Cognitive function in adolescence and the risk of early-onset stroke

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ABSTRACT

Background Stroke is increasingly prevalent at younger ages but the risk factors are uncertain. We examined the association between adolescent cognitive function and early-onset stroke.

Methods This was a nationwide population-based cohort study of 1 741 345 Israeli adolescents (42% women) who underwent comprehensive cognitive function tests at age 16–20 years, before mandatory military service, during 1987–2012. Cognitive function (range: 1–9) was categorised as low (1–3, corresponding to IQ score below 89), medium (4–7, IQ score range: 89–118), or high (8–9, IQ score above 118). Participant data were linked to the Israeli National Stroke Registry. Cox proportional hazard models were used to estimate risks for the first occurrence of ischaemic stroke during 2014–2018.

Results During 8 689 329 person-years of follow-up, up to a maximum age of 50 years, 908 first stroke events occurred (767 ischaemic and 141 haemorrhagic). Compared with a reference group of people with high cognitive function, body mass index-adjusted and sociodemographic-adjusted HRs (95% CIs) for early-onset stroke were 1.78 (1.33–2.38) in medium and 2.68 (1.96–3.67) in low cognitive function groups. There was evidence of a dose–response relationship (*P* for trend <0.0001) such that one-unit of lower cognitive function z-score was associated with a 33% increased risk of stroke (1.33; 1.23–1.42). These associations were similar for ischaemic stroke but lower for haemorrhagic stroke; persisted in sensitivity analyses that accounted for diabetes status and hypertension; and were evident before age 40 years.

Conclusions Alongside adolescent obesity and hypertension, lower cognitive function may be a risk factor for early-onset stroke.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While cognitive impairment and dementia are well-documented poststroke complications, the contribution of low cognitive function to the risk for stroke is less clear. Previous studies mainly assessed cognitive performance at mid-adulthood, when other comorbidities may be apparent and did not focus on the risk for early-onset stroke (<50 years).

WHAT THIS STUDY ADDS

⇒ We demonstrated that adolescents with medium and low cognitive function had twofold and threefold increased risks, respectively, for early-onset ischaemic stroke, after controlling for various confounders. The observed associations withheld extensive sensitivity analyses, including controlling for diabetes status, and limiting the age of stroke to 40 years or younger.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In light of the increasing incidence of early-onset stroke, the robust association between lower cognitive performance in adolescence and an increased risk of early-onset stroke underscores the need for comprehensive assessments beyond traditional stroke risk factors. The insights from our study suggest that cognitive performance might aid in identifying individuals at higher stroke risk, thus facilitating timely interventions to address potential mediators such as health illiteracy, education, and health behaviours.

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INTRODUCTION

Stroke represents a major public health concern due to its association with high rates of hospitalisation, long-term disabilities and mortality.[1] While stroke incidence in older people appears to be declining, recent evidence suggests an increasing incidence of stroke in adults aged under 50 years.[2 3] The implications of this rising incidence in early-onset stroke are important, as even in this younger population, about one-half of stroke survivors are projected to experience long-term physical and psychological impairments.[4] These findings bring into sharp focus the need to identify risk factors for early-onset stroke.[4 5]

While cognitive impairment and dementia are well-documented poststroke complications,[1] the contribution of low cognitive function to the risk for stroke is less clear. Data from prospective studies indicate that cognitive impairment sometimes precedes the stroke event, and may reflect a predictor associated with increasing risk for stroke. Those studies evaluated cognitive impairment by

Table 1 Characteristics of the study population at baseline and at the beginning of follow-up

	Low cognitive function (1–3)	Medium cognitive function (4–7)	High cognitive function (8–9)	Total
Individuals, number (%)	312 769 (18.0)	1 220 514 (70.1)	208 062 (11.9)	1 741 345
Female, number (%)	110 655 (35.4)	557 267 (45.7)	70 798 (34.0)	738 720 (42.4)
At adolescence				
Age at evaluation, years	17.5±0.6	17.3±0.4	17.3±0.5	17.3±0.5
Mean BMI, kg/m^2				
Male	22.1±4.1	21.9±3.6	21.7±3.3	21.9±3.7
Female	22.1±4.1	21.8±3.5	21.6±3.2	21.8±3.6
Overweight and obesity, %	17	14	12	15
Completed high school, %	82	96	99	94
Residential socioeconomic position, %				
Low	35	24	19	26
Medium	52	54	50	53
High	13	22	31	22
Unimpaired health,* %	64	69	69	68
At the beginning of follow-up†				
Age				
(mean±SD)	30.1±7.4	31.3±7.4	30.8±7.1	31.0±7.4
Range, years	17.6–46.5	17.3–47.0	17.1–46.7	17.1–47.0
Diagnosed with diabetes, number (%)	5601 (1.8)	14 738 (1.2)	1697 (0.8)	22 036 (1.3)

*Unimpaired health at adolescence was defined as the lack of a chronic illness that requires medical treatment, of a history of cancer or of major surgery.
†Follow-up started at 1 January 2014, and ended at a stroke event, death or 31 December 2018, whichever came first (allowing maximum follow-up of 5 years).
BMI, body mass index.

