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Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia

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ABSTRACT

Background: Risk factors for dementia can be divided into those that lead to pathologic insults and those that render the brain more vulnerable to such insults. Dementia prevention strategies need to be informed as to whether to prioritize reducing risk of pathology or to reduce the vulnerability of the brain to pathologic insult. Lower premorbid cognitive ability is associated with both increased vascular risk and reduced cognitive reserve, a measure of brain vulnerability. We investigated differential effects of premorbid cognitive ability on dementia subtypes to clarify which causal pathway was predominant.

Methods: A total of 297 cases of late onset dementia were identified from local case registers, born in 1921, and thus may have participated in the Scottish Mental Survey of 1932 (SMS1932). A total of 183 had mental ability scores identified in the SMS1932. A total of 173 of these were matched by birth records to one set of controls (controls1) by date of birth, sex, and district of birth registration. A further set of controls (controls2) was generated additionally matched on paternal occupation.

Results: Vascular dementia cases had significantly lower premorbid cognitive ability (OR 0.62, 95% CI 0.41–0.94, for every 10-point increase [0.7 SD] in mental ability score vs controls2), but there was no significant difference in the premorbid cognitive ability of Alzheimer disease cases (OR 1.02, 95% CI 0.82–1.28) vs controls2.

Conclusion: Lower premorbid cognitive ability is a risk factor for vascular dementia, but not Alzheimer disease. This suggests its effect acts mainly through vascular pathology rather than brain vulnerability. *Neurology*® 2008;71:1051–1056

GLOSSARY

AD = Alzheimer disease; **CBF** = cerebral blood flow; **LMTC** = Lothian Memory Treatment Centre; **MHT** = Moray House Test; **REH** = Royal Edinburgh Hospital; **SMS1932** = Scottish Mental Survey of 1932; **VaD** = vascular dementia.

Dementia is predicted to be one of the greatest worldwide disease burdens in the 21st century with one new case occurring every 7 seconds.[1] Moreover, in the United Kingdom at least, costs of dementia are predicted to far outstrip those that would be predicted due to rising prevalence associated with demographic change.[2] Relatively small changes in prevalence are likely to result in substantial cost savings[2] and could be achieved by modest delays to the onset of dementia.[3] Alzheimer disease (AD), the commonest cause of dementia, has an insidious onset with a preclinical phase preceding diagnosis by many years.[4] Neuropathologic features of AD, plaques and tangles, are thus typically present for some time before the diagnostic threshold for dementia is reached. Concomitant vascular lesions increase the likelihood of a clinical diagnosis of dementia,[5] though both neuropathologic features of AD and vascular lesions are common in the brains of people without dementia.[6] These findings indicate limitations with using neuropathologic standards for clinical diagnostic criteria for both AD and vascular dementia (VaD) but, at present, alternative gold standards are unavailable. The hypothesis that vascular lesions add to the pathologic load that pushes someone over the dementia threshold is supported by

data from studies that show vascular risk factors in midlife are associated with increased AD incidence in old age.[7,8] One prevention strategy, therefore, takes a life course perspective, aiming to reduce vascular risk in middle age. A complementary approach does not focus on the pathologic load, but on characteristics of the individual that might increase the load needed to cross the diagnostic threshold. This strategy usually invokes the concept of cognitive reserve[9,10] that posits that aspects of the brain's structure and function serve to buffer the effects of neuropathology.[11] Hence increasing cognitive reserve could delay dementia onset for the same pathologic load. Many factors are thought to contribute to cognitive reserve, but a key index that captures the effects of many of these is premorbid cognitive ability.[11]

