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Cognitive ability in young adulthood predicts risk of early-onset dementia in Finnish men

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Abstract

Objective

To test if the Finnish Defence Forces Basic Intellectual Ability Test scores at 20.1 years predicted risk of organic dementia or Alzheimer disease (AD).

Methods

Dementia was defined as inpatient or outpatient diagnosis of organic dementia or AD risk derived from Hospital Discharge or Causes of Death Registers in 2,785 men from the Helsinki Birth Cohort Study, divided based on age at first diagnosis into early onset (<65 years) or late onset (≥65 years). The Finnish Defence Forces Basic Intellectual Ability Test comprises verbal, arithmetic, and visuospatial subtests and a total score (scores transformed into a mean of 100 and SD of 15). We used Cox proportional hazard models and adjusted for age at testing, childhood socioeconomic status, mother's age at delivery, parity, participant's birthweight, education, and stroke or coronary heart disease diagnosis.

Results

Lower cognitive ability total and verbal ability (hazard ratio [HR] per 1 SD disadvantage >1.69, 95% confidence interval [CI] 1.01–2.63) scores predicted higher early-onset any dementia risk across the statistical models; arithmetic and visuospatial ability scores were similarly associated with early-onset any dementia risk, but these associations weakened after covariate adjustments (HR per 1 SD disadvantage >1.57, 95% CI 0.96–2.57). All associations were rendered non-significant when we adjusted for participant's education. Cognitive ability did not predict late-onset dementia risk.

Conclusion

These findings reinforce previous suggestions that lower cognitive ability in early life is a risk factor for early-onset dementia.

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Glossary

AD = Alzheimer disease; **HBCS** = Helsinki Birth Cohort Study; **ICD** = *International Classification of Diseases*.

The global number of people with some form of dementia is estimated to increase rapidly in the upcoming decades, totaling up to over 80 million individuals by 2040.[1] Identified risk factors for dementia include the ε4 allele of the *APOE* gene,[2] age,[3] and factors related to poorer health and lifestyle, such as diabetes, hypertension, obesity, hearing impairment, lower education, physical inactivity, smoking, depression, and social isolation.[3] In addition, lower cognitive ability in childhood[4,5] and young adulthood,[6] decades before the disease manifests, may predict increased dementia risk. Lower intelligence at the age of 11 years[4,5] in Scottish schoolchildren predicted a higher risk of late-onset dementia, but not early-onset dementia. Lower intelligence at the age of 18 years in Swedish male conscripts predicted higher risk of early-onset dementia,[6] and lower linguistic ability derived from autobiographies written by US nuns at mean age 22 years predicted higher risk of Alzheimer disease (AD) between ages 75 and 95 years.[7,8]

However, it remains unknown if the discrepant findings regarding dementia onset reflect the age at intelligence measurement: even though intelligence is shown to display high rank-order stability across decades,[9] intelligence measured at the age of 11 years[4,5] has not yet reached its peak, whereas at the age of 18 years[6] fluid intelligence is closer to it. On the other hand, in the study where intelligence was measured at the age of 18 years,[6] late-onset dementia could not be studied as the cohort was not mature enough. Further, the study that showed an association between linguistic ability and risk of AD did not differentiate the diagnoses by onset. In this study, we tested if intelligence in young adulthood in Finnish male conscripts predicted early and late-onset any dementia and AD with diagnoses derived from the Finnish national medical registries over the lifespan or until age 79 years. We also report associations between intelligence and late-onset dementia, with intelligence retested 5 decades later but prior to dementia diagnoses.

Methods

Participants

The participants come from the Helsinki Birth Cohort Study (HBCS) comprising 4,630 men born between 1934 and 1944 in Helsinki, Finland, who attended child welfare clinics and lived in Finland in 1971, when a personal identification number was allocated to all Finnish residents.[10–12] Cognitive ability data in young adulthood (mean age 20.1 years, SD 1.4, range 17.0–28.1) were available for 2,785 (60.2% of the original cohort) men who performed their compulsory military service in the Finnish Defence Forces between 1952 and 1972 and underwent compulsory cognitive ability testing, usually within the first 2 service weeks.[12] Data on dementia diagnoses were available until December 2013 on all of these men; 79 (2.8%) had been diagnosed with any dementia, and 48 (1.7%) with AD.