Mini Mental Examinations or by equivalent tests, and were performed on patients older than 65 years, with a relatively short follow-up interval.[6] There are prima facie reasons to anticipate an association between cognitive function and early-onset stroke. Low cognitive function may be inter-related with social determinants of health including education and socioeconomic status that were shown to be strongly related to incidence stroke with up to 50% increased risk.[7 8] Lower cognitive function in childhood and adolescence is associated with higher risks of future hypertension[9] and obesity.[10] While in various populations, lower cognitive function in adolescence has been related to later cardiometabolic events,[11–13] particularly type 2 diabetes and coronary heart disease, the few studies that assessed stroke risk have reported inconsistent results.[14–19]

Accordingly, in the present study we examined the association of cognitive function in adolescence with early-onset stroke in a nationally representative cohort of 1.7 million male and female adolescents.

METHODS

Study population

Prior to mandatory military service, Israeli adolescents undergo extensive evaluation to assess their suitability. In this study, all the adolescents (aged 16–20 years) who underwent this prerecruitment evaluation during 1987–2012 were included. This cohort was used recently to examine associations of adolescent body mass index (BMI)[20] and adolescent hypertension[21] with young adult stroke. The study exclusion criteria were missing cognitive performance data or death before 1 January 2014, when the Israeli National Stroke Registry (INSR) was established.

Assessment of cognitive function and covariates in adolescence

The military prerecruitment evaluation included a general intelligence test conducted by trained personnel. This multiple-choice exam comprised four subtests: (1) *Otis-R*, a measure of the ability to understand and carry out verbal instructions; (2) *Similarities-R*, which assesses verbal abstraction and categorisation; (3) *Arithmetic-R*, which assesses mathematical abilities, concentration and concept manipulation; (4) and *Raven's Progressive Matrices-R*, which measures non-verbal abstract reasoning and visual–spatial problem-solving abilities. For each of the subtests, a higher score indicates a higher level of performance. The sum of the four cognitive scores forms a general cognitive function measure on a 9-point scale. Scores from this test were shown to correlate highly ($r \geq 0.8$) with the Weschler Adult Intelligence Scale, a well-established test of general intelligence. For the main analyses, cognitive functions were grouped into three categories, as done previously[12]: low (1–3; IQ score below 89), medium (4–7; IQ score range: 89–118) and high (8–9; IQ score above 118). In a secondary analysis, we performed a continuous analysis in which the cognitive score (on a 9-point scale) was converted into z-scores according to sex and year of evaluation.

Weight, height and systolic and diastolic blood pressure were also measured at the time of the adolescent medical evaluations, as described elsewhere.[20] BMI was calculated as the weight in kilograms divided by the square of the height in metres and treated as a continuous variable. Education was dichotomised into complete and incomplete high school education (≥11/<11 years of schooling).[20] Residential socioeconomic position was derived from the Israeli Central Bureau of Statistics using data based on each individual's city of residence at the time of the adolescent medical evaluation. Cities are scored on a scale from 1 to 10, considering factors such as age distribution, unemployment rates, available workforce, education levels, average income per capita and the proportion of residents receiving income support.[22] For this study, the socioeconomic position scores were categorised into three groups: low (1–4), medium (5–7) and high (8–10).[23] The occurrence of diabetes was recorded from late adolescence through the beginning of follow-up using three

Table 2 The association of cognitive function in adolescence with incident early-onset stroke