Premorbid cognitive ability is not only a key index of cognitive reserve, but predicts survival,[12] cardiovascular disease,[13] and midlife blood pressure.[14] Theoretically, an association between lower premorbid cognitive ability and dementia would be expected to act not only by reduced cognitive reserve, but also by greater pathologic load, especially with respect to vascular lesions. No such association has been detected for early onset dementia, but lower IQ at age 11 has been associated with increased risk of late-onset dementia.[15] However, this study comprised only 50 late-onset cases, so was inadequately powered to determine effects of childhood IQ on AD and VaD separately. The Nun Study also found an association between linguistic ability at about 22 years of age and late-onset dementia, but this was based on just 39 neuropathology cases, only 59% of whom fulfilled clinical diagnostic criteria for dementia.[16] Intuitively, a causal chain linking lower premorbid cognitive ability to midlife vascular risk factors and thence to dementia in old age might be hypothesized. But demonstrating an association between midlife vascular factors and late-onset dementia may be misleading because vascular risk is associated with lower premorbid cognitive ability and thus with reduced cognitive reserve. These bidirectional relationships between cognition and vascular risk may be one reason why lowering blood pressure fails to re-

duce cognitive decline as much as expected.[17] However, a priori vascular risk factors might be expected to be more influential on VaD than AD incidence, so investigating differential effects of premorbid cognitive ability on different dementia subtypes may help clarify where prevention effort is best directed.

METHODS **Measure of premorbid cognitive ability.** This is provided by the Scottish Mental Survey of 1932 (SMS1932).[18,19] On June 1, 1932, almost every child at school in Scotland who was born in the calendar year 1921 took a group-administered mental ability test. In total 87,498 children (44,210 boys and 43,288 girls) took the test, representing about 95% of the relevant population. The test used was a version of the Moray House Test No. 12 (MHT), which consists of 71 items in categories including following directions, same-opposites, analogies, reasoning, arithmetical, spatial, mixed sentences, and proverbs. The maximum possible score is 76. To assess the criterion validity of the MHT, a random subset of the birth year (500 boys and 500 girls) were given the Stanford-Binet test, administered individually. The correlation between the Stanford-Binet test and MHT was 0.81 for boys and 0.78 for girls, thus validating the MHT as a test of general mental ability. The results of the SMS1932 were recorded in handwritten ledgers based on geographic area. These contain the pupils' names, schools, and MHT scores. These ledgers are stored in the Scottish Council for Research in Education archive at the University of Glasgow, Scotland. The data had been transcribed onto a computerized database. This database was made available by the Scottish Centre for Research in Education (SCRE) to the research team involved in follow-up studies of the SMS1932.

Definition of cases. Selection of cases and controls followed the methods of an earlier study of early onset dementia.[15] Like one subgroup in the earlier study, all cases and controls in this study had an MHT score available on the SMS1932 database and thus were all born in 1921. This sample was thus drawn from the same birth cohort, but with cases developing AD after rather than before 65 years of age. Hence there was no overlap in cases between the earlier study and this one. A case was defined as someone who had had an International Classification of Diseases (ICD)-10[20] diagnosis of dementia made after the age of 65 years. A total of 297 cases were identified from dementia case registers in Edinburgh maintained by the main psychiatric hospital, the Royal Edinburgh Hospital (REH), and a tertiary memory clinic, Lothian Memory Treatment Centre (LMTC). Referrals were made to the LMTC from the whole of the region of Lothian which has Edinburgh as its major city. The latest date for case identification was August 2003 when cases would have been 82 years old. The expected prevalence of dementia in the population from which cases were drawn[21,22] was estimated as 392 cases. Hence ascertainment was 75.8%, but this represents an upper limit because there may have been a small number of cases who had died since being entered on the case registers inflating this figure. LMTC AD cases had been classified according to NINCDS diagnostic criteria.[23] Its diagnostic criteria for VaD had varied between National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences[24] and ICD-10. In view of this all cases were reviewed and classified according to ICD-10 diagnostic guidelines as AD or VaD. The ICD-10 criteria were op-

Table 1 Demographic data and mean MHT scores in cases in different diagnostic groups