For a subsample of 930 men (53.2% of the 1,750 men who were invited; of the 1,036 men who were not invited, 646 had died, 206 had declined participation in any further follow-up, and 183 lived abroad), we had data on cognitive ability from an invitation-based retest at 67.9 years (SD 2.5, range 64.5–75.7), measured with the same test battery as at 20.1 years. They had participated in the test 2.8 years (SD 1.00, range 1.1–4.1) before the mean age at late-onset any dementia diagnosis in this subsample.

Detailed nonparticipant analyses of the men with Defence Forces data in young and late adulthood have been published.[13] Men with Defence Forces data in young adulthood (n = 2,785) differed from the rest of the men (n = 1,845) as follows: men with Defence Forces data more likely had fathers in manual worker occupations, they were longer and had a lower ponderal index at birth, their highest attained level of education was less often upper tertiary, and while they were more likely to have missing data on father's occupational status (p values < 0.022), they did not differ in the extent of missing data in the other variables. Men with Defence Forces data in late adulthood differed from the rest of the men as follows: men with Defence Forces data more likely had fathers in senior clerical occupations, their highest attained level of education was more often upper tertiary, and they less likely had any dementia or stroke or coronary heart disease diagnosis (p values < 0.008); they did not differ in the extent of missing data in any variables.

Standard protocol approvals, registrations, and patient consents

The HBCS has been approved by the Ethics Committee of the National Public Health Institute and the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa. The Finnish Defence Command has given permission for data linkage (permit AL18521). As only register data were used, no individual consent was required. All participants in the cognitive ability retest have signed informed consent.

Cognitive ability

The Finnish Defence Forces Basic Intellectual Ability Test comprises time-limited verbal, arithmetic, and visuospatial (analogous to Raven progressive matrices[14]) subtests and a total score. Each series comprises 40 multiple-choice items with progressive difficulty, and have been in use, with some modifications, since 1955. Psychometric test properties have

been described previously.[12,15] Test scores have been associated with, for example, cardiovascular disease and stroke risk[16] and *APOE* polymorphisms.[17] For all analyses, the cognitive ability test scores were converted to IQ-type scores with mean 100 and SD 15.

Intraclass correlations between the scores at the young and late adulthood testings were 0.77, 0.65, 0.74, and 0.62 (p values < 0.001) and average mean-level changes were 0.23 (SD 4.57, range −22.67 to 18.00), −2.60 (SD 6.40, range −30.00 to 33.00), 2.19 (SD 4.90, range −21.00 to 20.00), and 1.10 (SD 7.10, range −28.00 to 38.00) raw score points in the total, verbal, arithmetic, and visuospatial subtest scores, respectively.

Dementia diagnoses

Diagnoses of any organic dementias, given in inpatient (1969–2013) and outpatient (1998–2013) care (codes 290.00–290.10 from ICD-8, 290, 2912A, 2928C, 2941A, 3310A, and 3311A from ICD-9, and F00, F01, F03, F051, and G30 from ICD-10) and AD (codes 331.0 and 290.1 from ICD-9, and G30 and F00 from ICD-10) until December 31, 2013, were derived from the Finnish Hospital Discharge and Causes of Death Registers. In Finland, dementia is diagnosed by specialized memory clinics after referral by physicians in private or public health care based on clinical assessment and cognitive testing. As dementia prevalence in our sample (2.8%) matched the nationwide estimate for men of the corresponding age group (2.4%),[18] we considered completeness of case ascertainment to be adequate. According to prior studies,[4–6] diagnoses were divided into early-onset and late-onset dementias based on first diagnosis before or after age 65 years. Of the 79 men with any dementia diagnosis, 20 had early-onset and 59 late-onset diagnosis; of the 48 men with AD, 6 had early-onset and 42 late-onset AD. In the subsample who participated in the cognitive ability retest, 13 had a late-onset any dementia, 11 had AD.

Covariates

Covariates included birthweight (g), mother's age (years) at delivery and parity (primiparous/multiparous) extracted from hospital records, father's occupational status in childhood (manual worker/junior clerical/senior clerical) extracted from hospital, child welfare or school health care records, highest own attained level of education in adulthood (basic/primary or less/upper secondary/lower tertiary/upper tertiary) recorded at 5-year intervals between 1970 and 2000 derived from Statistics Finland, and diagnoses of stroke (codes 430–434 and 436–437 from ICD-8 and 9, 438 from ICD-9, and I60–I69 from ICD-10)[19] and coronary heart disease (codes 410–414 from ICD-8 and ICD-9 and I21–I25 from ICD-10)[10] until December 31, 2013, derived from the Hospital Discharge and Causes of Death Registers, and participant's age at the cognitive ability testings. We conducted additional analyses replacing the participant's education with occupation in adulthood, but these are not shown as the results did not differ.