	Low cognitive function (1–3)	Medium cognitive function (4–7)	High cognitive function (8–9)	Total
Individuals, number	312 769	1 220 514	208 062	1 741 345
Cumulative time of follow-up, person-years	1 560 076	6 090 679	1 038 574	8 689 329
Any stroke				
Incident cases, number	255	601	52	908
Incidence rate, per 100 000 person-years	16.35	9.87	5.01	10.45
Mean age at diagnosis	39.4±7.0	39.6±6.6	38.7±6.5	39.5±6.7
Died after incident stroke, number (%)	14 (5.5)	29 (4.8)	2 (3.8)	45 (5.0)
HR (95% CI)				
Minimally adjusted	3.37 (2.50–4.55)	1.88 (1.42–2.50)	1 (reference)	
Fully adjusted*	2.68 (1.96–3.67)	1.78 (1.33–2.38)	1 (reference)	
1-unit decrement in cognitive function z-score†	HR of 1.33 (95% CI: 1.23 to 1.42); p value <0.0001			
Ischaemic stroke				
Incident cases, number	222	505	40	767
Incidence rate, per 100 000 person-years	14.23	8.29	3.85	8.83
Mean age at diagnosis	39.8±6.8	40.0±6.3	39.7±6.0	39.9±6.4
Died after incident stroke, number (%)	10 (4.5)	17 (3.4)	1 (2.5)	28 (3.7)
HR (95% CI)				
Minimally adjusted	3.81 (2.72–5.33)	2.03 (1.47–2.80)	1 (reference)	
Fully adjusted*	2.97 (2.08–4.24)	1.92 (1.38–2.68)	1 (reference)	
1-unit decrement in cognitive function z-score†	HR of 1.33 (95% CI: 1.23 to 1.44); p value <0.0001			
Intracerebral haemorrhage				
Incident cases, number	33	96	12	141
Incidence rate, per 100 000 person-years	2.12	1.58	1.16	1.62
Mean age at diagnosis	36.4±7.8	37.5±7.5	35.2±7.1	37.1±7.5
Died after incident stroke, number (%)	4 (12.1)	12 (12.5)	1 (8.3)	17 (12.1)
HR (95% CI)				
Minimally adjusted	1.89 (0.98–3.66)	1.39 (0.76–2.5)	1 (reference)	
Fully adjusted*	1.74 (0.87–3.47)	1.34 (0.73–2.44)	1 (reference)	
1-unit decrement in cognitive function z-score†	HR of 1.32 (95% CI: 1.10 to 1.58); p value =0.003			

The minimally adjusted model included sex and age at the beginning of follow-up. The fully adjusted model was additionally adjusted for residential socioeconomic position, high school completion and adolescent body mass index.
*The fully adjusted model included 866 cases of any stroke, 732 cases of ischaemic stroke and 134 cases of intracerebral haemorrhage among 1 709 673 persons in total.
†Cognitive function z-scores were standardised and computed according to sex and year of assessment. The analyses were fully adjusted.

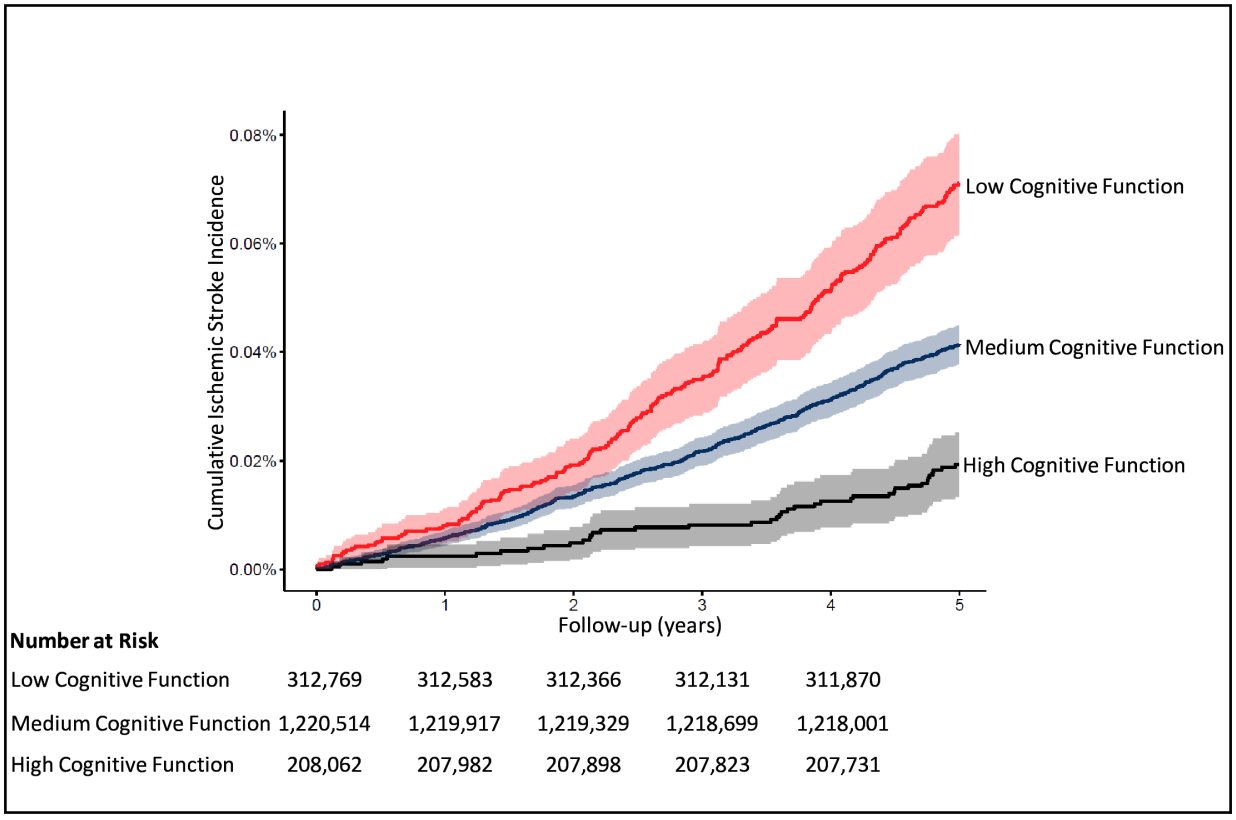
data sources: the medical evaluation at adolescence; the Israeli National Diabetes Registry, a national registry managed by the Ministry of Health[24]; and comorbidities that were collected in the INSR. These sources collectively capture nearly all diabetes diagnoses among permanent residents in Israel.[20]

