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Cardiovascular and cognitive fitness at age 18 and risk of early-onset dementia

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Patients with early-onset dementia are a significantly under-recognized subgroup of patients with an increasing prevalence. Epidemiological studies are limited and studies of modifiable risk factors, such as physical fitness, are lacking. We aimed to investigate the associations between cardiovascular fitness individually and in combination with cognitive performance at age 18 and risk of early-onset dementia and mild cognitive impairment later in life. We performed a population-based cohort study of over 1.1 million Swedish, 18-year-old, male conscripts, who underwent conscription exams between 1968 and 2005. These males were then followed for up to 42 years. Objective data on cardiovascular fitness and cognitive performance were collected during conscription exams and were subsequently linked with hospital registries to calculate later risk of early-onset dementia and mild cognitive impairment using Cox proportional hazards models controlling for several confounders. The scores from the exams were divided into tertiles (low, medium, high) for the analyses. The mean follow-up time for the analyses was 25.7 years (standard deviation: 9.3) and the median was 27 years. In total, 30 195 315 person-years of follow-up were included in the study. In fully adjusted models, both low cardiovascular fitness and cognitive performance (compared to high) at age 18 were associated with increased risk for future early-onset dementia (cardiovascular fitness, $n = 662$ events: hazard ratio 2.49, 95%, confidence interval 1.87–3.32; cognitive performance, $n = 657$ events: hazard ratio 4.11, 95%, confidence interval 3.19–5.29) and mild cognitive impairment (cardiovascular fitness, $n = 213$ events: hazard ratio 3.57, 95%, confidence interval 2.23–5.74; cognitive performance, $n = 212$ events: hazard ratio 3.23, 95%, confidence interval 2.12–4.95). Poor performance on both cardiovascular fitness and cognitive tests was associated with a >7-fold (hazard ratio 7.34, 95%, confidence interval 5.08–10.58) and a >8-fold (hazard ratio 8.44, 95%, confidence interval 4.64–15.37) increased risk of early-onset dementia and early-onset mild cognitive impairment, respectively. In conclusion, lower cardiovascular fitness and cognitive performance in early adulthood were associated with an increased risk of early-onset dementia and mild cognitive impairment later in life, and the greatest risks were observed for individuals with a combination of low cardiovascular fitness and low cognitive performance.

Keywords: mild cognitive impairment; exercise; epidemiology; longitudinal, dementia

Abbreviations: BMI = body mass index; ICD = International Classification of Diseases; MCI = mild cognitive impairment

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Introduction

Dementia is an increasing threat to an ageing population, with a global prevalence of dementia >35 million (WHO and Alzheimer's, 2012). Dementia is not one single disease, but rather a heterogeneous syndrome defined by measurable cognitive decline to the point where physical, social and intellectual functions are clearly impaired (Haan and Wallace, 2004). Mild cognitive impairment (MCI) is a clinical diagnosis of cognitive impairment in subjects who have not developed dementia. MCI may be a precursor of dementia and has, as dementia, heterogeneous aetiologies (Etgen *et al.*, 2011). Individuals diagnosed with MCI may also progress to different types of dementia, experience MCI until death, or even recover to normal cognition (Abner *et al.*, 2012).

Focusing on the high dementia prevalence in older populations may underestimate the importance of its occurrence in younger patients. Early-onset dementia (onset before 65 years of age) has attracted relatively little attention, is often misdiagnosed, and has been associated with higher mortality compared with late-onset dementias (Sampson *et al.*, 2004; Koedam *et al.*, 2008). A study from the USA evaluated patients with memory complaints from 2001 to 2004 and found that ~30% of these memory clinic patients with confirmed dementia had an age of onset <65 years (McMurtray *et al.*, 2006). Although this figure does not represent the general prevalence in a population (0.06–0.1%) (Harvey *et al.*, 2003; Sampson *et al.*, 2004; Borroni *et al.*, 2011; Nordstrom *et al.*, 2013), it highlights the importance of also studying early-onset diagnoses. Moreover, the number of individuals with early-onset dementia continues to rise (Werner *et al.*, 2009). Many neurological diseases and conditions have been identified as causes of early-onset dementia (Werner *et al.*, 2009), and studies of early-onset Alzheimer's disease focus on gene variants of susceptibility genes, such as amyloid precursor protein gene and presenilins in affected families (Rademakers *et al.*, 2003). However, familial Alzheimer's disease only accounted for <0.1% of all early-onset cases, demonstrating the need for investigation of modifiable risk factors (Whalley, 2001).

Studies of late-onset dementia report significant benefits of long-term, regular, physical and cognitive activity on later cognition, dementia risk and dementia progression (Fratiglioni *et al.*, 2004; Richards *et al.*, 2004; Rovio *et al.*, 2005; Ahlskog *et al.*, 2011). Apart from a recent study that identified risk factors for early-onset dementia in males, including cognitive performance at adolescence (Nordstrom *et al.*, 2013), there are surprisingly few epidemiological studies of early-onset dementia compared to late-onset, and studies focusing specifically on the effects of physical activity on early-onset dementia and MCI are currently lacking (Harvey *et al.*, 2003; McMurtray *et al.*, 2006; Werner *et al.*, 2009; Nordstrom *et al.*, 2013). The present study presents a large, population-based, cohort study with a follow-up interval of up to 42 years. The study aimed to determine whether cardiovascular fitness, separately or in combination with cognitive performance objectively measured in 18-year-old males, was associated with risk of developing early-onset dementia and MCI, i.e. before age 60. With >1.1 million subjects included, the current study provides valuable insights into future preventive and treatment strategies for dementia.

Materials and methods

Study population

The study cohort consisted of 18-year-old Swedish males, who enlisted for mandatory military service from 1968–2005 (i.e. born between 1950 and 1987, $n = 1\,353\,723$). During that time, Swedish law required all 18-year-old Swedish males to enlist. Exemptions were granted only for incarcerated males, severe chronic medical or mental conditions, or handicaps documented by a medical certificate (~2–3% of the yearly male population). Conscripts with complete information on cardiovascular fitness ($n = 1\,174\,483$) and cognitive performance ($n = 1\,172\,190$) at age 18 were included in the current study. The Ethics Committee of the University of Gothenburg and Confidentiality Clearance at Statistics Sweden approved this study.