Statistical analyses

Cox proportional hazard models examined the associations between cognitive ability in young adulthood and risk of any dementia and AD and early- and late-onset diagnoses, and examined associations between cognitive ability in late adulthood and age-related change in cognitive ability between 20.1 and 67.9 years and risk of any late-onset dementia (11 of 13 any late-onset dementia cases had AD; AD is not analyzed separately). The participants were followed up until first hospitalization for any dementia, death, migration, or until December 31, 2013. All analyses were adjusted for age at cognitive ability testing and in further models for the other covariates. We included in the analyses all participants with complete data for each model (missing data by study variable are in table 1; footnotes in tables 2 and 3 show sample sizes for different models). We had 85% statistical power at α level 0.05 to detect a difference in young and late adulthood cognitive ability of 0.34 and 0.84 SD units between any and no dementia diagnoses, respectively. The corresponding detectable SD unit differences in young adulthood cognitive ability were 0.67 and 0.39 for early- and late-onset any dementia, and 1.23 and 0.47 for early- and late-onset AD, respectively.

Data availability

Any requests for data use should be addressed to the Finnish Defence Forces, Finnish national register authorities, and individual Helsinki Birth Cohort Study researchers. Data requests may be subject to further review by the Finnish Defence Forces, Finnish national register authorities, and by the ethical committees.

Results

Cognitive ability at 20.1 years and risk of dementia

Participant characteristics according to any dementia diagnoses are presented in table 1.

Table 2 shows that the cognitive ability total and verbal and arithmetic subtest scores were not significantly associated with any-onset any dementia diagnosis. Lower scores in the visuospatial subtest were associated with a higher risk of any-onset any dementia, but this association did not survive covariate adjustments.

In analyses examining the associations between cognitive ability at 20.1 years and any early-onset and late-onset dementia, we found that lower cognitive ability total and verbal, arithmetic, and visuospatial subtest scores were associated with a higher risk of any early-onset dementia in models adjusting for age at cognitive ability testing (figure 1). All of these associations remained significant in the models additionally adjusting for the covariates, but were rendered nonsignificant in the model adjusting for the participants' highest lifetime attained education (table 2). Cognitive ability scores were not associated with risk of any late-onset dementia or with risk of any-onset, early-onset, or late-onset AD (table 3).

Table 1 Participant characteristics according to dementia diagnosis

Characteristic	Defence forces data at 20.1 years available: Dementia diagnosis			Defence forces data at 67.9 years available: Dementia diagnosis		
	No (2,706)	Any dementia (79)	*p* Value[a]	No (917)	Any dementia (13)	*p* Value[a]
Mother's age at delivery, y	28.4 (5.5)	28.4 (5.0)	0.986	28.5 (5.5)	27.5 (4.9)	0.501
Data not available	2 (0.1)	0 (0.0)		1 (0.1)	0 (0.0)	
Parity			0.293			0.068
Primiparous	1,327 (49.0)	34 (43.0)		445 (48.5)	3 (23.1)	
Multiparous	1,379 (51.0)	45 (57.0)		472 (51.5)	10 (76.9)	
Data not available	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Father's occupational status			0.569			0.638
Senior clerical	439 (16.5)	15 (19.2)		196 (21.8)	4 (30.8)	
Junior clerical	639 (24.1)	15 (19.2)		219 (24.3)	2 (15.4)	
Manual worker	1,578 (59.4)	48 (61.5)		486 (53.9)	7 (53.8)	
Data not available	50 (1.8)	1 (1.3)		16 (1.7)	0 (0.0)	
Birthweight, kg	3.5 (0.5)	3.4 (0.6)	0.855	3.5 (0.5)	3.5 (0.5)	0.714
Data not available	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Highest own achieved level of education			0.086			0.334
Upper tertiary	322 (11.9)	13 (16.5)		172 (18.8)	3 (23.1)	
Lower tertiary	597 (22.1)	10 (12.7)		278 (30.3)	1 (7.7)	
Upper secondary	697 (25.8)	18 (22.8)		226 (24.6)	5 (38.5)	
Basic or less	1,025 (37.9)	38 (48.1)		241 (26.3)	4 (30.8)	
Data not available	65 (2.4)	0 (0.0)		0 (0.0)	0 (0.0)	
Stroke or coronary heart disease diagnosis	486 (18.0)	29 (36.7)	0.000	132 (14.4)	4 (30.8)	0.015
Data not available	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Age at cognitive ability testing, y	20.1 (1.4)	20.3 (1.3)	0.190	67.9 (2.5)	69.6 (3.0)	0.044
Data not available	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Cognitive ability score						
Total score	100.1 (5.0)	98.1 (16.3)	0.251	100.2 (14.9)	88.2 (15.9)	0.004
Data not available	16 (0.6)	1 (1.3)		0 (0.0)	0 (0.0)	
Verbal subtest	100.0 (15.0)	99.0 (15.5)	0.547	100.0 (15.0)	96.7 (14.9)	0.429
Data not available	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Arithmetic subtest	100.1 (15.0)	97.9 (15.7)	0.204	100.2 (14.9)	85.1 (13.0)	0.000
Data not available	16 (0.6)	1 (1.3)		0 (0.0)	0 (0.0)	
Visuospatial subtest	100.0 (15.0)	97.7 (16.1)	0.159	100.1 (15.0)	91.6 (15.4)	0.041
Data not available	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	