	Type of dementia		
	AD	VaD/mixed	Dementia (unspecified)
No.	86.0	40.0	44.0
Age at SMS, y	10.9 (0.29)	10.9 (0.27)	10.9 (0.27)
Female sex, n (%)	58.0 (67)	22.0 (55)	22.0 (50)
Born Lothian, n (%)	63.0 (73)	31.0 (78)	33.0 (75)
Maternal age, y	30.7 (7.0)	30.2 (5.7)	30.6 (6.5)
Paternal age, y	33.7 (8.2)	32.0 (6.2)	33.0 (7.1)
Years parents married at birth of subject, median (interquartile range)	3.9 (1.2–10.5)	5.0 (1.2–10.0)	3.5 (1.3–9.5)
Paternal occupational category, n (%)			
I	2.0 (2)	0.0	3.0 (7)
II	7.0 (8)	4.0 (11)	4.0 (9)
III	50.0 (59)	25.0 (66)	24.0 (55)
IV	16.0 (19)	6.0 (18)	8.0 (18)
V	10.0 (12)	3.0 (18)	5.0 (11)
MHT score	40.0 (14.5)	35.0 (13.1)	38.7 (15.6)

MHT = Moray House Test; AD = Alzheimer disease; VaD = vascular dementia; SMS = Scottish Mental Survey.

erationalized to make a diagnosis of VaD with an emphasis on dementia with features of 1) sudden onset of symptoms and stepwise deterioration, 2) important vascular risk factors, focal neurologic signs, and supporting neuroimaging and neuropsychological assessment, or 3) a temporally appropriate clinical history of stroke or TIA. Some cases had features of both AD and VaD. ICD-10 does not have a separate coding for mixed AD/VaD, but states, "In a certain proportion of cases, the features of AD and vascular dementia may both be present. In such cases, double diagnosis (and coding) should be made. When the vascular dementia precedes the AD, it may be impossible to diagnose the latter on clinical grounds."[20] We classified cases that satisfied both AD and VaD criteria as "mixed" and those that did not fulfill either AD or VaD ICD-10 diagnostic criteria as "unspecified dementia."

Definition of controls. Controls used were population controls obtained from the national birth register held at Register House, Edinburgh. Therefore cases and controls had to have personal details matched to that of individuals on both the SMS1932 database (SMS1932) and the national register for births, deaths, and marriages. Of the 297 cases with late onset dementia there were 44 females whose maiden name was not known; therefore these cases were not able to be matched to the SMS. A further 65 cases could not be matched to the SMS; a high proportion of these cases are likely to have migrated to Scotland after the age of 11, and so would not have taken part in the SMS1932. A total of 183 cases were matched to the SMS1932. Of these, seven were not matched to the birth register, probably indicating migration to Scotland before age 11 years. Three were adopted, and so were excluded as no data were known about paternal occupation required for matching controls. This left 173 cases with which controls could be matched.

Each dementia case was matched individually in two ways to population controls from the birth register. This was to try to avoid potential overmatching due to the correlation between

childhood IQ and paternal social class that may have affected the early onset study.[15] Thus, eventually, there were two control groups. Control group 1 was matched on age, sex, and district of birth registration. Control group 2 was matched on age, sex, district of birth registration, and father's occupation. To increase power, each control group contained two individuals as controls—the person closest before and closest after the case on the register of births who met the matching criteria. Not infrequently those in control group 1 were the same as those in control group 2; that is, the controls in group 1 often shared paternal occupation with the case. Variables available that were not used for matching were paternal age at subject's birth, maternal age at subject's birth, length of time parents had been married at subject's birth, and age of the subject at SMS1932.

Statistical analysis. After initial data description, comparisons between cases and controls were made with t tests and then OR with 95% CI estimated using conditional logistic regression. Conditional logistic regression represents an extreme form of stratification to control for confounding exposures where each case is matched to specific controls.

