Contents lists available at ScienceDirect

EClinicalMedicine

Research Paper

Adolescent cognitive function and incident early-onset type 2 diabetes

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ARTICLE INFO

ABSTRACT

Background: Cognitive function among apparently healthy adolescents has been associated with cardiovascular morbidity and mortality. We examined the relationship between global and subdomain cognitive scores in adolescence and early-onset type 2 diabetes (T2D) in men and women.
Methods: A nationwide, population-based study of 971,677 Israeli born adolescents (56% men; mean age 17.4 years) who were medically examined and their cognitive performance was assessed before compulsory military service during 1992−2010. Data included global and subdomain cognitive Z-scores (problem-solving, verbal abstraction and categorization, verbal comprehension, and mathematical abilities). Data were linked to the Israeli National Diabetes Registry. The relations between global and subdomain scores and incident T2D was determined using Cox proportional hazard models and logistic regression models. Analyses were conducted separately for men and women.
Findings: During 16,095,122 person-years, 3,570 individuals developed T2D. After adjustment, those in the low compared to the high quintile of global cognitive Z-score had the highest risk for T2D; HR 2.46, (95% CI 2.10−2.88) for men and 2.33 (95% CI 1.88−2.89) for women. A one-unit lower global cognitive Z-score was associated with 1.41 (95% CI 1.34−1.48) and 1.46 (95% CI 1.36−1.56) increased risks for men and women, respectively. The relationship was noted for the cognitive subdomains scores as well as for the global cognitive score, with no heterogeneity across cognitive subdomains.
Interpretation: This large nationally representative cohort suggests relationship between global, as well as subdomain cognitive scores in late adolescence, and incident early onset T2D in both sexes, which was independent of socioeconomic status.

1. Introduction

Early-onset type 2 diabetes, defined as onset of diabetes by age 40 years, is increasing disproportionally worldwide [1]. Early-onset type 2 diabetes has a worse clinical course, with risk for long-term complications [1], and might be associated with novel risk factors such as intelligence and cognition variability [2]. Cognitive epidemiology, emerged in the early 2000s, studies how and why individual differences in intelligence (especially when measured in childhood or young adulthood) associate with later differences in health, illness and death [2].

While diabetes is recognized as a risk factor for cognitive impairment later in life [3], evidence suggests that the association may be bidirectional. Accordingly, cognitive function among apparently healthy adolescents has been associated with incident type 2 diabetes [4−7], the metabolic syndrome [4−6,8−10], cardiovascular morbidity [11,12] and mortality [13]. Some studies have assessed cognitive function in adolescence and the risk for type 2 diabetes

Research in context

Evidence before this study

Cognitive function among apparently healthy adolescents has been associated with incident type 2 diabetes, the metabolic syndrome, cardiovascular morbidity and mortality in some publications, yet only a few studies provided data with respect to specific cognitive subdomains.

Added value of this study

In a large nationally representative cohort of nearly 1 million born adolescents, we demonstrated the importance of cognitive performance during late adolescence in predicting diabetes in young adulthood, in both sexes, and in all cognitive subdomains examined (problem-solving, verbal abstraction and categorization, verbal comprehension and mathematical abilities).

Implications of all the available evidence

We observed an inverse relationship in both sexes, of global and subdomain cognitive scores in late adolescence with early onset type 2 diabetes. These relationships were independent of adolescent sociodemographic background or BMI. The findings support the hypothesis that cognitive abilities at adolescence are a risk marker for future metabolic health.

[4−6]. However, only a few studies provided data with respect to specific cognitive subdomains [6,8−10].

Here, we used a nationally representative study sample of approximately 1 million adolescents who were screened for cognitive status as part of their assessment for mandatory military service. Cognitive assessment included measures of problem-solving abilities, verbal abstraction and categorization, verbal comprehension, and mathematical abilities, as well as a measure summing all these into a global cognitive score. These data were linked to the Israel National Diabetes Registry (INDR) to assess relations between these scores and the risk for type 2 diabetes in young adulthood.

2. Methods

2.1. Study population

This was a retrospective historical cohort study of 1,112,274 Israeli-born adolescents aged 16−19 years, who underwent compulsory evaluation, including medical and cognitive assessments aimed to determine military service placement, between January 1, 1992 and December 31, 2010. Exclusion criteria were the absence of full cognitive data, death before establishment of the INDR in 2012, and a history of diabetes or dysglycemia, based on review of medical history, an interview, and a physical examination (Fig. 1). Thus, the study sample comprised 971,677 adolescents (56% men) with complete information on all cognitive domains. This represents 87.4% of the data available for Israeli-born adolescents. The date of diabetes diagnosis was available for only 3570 (63%) of 5649 individuals with type 2 diabetes.