Values are mean (SD) or n (%).
[a] *p* Values correspond to group comparisons with χ^2 test for parity, father's occupational status and highest own achieved level of education, analysis of variance for other variables.

Table 2 Cognitive ability at 20.1 years and dementia risk

Cognitive ability in SD units	Model 1[a,b] HR (95% CI)	*p* Value	Model 2[a,c] HR (95% CI)	*P* Value	Model 3[a,d] HR (95% CI)	*p* Value	Model 4[a,e] HR (95% CI)	*p* Value
Any-onset								
Total	1.23 (0.97–1.55)	0.083	1.21 (0.95–1.54)	0.132	1.15 (0.87–1.51)	0.328	1.22 (0.97–1.54)	0.095
Verbal	1.14 (0.91–1.43)	0.259	1.11 (0.88–1.41)	0.385	1.06 (0.82–1.37)	0.657	1.14 (0.90–1.43)	0.276
Arithmetic	1.22 (0.97–1.54)	0.086	1.21 (0.97–1.54)	0.126	1.14 (0.87–1.50)	0.328	1.22 (0.96–1.53)	0.098
Visuospatial	1.27 (1.01–1.60)	0.041	1.25 (0.98–1.58)	0.072	1.19 (0.93–1.54)	0.175	1.27 (1.00–1.60)	0.047
Early onset (before 65 years of age)								
Total	1.87 (1.14–3.06)	0.013	1.77 (1.07–2.95)	0.027	1.47 (0.85–2.55)	0.167	1.85 (1.12–3.03)	0.015
Verbal	1.79 (1.08–2.96)	0.024	1.69 (1.01–2.63)	0.046	1.45 (0.85–2.48)	0.177	1.77 (1.07–2.94)	0.026
Arithmetic	1.71 (1.05–2.80)	0.032	1.63 (0.98–2.69)	0.058	1.33 (0.78–2.27)	0.297	1.69 (1.03–2.94)	0.036
Visuospatial	1.65 (1.02–2.68)	0.042	1.57 (0.96–2.57)	0.071	1.34 (0.80–2.23)	0.269	1.63 (1.03–2.65)	0.048
Late onset (65 years of age or later)								
Total	1.08 (0.83–1.40)	0.581	1.07 (0.81–1.41)	0.645	1.06 (0.77–1.45)	0.715	1.07 (0.82–1.39)	0.605
Verbal	1.00 (0.77–1.29)	0.991	0.98 (0.75–1.28)	0.886	0.97 (0.72–1.30)	0.827	1.00 (0.77–1.29)	0.976
Arithmetic	1.10 (0.85–1.43)	0.465	1.10 (0.84–1.45)	0.499	1.09 (0.80–1.49)	0.571	1.10 (0.84–1.43)	0.490
Visuospatial	1.17 (0.90–1.52)	0.242	1.16 (0.88–1.52)	0.292	1.15 (0.86–1.55)	0.335	1.17 (0.90–1.52)	0.255

Abbreviations: CI = confidence interval; HR = hazard ratio.
HRs given per 1 SD disadvantage in cognitive ability.
[a] Across the statistical models, the number of participants available for analysis with any-onset, early-onset, and late-onset any dementia diagnosis varied between 77–79, 19–20, and 58–59, respectively, and the number of participants with no dementia diagnosis varied between 2,626 and 2,706.
[b] Model 1 adjusted for age at cognitive ability testing.
[c] Model 2 adjusted for age at cognitive ability testing, father's occupation in childhood, mother's age at delivery, birthweight, and parity.
[d] Model 3 adjusted for age at cognitive ability testing and own highest attained education.
[e] Model 4 adjusted for age at cognitive ability testing and diagnoses of stroke or coronary heart disease.