Swedish Military Service Conscription Register data

Cardiovascular fitness test

Cardiovascular fitness was assessed using the cycle ergometer test. The procedure, including elements of validity and reliability, has been described in detail and used in previous studies (Nordesjö and schele, 1974; Aberg *et al.*, 2009). Briefly, after a normal resting electrocardiogram, 5 min of submaximal exercise was performed at work rates of 75–175 W, depending on body weight. The work rate was continuously increased by 25 W/min until volitional exhaustion. The subject was instructed to maintain pedal cadence between 60–70 rpm. Heart rate was continuously measured. The final work rate (W_{max}) was recorded and divided by body mass. W_{max}/kg was used because of better correlation with measured maximum oxygen consumption (V_{O2max}) (correlation coefficient ~0.9) than predicted maximum oxygen consumption (correlation coefficient ~0.6–0.7) (Nordesjö and schele, 1974). The resulting W_{max}/kg was transformed into stanine scores, with 1 representing lowest and 9 representing maximal performance, which served as a measure of cardiovascular fitness.

Cognitive performance tests

The cognitive performance tests have been previously described (Carlstedt, 2000) and data from these tests have been included in other studies (Aberg *et al.*, 2009). Individuals were tested for performance in four cognitive domains: logical, verbal, visuospatial and technical cognition. The logical intelligence test measured the capacity to understand written instructions and apply them to a problem-solving task. The verbal intelligence test measured the ability to correctly choose a synonym or opposite of a given set of words. The visuospatial intelligence test assessed the capability to identify the correct 3D object from a series of 2D drawings. The technical intelligence test represented complex problem solving requiring knowledge of basic physics and mathematics. Results from all four subtests were also combined with equal importance and weighted on the basis of the mean score, yielding a measure of general cognitive performance (Carlstedt, 2000). All test results, including the general cognitive performance derived from the four subtests, were standardized against

data from previous years to follow a Gaussian distribution, resulting in scores from 1 (lowest) to 9 (highest).

Diagnoses recorded at conscription

Males underwent extensive and highly standardized physical and psychological examinations by medical doctors and psychologists during the conscription examination. Those who met criteria for previous or ongoing dementia or MCI disorders or symptoms (ICD-9: 290, 294, 331 310W; ICD-10: F00-F03, G30, G31, G91.2, F06.7 R41.8A) at conscription were excluded from the current analyses ($n = 20$).

Register linkage

Swedish citizens have a unique personal identification number, which allows for linkage of data from the Swedish Military Service Conscription Register to other registers. Information from the various registers described below was compiled for each individual and anonymized to perform statistical analyses.

Swedish National Hospital Discharge Register

The Swedish National Hospital Discharge Register includes virtually all in-patient care, as well as specialist out-patient care, since 1964. Dementia diagnoses from this register have been previously validated (Nordstrom *et al.*, 2013). Discharge diagnoses are coded by the physician in accordance with the International Classification of Diseases (ICD), versions 9 or 10 (WHO, 1978, 1992). The follow-up period began at date of conscription (baseline); however, individuals diagnosed according to ICD-8 (enlisted for conscription between 1968 and 1978 and diagnosed 1–10 years after, $n = 5$) were excluded from analyses because of uncertain dementia diagnostics tools at the time.

Diagnostics codes were identified for first disorder onset from 1978 to 31 December 2010. Because the oldest individuals in the study at time of diagnosis were 60 years old, only males with an early-onset dementia were included. MCI was defined as mild cognitive disorder (ICD-10: F06.7), subjective complaints of mild cognitive disorder (ICD-10: R41.8A), and other specified non-psychotic mental disorders following organic brain damage, including mild memory disturbance (ICD-9: 310W). Early-onset of all dementias was defined by combining first onset of several dementia disorders and syndromes, including Alzheimer's disease, vascular dementia, and dementia as a result of other diseases (ICD-9: 290, 294, 331; ICD-10: F00-F03, G30, G31, G91.2).

Longitudinal Integration Database for Health Insurance and Labor Market Studies

The Longitudinal Integration Database for Health Insurance and Labor Market Studies (Swedish acronym LISA; http://www.scb.se/Pages/List____257743.aspx) at Statistics Sweden includes all registered residents of Sweden aged 16 years and older and has been previously used in studies (Aberg *et al.*, 2009). Information on parental and individuals own education (80% coverage) was rated into three levels: pre-high school education, high school education, and college and/or postgraduate education.

Cause of Death Register

The Swedish Cause of Death Register, which covers almost all deaths since 1961, is annually updated based on death certificate diagnoses.

Statistical analyses

All statistical calculations were performed using SAS version 8.1 (SAS Institute). Proportional hazards assumptions were investigated using R version 3.0.2 (R Foundation for Statistical Computing). Cox proportional hazards models were used to assess the influence of cardiovascular fitness and cognitive performance at age 18 for the first occurrence of early-onset dementia and MCI later in life. The follow-up period began at the date of conscription (baseline) and subjects were later censored at time of first-onset dementia or MCI diagnosis, death from other causes, or at the end of follow-up period, i.e. 31 December 2010 (maximum 42-year follow-up). Results from the cardiovascular fitness test and the tests of the four cognitive domains (logical, verbal, visuospatial and technical) were standardized against data from previous years and evaluated on a normalized scale ranging from stanine score 1–9. For the measure of general cognitive performance, the test scores of the four cognitive domains were summed with equal importance. Cardiovascular fitness and cognitive performance were categorized as low (stanine score 1–3), medium (stanine score 4–6), and high (stanine score 7–9); the high group served as the reference category. The standardization to a 9-point stanine scale and then grouping the scores into three groups (low, medium, high) provided long-term stability of the data sets and have been used previously (Gunnell *et al.*, 2005). As cardiovascular fitness in contrast to cognitive performance was not normally distributed (Table 1), separate subanalyses were performed with low cardiovascular fitness as stanine score 1–4, medium as stanine score 5–7 and high as stanine score 8–9.

