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Childhood cognitive ability and incident dementia: the 1932 Scottish Mental Survey cohort into their tenth decade

Running head: Childhood IQ and dementia

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Availability of data and code for replication: The SMS1932 data are available to collaborating researchers through the Centre for Cognitive Ageing & Cognitive Epidemiology, University of Edinburgh (www.ccace.ed.ac.uk) and the linked health data are available from the Information Services Division of NHS National Services Scotland subject to application to the Public Benefit and Privacy Panel. Code is available from the authors on request.

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ABSTRACT

Background: The prevention of dementia is a global priority but its etiology is poorly understood. Early life cognitive ability has been linked to subsequent dementia risk but studies to date have been small and none has examined sex differences. **Methods:** In the 1932 Scottish Mental Survey cohort, we related intelligence test scores at age 11 years in 16,370 boys and 16,097 girls (born in 1921) to incident dementia aged ≥65 years as ascertained using probabilistic linkage to electronic health records up to the age of 92 years (1231 cases in men, 2163 in women; median follow up 15 years). **Results:** Compared to the highest intelligence group (≥115), dementia risk was raised in the lowest-scoring category (<85) and these associations were stronger for women (hazard ratio; 95% confidence interval: 1.51, 1.29 to 1.76) than men (1.19, 0.98 to 1.44; P-value for interaction by gender: 0.054). There was evidence of a dose-response association between childhood IQ and dementia in women (IQ 100-114.9 compared to ≥115: 1.18, 1.03 to 1.34; IQ 85-99.9: 1.32, 1.15 to 1.51; P-value for trend<0.001) but not in men (1.05, 0.89 to 1.24; 1.01, 0.85 to 1.21; 0.44) **Conclusions:** Childhood intelligence is related to subsequent dementia risk but this association is not the same in men and women.

Keywords: Dementia, cognitive ability, cohort study, survival analysis, life course epidemiology, risk factors, dementia prevention

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Introduction

Dementia is a major, growing global public health concern.[1] Potentially modifiable risk factors from different stages of the life course include low educational attainment (early life), hypertension, obesity, diabetes, and smoking (mid-life) and depression and, possibly, cognitive inactivity (later life).[2,3] Lower cognitive ability in early life, independent of educational achievement, has been linked to all dementias combined, in addition to sub-types (Alzheimer's and vascular).[4-7] Studies to date have, however, been small in size, leading to endpoint rarity and limited statistical power. Thus, no study to date has examined sex differences. Accordingly, we examined the association between childhood cognitive ability and dementia in a cohort study of over thirty-five thousand men and women.

Methods

Derivation of the cohort is described in detail elsewhere.[8] Briefly, participants in the 1932 Scottish Mental Survey (SMS1932)[9] – almost all children born in 1921 and attending school in June 1932 – were traced through linkage with electronic health records in Scotland using probabilistic linkage techniques. We excluded individuals who died before the age of 65 years thus forming a cohort who had not been diagnosed with dementia at this age who were followed up from age 65 years.

Incident dementia diagnoses were ascertained from any mention of dementia ICD codes (ICD-9: 290.0-290.4, 290.8, 290.9, 291.1, 291.2, 294.1, 294.2, 294.8, 294.9, and 331.0 to 331.9; ICD-10: F00-F05.1, F09, G30, and G31) in general or psychiatric hospital discharge records (Scottish Morbidity Records 01 and 04, respectively), death certificates, and, for a subset, primary care records. Scottish Morbidity Records began to be recorded electronically in 1981 and thus are only available from when participants were aged 60 years or older; since we were interested in incident dementia we only recorded dementia as an outcome if it was

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recorded from age 65 years onwards to ensure that prevalent cases at baseline were excluded. Death certificates were available for the full period of follow up but were only used to ascertain dementia from age 65 years onwards; death at any age was recorded. Primary care records were ascertained cross-sectionally at the linkage date for patients registered with the NHS Greater Glasgow & Clyde Nursing Homes Medical Practice, which provided primary care services solely to nursing homes within that health board.

Childhood cognitive ability was measured at around age 11 years, when all participants sat the Moray House Test no. 12, from which an IQ score was derived, corrected for age in days at the time of testing.[10] Ethical approval was granted by South East Scotland Research Ethics Committee 3 and use of the data was approved by NHS Caldicott Guardians, the Community Health Index Advisory Group, and by the Privacy Advisory Committee to NHS National Services Scotland and the Registrar General.