RESULTS Eighty-six (49.7%) cases had AD, 32 (18.5%) VaD, 8 (4.6%) mixed AD/VaD, 44 (25.4%) unspecified dementia, 2 (1.2%) PD, and one (0.6%) as "other neurodegenerative." Demographic data were similar for all main dementia subtypes (table 1). Maternal age at birth was similar for AD cases (mean 30.7 years, SD [SD] 7.0), VaD cases (30.2 years, SD 5.7), and unspecified dementia (30.6 years, SD 6.5), as was paternal age at birth (AD 33.7 years, SD 8.2; VaD 32.0 years, SD 6.2; unspecified dementia 33.0 years, SD 7.1). AD cases' parents had been married for a median 3.9 years (interquartile range 1.2–10.5 years) at the case's birth, VaD cases' parents for 5.0 (1.2–10.0) years, and unspecified dementia parents for 3.5 (1.3–9.5) years. There was a trend for VaD cases to have lower MHT scores than AD cases (t = 1.87, p = 0.06). Among cases, a significant migration effect was found. Cases born outside Lothian (n = 43) had higher MHT scores than controls (44.6 vs 35.6 control group 1 and 35.0 control group 2) and cases born in Lothian (44.6 vs 36.2, n = 130, F = 11.3, p < 0.001). This was in the context of the trend for people born in Lothian already to have higher MHT scores than those born elsewhere in Scotland.[19] Since we were unable to identify suitable controls who also migrated into Lothian, cases who migrated into Lothian were excluded from further analysis.

Comparison of MHT scores by dementia type showed that VaD cases had significantly lower scores than both control group 1 (p = 0.02) and control group 2 (p = 0.01), but there was no significant difference for AD cases (table 2). Conditional logistic regression confirmed that higher MHT score age 11 was associated with significantly lower odds of VaD (OR 0.62, 95% CI 0.41–0.94 for a 10-point in-

Table 2	Mean MHT score in cases and controls in people born in Lothian			
Type of dementia	No.	Mean MHT (SD)	t	p Value
AD				
Case	63	37.7 (14.0)		
Control group 1	126	38.7 (15.0)	−0.5	0.64
Control group 2	122	37.6 (14.9)	0.1	0.95
VaD				
Case	31	34.0 (13.5)		
Control group 1	62	41.4 (14.5)	−2.4	0.02
Control group 2	62	40.9 (11.8)	−2.5	0.01
Unspecified dementia				
Case	36	35.4 (16.0)		
Control group 1	72	40.7 (13.9)	−1.8	0.08
Control group 2	70	36.1 (14.6)	−0.2	0.84

MHT = Moray House Test; AD = Alzheimer disease; VaD = vascular dementia.

crease in MHT score [0.7 standard deviations] compared with control group 2, table 3): no other independent variable (paternal age at subject's birth, maternal age at subject's birth, length of time parents had been married at subject's birth, age of subject at SMS) had any significant effect in the model. Results for unspecified dementia cases were intermediate between AD and VaD. There was a trend for cases to

Table 3	Relationship between MHT score and dementia subtypes	
Type of dementia	OR (95% CI)	p Value
AD		
Control group 1*	0.97 (0.79–1.19)	0.76
Control group 2†	1.02 (0.82–1.28)	0.86
VaD		
Control group 1‡	0.68 (0.50–0.94)	0.021
Control group 2§	0.62 (0.41–0.94)	0.023
Unspecified dementia		
Control group 1¶	0.76 (0.56–1.04)	0.085
Control group 2‖	1.00 (0.76–1.33)	0.99

*A total of 63 cases and 119 controls matched on sex, birth registration district, and age at SMS.
†A total of 61 cases and 119 controls matched on sex, birth registration district, and paternal occupational category.
‡A total of 31 cases and 60 controls matched on sex, birth registration district, and age at SMS.
§A total of 31 cases and 60 controls matched on sex, birth registration district, and paternal occupational category.
¶A total of 33 cases and 63 controls matched on sex, birth registration district, and age at SMS.
‖A total of 32 cases and 61 controls matched on sex, birth registration district, and paternal occupational category.
MHT = Moray House Test; AD = Alzheimer disease; VaD = vascular dementia; SMS = Scottish Mental Survey.

have lower MHT scores than control group 1 (mean 35.4 vs 40.7, $p = 0.08$) but not control group 2 ($p = 0.84$).