Israeli National Stroke Registry

The INSR database is a national registry managed by the Israel Center for Disease Control in the Ministry of Health. Since 1 January 2014, all Israeli hospitals have been mandated to quarterly report patients with a primary discharge diagnosis of ischaemic or intracerebral haemorrhage (indicated by International Classification of Diseases, Ninth Revision (ICD-9); online supplemental table S1). Events prior to 2014 were not available. The positive predictive value of the INSR is 95% for case identification and 97% for differentiating between ischaemic stroke and intracerebral haemorrhage.[20 25] The INSR also collects comorbidity data using ICD codes from hospital discharge forms and from health maintenance organisation records.[20] Outcomes of the study were an incident first event of any stroke, of an ischaemic stroke and of an intracerebral haemorrhage, as documented by the INSR. The database of the Israel Defense Forces was linked to the INSR using civilian identification numbers through 31 December 2018. The follow-up period was from 1 January 2014, the first date of recoding in the INSR, until the stroke event, death or 31 December 2018, whichever came first.

Statistical analysis

Age at the beginning of follow-up was the age at 1 January 2014. Age was treated as a continuous linear variable, given the lack of interaction with cognitive function groups and the insignificant contribution when the quadratic term for age was added to the model. The χ^2 test were used to compare the proportion of categorical variables across cognitive function groups. The incidence rate of first stroke events was calculated per person-years of follow-up. Kaplan-Meier curves were plotted to present the cumulative incidence of the first ischaemic stroke event. Cox proportional hazard models were used to estimate the HRs and 95% CIs for incident stroke, considering the group with high cognitive function as the reference. Cox proportional hazard models were prespecified adjusted for sex and age at the beginning of follow-up (minimally adjusted model). Additional adjustments were made for residential socioeconomic position, education level and adolescent BMI (fully adjusted model).[20] HRs were further adjusted for diabetes status at the beginning of the follow-up (diabetes adjusted model).



Number at Risk

Low Cognitive Function	312,769	312,583	312,366	312,131	311,870
Medium Cognitive Function	1,220,514	1,219,917	1,219,329	1,218,699	1,218,001
High Cognitive Function	208,062	207,982	207,898	207,823	207,731

Figure 1 Kaplan-Meier curves of the cumulative incidence of first ischaemic stroke events during the follow-up period.

Subgroups and sensitivity analyses

As the strongest cognitive function–stroke relations were apparent for ischaemic stroke, this was the focus of our sensitivity and subgroup analyses. We carried out a series of seven planned analyses (all adjusted as in the fully adjusted model). (1) We stratified by sex. (2) To minimise confounding by coexisting morbidities, the sample was limited to study members with unimpaired health in adolescence, defined as a lack of prescribed medical treatment for chronic illness and the absence of a history of any chronic disease or of a major operation. (3) To better control for abnormal blood pressure, we restricted the cohort to those whose adolescent medical evaluations indicated optimal blood pressure. This was defined as <90th percentile for sex, age and height; and also systolic and diastolic values lower than 120 and 80 mm Hg, respectively.[21] (4) We assessed the cognitive function–stroke relation of each of the cognitive subdomains. (5) We included a subgroup analysis of six categories, based on stratifications of BMI status (low-normal/high; using the 85th percentile as a cut-off) and cognitive function groups (low/medium/high); low-normal BMI and high cognitive function were the reference categories. We performed this subgroup analysis despite the absence of an interaction between BMI and the cognitive function–stroke association (p for interaction=0.320). The reason is the potential clinical significance of an association with BMI, and based on a previous work of this cohort that showed an association of BMI with a threefold increased risk for stroke.[20] (6) We further stratified the groups of cognitive function (low/medium/high) by both BMI status (low-normal/high) and by blood pressure status (optimal/non-optimal; using the 90th percentile and 120/80 mm Hg cut-off for systolic/diastolic values. (7) To better assess the period at risk, the outcome was set as ischaemic stroke diagnosed before age 40 years.