Follow-up extended from the initial pre-military evaluation until type 2 diabetes diagnosis, death or 31 December 2016, whichever came first.

2.2. Ethical statement

The Institutional Review Boards of Sheba Medical Center Ethics Committee and the Institutional Review Board of the Israel Defense Forces Medical Corps approved this study and waived the need for informed consent, with assurance of strict maintenance of anonymity of the persons included, during database analyses.
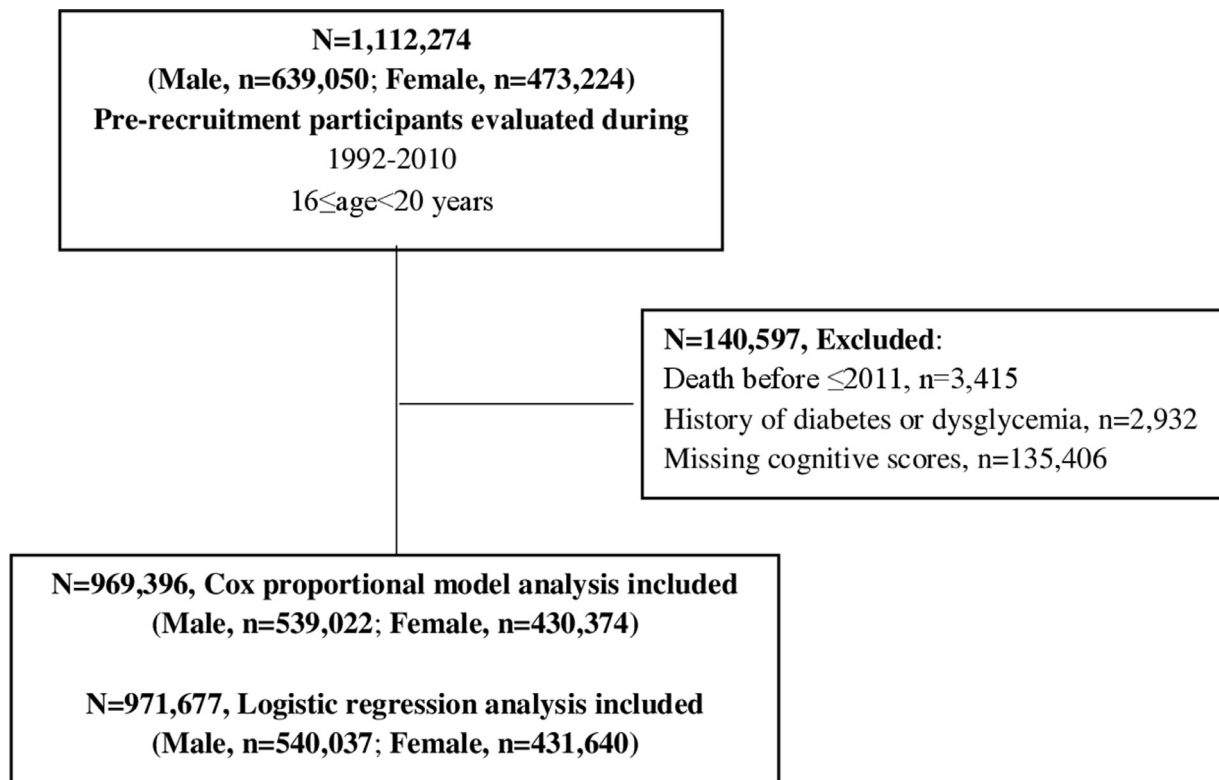

Fig. 1. Study flowchart.

2.3. Evaluation of cognitive function at baseline

Cognitive assessment was conducted as part of the pre-military assessment and was administered by trained personnel. The cognitive assessment included four subdomains: Raven's Progressive Matrices-R, which measures nonverbal abstract reasoning and visual-spatial problem-solving abilities; Similarities-R, which assesses verbal abstraction and categorization; the Otis-R, verbal comprehension, which is a measure of the ability to understand and carry out verbal instructions; and Arithmetic-R, which assesses mathematical reasoning, concentration, and concept manipulation [14]. The sum of the scores of the four tests form a validated global score of overall intelligence [15]. The standardized sum of the scores of the four tests form a validated global score of overall intelligence [15]. Scored on a 90-point scale (stanine), this overall score has demonstrated high correlation ($r > 0.8$) with the Wechsler Adult Intelligence Scale Total Intelligence Quotient (IQ) [14,15].