Cognitive ability at 67.9 years, age-related cognitive change, and risk of dementia

Lower cognitive ability total and arithmetic subtest scores at 67.9 years predicted a higher risk of any late-onset dementia in all models adjusting for covariates (table e-1, links.lww.com/WNL/A560). Dementia risk was also higher in men who showed more aging-related change in cognitive ability over 5 decades in all adjusted models (figure 2 and figure e-1, links.lww.com/WNL/A559).

Discussion

Our study shows that men who had lower cognitive ability scores at the age of 20 years had a higher risk of any early-onset dementia. This association was independent of childhood socioeconomic status, maternal age at delivery, participant's birthweight, and diagnoses of stroke or cardiovascular disease before the dementia diagnosis. This association was present across all the tested domains of cognition, suggesting a widespread protective effect of better cognitive function in young adulthood.

Cognitive ability at age 20 years was not associated with the risk of early-onset AD. The hazard ratios (HRs) for AD, however, were similar to those of any dementia, despite not reaching the conventional level of significance because of the lower statistical power. Notably, the majority of participants with early-onset dementia had AD, hence the associations with early-onset dementia were largely driven by AD. Further, we found that young adulthood cognitive ability did not predict any late-onset dementia or late-onset AD. While the number of cases with any dementia or AD in our sample was overall small, the sample size cannot entirely explain why we did find associations with early- but not with late-onset dementia: we had nearly 3 and 7 times more cases with late- than early-onset any dementia and AD, respectively.

Our findings align with the prior study that showed that lower cognitive ability in young adulthood predicted higher risk of early-onset dementia in Swedish male conscripts[6] and with the study in Scottish schoolchildren that showed that cognitive ability at age 11 years was not associated with late-onset AD,[5] but disagree with the findings from the same cohort showing that lower cognitive ability at age 11 years predicted higher risk of any late-onset dementia[4] and vascular dementia,[5] but not