DISCUSSION In this sample, lower premorbid cognitive ability increased risk of VaD but not AD. This association was independent of early childhood social status and the environmental factors captured here. The data support the hypothesis that lower premorbid cognitive ability acts as a risk factor for dementia, through pathways of vascular risk rather than more generic cognitive reserve. If premorbid cognitive ability was acting primarily as an index of cognitive reserve, a similar effect on AD and VaD would have been expected. By contrast, if the effect was primarily through midlife vascular risk, low premorbid cognitive ability would, as reported here, have a greater impact on VaD. What has hitherto been considered as a direct measure of brain structure and function[25] may, instead, be mediated by vascular disease. This would be consistent with neuropathologic findings from the Nun study where vascular lesions made a major contribution to AD diagnosis.[16] The same may be applicable to educational attainment, which is closely related to premorbid cognitive ability,[26] and is also associated with dementia risk.[27] Education correlates with the extent of the parietotemporal regional cerebral blood flow (CBF) deficit in AD and this has been put forward as evidence of cognitive reserve.[28] However, such CBF deficits might also result from subtle vascular changes. The Framingham study demonstrated an association of education with non-AD dementia, but not with AD.[29] Similarly, a study in Stockholm found an association between lower educational attainment and unspecified dementia but not AD.[30] It might be argued that vascular load is, itself, a component of cognitive reserve, but this would push the concept beyond the point of absurdity in the case of a vascular disease like VaD.

In this study, we identify a risk factor for VaD as early as 11 years, well before completion of formal education, emphasizing the lifelong nature of risk and that prevention strategies could be implemented from childhood onwards. The unique availability of childhood cognitive data for a cohort now at high risk of dementia together with data that show associations between childhood cognitive ability and midlife vascular disease independent of socioeconomic status and smoking[13,14] allow causal pathways that stretch throughout the life course to be identified. These data favor vascular risk reduction as a priority.

Case representativeness was limited by use of case registers rather than independent identification in the community. This also resulted in a

smaller sample size than would have been obtained by community screening: limited numbers may have meant that we missed a true difference in MHT score between AD cases and controls because of inadequate power to detect an effect size <0.5 standard deviations. Ascertainment is likely to have been biased toward those seeking medical help. If this were the case, we would have expected MHT score among people identified as having dementia to be higher than the population average. The mean MHT scores of cases born in Lothian of 36.2 was identical to the mean for the population of Lothian as a whole, slightly lower than the mean for the population of Edinburgh (37.3), but higher than the Scottish mean of 34.5 (SD 15.5).[18] It would be expected to be higher than the mean for all those scored in 1932 because attrition affects people with lower childhood IQs to a greater extent.[12] Controls were chosen by matching at birth, but were known to have survived to 11 years of age as they participated in the SMS1932. VaD controls had higher mean MHT scores than AD controls. The paternal occupation profile was similar in terms of social class (table 1) and consistent with the national average, but there may have been subtle differences in actual occupation within the predominant skilled social class III that explain this difference.[31] A number of controls may have developed dementia, but this means that the ORs more accurately reflect risk relative to the general population rather than a select nondemented group. Moreover, as indicated in the Introduction, clinical diagnostic criteria of AD and VaD cover a spectrum of neuropathology and a proportion of controls may have had changes within their brains without any manifestations of dementia. The differentiation of VaD from AD using clinical criteria is known to be difficult. The diagnostic accuracy of the ICD-10 criteria is low.[32-34] The sensitivity of the ICD-10 criteria, as well as others, is very low. Thus while the clinical criteria used here identified subjects with clinical cerebrovascular syndromes, we do not know the extent of the link between the clinical diagnosis of VaD and cerebrovascular pathology. The matching also meant that we had no data to compare effects of education and occupation, though childhood IQ is strongly correlated with both in Western societies.[35] Whether the same pathways linking IQ and dementia are relevant to non-Western societies, which will see the largest increase in dementia, requires further research. This is important before public health measures to reduce dementia incidence based on preventing vascular pathology are implemented in less-developed countries.

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