All cognitive scores were standardized for sex and year of assessment. Thus, Z-scores for the global and subdomains raw scores were computed according to sex and year of assessment and were then categorized into quintiles (1st is low, 5th is high) similar a previous study from this cohort [16].

2.4. Covariates

Medical evaluation is performed by a physician as part of the compulsory pre-army assessment. This includes a detailed interview, review of medical history and a physical examination. Measurement of weight, height, and systolic and diastolic blood pressure were performed for most of the adolescents (98.5%) as described elsewhere [17,18]. Mean arterial pressure was calculated: ($Systolic\ BP + 2 * Diastolic\ \frac{BP)}{3}$.

Demographic data of all the adolescents were available from the pre-military assessment. These included data on birth year, sex, education, country of origin (classified by the father's or grandfather's country of birth) and residential socioeconomic status (SES). Residential SES was based on locality of residence at the time of examination and was determined according to a 1-to-10 ordinal scale reflecting SES characteristics of residential areas, as defined by the Israeli Bureau of Statistics [19]. Adolescents were classified into three categories of residential SES: low (1−4), intermediate (5−7), and high (8−10) as reported previously [17]. Data on years of attained education were received from the Israeli Ministry of Education and dichotomized as previously described using a cutoff of 11 years of formal schooling (Supplementary Appendix) [17].

The Israel National Diabetes Registry (INDR)

The primary outcome of the study was early-onset type 2 diabetes as indicated by the INDR. This registry was established in 2012 and is managed by the Israel Center for Disease Control. The INDR receives an annual dataset of the persons with diabetes from each of the four health maintenance organizations that provide medical services to almost all Israeli permanent residents. The pre-military assessment of adolescents was linked to the INDR using a coded de-identified civilian identification number [17,18]. The dataset reported to the INDR includes individual data on persons who met at least one of the following criteria in the previous year: (1) a single test of glycated hemoglobin (HbA1c) greater than or equal to 6.5%; (2) serum glucose concentrations of 200 mg/dL or higher in two tests performed at least 1 month apart in the same year; (3) at least three purchases of glucose lowering medication (including insulin) in different months. The sensitivity of detecting diabetes in the INDR is 95%, specificity 94.3% and the positive predictive value is 93% [17]. The INDR does not receive data regarding the type of diabetes. Therefore, an algorithm to classify type 1 versus type 2 diabetes was applied. Using the following criteria, individuals were deemed to have type 1 diabetes: (1) treatment with insulin was initiated before age 18 years; (2)

treatment with short acting insulin was initiated at least one year before any oral anti-diabetic drug, or treatment with oral anti-diabetic drugs was never administered. Diabetes was designated as "uncertain type" if information on the initiation of antidiabetic medications was missing. All other incidences of diabetes were recorded as type 2.

2.5. Statistical analysis

Analyses were conducted separately for men and for women. The global cognitive Z-score was analyzed as a continuous variable and as categorical variable for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile. The one sample Kolmogorov-Smirnov test was applied to test for a normal distribution of continuous variables. The characteristics of the cohort were expressed as counts with percentages and as means ± standard deviations (SD). Chi-square and analysis of variance or Kruskal-Wallis tests were performed to determine significant differences in baseline characteristics among the global cognitive Z-score quintiles. Baseline characteristics of individuals who were not included in the study (Fig. 1) were compared to those included using chi-square and analysis of variance or Kruskal-Wallis tests (Supplementary Table S1). Kaplan-Meier cumulative probability curves for the incidence of type 2 diabetes by quintiles of global cognitive Z-scores were plotted by sex.

Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for incident type 2 diabetes, using Z-scores of cognitive performance (global score or subdomains) as either categorical or continuous variables. Multivariable models were pre specified to include age at examination, birth year, education, country of origin, BMI, height, mean arterial pressure and residential SES. The assumption of proportional hazards was assessed by log−log plots, and the ratio of hazards was the same across time. Interactions with SES and sex were assessed.

In addition, we conducted two sensitivity analyses. First, the study sample was restricted to individuals with unimpaired health status at study entry (absence of a medical history of cancer or major surgery, absence of mental disorders or a need for a chronic medical treatment or follow-up), to minimize confounding by coexisting medical illness [17,18]. Second, the outcome was defined as the onset of type 2 diabetes before age 30 years, to better characterize the hazard associated in early young adulthood.