To assess effects of variation in diagnosis rate and differences in conscription procedures over calendar time, we adjusted for calendar years of conscription by stratifying the Cox model by decade (60's, 70's, etc.). To reduce the risk for possible reverse causation, subanalyses were also performed in individuals, who fulfilled criteria for previous or ongoing neurological disorders or symptoms (ICD-8 and 9 codes 320-389, 780, 781; ICD-10 codes G00-G99) or psychiatric disorders or symptoms (ICD-8 and 9 codes 290-319; ICD-10 codes F00-F99) at conscription, and were excluded. To further reduce baseline misclassification, separate analyses were performed, excluding incident cases during the first 10 and 20 years after conscription. Because differences among regions and test centres could introduce bias, geographical region (where the conscript resided) and conscription test centres were considered as possible confounders and were accounted for in the adjustments. Mid-life body mass index (BMI) is a risk factor for later dementia; therefore, BMI was included as a confounder (Anstey *et al.*, 2011). Parental education levels (mother and father separately), as well as conscript's own education, were included as confounders. Moreover, separate analyses were performed including presence of cerebrovascular disease (ICD-10: I60-I69, G46, G45.9; ICD-8/9: 430-438), diabetes (ICD-10: E10-E14; ICD8/9: 250) or hypertension (ICD-10: I10-I15; ICD-9: 401-405; ICD-8: 400-404) before the dementia or MCI diagnosis as additional explanatory variables to the adjusted models. In a final set of analyses we looked at combinations of different subgroups of cardiovascular fitness and cognitive performance to study the relations between fitness and cognition on the future risk of early-onset dementia and MCI separately. We then combined all nine subgroups of low, medium and high cardiovascular fitness and cognitive performance, using the high cardiovascular fitness/high cognitive performance group as the reference category. We also investigated the overall statistical interaction between cardiovascular fitness and cognitive performance on risk of early-onset dementia and MCI.

Table 1 Numbers and proportions with first onset dementia and MCI during the observation period, shown by level of cardiovascular fitness and cognitive performance at age 18

	Total number of conscripts	Number of all dementia diagnoses (%)	Number of MCI diagnoses (%)
Cardiovascular fitness			
1	994	2 (0.2)	0 (0)
2	5 589	8 (0.14)	6 (0.11)
3	39 686	55 (0.14)	19 (0.05)
4	114 112	81 (0.07)	27 (0.02)
5	192 655	158 (0.08)	43 (0.02)
6	323 976	133 (0.04)	54 (0.02)
7	171 751	91 (0.05)	26 (0.02)
8	117 773	45 (0.04)	10 (0.01)
9	207 947	89 (0.04)	28 (0.01)
All levels	1 174 483	662 (0.06)	213 (0.02)
Cognitive performance			
1	31 472	64 (0.20)	28 (0.09)
2	71 951	82 (0.11)	24 (0.03)
3	119 063	114 (0.10)	28 (0.02)
4	178 285	125 (0.07)	38 (0.02)
5	257 944	110 (0.04)	36 (0.01)
6	208 085	73 (0.04)	25 (0.01)
7	157 167	48 (0.03)	22 (0.01)
8	95 902	27 (0.03)	9 (0.01)
9	52 321	14 (0.03)	2 (0.00)
All levels	1 172 190	657 (0.06)	212 (0.02)

The proportional hazard assumption was investigated using plots and tests based on Schoenfield residuals (Therneau and Grambsch, 2000). In a large sample, the assumption may be reasonable despite being rejected by formal tests (Moeschberger and Klein, 2003). Therefore we investigated potential violations further by either using a stratified Cox model or by modelling the covariate-time interaction explicitly. If the changes in estimates were only minor, the assumption was deemed to be justified. The hazard assumptions for the analyses regarding cardiovascular fitness and cognitive performance on later risk of early-onset dementia and MCI all held for our data, except for the analysis of cognitive performance and later risk of MCI. Therefore, we further examined these hazards by a Kaplan-Meier plot and found that hazards were unproportional among individuals with a high cognitive performance after 30 years of follow-up (Supplementary Fig. 1). This correlates with the increased number of MCI cases that start after 30 years in this group compared with the low and medium cognitive fitness group who have more cases earlier on. Because of the large number of observations, *P*-values were small [in all analyses in which the 95% confidence interval (CI) did not include 1, the *P*-values were <0.0001]. Therefore *P*-values are not reported and the risk for type I errors is considered to be low.

Results

Of the number of males at the military conscription ($n = 1\,353\,723$) with information on cardiovascular fitness ($n = 1\,174\,483$; 179 240 males were excluded from the analyses) and cognitive performance ($n = 1\,172\,190$; 181 533 males were excluded from the analyses), 662 and 657 were diagnosed with early-onset dementia and 213 and 212 with early-onset MCI, respectively. The mean follow-up time for the analyses was 25.7 years [standard deviation (SD): 9.3] and the median was 27 years. In total, 30 195 315 person-years of follow-up were included in the study. During the follow-up time 24 728 individuals died and 48 006 individuals emigrated. Of the males with information of cardiovascular fitness and cognitive performance, 41 443 and 40 436, respectively, lacked full information from the other national databases. A flowchart of the completeness of data for the individuals included in the analyses is shown in Supplementary Fig. 2. Fourteen per cent of the individuals in the cohort had pre-high school as highest education, 53% had finished high school and 32% had a college and/or postgraduate education. The distribution of the parents' education was as follows: 40% of the mothers and 41% of the fathers had pre-high school as highest education, 34% of the mothers and 24% of the fathers had finished high school and 26% of the mothers and 35% of the fathers had a college and/or postgraduate education. Of the individuals with early-onset dementia, 89 also had cerebrovascular disease, 37 had diabetes and 47 had hypertension before their dementia diagnosis. Of the individuals with early-onset MCI, 52 also had cerebrovascular disease, 12 had diabetes and 29 had hypertension before their MCI diagnosis.

Table 1 shows the distribution of early-onset dementia and MCI diagnoses among the different cardiovascular fitness and cognitive performance stanine scores.