Table 3 Cognitive ability at 20.1 years and Alzheimer disease risk

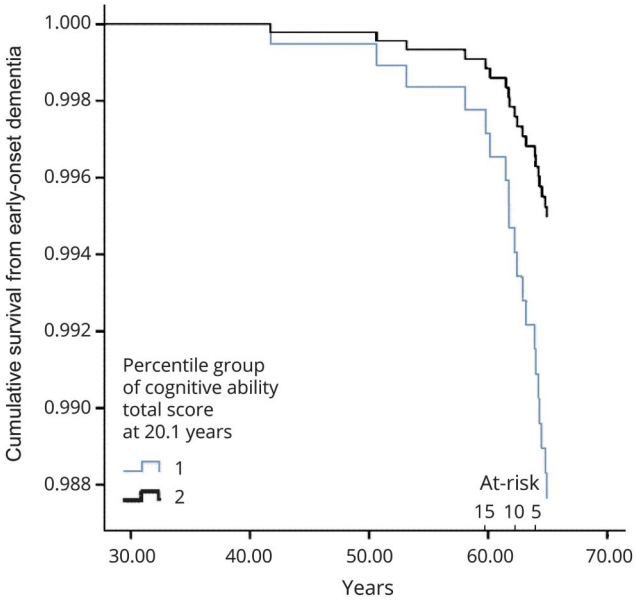
	Model 1[a,b]		Model 2[a,c]		Model 3[a,d]		Model 4[a,e]	
Cognitive ability in SD units	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
Any-onset								
Total	1.11 (0.83–1.49)	0.468	1.13 (0.84–1.54)	0.425	1.19 (0.84–1.69)	0.332	1.11 (0.83–1.48)	0.480
Verbal	1.07 (0.80–1.44)	0.635	1.09 (0.80–1.47)	0.596	1.13 (0.81–1.57)	0.469	1.07 (0.80–1.43)	0.643
Arithmetic	1.11 (0.83–1.49)	0.472	1.13 (0.84–1.56)	0.414	1.18 (0.84–1.66)	0.347	1.10 (0.83–1.48)	0.486
Visuospatial	1.15 (0.86–1.53)	0.362	1.15 (0.85–1.56)	0.358	1.19 (0.86–1.64)	0.297	1.14 (0.85–1.53)	0.371
Early-onset (before 65 years of age)								
Total	1.72 (0.71–4.16)	0.232	1.97 (0.80–4.89)	0.142	2.00 (0.74–5.45)	0.174	1.72 (0.71–4.18)	0.228
Verbal	2.32 (0.86–6.26)	0.098	2.55 (0.95–6.87)	0.063	2.68 (0.93–7.76)	0.069	2.32 (0.86–6.27)	0.097
Arithmetic	1.42 (0.60–3.35)	0.429	1.62 (0.66–3.70)	0.295	1.55 (0.56–4.13)	0.384	1.42 (0.60–3.36)	0.424
Visuospatial	1.25 (0.54–2.89)	0.602	1.36 (0.58–3.21)	0.480	1.30 (0.53–3.20)	0.571	1.21 (0.53–2.76)	0.644
Late-onset (65 years of age or later)								
Total	1.05 (0.77–1.43)	0.743	1.05 (0.76–1.45)	0.773	1.11 (0.76–1.61)	0.587	1.05 (0.77–1.43)	0.756
Verbal	0.98 (0.72–1.33)	0.897	0.97 (0.71–1.34)	0.860	1.01 (0.71–1.44)	0.947	0.98 (0.72–1.33)	0.890
Arithmetic	1.08 (0.79–1.47)	0.635	1.08 (0.79–1.49)	0.631	1.14 (0.79–1.64)	0.496	1.07 (0.79–1.46)	0.650
Visuospatial	1.13 (0.83–1.54)	0.437	1.12 (0.81–1.55)	0.479	1.17 (0.83–1.66)	0.363	1.13 (0.83–1.54)	0.445

Abbreviations: CI = confidence interval; HR = hazard ratio.
HRs given per 1 SD disadvantage in cognitive ability.
[a] Across the statistical models, the numbers of participants available for analysis with any-onset, early-onset, and late-onset Alzheimer disease diagnosis were 48, 6, and 42, respectively, and the number of participants with no dementia diagnosis varied between 2,626 and 2,706.
[b] Model 1 adjusted for age at cognitive ability testing.
[c] Model 2 adjusted for age at cognitive ability testing, father's occupation in childhood, mother's age at delivery, birthweight, and parity.
[d] Model 3 adjusted for age at cognitive ability testing and own highest attained education.
[e] Model 4 adjusted for age at cognitive ability testing and diagnoses of stroke or coronary heart disease.

early-onset dementia.[4,5] These time-varying patterns of findings may suggest that contribution of different mechanisms mediating the association between cognitive ability and dementia risk may differ between different points in the lifespan. Indeed, heritability estimates of cognitive ability suggest an overall pattern of increase from childhood to adulthood, and relative stability after reaching adulthood.[20,21] Further studies are warranted to unravel if this interpretation is true, or if other underlying factors that may compromise brain development until the cognitive peak is reached are involved.

Among the men who had cognitive ability scores in old age available, we found higher risks of late-onset dementia in men with lower scores 1–4 years before their late-onset any dementia diagnosis, and men who showed more aging-related change in cognitive ability between young adulthood and old age. The total cognitive ability and arithmetic subtest scores, but not the verbal or visuospatial subtest scores in old age, predicted a higher risk of any late-onset dementia, indicating that the association with the total score is driven by the association with the arithmetic subtest score. A higher risk of late-onset dementia was predicted by greater change in the total cognitive ability and arithmetic and visuospatial subtest scores between young adulthood and old age, but not in the verbal subtest score. These associations were independent of paternal socioeconomic status in childhood, birthweight, mother's age

Figure 1 Cumulative risk of early-onset any dementia in men with cognitive ability total score at mean age of 20.1 years below (percentile group 1) and above (2) the median



Numbers at risk indicate the number of participants left yet to receive a dementia diagnosis.

at delivery, parity, the participant's education, and diagnoses of stroke or cardiovascular disease before the late-onset dementia diagnosis. These findings support the validity of our cognitive ability measure, which is not in clinical use and available for critical psychometric evaluation. The findings should, however, be interpreted with caution. As dementia has a long preclinical phase, a likely explanation of these associations is reverse causality: lower cognitive ability in older age in our study likely reflects premorbid dementia in some participants who have not yet received a dementia diagnosis. Favoring this interpretation, it should be noted that the participants were still sufficiently functional to independently participate in the voluntary cognitive ability retest in old age.