Logistic regression models were applied to account for individuals without a known date of type 2 diabetes diagnosis. Thus, all analyses applied by the Cox proportional hazard models were repeated and odds ratios (ORs) and 95% CIs for type 2 diabetes were calculated. Additionally, we conducted an analysis that included uncertain diabetes type, as a valid outcome to address bias related to misclassification.

The explained variability (adjusted R square), i.e., the explanatory power of the regression models in the fully-adjusted models for each of the cognitive subdomain scores was also imputed. Heterogeneity in the relationship between the particular cognitive subdomain scores and incident diabetes (i.e. the HRs for diabetes for cognitive subdomain Z-scores) was assessed using Higgins & Thompson's heterogeneity H-index, Higgins & Thompson's I-squared statistics within a visual forest plot. All the tests used were two-tailed, and $p < 0.05$ was considered statistically significant. Data were analyzed with SPSS software, version 25.0 (SPSS Inc, Chicago, Illinois) and in WIN-PEPI for windows (version 11.65).

2.6. Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Study characteristics

The characteristics of the study population by quintiles of global cognitive Z-score groups are shown in Table 1. In general, adolescents in the lowest quintile were less educated, had higher BMI and were categorized in lower residential SES categories. A significant interaction was found between cognitive function, sex and T2D (*P* for interaction<0.001). A total of 3570 (0.4%) adolescents (2425 men and 1145 women) were diagnosed with type 2 diabetes during a mean follow-up of 16.6 ± 5.5 years; the mean age at diagnosis was 35.4 ± 3.8 years for men and 33.8 ± 4.5 years for women.

Baseline characteristics of 140,597 individuals who were not included in the study, because of history of diabetes or dysglycemia, died before establishment of the INDR and those with missing cognitive data, were compared to those included (Supplementary Table S1). Compared with patients who were not included, those included were more educated, less obese and had a higher SES status.

3.2. The relationship between global cognitive function and early-onset type 2 diabetes

During 16,095,122 person-years, 3570 individuals developed T2D. Kaplan-Meier cumulative probability curves for the incidence of type 2 diabetes by quintiles of global cognitive Z-scores demonstrated graded decreasing HRs from lower to higher quintiles in both sexes (Fig. 2). HRs for incident type 2 diabetes were calculated after adjustment for age at examination, birth year, education, country of origin, BMI, height, mean arterial pressure and residential SES. For men, the adjusted HRs were 2.46 (95% CI 2.10−2.88), 1.87 (95% CI 1.61−2.17), 1.45 (95% CI 1.24−1.70) and 1.26 (95% CI 1.05−1.52) for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile (Table 2). A similar trend was noted when cognitive function was treated as a continuous variable (Fig. 3). Thus, after adjustment for the variables mentioned above, every one-unit decrement in global cognitive Z-score was associated with a 1.41 (95% CI 1.34−1.48) greater hazard for the development of type 2 diabetes. For women, after the adjustments cited above, the HRs were 2.33 (95% CI 1.88−2.89), 1.58 (95% CI 1.26−1.98), 1.23 (95% CI 0.95−1.59) and 1.08 (95% CI 0.85−1.39) for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile (Table 2). After adjustment for the variables mentioned above, every one-unit decrement in global cognitive Z-score was associated with a 1.46 (95% CI 1.36−1.56) greater hazard for the development of type 2 diabetes.

3.3. The relationship between cognitive subdomains and early-onset type 2 diabetes

Lower vs. higher scores on the cognitive subdomains were all associated with increased adjusted HRs for type 2 diabetes in both

Table 1

Baseline characteristics by quintiles of cognitive global Z-scores of adolescents with known dates of diabetes diagnosis.