Cardiovascular fitness and cognitive performance at age 18 and future early-onset dementia or mild cognitive impairment

Low and medium cardiovascular fitness (compared with high) were associated with an increased risk of being diagnosed with early-onset dementia and MCI later in life (Table 2). Association strength remained significant in models that controlled for calendar year, conscription test centre, region, BMI, parental education, individual's education level, and cognitive performance at age 18. The hazard ratio in the low cardiovascular fitness group was attenuated by 23% for early-onset dementia (comparing hazard ratio 1.92 adjusted for cognitive performance, with hazard ratio 2.49 unadjusted for cognitive performance; Table 2) and 17% for MCI dementia (comparing hazard ratio 2.96 adjusted for cognitive performance, with hazard ratio 3.57 unadjusted for cognitive performance; Table 2), respectively, when controlling for cognitive performance at conscription. Data were re-analysed using a different grouping of cardiovascular fitness (see 'Statistical analysis' section) and this procedure yielded similar hazard ratios (results not shown). Therefore, stanine score 1–3 was used as 'low', stanine score 4–6 as 'medium' and stanine score 7–9 as 'high' cardiovascular fitness in all following analyses.

Low cognitive performance (compared with high) was also associated with an increased risk for early-onset dementia and MCI later in life (Table 2). For early-onset dementia, but not for MCI,

Table 2 Hazard ratios for all dementias and MCI in relation to cardiovascular fitness ($n = 1\,174\,483$) and cognitive performance ($n = 1\,172\,190$) in 18-year-old male conscripts with age-adjusted and fully adjusted models

	Hazard ratio (95% CI)				
All dementias, *n* = 662					
Cardiovascular fitness	**Age adjusted**	**Adjusted[a]**	**Adjusted[b]**	**Adjusted[c]**	**Adjusted[d]**
Low*	2.68 (2.03–3.53)	2.72 (2.05–3.62)	2.49 (1.87–3.32)	2.19 (1.64–2.92)	1.92 (1.43–2.58)
Medium*	1.42 (1.21–1.68)	1.50 (1.26–1.77)	1.42 (1.20–1.69)	1.34 (1.12–1.59)	1.28 (1.08–1.53)
MCI, *n* = 213					
Cardiovascular fitness	**Age adjusted**	**Adjusted[a]**	**Adjusted[b]**	**Adjusted[c]**	**Adjusted[d]**
Low*	3.59 (2.26–5.70)	3.83 (2.39–6.12)	3.57 (2.23–5.74)	3.19 (1.98–5.14)	2.96 (1.83–4.78)
Medium*	1.69 (1.25–2.28)	1.75 (1.28–2.38)	1.68 (1.23–2.29)	1.57 (1.15–2.14)	1.52 (1.11–2.07)
All dementias, *n* = 657					
Cognitive performance	**Age adjusted**	**Adjusted[a]**	**Adjusted[b]**	**Adjusted[c]**	**Adjusted[e]**
Low*	4.04 (3.18–5.14)	4.24 (3.32–5.41)	4.11 (3.19–5.29)	3.39 (2.60–4.42)	3.82 (2.96–4.93)
Medium*	1.72 (1.36–2.18)	1.79 (1.41–2.27)	1.78 (1.39–2.26)	1.62 (1.26–2.07)	1.72 (1.35–2.20)
MCI, *n* = 212					
Cognitive performance	**Age adjusted**	**Adjusted[a]**	**Adjusted[b]**	**Adjusted[c]**	**Adjusted[e]**
Low*	3.41 (2.27–5.12)	3.36 (2.24–5.06)	3.23 (2.12–4.95)	2.47 (1.57–3.87)	2.85 (1.86–4.39)
Medium*	1.51 (1.02–2.24)	1.51 (1.02–2.24)	1.49 (0.99–2.22)	1.25 (0.82–1.89)	1.41 (0.95–2.12)

*Reference category: high.
[a]Adjusted for calendar year, BMI, region, conscription test centre.
[b]Adjusted for calendar year, BMI, region, conscription test centre, parental education.
[c]Adjusted for calendar year, BMI, region, conscription test centre, own education.
[d]Adjusted for calendar year, BMI, region, conscription test centre, parental education, cognitive performance at age 18.
[e]Adjusted for calendar year, BMI, region, conscription test centre, parental education, cardiovascular fitness at age 18.

medium cognitive performance (compared to high) was also associated with an increased risk. The hazard ratio in the low cognitive performance group was attenuated by 7% for early-onset dementia (comparing hazard ratio 3.82 adjusted for cardiovascular fitness, with hazard ratio 4.11 unadjusted for cardiovascular fitness; Table 2) and 12% for MCI (comparing hazard ratio 2.85 adjusted for cardiovascular fitness, with hazard ratio 3.23 unadjusted for cardiovascular fitness; Table 2), when controlling for cardiovascular fitness at conscription.

To reduce the risk for possible reverse causation, individuals with any neurological or psychiatric disorders/symptoms at baseline, as well as incident cases in the first 10 and 20 years after conscription, were excluded. This resulted in only slight changes in hazard ratios, and a significantly increased risk in individuals with low cardiovascular fitness and cognitive performance remained in all analyses (Table 3). Separate analyses were performed also including presence of cerebrovascular disease, diabetes or hypertension before the dementia or MCI diagnosis as additional explanatory variables. The association between cardiovascular fitness and early-onset dementia was attenuated when adjusting for cerebrovascular disease (attenuated by 25%; comparing hazard ratio 2.05 from Table 4 adjusted for cerebrovascular disease, with hazard ratio 2.72 from Table 2 unadjusted for cerebrovascular disease), but only slightly when adjusting for diabetes (attenuated by 11%; comparing hazard ratio 2.41 from Table 4 adjusted for cerebrovascular disease, with hazard ratio 2.72 from Table 2 unadjusted for cerebrovascular disease) and hypertension (attenuated by 5%; comparing hazard ratio 2.58 from Table 4 adjusted for cerebrovascular disease, with hazard ratio 2.72 from Table 2 unadjusted for cerebrovascular disease). The association of cognitive performance and early-onset dementia when adjusting for cerebrovascular disease, diabetes and hypertension, was similar to not adjusting. The associations of early-onset MCI and cardiovascular fitness as well as cognitive performance, when adjusting for cerebrovascular disease, diabetes and hypertension, were both similar to not adjusting.