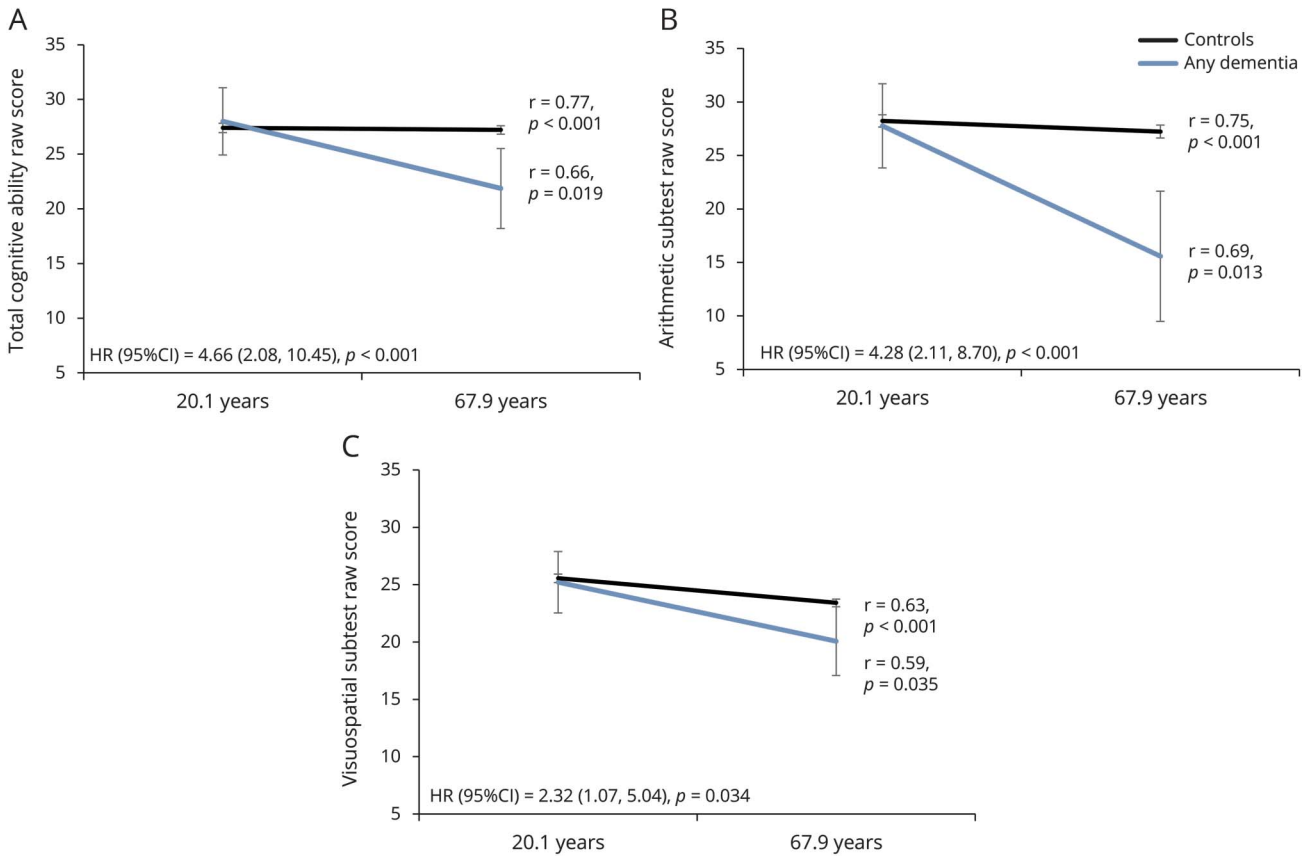
High rank-order stability of cognitive ability across the lifespan in participants with dementia is, however, in accordance with the concept of cognitive reserve, which reflects the protective effect of experience on brain structure and cognitive skills, and is distinct from the disease process.[22] In this study, the association between cognitive ability at 20 years and risk of early-onset dementia was rendered nonsignificant when we adjusted for the participant's education. This may reflect the close relationship between cognitive ability and education, both of which are markers of cognitive reserve.[22] Higher early-life cognitive ability[23,24] and education[25] are associated with increased life expectancy, and may protect against disease in later life by increasing health-promoting behaviors,[23,24] and promoting social participation and activities that contribute to accumulation of cognitive reserve[26] over the lifespan. Indeed, the increase in the heritability of cognitive ability from childhood to early adulthood has been suggested to be due to increasing selection of environments, such as education, that are compatible with the individual's genetic predispositions.[20]