RESULTS

From an initial cohort of 1 794 574 individuals, 53 229 were excluded (online supplemental figure S1). Of the analytical sample of 1 741 345 individuals (738 720 women, 42%), 12% had high cognitive function, 70% medium cognitive function, and 18% low cognitive function. Baseline characteristics are presented in table 1 according to these three groups. Cognitive function and baseline characteristics were similar between the individuals who died before the beginning of the follow-up, and were thus excluded from the cohort, and between the analytical cohort (online supplemental table S2). The mean (±SD) age was 17.3 (±0.5) years at the time of the cognitive function assessment; and 31.0 (±7.4) years at the beginning of the follow-up. The group with low cognitive function had the least favourable characteristics, and the group with high cognitive function had the most favourable characteristics. Accordingly, the former compared with the latter were more likely to be with overweight or obesity (17% vs 12%; p<0.001), less likely to have completed high school (82% vs 99%; p<0.001) and more likely to have resided in a neighbourhood with a low socioeconomic position (35% vs 19%; p<0.001).

The association of cognitive function in adolescence with any type of stroke

During a cumulative follow-up of 8 689 329 person-years, 908 incident cases of stroke were recorded (767 ischaemic and 141 intracerebral haemorrhage). The mean age at stroke occurrence was 39.5±6.7 years (maximum age 50 years). Among those with incident stroke, 45 resulted in death (5% of all stroke cases), and 62% of these occurred within 30 days of stroke (table 2). In the lower cognitive function groups, the incidences of both types of stroke were higher, yet particularly that of ischaemic

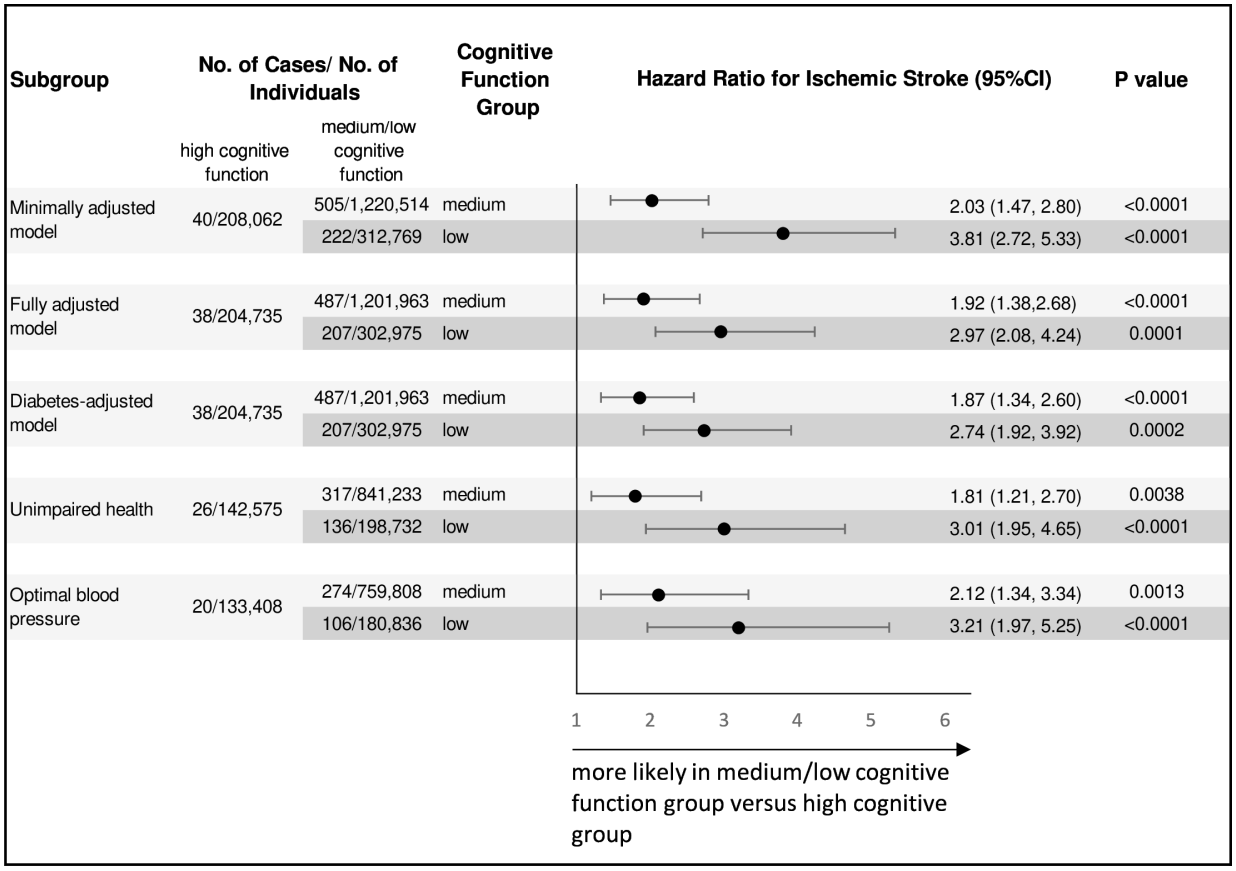


Figure 2 Adolescent cognitive function and subsequent risk for an ischaemic stroke event. The diabetes-adjusted model includes the fully adjusted model plus adjustment for diabetes status. Optimal blood pressure values at adolescence were defined as single measurements of blood pressure at the time of medical evaluation, which were <90 th percentile for sex, age and height; or lower than 120/80 mm Hg.

