testing as well as by survivorship bias. Lastly, though this study represents the largest ACHD population examined for neurocognitive outcomes to date, the modest sample sizes for select neurocognitive tests were still relatively underpowered.

CONCLUSIONS

In a study population of middle- and older-aged volunteers in the UKB, we find that individuals with mild-to-moderate ACHD have decreased neurocognitive function, most significantly in cognitive flexibility, analogous to deficits observed in children with CHD. These differences appear to be driven by increased burden of cerebro- and cardiovascular disease among individuals with ACHD. Given the impact of neurocognition on quality of life measures such as employability, further longitudinal studies on neurocognitive function in the ACHD population are paramount for directing better preventive clinical care.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S4

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Supplemental Material

Table S1. Illness Definitions by HES and Self-Reported Data in the UKB.

Diagnosis	ICD 9	ICD 10	Self-reported Medical History	Self-reported Operative History
Mood disorders (depression, anxiety, panic attacks, suicidality, mania, bipolar disorders)	296*, 300*, 311*	F25*, F30*, F31*, F32*, F33*, F34*, F38*, F39*, F40*, F41*	1286, 1287, 1288, 1290, 1291	
Dementia & degenerative disorders (Alzheimer's disease, vascular dementia, other degenerative neurologic conditions)	331*, 290*, 294.1	F00*, F01*, F02*, F03*, G30*, G31*	1263	
Parkinson's Disease	332*	G20*	1262	
Intellectual disability (organic brain damage, developmental delays, mental retardation)	310*, 315*, 317*, 318*, 319*	F04*, F06.7, F10.6, F70*, F71*, F72*, F73*, F78*, F79*		
Seizure disorders (epilepsy)	345*	G40*, G41*	1264	
Ischemic or Hemorrhagic Stroke	430*, 431*, 432*, 433*, 434*, 435*, 436*	I60*, I61*, I62*, I63*, G45*, I64*, G46*	1491, 1583, 1081, 1082	
Coronary Artery Disease (CAD) (history of unstable angina, myocardial infarction, chronic ischemic heart disease, prior percutaneous coronary interventions, and/or prior coronary artery bypass graft procedures)	410*, 411*, 412*, 413*, 414.0, 414.8, 414.9	I20*, I21*, I22*, I24.0, I24.8, I24.9, I25*	1074, 1075	1070, 1095, 1523

*Inclusive of diagnostic codes with trailing digits.

ICD 9 = International Classification of Diseases, 9th revision; ICD 10 = International Classification of Diseases, 10th revision; HES = Hospital encounter statistics; UKB = UK Biobank; CAD = Coronary artery disease;

Table S2. ACHD subgroups by lesion type (reproduced from Saha et al., Circulation 2019) Lesion types.

	No. (%)
Complex defects	**96 (100)**
Single ventricle, truncus arteriosus, TOF, TGA, TAPVR, AVCD	50 (52)
Unspecified cyanotic lesion	45 (48)
Non-complex defects	**924 (100)**
Left-to-right shunt only (ASD, VSD, AP window, PDA, PAPVR)	448 (48)
Left sided lesion only	90 (10)
Right sided lesion only	47 (5)
Mixed shunt, left-sided, and/or right-sided lesion	50 (5)
Heart surgery prior to age 18	185 (20)
Non-specific ICD code for congenital heart disease	71 (8)
Other (coronary artery malformation, venous malformation, conduction defect)	33 (4)

ACHD = adult congenital heart disease; ASD = atrial septal defect; AP = aorto-pulmonary; AVCD = atrioventricular canal defect; ICD = International Classification of Diseases; PAPVR = partial anomalous pulmonary venous return; PDA = patent ductus arteriosus; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; VSD = ventricular septal defect

Table S3. Demographic characteristics of ACHD participants ACHD complexity in the UK Biobank.

	Mild to moderate ACHD	Complex ACHD	p-value
n	924	96	
Demographic Factors			
Age at Enrollment (median, [IQR])	57 [49, 63]	58 [49, 64]	0.236
Male Sex (%)	428 (46.3)	54 (56.2)	0.081
Year of Birth (median [IQR])	1951 [1946, 1959]	1951 [1944, 1958]	0.243
Caucasian Ethnicity (%)	876 (94.8)	88 (91.7)	0.294
Townsend (median [IQR])	-1.92 [-3.44, 1.23]	-0.99 [-3.02, 1.86]	0.106
Smoking (%)			0.485
Never	514 (55.9)	48 (50.0)	
Current	90 (9.8)	12 (12.5)	
Previous	315 (34.3)	36 (37.5)	
Alcohol (%)			0.301
Seldom	344 (37.4)	38 (40.0)	
Daily	168 (18.2)	22 (23.2)	
Weekly	409 (44.4)	35 (36.8)	
Obese (%)	241 (26.4)	13 (13.7)	**0.010**
Systolic blood pressure (median, IQR])	134 [121, 147]	134 [118, 146]	0.302
Diastolic blood pressure (median [IQR])	79 [73, 87]	78 [71, 89]	0.470
Positive family history of cognitive disorder (%)	221 (24.6)	16 (18.0)	0.205
Quality of Life Measures			
Achieved college graduation (%)	278 (30.4)	30 (31.9)	0.855
Unemployed (%)	107 (11.6)	17 (17.7)	0.113
Hours worked per week (median [IQR])	37 [25, 41]	39 [28, 44]	0.317
Lives with a partner/spouse (%)	662 (88.3)	64 (90.1)	0.781
Comorbid Illness			
Dementia (%)	0 (0)	0 (0)	NA
Parkinsons (%)	1 (0.1)	0 (0)	1.000
Intellectual delay (%)	0 (0)	0 (0)	NA
Mood disorder (%)	71 (7.9)	6 (6.4)	0.760
Seizure disorder (%)	16 (1.7)	0 (0)	0.384
Ischemic or hemorrhagic stroke (%)	82 (9.0)	7 (7.6)	0.796
Coronary artery disease (%)	171 (19.1)	14 (14.6)	0.346

ACHD = Adult congenital heart disease; IQR = interquartile range

Table S4. Neurocognitive performance among ACHD and non-ACHD after exclusion of complex ACHD diagnoses.

	Least Squares Mean (95% CI)		
	Non-ACHD	**ACHD**	**p-value***
Neurocognitive testing (n)	497,983	924	
Completed at Enrollment			
Reaction time, milliseconds	492,245 558 (558, 559)	914 562 (555, 569)	0.327
Fluid Intelligence, n correct	164,041 6.0 (6.0, 6.0)	279 5.8 (5.6, 6.1)	0.141
Numeric memory, n digits remembered	51,324 6.5 (6.5, 6.5)	84 6.1 (5.7, 6.5)	0.083
Completed at Follow-Up			
Symbol Digit Substitution, n correct	116,903 19.8 (19.7, 19.8)	186 19.1 (18.4, 19.8)	0.083
Numeric Trail Making (TMT-A), seconds	103,270 39.04 (38.95, 39.13)	174 41.63 (39.48, 43.77)	0.073
Alpha-numeric Trail Making (TMT-B), seconds	103,268 66.66 (66.50, 66.82)	174 72.39 (68.79, 75.99)	**0.015**
Trail Making Difference, seconds	103,268 27.62 (27.49, 27.75)	174 30.76 (27.79, 33.74)	0.083

ACHD = adult congenital heart disease; CI = Confidence interval; TMT-A = Numeric Trail Making; TMT-B = Alpha-numeric Trail Making