Quintiles of global cognitive Z-scores						Characteristics
5th N = 182,569	4th N = 195,392	3rd N = 202,458	2nd N = 191,316	1st N = 197,661		
						Z-Score:
1.40 ± 0.4	0.57 ± 0.2	0.02 ± 0.2	−0.53 ± 0.2	−1.37 ± 0.4	mean ± SD	Global
0.97 ± 0.3	0.62 ± 0.4	0.27 ± 0.5	−0.25 ± 0.6	−1.36 ± 0.9	mean ± SD	Nonverbal abstract reasoning and visual-spatial problem-solving abilities
1.02 ± 0.3	0.63 ± 0.4	0.22 ± 0.5	−0.37 ± 0.6	−1.38 ± 0.7	mean ± SD	Verbal abstraction and categorization
1.12 ± 0.4	0.62 ± 0.4	0.13 ± 0.5	0.43 ± 0.5	−1.34 ± 0.7	mean ± SD	Verbal comprehension
1.32 ± 0.7	0.48 ± 0.6	−0.08 ± 0.5	−0.54 ± 0.5	−1.05 ± 0.5	mean ± SD	Mathematical reasoning concentration and concept manipulation
17.2 ± 0.3	17.2 ± 0.3	17.2 ± 0.3	17.3 ± 0.4	17.4 ± 0.5	mean ± SD	Age at examination
102,658 (56.2)	109,619 (56.1)	118,136 (58.4)	105,690 (55.2)	102,919 (52.1)	n (%)	Sex, men
181,875 (99.6)	193,883 (99.2)	198,644 (98.1)	182,661 (95.5)	173,002 (87.5)	n (%)	Education[1], ≥11 years
31,587 (17.4)	38,087 (19.6)	46,127 (22.8)	51,042 (26.8)	62,325 (31.6)	n (%)	SES groups[2], Low
90,890 (50.0)	103,003 (52.9)	110,474 (54.7)	104,517 (54.8)	106,566 (54.0)		Moderate
59,298 (32.6)	53,669 (27.6)	45,289 (22.4)	35,129 (18.4)	28,308 (14.4)		High
17,934 (9.9)	16,903 (8.7)	15,235 (7.6)	12,697 (6.7)	12,714 (6.5)	n (%)	Origin[3], Israel
16,969 (9.3)	15,223 (7.8)	14,248 (7.1)	11,860 (6.2)	11,011 (5.6)		USSR
34,053 (18.7)	47,393 (24.3)	56,477 (28.0)	59,245 (31.1)	31,330 (31.2)		Asia
26,734 (14.7)	41,302 (21.2)	55,662 (27.6)	63,190 (33.2)	78,704 (40.0)		Africa
85,996 (47.3)	73,629 (37.8)	59,244 (29.4)	41,716 (21.9)	29,024 (14.8)		West Ethiopia
126 (0.1)	325 (0.2)	865 (0.4)	1729 (0.9)	3917 (2.0)		
62.6 ± 11.6	62.7 ± 12.2	62.7 ± 12.3	62.2 ± 12.5	62.0 ± 13.2	mean ± SD	Weight[4] (kg)
170 ± 8.8	169 ± 8.9	169 ± 8.9	168 ± 8.8	167 ± 8.7	mean ± SD	Height[5] (cm)
10,014 (5.5)	11,003 (5.7)	12,595 (6.3)	13,092 (6.9)	14,525 (7.5)	n (%)	BMI[6]†, (kg/m^{2}), Underweight
						Normal
149,795 (82.6)	156,329 (80.6)	159,313 (79.5)	147,451 (77.9)	145,356 (75.2)		Overweight
15,242 (8.4)	18,120 (9.3)	19,084 (9.5)	18,925 (10.0)	20,970 (10.8)		Obese
6279 (3.5)	8445 (4.4)	9511 (4.7)	9697 (5.1)	12,476 (6.5)		
116 ± 12	115 ± 12	115 ± 12	116 ± 12	115 ± 12	mean ± SD	Systolic BP[7], mm Hg
71 ± 8	71 ± 8	71 ± 8	71 ± 8	71 ± 8	mean ± SD	Diastolic BP[8], mm Hg
85.9 ± 8.2	85.6 ± 8.1	85.9 ± 8.3	86.1 ± 8.3	85.9 ± 8.3	mean ± SD	Mean arterial pressure
376 (0.2)	387 (0.1)	637 (0.3)	960 (0.5)	1210 (0.6)		Diabetes type 2, n (%)
57 (0.03)	50 (0.03)	56 (0.02)	59 (0.03)	78 (0.04)		Uncertain diabetes type, n (%)

Missing: [1] −0.02%.

[2] −0.3%.

[3] −0.4%.

[4] −1.4%.

[5] −1.4%.

[6] −1.4%.

[7] −1.5%; [8] −1.5%. SES= socioeconomic status (residential); BMI= Body mass index; BP=blood pressure.