People with a record of dementia were censored at the age (years) at first mention of dementia in electronic health records or at death for people whose dementia was only mentioned on their death certificate. For non-cases, censoring took place either at their age at death from non-dementia causes or end of follow-up (June 2012), whichever came first. We used Cox proportional hazards models in the statistical package R version 3.2.3 to compute hazard ratios with accompanying 95% confidence intervals for the association between IQ aged 11 years and later dementia.[11,12] We divided individuals into four groups based on IQ score (>115 [the referent], 100-114.9, 85-99.9, and<85; IQ has, by definition, mean 100 and standard deviation [SD] 15) as well as reporting the hazard ratio per SD lower IQ score.

In addition to producing unadjusted hazard ratios, to allow for clustering of cognitive abilities we constructed multi-level Cox-mixed effects models nesting individuals within schools and counties. We also included a contemporary county-level measure of socioeconomic position:

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mean number of people per room in dwellings extracted from the 1931 census (available at http://www.histpop.org/).

Finally, in order to explore the possibility of selection bias in relation to childhood cognitive ability and survival to age 65 years we explored the effect of using inverse probability weighting. In order to adjust for any differential drop-out before the age of 65 years relating to IQ age 11 years, we estimated the stabilized inverse probability weights using the IPW package in R and repeated the Cox models with appropriate weighting.[13]

Results

A total of 43,569 boys and 42,951 girls were named in the SMS1932 ledgers and 19,272 men (44%) and 18,325 women (43%) were traced through probabilistic linkage to electronic health records. Mean IQ at baseline in study members traced and those who were not was very similar for men (99.4 vs 100.3) and women (100.0 vs 100.2). After dropping study members missing data for IQ (some individuals were recorded even though they were absent on the day of the test) and excluding participants who died before the age of 65 years, the analytical sample was 16,370 men and 16,097 women. Mean (SD, range) IQ scores were 99.6 (15.1, 51.0-138.0) in men and 100.2 (14.6, 51.0-135.9) in women. During follow-up of up to 26 years (median 15, interquartile range 8-21) from the age of 65 years, 1231 men and 2163 women developed dementia.

In men, there was no evidence of a linear relationship between IQ aged 11 years and subsequent dementia risk (**table**). However, dementia risk was somewhat raised in the lowest IQ group (i.e., greater than one SD below the mean) compared to the highest (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.98 to 1.44). In women, there was clearer evidence of a relationship such that a dose–response association between IQ aged 11 years and subsequent dementia risk across the full range of scores was apparent (IQ 100-114.9

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compared to ≥115: 1.18, 1.03 to 1.34; IQ 85-99.9: 1.32, 1.15 to 1.51; HR per SD disadvantage 1.14, 95% CI, 1.09 to 1.19; $P_{trend}<0.001$). This was not the case in men (IQ 100-114.9 compared to ≥115: 1.05, 0.89 to 1.24; IQ 85-99.9: 1.01, 0.85 to 1.21; $P_{trend}=0.44$). The results of the multi-level model were almost identical to the unadjusted model. Similarly, using inverse probability weighting to account for possible survival bias to age 65 years in relation to IQ aged 11 years did not alter our conclusions (**eTable;** http://links.lww.com/EDE/B165).

Discussion

Our main findings are that an association between lower childhood IQ and increased dementia risk was clearly evident in women, but less so in men. An association between lower educational attainment with increased dementia risk has been seen in a series of studies.[3,14] However, fewer studies have focused specifically on early-life cognitive ability, which may capture individual differences better than years of schooling, for example. The findings from the Nun study were that two measures of linguistic ability in early life – idea density and grammatical complexity derived from autobiographical essays written by on entry into the Order – were associated with lower cognitive function in later life and Alzheimer's disease.[4,5] Studies using subsets of the SMS1932 cohort have previously shown an association between lower childhood cognitive ability and dementia. In a case–control study including 50 people from the SMS1932 with late-onset dementia (i.e. from age 65 years and older), people who developed dementia scored worse on the Moray House Test aged 11 years.[6] A further case-control study of 297 SMS1932 participants with late-onset dementia matched to controls identified an association between lower childhood mental ability and vascular dementia (OR per 10-point increase [0.7 SD] in mental ability score, 95% CI 0.62, 0.41 to 0.94) but not Alzheimer's dementia (1.02, 0.82 to 1.28).[7] However, previous studies