Different domains of cognitive performance at age 18 and future early-onset dementia or mild cognitive impairment

To determine whether risk for future early-onset dementia or MCI differentially correlated with one domain of cognitive performance more than others, logic cognition, verbal cognition, visuospatial cognition, and technical cognition at age 18 were analysed separately (Table 5). Although there were smaller differences in the hazard ratios, low performance in all four cognitive domains resulted in significantly increased risks for both early-onset dementia and MCI later in life. For both early-onset dementia and MCI, the hazard ratios were lowest for visuospatial cognition. The highest

Table 3 Subanalyses of hazard ratios for all early-onset dementias in relation to cardiovascular fitness and cognitive performance in 18-year-old male conscripts

	Hazard ratio (95% CI)		
	Age adjusted	Adjusted[e]	Adjusted[f]
Cardiovascular fitness			
[a]**Neurological diagnoses excluded** (n = 1 039 072)			
All dementias, n = 528			
Low*	2.77 (2.04–3.76)	2.78 (2.03–3.82)	2.57 (1.86–3.52)
Medium*	1.33 (1.11–1.60)	1.40 (1.16–1.70)	1.34 (1.10–1.62)
[b]**Psychiatric diagnoses excluded** (n = 1 117 831)			
All dementias, n = 531			
Low*	2.39 (1.72–3.32)	2.35 (1.67–3.31)	2.20 (1.56–3.10)
Medium*	1.35 (1.12–1.62)	1.39 (1.15–1.68)	1.34 (1.11–1.62)
[c]**10 years latency time** (n = 1 093 673)			
All dementias, n = 549			
Low*	2.70 (2.01–3.64)	2.88 (2.11–3.93)	2.59 (1.90–3.55)
Medium*	1.43 (1.19–1.71)	1.57 (1.30–1.89)	1.48 (1.23–1.79)
[d]**20 years latency time** (n = 824 500)			
All dementias, n = 340			
Low*	2.13 (1.41–3.21)	2.37 (1.54–3.65)	2.10 (1.36–3.24)
Medium*	1.59 (1.27–2.00)	1.71 (1.35–2.16)	1.59 (1.26–2.02)
Cognitive performance			
[a]**Neurological disease excluded** (n = 1 036 958)			
All dementias, n = 524			
Low*	3.67 (2.82–4.78)	3.88 (2.97–5.07)	3.75 (2.84–4.96)
Medium*	1.66 (1.29–2.14)	1.73 (1.34–2.24)	1.71 (1.32–2.23)
[b]**Psychiatric disease excluded** (n = 1 115 818)			
All dementias, n = 528			
Low*	3.20 (2.46–4.15)	3.36 (2.58–4.38)	3.32 (2.52–4.37)
Medium*	1.63 (1.27–2.08)	1.69 (1.32–2.17)	1.70 (1.32–2.18)
[c]**10 years latency time** (n = 1 091 563)			
All dementias, n = 545			
Low*	4.57 (3.47–6.00)	4.92 (3.74–6.49)	4.65 (3.50–6.18)
Medium*	1.94 (1.48–2.53)	2.05 (1.56–2.68)	2.00 (1.52–2.63)
[d]**20 years latency time** (n = 823 207)			
All dementias, n = 338			
Low*	5.29 (3.67–7.61)	5.60 (3.88–8.07)	4.92 (3.38–7.14)
Medium*	2.34 (1.64–3.34)	2.43 (1.70–4.47)	2.26 (1.57–3.24)

*Reference category: high.
[a]Subanalyses after exclusion of conscripts with any neurological diagnosis preceding or coinciding with conscription examination.
[b]Subanalyses after exclusion of conscripts with any psychiatric diagnosis preceding or coinciding with conscription examination.
[c]Subanalyses after exclusion of conscripts with a dementia diagnosis during the first 10 years following the conscription examination.
[d]Subanalyses after exclusion of conscripts with a dementia diagnosis during the first 20 years following the conscription examination.
[e]Adjusted for calendar year, BMI, region, conscription test centre.
[f]Adjusted for calendar year, BMI, region, conscription test centre, parental education.

hazard ratio for early-onset dementia was obtained with a low verbal cognitive performance and the highest hazard ratio for MCI with a low logic cognitive performance.

Relations between cardiovascular fitness and cognitive performance on future risk of early-onset dementia and mild cognitive impairment

To study the relationship between cardiovascular and cognitive performance on future risk of early-onset dementia and MCI, cardiovascular and cognitive performance were included in the same model (Table 6). A global test for interaction showed that there was no statistical interaction between cardiovascular fitness and cognitive performance on future risk of early-onset dementia and MCI. Poor performance (category 'low') on both the cognitive and cardiovascular fitness tests was associated with a >7-fold increased risk for early-onset dementia and a >8-fold increased risk for MCI, compared to a high performance in both. A high cardiovascular fitness (compared with low) in individuals with low cognitive performance reduced the risk of early-onset dementia with 48 % [(1 – hazard ratio (3.82 / 7.34)) × 100]. On the other hand, a high cognitive performance (compared with low)

Table 4 Hazard ratios for early-onset dementia and MCI in relation to cardiovascular fitness and cognitive performance at age 18: subanalyses with a diagnosis of cerebrovascular disease or diabetes or hypertension prior to dementia or MCI as additional separate confounders to fully adjusted models

	Hazard ratio (95% CI)		
	Adjusted[a]	Adjusted[b]	Adjusted[c]
Cardiovascular fitness			
All dementias, *n* = 651			
Low*	2.05 (1.54–2.72)	2.41 (1.81–3.20)	2.58 (1.94–3.43)
Medium*	1.34 (1.13–1.60)	1.48 (1.25–1.76)	1.47 (1.24–1.74)
MCI, *n* = 210			
Low*	3.60 (2.25–5.76)	3.84 (2.40–6.14)	3.78 (2.36–6.06)
Medium*	1.52 (1.11–2.08)	1.59 (1.16–2.17)	1.60 (1.17–2.18)
Cognitive performance			
All dementias, *n* = 646			
Low*	3.92 (3.08–5.02)	3.97 (3.10–5.07)	4.08 (3.20–5.21)
Medium*	1.68 (1.32–2.13)	1.78 (1.14–2.26)	1.76 (1.39–2.24)
MCI, *n* = 209			
Low*	3.32 (2.19–5.01)	3.29 (2.18–4.95)	3.38 (2.24–5.10)
Medium*	1.42 (0.95–2.11)	1.46 (0.98–2.17)	1.49 (1.00–2.21)

*Reference category: high.
[a]Adjusted for calendar year, BMI, region, conscription test centre, cerebrovascular disease .
[b]Adjusted for calendar year, BMI, region, conscription test centre, diabetes.
[c]Adjusted for calendar year, BMI, region, conscription test centre, hypertension.

in individuals with low cardiovascular fitness reduced the risk of early-onset dementia with 74 % [(1 – hazard ratio (1.92 / 7.34)) × 100].