Furthermore, we found that the association between cognitive ability at 68 years, unlike at 20 years, and dementia risk was independent of the participant's education. As the protective effect of education is accumulated during the lifespan, this may suggest that the relative contributions of cognitive ability and education to prediction of dementia risk may differ between young adulthood and in old age. The association between education and cognitive functioning in old age likely reflects acquired advantages in brain structure, which does not actively provide cognitive stimulation.[27] Indeed, while occupational complexity is associated with higher cognitive performance,[28] these effects are reduced after retirement[29] as cognitive stimulation must then be maintained with other activities.

Strengths of this study include measurement of cognitive ability at age 20 years and at age 68 years with the same test battery in a well-characterized lifespan longitudinal cohort of men, and availability of data on dementia diagnoses from national registers, which have been found in another Finnish cohort to identify dementia cases accurately.[30] Limitations include studying Finnish men only, and as the cohort was born in the 1930s and 1940s, generalizations to more recent cohorts cannot be made. This is an unavoidable limitation to studying cognitive aging in today's elderly. Dementia prevalence in this cohort is similar to the nationwide estimate based on literature reviews and meta-analyses for the corresponding WHO region, age group, and sex.[18] It has been estimated that inpatient data from the Hospital Discharge Register may miss approximately half of dementia cases,[30] so our study may underestimate dementia prevalence before outpatient data became available for the cohort in 1998. However, this cannot explain the lack of associations with late-onset dementia, as in 1998 the oldest members of the cohort were 64 years old, so any missed cases are early-onset dementias. It is also possible that participants with mild or early forms of dementia have not sought treatment and thus remain undiagnosed, or that some participants may have fulfilled the diagnostic criteria before the age of 65 years but received a late-onset diagnosis due to delays in seeking treatment; however, this more likely underestimates than overestimates the associations. Overall, the number of cases with any dementia and AD was small. Hence, our results stand in need of replication in larger cohorts and await our own cohort to age further. Finally, residual confounding cannot be excluded.

We found that lower cognitive ability at 20 years was associated with a higher risk of any early-onset dementia. Lower cognitive ability at 68 years 1–4 years before the diagnosis and larger change in cognitive ability from young adulthood to old age were associated with a higher risk of any late-onset dementia. Our study concurs with earlier studies in Scottish,[4,5] Swedish,[6] and US[7,8] men and women that have found an

Figure 2 Cognitive ability scores



Cognitive ability total (A), arithmetic (B), and visuospatial (C) subtest raw scores at 20.1 and 67.9 years in participants diagnosed with any late-onset dementia and those without any dementia diagnosis. Error bars represent 95% confidence intervals (CIs). Numbers are model 1 hazard ratios (HRs), 95% CIs, and *p* values from Cox regression analysis predicting any late-onset dementia risk with change in total cognitive ability and arithmetic and visuospatial subtest in SD units between 20.1 and 67.9 years, and Pearson correlation coefficients and *p* values between cognitive ability raw scores at 20.1 years and 67.9 years for participants with late-onset dementia and those without any dementia diagnosis.

association between dementia risk and cognitive ability measured decades before the time of diagnosis. Together with these studies, our study suggests that the associations between cognitive ability and dementia risk may be different depending on the age at cognitive testing and the time of dementia onset, which may be due to mediation by at least partially different heritable and nonheritable mechanisms.

Author contributions

K.R. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drafting/revising the manuscript for content: V.R., J.L., M.H., E.K., J.E., K.R. Study concept or design: V.R., J.L., M.H., E.K., J.E., K.R. Analysis or interpretation of data: V.R., J.L., K.R. Acquisition of data: J.L., M.H., J.E., E.K., K.R. Statistical analysis: V.R., J.L., K.R. Study supervision or coordination: V.R., J.L., M.H., E.K., J.E., K.R. Obtaining funding: J.L., J.E., K.R.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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