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in this area have either analyzed men and women together or just included one gender. Thus, we cannot compare our finding of different associations between the sexes with previous studies. However, sex differences in dementia are well described. Alzheimer's dementia (the commonest cause of dementia) is recognized to be more common in women.[15] Furthermore, we have previously reported different associations in men and women between height – a marker of early life experience and which is closely correlated with cognition and cognitive reserve - and dementia.[16]

Our study has some limitations. Linkage with electronic health records identified less than half of the original cohort, which may result from emigration, death prior to the start of the records in 1981, and the probabilistic linkage methods used. However, this rate is similar to the response in other studies (e.g., 56% in CFAS-II[17]). Furthermore, since dementia is primarily a disease which presents in later life, few participants will have developed overt dementia prior to the start of Scottish Morbidity Records in 1981. In any case, we only used incident dementia at or after the age of 65 years in order to exclude prevalent cases prior to that age. There were also very small differences in mean IQ scores between those who were and were not traced so minimizing concerns regarding selection bias. Furthermore, we took differential survival to age 65 years into account with the inverse probability weighting. However, differential survival after age 65 years – IQ is associated with mortality[18] – is a further potential bias.[19,20] Thus, the use of Cox models in the present study as opposed to an illness–death model, as has been suggested to be appropriate,[21] might potentially bias our findings.

The dementia outcome used is another limitation. Individually, almost any health register will miss a proportion of dementia cases – approximately 28% on death certificates and 46% in general hospital discharge records[22,23] – but using multiple sources, as in the present study, will reduce the proportion missed. Importantly, in one of the studies just referred to,

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premorbid intelligence (estimated from the National Adult Reading Test which has been validated in people with dementia[24]) was not associated with correct recording or otherwise of a dementia diagnosis – from a tertiary referral memory clinic - on death certificates (data available from the author on request).[22]

Dementia subtype is relatively infrequently recorded on electronic health records so such analyses were not possible herein. Finally, using the earliest mention of dementia in any health record gives some indication of when the condition began but the illness will have been first identified on or before that date. These limitations are compounded by under-diagnosis of dementia – approximately half of people with dementia do not have a diagnosis and so this could never be recorded in electronic health records.[25] Nevertheless, the number of people dementia detected in our cohort is broadly what would be expected: approximately 9% of all participants and about two thirds of the cases being female.[15,26] A final limitation is the limited range of covariates – socioeconomic, health, and psychiatric – captured in the present study.

The multi-level model allows us to take into account clustering of cognitive abilities within schools – i.e. that pupils in one school may be, on average, brighter than those in another school (mean IQ scores for school ranged from 51 to 136). However, this may be *over*-controlling, falsely taking away some of the variance in IQ.

Social class has been shown to be associated with intelligence measured at age 11.[27] Thus, childhood cognitive ability might be a risk marker for socioeconomic factors in early life. Therefore, it may be these factors which are, partly at least, important in determining dementia risk. However, further work is required to tease apart which are the important factors and, crucially, whether they are amenable to modification in order to reduce the risk of individuals developing dementia during their lives.

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Table. Hazard ratios with accompanying 95% confidence intervals for the association between IQ aged 11 years and subsequent dementia incidence in men and women: follow up of the 1932 Scottish Mental Survey cohort into the tenth decade possession

	N	N events	Total IQ score ≥115	100-114.9	85-99.9	<85	Per SD disadvantage	P_{trend}
Men								
Unadjusted[a]	16370	1231	1 (ref.)	1.05 (0.89, 1.24)	1.01 (0.85, 1.21)	1.19 (0.98, 1.44)	1.02 (0.97, 1.08)	0.44
Multi-level model[b]	16039[c]	1212	1	1.05 (0.90, 1.24)	1.02 (0.86, 1.22)	1.21 (1.00, 1.47)	1.03 (0.97, 1.09)	0.36
Women								
Unadjusted	16097	2163	1 (ref.)	1.18 (1.03, 1.34)	1.32 (1.15, 1.51)	1.51 (1.29, 1.76)	1.14 (1.09, 1.19)	<0.001
Multi-level model	15764[c]	2119	1	1.17 (1.02, 1.33)	1.30 (1.13, 1.49)	1.47 (1.26, 1.72)	1.13 (1.08, 1.18)	<0.001

[a] 'Unadjusted' denotes a Cox proportional hazards model with no adjustment for covariables

[b] 'Multi-level model' denotes a hierarchical Cox proportional hazards model with additional school- and county-level random effects in addition to adjustment for county-level socioeconomic position (mean number of people per room in dwellings) derived from the 1931 Census

[c] An additional 331 men and 333 women were missing data on school or county

SD indicates standard deviation.

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