Discussion

The present results show that both low cardiovascular and cognitive performance in early adulthood were associated with an increased risk of early-onset dementia and MCI later in life, and that the highest risks were observed for individuals with a combination of low cardiovascular fitness and low cognitive performance. Results for cognitive performance and early-onset dementia were in accordance with a previously described study (Nordstrom *et al.*, 2013), but associations of cardiovascular fitness and later risks of early-onset dementia and MCI have not been previously shown.

Prevalence rates for early-onset dementia ranging from 55–98/100 000 in the age-group 45–64 years have been previously reported (Harvey *et al.*, 2003; Sampson *et al.*, 2004; Borroni *et al.*, 2011; Nordstrom *et al.*, 2013). In the current study, the proportion of males without a dementia diagnosis at baseline, who later developed early-onset dementia (0.06%; 56/100 000), corresponded well with these numbers.

Given that changes in the brain, which lead to dementia, might start to develop years before manifestation of actual symptoms, it is of great importance to investigate potential risk factors early in life (Braak *et al.*, 1999). The current study relies on psychologists and physicians for baseline assessment of mental and physical health history, which allows for the exclusion of individuals with previous or pre-existing psychiatric or neurological disorders or symptoms. Excluding individuals with any dementia diagnosis during the first 10 and 20 years following conscription examination did not attenuate the observed risks of early-onset dementia or MCI. Moreover, we performed separate subanalyses including prior cerebrovascular disease, diabetes and hypertension as additional explanatory variables and the associations remained. However, these findings do not fully explain the causal effects. Although we have performed analyses excluding individuals with previous or pre-existing psychiatric and neurological disorders or symptoms at baseline and also adjusted the analyses for the individual's as well as parental education level, other early life experiences such as intrauterine factors or low socioeconomic status might still affect cardiovascular and cognitive performance at conscription and hence later risk of early-onset dementia and MCI. Further long-term intervention studies are needed to determine the effects of low performance at baseline on onset and clinical course of early-onset dementia and MCI.

The current study was based on clinical diagnoses, but lacks pathological confirmation of these diagnoses. To increase diagnostic reliability, only individuals diagnosed using the ICD-9 and ICD-10 code system were included, which excluded five individuals with ICD-8 diagnosis. Moreover, to specifically investigate a more exact diagnosis we studied the subgroup early-onset MCI.

Previous studies have documented significant benefits of long-term, regular exercise on cognition, late-onset dementia risk, and perhaps late-onset dementia progression (Dik *et al.*, 2003; Richards *et al.*, 2004; Hamer and Chida, 2009; Ahlskog *et al.*, 2011; Ratey and Loehr, 2011). However, epidemiological studies and intervention studies on the effects of physical activity on early-onset dementia are lacking. Given the patients' younger age, these individuals might respond better to exercise programmes compared with older patients.

Table 5 Hazard ratios for all dementias and MCI in relation to performance on logical, verbal, visuospatial, and technical cognition measurements in 18-year-old male conscripts

Performance	Hazard ratio (95% CI)			
	Age adjusted	Adjusted[a]	Adjusted[b]	Adjusted[c]
Logic cognition test				
All dementias				
Low*	3.39 (2.66–4.31)	3.43 (2.70–4.39)	3.29 (2.56–4.24)	2.63 (2.02–3.43)
Medium*	1.53 (1.21–1.93)	1.54 (1.22–1.95)	1.52 (1.20–1.93)	1.36 (1.07–1.74)
Verbal cognition test				
All dementias				
Low*	3.74 (2.88–4.85)	3.99 (3.06–5.20)	3.84 (2.93–5.04)	3.14 (2.37–4.17)
Medium*	1.72 (1.34–2.22)	1.81 (1.40–2.34)	1.80 (1.39–2.33)	1.63 (1.25–2.12)
Visuospatial cognition test				
All dementias				
Low*	2.92 (2.29–3.73)	3.14 (2.45–4.03)	2.97 (2.31–3.82)	2.55 (1.98–3.29)
Medium*	1.69 (1.36–2.11)	1.75 (1.40–2.19)	1.71 (1.36–2.14)	1.61 (1.28–2.02)
Technical cognition test				
All dementias				
Low*	3.28 (2.53–4.27)	3.37 (2.58–4.40)	3.23 (2.46–4.25)	2.73 (2.07–3.60)
Medium*	1.65 (1.27–2.14)	1.71 (1.32–2.23)	1.68 (1.29–2.19)	1.53 (1.17–1.99)
Logic cognition test				
MCI				
Low*	4.99 (3.04–8.18)	4.88 (2.97–8.01)	4.88 (2.93–8.13)	3.75 (2.20–6.41)
Medium*	2.39 (1.48–3.86)	2.38 (1.47–3.83)	2.40 (1.48–3.89)	2.04 (1.24–3.43)
Verbal cognition test				
MCI				
Low*	3.21 (2.06–4.98)	3.20 (2.05–4.99)	3.11 (1.97–4.92)	2.31 (1.43–3.74)
Medium*	1.45 (0.95–2.23)	1.47 (0.96–2.26)	1.47 (0.95–2.26)	1.21 (0.78–1.89)
Visuospatial cognition test				
MCI				
Low*	2.38 (1.58–3.56)	2.52 (1.67–3.79)	2.40 (1.58–3.63)	1.96 (1.28–3.00)
Medium*	1.23 (0.82–1.77)	1.27 (0.88–1.84)	1.25 (0.86–1.80)	1.13 (0.76–1.63)
Technical cognition test				
MCI				
Low*	3.07 (1.93–4.89)	3.02 (1.89–4.80)	2.91 (1.18–4.68)	2.29 (1.41–3.72)
Medium*	1.60 (1.01–2.52)	1.60 (1.01–2.52)	1.57 (0.99–2.49)	1.34 (0.84–2.13)

*Reference category: high.
[a]Adjusted for calendar year, BMI, region, conscription test centre.
[b]Adjusted for calendar year, BMI, region, conscription test centre, parental education.
[c]Adjusted for calendar year, BMI, region, conscription test centre, own education.