stroke, which increased from 3.85 to 14.23 cases/10^6 person-years (table 2). Medium and low cognitive function were associated with adjusted HRs of 1.78 (95% CI: 1.33 to 2.38) and 2.68 (95% CI: 1.96 to 3.67), respectively, for any stroke (fully adjusted model, table 2). When cognitive function was treated as a continuous variable (table 2), the adjusted HRs for every one-unit decrement in global cognitive function z-score were 1.33 (95% CI: 1.23 to 1.42), p<0.0001 for any stroke; 1.33 (95% CI: 1.23 to 1.44), p<0.0001 for ischaemic stroke and 1.32 (95% CI: 1.10 to 1.58), p=0.003 for intracerebral haemorrhage. Notably, when the analysis was based on categories of cognitive function, intracerebral haemorrhage was not associated with any of these categories (table 2).

The association of cognitive function in adolescence with ischaemic stroke

Crude incidence rates for ischaemic stroke across each individual cognitive score from 1 to 9 are detailed in online supplemental figure S2. Kaplan-Meier cumulative survival curves for the incidence of ischaemic stroke events by cognitive function categories (low, medium and high) are shown in figure 1. Stepwise adjusted models of sociodemographic variables and BMI for ischaemic stroke are presented in online supplemental table S3. Compared with the high cognitive function group, for the low and medium cognitive function groups, the risk of incident ischaemic stroke was higher after minimal adjustment. Further adjustments for residential socioeconomic position, education and adolescent BMI (fully adjusted model) marginally attenuated these point estimates to 1.92 (95% CI: 1.38 to 2.68) for medium cognitive function and 2.97 (95% CI: 2.08 to 4.24) for low cognitive function (table 2, figure 2). Adjustment for diabetes status yielded similar results (figure 2, p for interaction=0.674). Among men and women with low cognitive function in adolescence, the adjusted HRs were 2.89 (95% CI: 1.90 to 4.39) and 3.19 (95% CI: 1.61 to 6.32), respectively (p for interaction=0.776, online supplemental table S4). The results persisted when the study sample was restricted to those with unimpaired health in adolescence and to those with optimal blood pressure at adolescence (figure 2). Similar point estimates were demonstrated for each subdomain of cognitive function (online supplemental table S5).

Crude incidence rates for ischaemic stroke per 100 000 person-years gradually increased from categories of high to low cognitive function, and from categories of low-normal to high BMI (figure 3A). The fully adjusted HR for ischaemic stroke was 2.61 (95% CI: 1.77 to 3.85) among those with low cognitive function and low-normal BMI in adolescence, compared with a reference group of individuals with high cognitive function and low-normal BMI in adolescence. The HR was 6.64 (95% CI: 4.32 to 10.22, figure 3B) among those with low cognitive function and high BMI in adolescence. We consistently observed that further stratification of the latter matrix to adolescent blood pressure status resulted in higher stroke incidence among those with non-optimal blood pressure in adolescence. The highest rate, 26.33 cases/10^6 person-years, was computed for those with low cognitive function, high BMI, and non-optimal blood pressure in adolescence (online supplemental figure S3).

Of the 767 cases of ischaemic stroke, 311 (41%) occurred before the age of 40 years. Fully adjusted HRs for incident