†BMI classified according to percentiles: underweight (<5th) normal (5th≤BMI<85th), overweight (85th ≤BMI<94th) and obese (≥95th).
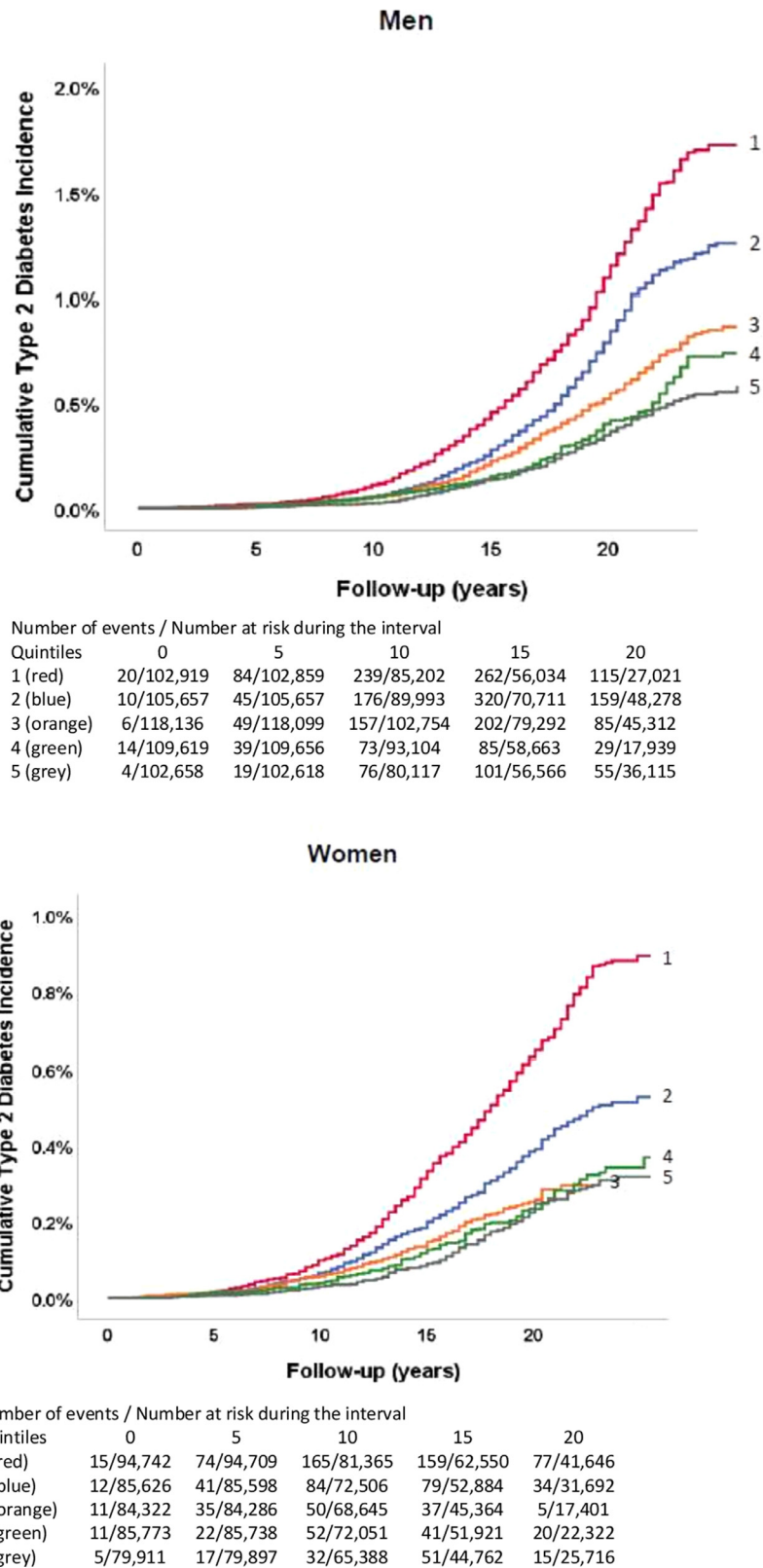
Men

Number of events / Number at risk during the interval

Quintiles	0	5	10	15	20
1 (red)	20/102,919	84/102,859	239/85,202	262/56,034	115/27,021
2 (blue)	10/105,657	45/105,657	176/89,993	320/70,711	159/48,278
3 (orange)	6/118,136	49/118,099	157/102,754	202/79,292	85/45,312
4 (green)	14/109,619	39/109,656	73/93,104	85/58,663	29/17,939
5 (grey)	4/102,658	19/102,618	76/80,117	101/56,566	55/36,115

Women

Number of events / Number at risk during the interval

Quintiles	0	5	10	15	20
1 (red)	15/94,742	74/94,709	165/81,365	159/62,550	77/41,646
2 (blue)	12/85,626	41/85,598	84/72,506	79/52,884	34/31,692
3 (orange)	11/84,322	35/84,286	50/68,645	37/45,364	5/17,401
4 (green)	11/85,773	22/85,738	52/72,051	41/51,921	20/22,322
5 (grey)	5/79,911	17/79,897	32/65,388	51/44,762	15/25,716

