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Featured Article

Cognitive ability in young adulthood and risk of dementia in a cohort of Danish men, brothers, and twins

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Abstract

Introduction: We examined the association between cognitive ability in young adulthood and dementia in Danish men, brothers, and male twins.

Methods: In total, 666,986 men born between 1939 and 1959 were identified for dementia diagnosis in national registries from 1969 to 2016. The association between cognitive ability from draft board examination and dementia was examined using Cox regression.

Results: During a 44-year follow-up, 6416 (0.96%) men developed dementia, 1760 (0.26%) and 970 (0.15%) of which were classified as Alzheimer's and vascular dementia, respectively. Low cognitive ability was associated with increased risk of dementia (hazard ratio $[HR]_{\text{per SD decrease}}$ 1.33 [95% confidence interval {CI} = 1.30–1.35]) with the strongest associations for vascular dementia ($HR_{\text{per SD decrease}}$ 1.47 [95% CI = 1.31–1.56]) and a weaker for Alzheimer's disease ($HR_{\text{per SD decrease}}$ 1.07 [95% CI = 1.03–1.13]). The intrabrother and twin analyses (taking shared family factors into account) showed attenuated risk estimates but with wide CIs.

Discussion: Low early-life cognitive ability increases the risk of dementia before the age of 78 years. The association is partly explained by shared family factors.

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Keywords: Cohort study; Twin study; Cognitive ability; Dementia; Alzheimer's disease; Vascular dementia

1. Introduction

Dementia is a leading cause of disability, and with an increasing elderly population worldwide, the prevalence of dementia is expected to increase, despite reductions in incidence [1–4]. Alzheimer's disease (AD) is the most common cause of dementia in the elderly, followed by vascular dementia (VaD). The increasing awareness of shared modifiable risk factors such as cardiovascular risk factors [3] calls for an identification of such risk factors and effective strategies for prevention of dementia. In a life-course perspective, general early-life cognitive ability has been proposed as a potential risk factor for dementia. Low early-life cognitive ability reflects prenat al brain development [5–7] and is associated with subsequent morbidity and mortality [8–11]. This might increase the risk of dementia, which acts not only through cognitive reserve but also through poorer lifestyle and comorbidity, potentially influencing thrombotic and atherosclerotic processes and might

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increase the risk of vascular lesions [6]. However, the influence of early-life cognitive ability and lifestyle on risk of developing AD and VaD is scarcely investigated, mainly due to the lack of access to information on early-life cognitive ability. In the study of 93 nuns from Milwaukee, USA, linguistic ability at the age of 22 years was associated with cognitive test scores and a diagnosis of AD at the age of 75 to 95 years [12]. In the Scottish 1921 birth cohort, 50 patients with dementia diagnosed after the age of 65 years had lower mental ability at the age of 11 years compared with controls, but this was not the case for 59 patients with early-onset dementia [13]. Furthermore, analysis of the Scottish birth cohort also showed that the 31 cases with VaD had lower early-life mental ability than matched controls, but there was no significant difference for 63 cases with AD [14]. More recently, two studies based on the Swedish Military Conscription Register [15,16] have shown that low cognitive ability in young adulthood was associated with dementia before the age of 60 years (dementia cases: $n = 487$ [15] and $n = 657$ [16]).

Family studies have suggested that more than 50% of the between-subject variation in both early-life cognitive ability [17] and AD can be ascribed to genetic factors [17–19]. Environmental factors shared within families and attributed to cognitive ability include parental lifestyle and socioeconomic conditions [20]. Twin and sibling studies offer a unique design for controlling, in part, for shared genetic and familial factors [21,22] by taking advantage of the fact that twins and full siblings are almost always brought up together and that monozygotic (MZ) twins are perfectly matched genetically, whereas dizygotic (DZ) twins and full siblings share on average 50% of their segregating genes. To date, no studies have investigated the impact of shared familial factors on the association between early-life cognitive ability and late-life dementia.

The objectives of the study were to examine the association between cognitive ability in young adulthood and AD or VaD diagnosis and age of onset in men. We also wanted to assess whether this association could be replicated within brothers and male twin pairs. We hypothesize that low early-life cognitive ability increases the risk of dementia, and that familial factors including genetic constitution account for a considerable part of the expected association.

2. Methods

2.1. Study population

The Danish Conscription Database (DCD) comprises 728,158 Danish men born between 1939 and 1959, who were conscripted for mandatory military service from 1957 until 1984 and were alive on April 1, 1968 when the Danish Civil Registration System was established. Through data linkage with the Danish Twin Registry and the Danish Civil Registration System, 14,408 male twins (4108 intact male twin pairs $n = 8216$) and 81,002 brothers were identified in the DCD. Of the 728,158 men, 63,172 (0.9 %) were excluded; 52,843 had no conscript examination data, whereas 5691, 1181, and 1458 had no information on cognitive ability, education, or height. Available for analysis were 666,986 men including 74,761 brothers and 7310 male twins ($n = 3655$ pairs with information on zygosity for 1085 MZ and 2226 DZ pairs) with complete information on all data. The missing observations were mainly due to the lack of registry information for men who volunteered for military service or had been exempted from the draft board examination because of the medical conditions such as intellectual disability, psychiatric disorders, epilepsy, or type 1 diabetes. The percentage of missing observation was highest (8.2%) for men born after 1955 and lowest (5.9%) for those born before 1944. The DCD has been described in detail, previously [23]. All data linkages and analyses were approved by the Danish Data Protection Agency.

2.2. Assessment of cognitive ability

Cognitive ability was assessed by the draft board intelligence test, the Børge Prien Prøve (BPP), which has been described previously [23,24] and used in other studies [9]. It is a group-administered paper and pencil test comprising four subtests (letter matrices, 19 items; verbal analogies, 24 items; number series, 17 items; and geometric figures, 18 items) to be completed within 45 minutes. This version of BPP has been used without changes since 1957. The numbers of correct answers in the four subtests are summed to a total score with a 0 to 78 range. The total BPP score has been shown to correlate with the full-scale Wechsler Adult Intelligence Scale ($r = 0.82$) [25].

2.3. Dementia outcome measures

Information on any admission to a psychiatric or somatic ward from 1969 or 1977, respectively, until 2016 was obtained by linking the DCD to the Danish Psychiatric Central Registry and the Danish National Patient Registry using the person identification number as a key. These registers hold individual-level data on type of patient contact (inpatients, and, from 1995 onward, emergency and outpatients), diagnosis, and date of admission for all hospital admissions [26]. Mortality from all and specific causes of death was followed from April 1968 until April 2016 in the Danish Cause of Death Register. Hospital diagnosis and registered causes of death have been classified according to 8th revision of the International Classification of Disease (ICD-8) for the period 1969 to 1993, and according to the ICD-10 from 1994 onward. In the present study, the outcome of interest was the first hospital discharge or death from a main diagnosis of dementia (ICD-8: 290.00–290.99 and ICD-10: F00.0–F03.9; G30.0–G30.9) from 1969 until 2016. Dementia cases were subdivided into AD (ICD-8: 290.10 and ICD-10: F00.0–F00.9; G30.0–G30.9) and VaD (ICD-10: F01.0–F01.9) cases.

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