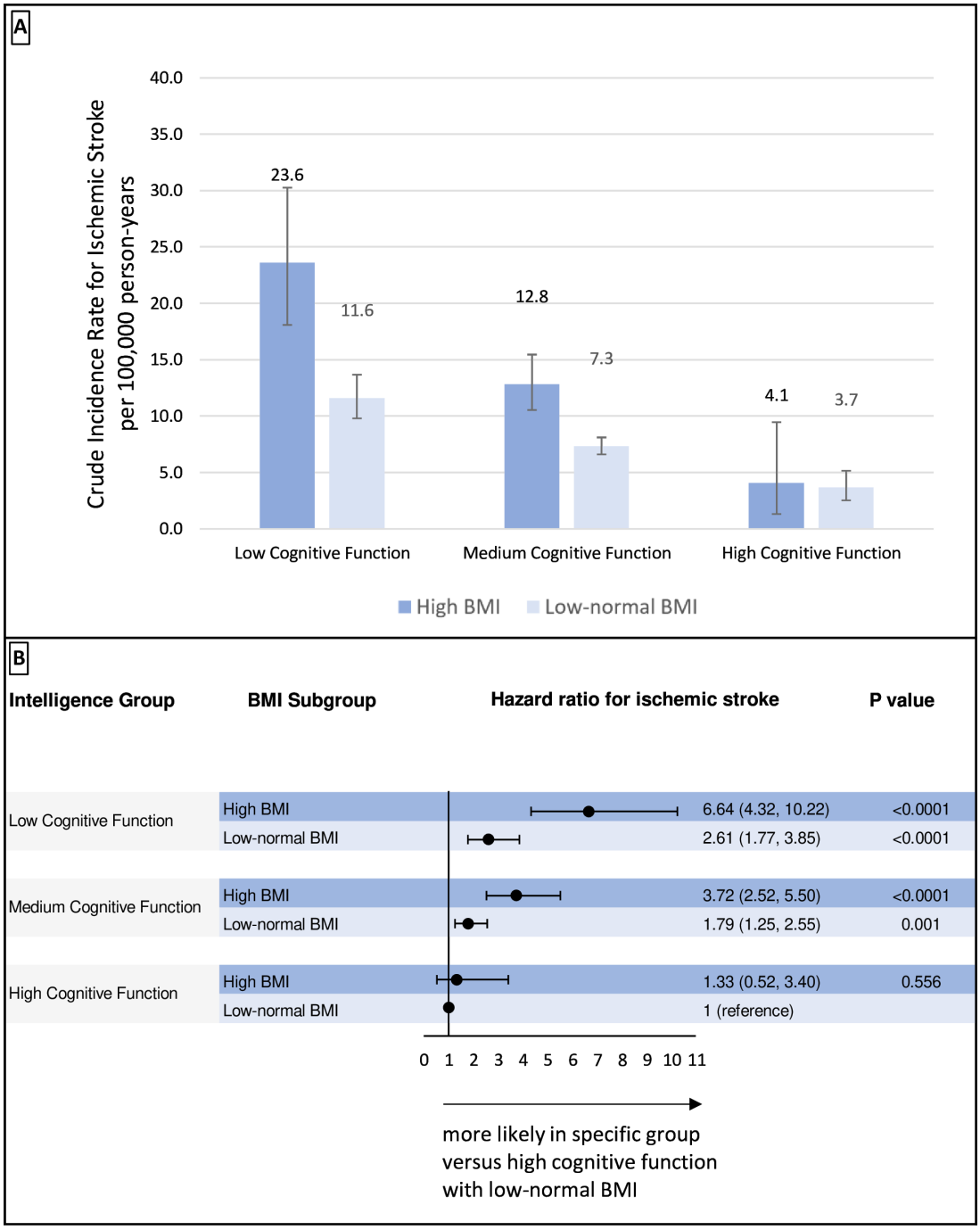


Figure 3 Ischaemic stroke risk stratified by BMI and cognitive function at adolescence. (A) Crude incidence rates for ischaemic stroke per 100 000 person-years across BMI and cognitive function groups. (B) Adjusted HRs (95% CI) for ischaemic stroke by BMI and cognitive function groups. Adolescents with high cognitive function and low-normal BMI served as the reference. BMI, body mass index.

stroke before age 40 years were 1.96 (95% CI: 1.19 to 3.22) and 3.28 (95% CI: 1.92 to 5.59) among those with medium and low cognitive function in adolescence, respectively.

DISCUSSION

In this nationwide population-based cohort study, we demonstrated that lower cognitive performance measured at adolescence was associated with a higher risk of a first ischaemic stroke event. Among individuals with medium and low cognitive function in adolescence, the HRs for ischaemic stroke were increased twofold and threefold, respectively, after controlling for adolescent BMI, the age at the beginning of the follow-up, and sociodemographic confounders. The observed association held after extensive sensitivity analyses, including controlling for diabetes status and limiting the age of stroke to up to 40 years.

Aggregated data from cohort studies of middle-aged and older-aged populations suggested that each SD lower cognitive score was associated with an increased risk of stroke of about 1.2-fold.[6] Only a few reports have assessed the link between cognitive function measured at adolescence and incident stroke. Most were cohorts that followed racially homogeneous children and adolescents born in specific years of the first half of the twentieth century, to their sixth to eighth decade.[26] While some reported an inverse relation,[14–16] others reported null associations.[17–19]

Among studies with significant associations, the ranges of HRs of point estimates were 1.2 to 1.7 for z-score unit decrements in cognitive function. This is comparable to the adjusted HR of 1.3 in our study. The evidence is limited as to whether the association exists with early-onset stroke.[19 27 28] Studies that reported a null association may have been underpowered, given the low stroke incidence of this age group.[19 27] None of the studies assessed the association at the level of cognitive function subdomains or examined if the association persists when accounting for metabolic mediators such as diabetes.