Fig. 2. . Kaplan-Meier cumulative probability curves showing the incidence of type 2 diabetes by quintiles (1−5) of global cognitive Z-scores by sex. Quintile 1 is low; quintile 5 is high.

sexes. In men, after adjustment for the variables mentioned above, every one-unit SD decrement in cognitive Z-scores for problem-solving abilities, verbal abstraction and categorization, verbal comprehension, and mathematical abilities was associated with 1.31 (95% CI 1.26−1.36), 1.33 (95% CI 1.28−1.39), 1.27 (95% CI 1.22−1.33) and

1.35 (95% CI 1.29−1.41) greater hazard for incident diabetes, respectively (Fig. 3). In women, after adjustment for the variables mentioned above, every one-unit SD decrement in cognitive Z-scores for problem-solving abilities, verbal abstraction and categorization, verbal comprehension, and mathematical abilities was associated with

Table 2
Hazard ratios (HRs) and 95% confidence interval (CIs) for associations between global cognitive Z-scores and early-onset type 2 diabetes.

Cognitive Z-scores		Model 1 HR (95%CI)	Model 2 HR (95%CI)
		Men	
Global Z-score quintiles	1	3.20 (2.78−3.70)*	2.46 (2.10−2.88) *
	2	2.25 (1.95−2.60) *	1.87 (1.61−2.17) *
	3	1.54 (1.33−1.79) *	1.45 (1.24−1.70) *
	4	1.17 (0.98−1.40)	1.26 (1.05−1.52) *
	5 (high)	1 (ref.)	1 (ref.)
		Women	
Global Z-score quintiles	1	2.97 (2.43−3.63) *	2.33 (1.88−2.89) *
	2	1.79 (1.44−2.22) *	1.58 (1.26−1.98) *
	3	1.27 (1.00−1.62) **	1.23 (0.95−1.59)
	4	1.14 (0.90−1.45)	1.08 (0.85−1.39)
	5 (high)	1 (ref.)	1 (ref.)

*$P < 0.001$ ** $p < 0.05$; Model 1: Unadjusted; Model 2: Adjusted for age at examination and birth year (continuous), education, country of origin, BMI (continuous), height (continuous), mean arterial pressure (continuous) and residential socioeconomic status.

1.33 (95% CI 1.25−1.40), 1.34 (95% CI 1.27−1.42), 1.34 (95% CI 1.26−1.42) and 1.34 (95% CI 1.25−1.43) greater hazard for incident diabetes, respectively (Fig. 3). No heterogeneity was noted in the relations between incident diabetes and the four cognitive subdomain scores among men (I^2 = 28% and H-index=1.2, P = 0.244) and among women (I^2 = 0% and H-index=1.0, P = 0.997) (Fig. 3).

For men, when restricted to those diagnosed with T2D by age 30 years, the adjusted HRs were 2.62 (95% CI 2.12−3.25), 2.05 (95% CI 1.68−2.51), 1.58 (95% CI 1.28−1.94) and 1.41 (95% CI 1.11−1.80) for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile. For women, when restricted to those diagnosed with T2D by age 30 years, the adjusted HRs were 2.79 (95% CI 2.13−3.65), 1.67 (95% CI 1.25−2.22), 1.16 (95% CI 0.83−1.62) and 1.03 (95% CI 0.75−1.42) for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile. (Supplementary Table S2).

Similar point estimates were obtained in both sexes when analyses were limited to adolescents with unimpaired health at study entry (Supplementary Table S2). For men, the adjusted HRs were 2.14 (95% CI 1.56−2.93), 1.39 (95% CI 1.01−1.91), 1.35 (95% CI 0.98−1.85) and 1.23 (95% CI 0.88−1.72) for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile. For women, the adjusted HRs were 2.76 (95% CI 1.87−4.01), 2.03 (95% CI 1.36−3.04), 1.63 (95% CI 1.07−2.47) and

1.34 (95% CI 0.87−2.07) for comparisons of the first, second, third and fourth quintiles, respectively, with the fifth (reference) quintile.

Similar point estimates were obtained when logistic regression models were applied to account for incidences of type 2 diabetes without diagnosis dates (Supplementary Tables S3 and S4).