The cross-sectional correlation of low cardiovascular fitness and low cognitive performance at age 18 (Aberg *et al.*, 2009) indicates the possibility that the association between low cardiovascular fitness in young adulthood and early-onset dementia later in life was mediated via an effect of low cognitive ability at baseline. However, after including parental education level, the individual's education level, or cognitive performance at age 18 as additional confounders, associations between cardiovascular fitness and later early-onset dementia and MCI remained significant.

Low performance in any of the cognitive domains (logic, verbal, visuospatial or technical) was associated with higher risks of early-onset dementia and MCI, respectively. Although performance of individuals, who later developed early-onset dementia, on these cognitive domains was recently published, separate risk analyses were not performed. The present results for verbal intelligence scores were in accordance with findings from the Nun Study (Riley *et al.*, 2005), which suggested a strong inverse relationship between early-life linguistic ability and late-life cognitive function, including MCI.

The current study was performed with some limitations. The Swedish National Hospital Discharge Register allowed analyses of virtually all in-patient and specialist care for dementia diagnoses. Nevertheless, the incidence of early-onset dementias and MCI as well as cerebrovascular disease, diabetes and hypertension could be underestimated, because it is possible that some subjects were never admitted to a hospital-based health care and would be missed by the discharge register. Moreover, as MCI only during the last decade has been recognized in clinical practice and commonly used in medical literature, the prevalence of cognitive impairment as a result of MCI may have been falsely low. This probably means that our findings would have been even stronger if the MCI diagnostics had been applied also during the early time

Table 6 Hazard ratios for all early-onset dementias and MCI in relation to combinations of separate subgroups of cardiovascular fitness and cognitive performance (IQ) in 18-year-old male conscripts

		Hazard ratio (95% CI)		
		Age adjusted	Adjusted[a]	Adjusted[b]
All dementias, $n = 657$				
Low fitness	Low IQ	7.67 (5.41–10.88)	7.74 (5.42–11.06)	7.34 (5.08–10.58)
	Medium IQ	3.42 (2.39–4.91)	3.42 (2.37–4.95)	3.31 (2.28–4.80)
	High IQ	2.06 (1.55–2.73)	2.00 (1.49–2.68)	1.92 (1.43–2.58)
Medium fitness	Low IQ	4.74 (3.59–6.27)	5.07 (3.82–6.73)	4.90 (3.65–6.57)
	Medium IQ	2.12 (1.60–2.81)	2.25 (1.69–3.00)	2.21 (1.65–2.95)
	High IQ	1.27 (1.08–1.51)	1.31 (1.10–1.56)	1.28 (1.08–1.52)
High fitness	Low IQ	3.73 (2.92–4.75)	3.88 (3.03–4.96)	3.82 (2.96–4.93)
	Medium IQ	1.66 (1.31–2.11)	1.72 (1.35–2.18)	1.73 (1.35–2.20)
	High IQ	Reference category	Reference category	Reference category
MCI, $n = 213$				
Low fitness	Low IQ	8.75 (4.91–15.61)	8.83 (4.93–15.79)	8.44 (4.64–15.37)
	Medium IQ	4.18 (2.31–7.58)	4.31 (2.37–7.86)	4.18 (2.28–7.69)
	High IQ	2.92 (1.83–4.66)	3.05 (1.89–4.91)	2.96 (1.83–4.78)
Medium fitness	Low IQ	4.52 (2.80–7.33)	4.46 (2.75–7.25)	4.32 (2.62–7.15)
	Medium IQ	2.16 (1.33–3.51)	2.18 (1.34–3.55)	2.14 (1.30–3.52)
	High IQ	1.51 (1.11–2.05)	1.54 (1.13–2.11)	1.51 (1.11–2.07)
High fitness	Low IQ	3.00 (1.99–4.52)	2.90 (1.91–4.39)	2.85 (1.86–4.38)
	Medium IQ	1.43 (0.96–2.12)	1.42 (0.95–2.10)	1.41 (0.95–2.11)
	High IQ	Reference category	Reference category	Reference category

[a]Adjusted for calendar year, BMI, region, conscription test centre.
[b]Adjusted for calendar year, BMI, region, conscription test centre, parental education.

period of our study. We performed separate analyses, which excluded individuals who emigrated ($n = 48\,006$) during the follow-up and they yielded similar results (data not shown). However, the loss of follow-up because of emigration might still impact the results. The exclusion of individuals because of missing data on cardiovascular fitness ($n = 179\,240$) or cognitive performance ($n = 181\,533$) at baseline might also influence the results. Potential confounders, not captured in the current study, also exist, such as alcohol consumption, infections, and genetics, which could partially explain the observed associations between cardiovascular fitness and early-onset dementia (Rademakers *et al.*, 2003; Sampson *et al.*, 2004; Werner *et al.*, 2009). It was not determined whether factors included as confounders in the analyses, such as BMI, instead might represent intermediate variables. In addition, only males were examined. Therefore, the present findings cannot be extrapolated to the female population; however, benefits of physical activity are similarly ranked for both genders (Rovio *et al.*, 2005).

Several potential mechanisms exist through which cardiovascular fitness could affect cognitive function later in life (Ahlskog *et al.*, 2011). Previous studies have shown that cardiovascular fitness could influence neurodegenerative disease mechanisms or facilitate neuroprotective, neurotrophic factors and neuroplasticity in the brain, often by influencing cardiovascular disease and vascular risk factors (Christie *et al.*, 2008; Carotenuto *et al.*, 2012). For example, cardiovascular exercise increases the expression and concentration of neurotropic factors in the brain involved in neuroplasticity and learning- and memory functions, such as brain-derived neurotropic factor (BDNF) and insulin-like growth factor 1 (IGF1) (Ahlskog *et al.*, 2011). It has been suggested that experiences early in life, such as physical activity, form a brain reserve and that differences in brain reserve capacity leads to differences in the clinical expression of a particular degree of damage to the brain (Valenzuela, 2008; Nithianantharajah and Hannan, 2009). By enhancing neuroplasticity in the young brain, cardiovascular fitness might help build up a future brain reserve and have a protective or disease-slowing effect on MCI and dementia.