The association between low cognitive function and stroke may be mediated or confounded by various risk factors.[29] These include health-related behaviours (eg, smoking and tobacco use, physical inactivity and nutrition), cardiometabolic morbidities and social determinants.[1] Higher cognitive function tends to correlate with a lower likelihood of being a current smoker and a greater likelihood of quitting among those who have taken up the habit,[30 31] engaging in aerobic physical activity and strength training[32 33] and having a healthier diet.[33] The lack of lifestyle data is a limitation of the present study. Taking into account type 2 diabetes status, which was recently shown to be associated with low cognitive function,[13] did not materially change the results. Although we also controlled for high-school education and for residential socioeconomic position, data regarding higher education and major components of socioeconomic position were unavailable. Our research design did not allow for a direct assessment of these intermediate risk factors. Future studies are needed to better understand how early-life cognitive function impacts stroke risk later in life.

This study may have public health implications. Among individuals with low cognitive function in late adolescence (18% of the study population), the risk of early-onset stroke was markedly increased. Notably, the HR for low cognitive function group (2.97) was comparable to the HRs of adolescent obesity (3.43)[20] and adolescent hypertension (2.20),[21] reported in previous reports of this cohort that used similar study design and model adjustments. We also demonstrated that the risk differed across strata of BMI. As described, relative to stroke in older age groups, early-onset stroke is associated with higher risks of recurrence, cardiovascular complications, long-term healthcare resource consumption, poor functional outcomes and death.[4 34] Without risk factor intervention in early adulthood, stroke risk accumulates.[5] Given the longstanding disproportionate burden of stroke among people who are socially disadvantaged, avenues for promoting health equities in stroke might require targeting multiple risk factors, including BMI.[35] Cognitive function may serve as a means of stratifying individuals at greater risk for stroke and for intervention via possible mediators such as health illiteracy, education and health-related behaviours.[19] Provision of early social and health support for individuals with lower cognitive function might be essential for mitigating their elevated risk.

The stratification of the cognitive function–stroke association by BMI status is also of clinical interest. Evidence suggests an association between high BMI and low cognitive function,[36] possibly driven by alterations in brain structure and reduced functional connectivity, and mediated by biomarkers of poor health.[37] Glucagon-like peptide-1 receptor agonists, medications used in the treatment of type 2 diabetes and obesity, appear to promote weight reduction[38] and blood pressure lowering[39] and hence stroke prevention among people with type 2 diabetes.[40] As the highest incidence for stroke was observed among individuals with low cognitive function and abnormally high blood pressure and BMI in adolescence, this may entail a potential target population for mitigation of metabolic risk factors and lowering future stroke risk.

This study has several limitations. First, incident cases of stroke that occurred before 1 January 2014 were unavailable for us. We believe that this caveat did not bias our findings as the results were consistent for stroke events that occurred before and after age 40 years. Also, we did not observe meaningful differences in sociodemographic or medical baseline characteristics among those who died before 2014. Furthermore, we previously demonstrated on a subpopulation of this cohort that low cognitive function was associated with an approximately twofold increased risk for stroke-specific mortality.[12] Second, as mentioned earlier, we lacked data regarding lifestyle habits such as smoking, alcohol consumption and physical activity. Third, although point estimates were adjusted for high school completion, quality of education as well as higher education level were unavailable to us. Fourth, the residential socioeconomic position variable lacks data of other components of socioeconomic status such as household income, employment status and wealth. Additionally, its classification provides a single score to entire cities, which may not reflect the diversity within neighbourhoods. Lastly, this socioeconomic position data pertain solely to adolescence and does not consider socioeconomic changes occurring later in life. Fifth, other than diabetes, we could not account for cardiometabolic comorbidities such as hypertension that may mediate the association between cognitive function and stroke. Sixth, imaging data were unavailable, thus differentiating stroke into clinical categories was not possible. The strengths of our study include the systematic medical and sociodemographic evaluations, and comprehensive cognitive function assessment, that were done as part of a nationwide medical screening in an unselected population; and linkages between nationwide databases with valid diagnoses of stroke. The consistency of the association, despite the socioeconomic and ethnic heterogeneity of our cohort, suggests that our findings may be generalised to other Western populations. Previous reports from our dataset also reported point estimates between adolescent cognition and various metabolic outcomes[12 13] that were consistent to those reported by other European cohorts. This further supports the external validity of our findings.[29]

CONCLUSIONS

In conclusion, lower cognitive function measured at adolescence was strongly associated with an increased risk for early-onset stroke. This relation was independent of adolescent sociodemographic background, BMI and health status. Our findings support the addition of cognitive function to the more traditional stroke risk factors, to provide more effective health education and healthcare.

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