When cognitive performance and cardiovascular fitness were respectively used as additional confounders for each other, the associations with future risk of early-onset dementia and MCI remained. We also found that there was no 'statistical' interaction of cardiovascular fitness and cognitive performance on later risk of dementia and MCI. However, this implies that there is a 'biological' interaction, because of the fact that the analyses were performed using a multiplicative model. When analysing combinations of different subgroups, a combination of low cardiovascular fitness and low cognitive performance at age 18 resulted in a >7-fold and a >8-fold increase in risk for later dementia and MCI, respectively (Supplementary Fig. 3). This shows that both cardiovascular fitness and cognitive performance in adolescence are important predictors for later dementia and MCI. However, high cognitive performance seemed to be more important than a high cardiovascular fitness for reducing the risk of dementia and MCI later in life. Nevertheless, high or medium cardiovascular fitness reduced the risk of early-onset dementia in individuals with low cognitive performance. These results highlight the importance of cardiovascular fitness, independent of a cognitive performance and it would be of interest to target high-risk groups with low cognitive performance for intervention

with cardiovascular training. A greater understanding of the mechanisms underlying these associations is needed to increase opportunities and strategies for prevention.

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Supplementary material

Supplementary material is available at *Brain* online.

References

Aberg MA, Pedersen NL, Toren K, Svartengren M, Backstrand B, Johnsson T, et al. Cardiovascular fitness is associated with cognition in young adulthood. Proc Natl Acad Sci USA 2009; 106: 20906–11.

Abner EL, Kryscio RJ, Cooper GE, Fardo DW, Jicha GA, Mendiondo MS, et al. Mild cognitive impairment: statistical models of transition using longitudinal clinical data. Int J Alzheimers Dis 2012; 2012: 291920.

Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clin Proc 2011; 86: 876–84.

Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev 2011; 12: e426–37.

Borroni B, Alberici A, Grassi M, Rozzini L, Turla M, Zanetti O, et al. Prevalence and demographic features of early-onset neurodegenerative dementia in Brescia County, Italy. Alzheimer Dis Assoc Disord 2011; 25: 341–4.

Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur Arch Psychiatry Clin Neurosci 1999; 249 (Suppl 3): 14–22.

Carlstedt B. Cognitive abilities - aspects of structure, process and measurement. PhD thesis. University of Gothenburg, Department of Education; 2000.

Carotenuto A, Rea R, Colucci L, Ziello AR, Molino I, Carpi S, et al. Late and early onset dementia: what is the role of vascular factors? A retrospective study. J Neurol Sci 2012; 322: 170–5.

Christie BR, Eadie BD, Kannangara TS, Robillard JM, Shin J, Titterness AK. Exercising our brains: how physical activity impacts synaptic plasticity in the dentate gyrus. Neuromolecular Med 2008; 10: 47–58.

Dik M, Deeg DJ, Visser M, Jonker C. Early life physical activity and cognition at old age. J Clin Exp Neuropsychol 2003; 25: 643–53.

Etgen T, Sander D, Bickel H, Forstl H. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Dtsch Arztebl Int 2011; 108: 743–50.

Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004; 3: 343–53.

Gunnell D, Magnusson PK, Rasmussen F. Low intelligence test scores in 18 year old men and risk of suicide: cohort study. BMJ 2005; 330: 167.

Haan MN, Wallace R. Can dementia be prevented? Brain aging in a population-based context. Annu Rev Public Health 2004; 25: 1–24.

Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 2009; 39: 3–11.

Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 2003; 74: 1206–9.

Koedam EL, Pijnenburg YA, Deeg DJ, Baak MM, van der Vlies AE, Scheltens P, et al. Early-onset dementia is associated with higher mortality. Dement Geriatr Cogn Disord 2008; 26: 147–52.

McMurtray A, Clark DG, Christine D, Mendez MF. Early-onset dementia: frequency and causes compared to late-onset dementia. Dement Geriatr Cogn Disord 2006; 21: 59–64.

Moeschberger ML, Klein JP. Survival analysis: Techniques for censored and truncated data. New York: Springer; 2003.

Nithianantharajah J, Hannan AJ. The neurobiology of brain and cognitive reserve: mental and physical activity as modulators of brain disorders. Prog Neurobiol 2009; 89: 369–82.

Nordesjö LO, Schéle R. Validity of an ergometer cycle test and measures of isometric muscle strength when prediction some aspects of military performance. Swedish J Defence Med 1974; 10: 11–23.

Nordstrom P, Nordstrom A, Eriksson M, Wahlund LO, Gustafson Y. Risk factors in late adolescence for young-onset dementia in men: a nationwide cohort study. JAMA Intern Med 2013; 173: 1612–1618.

Rademakers R, Cruts M, Van Broeckhoven C. Genetics of early-onset Alzheimer dementia. ScientificWorldJournal 2003; 3: 497–519.

Ratey JJ, Loehr JE. The positive impact of physical activity on cognition during adulthood: a review of underlying mechanisms, evidence and recommendations. Rev Neurosci 2011; 22: 171–85.

Richards M, Shipley B, Fuhrer R, Wadsworth ME. Cognitive ability in childhood and cognitive decline in mid-life: longitudinal birth cohort study. BMJ 2004; 328: 552.

Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging 2005; 26: 341–7.

Rovio S, Kareholt I, Helkala EL, Viitanen M, Winblad B, Tuomilehto J, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol 2005; 4: 705–11.

Sampson EL, Warren JD, Rossor MN. Young onset dementia. Postgrad Med J 2004; 80: 125–39.

Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer; 2000.

Valenzuela MJ. Brain reserve and the prevention of dementia. Curr Opin Psychiatry 2008; 21: 296–302.

Werner P, Stein-Shvachman I, Korczyn AD. Early onset dementia: clinical and social aspects. Int Psychogeriatr 2009; 21: 631–6.

Whalley LJ. Early-onset Alzheimer's disease in Scotland: environmental and familial factors. Br J Psychiatry Suppl 2001; 40: s53–9.

WHO. World Health Organization: international statistical classification of diseases and related health problems (ICD-9). Geneva, Switzerland: WHO; 1978.

WHO. World Health Organization: the ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva, Switzerland: WHO; 1992.

WHO. Alzheimer's DI. Dementia: a public health priority. Geneva, Switzerland: WHO, 2012.