4. Discussion

This nationwide study demonstrates a graded inverse relationship between cognitive performance in late adolescence and the risk for incident diabetes in young adulthood. This relation was evident in both men and women; the point estimates were similar despite a significant interaction with sex. In men, comparison of all global cognitive Z-scores quintiles to fifth (reference) quintile was associated with a significant reduction in T2D risk. In women this was only evident in the first and second quintiles compared to the fifth quintile comparison. The relation persisted when the analysis was limited to those with unimpaired health and when the outcome was limited to a diagnosis of type 2 diabetes before age 30 years. The point estimates were slightly attenuated after adjustment for sociodemographic variables and adolescent BMI, further strengthening the hypothesis of a relationship between cognitive status in adolescence and incident type 2 diabetes. The similarity of the relations for cognitive subdomain scores, without any significant heterogeneity, as well as to the relation for global cognitive scores, further supports the hypothesis that global cognitive score is a significant marker of future metabolic health.

Our results are consistent with previous studies that reported an inverse association between cognitive function in adolescence and incident T2D. In the British National Child Development Study [6], a one-unit SD decrement in general ability score at age 11 years was associated with a 37% increased risk for type 2 diabetes at age 42 years. In the Lothian Birth Cohort [5], lower childhood cognitive functions at age 11 years, overall and in specific cognitive subdomains, were associated with higher HbA1c levels and self-reported type 2 diabetes at age 70 years [5]. The Vietnam Experience Study [8], comprised a large cohort of former US male military personnel whose IQ was assessed at entry to the service at around age 20 years. Lower IQ test scores were associated with a higher prevalence of the metabolic syndrome and most of its components (hypertension, high BMI, high triglycerides and high blood glucose) at a mean age of 38.3 years. A one SD higher IQ score was associated with a decrease in blood glucose level by about 20% [8]. Data of young men from the Danish National Health Service study [10] reported a greater hazard for the development of type 2 diabetes before age 55 years among
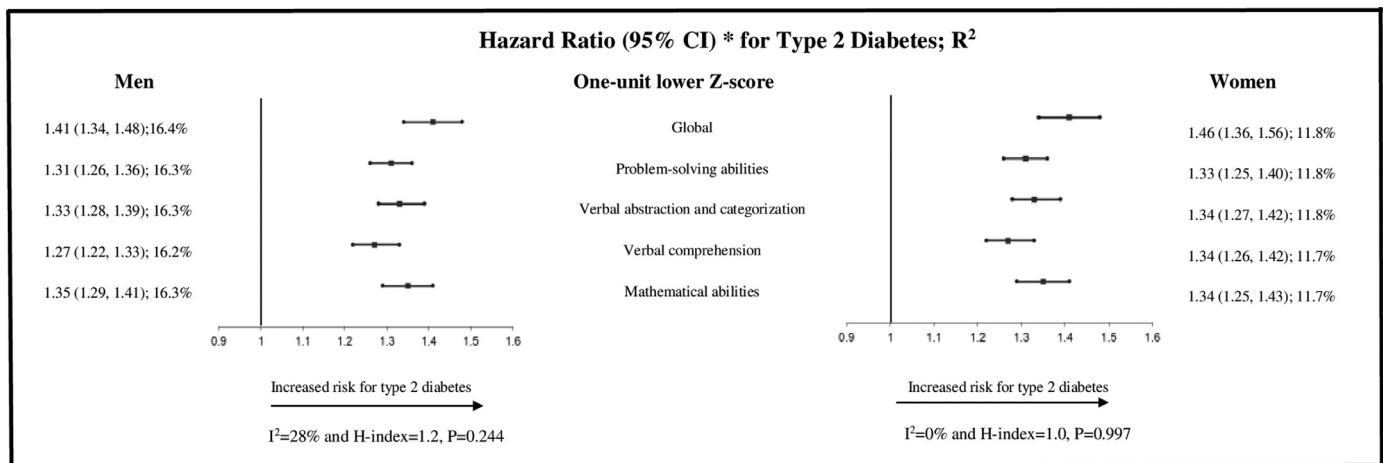
Fig. 3. The relations between one-unit lower cognitive Z-scores in global and cognitive subdomain scores in adolescence and early-onset type 2 diabetes.

those with low vs. very high cognitive scores, 1.76 (95% CI 1.28, 2.40) [10]. In a sub-cohort of the present study,[7] of career men military personnel, the risk for T2D in young adulthood was increased two-fold among those with lower vs. higher cognitive scores at age 17 years, independent of any lifestyle data, baseline glucose or tri-glyceride level, family history of diabetes or adult BMI. The current analysis confirms the results of these studies but also extends them, by providing data separately for men and women, and for the cogni-tive subdomains. Indeed, a recent article summarizing studies that assessed associations of cognitive function with diabetes- and cardio-vascular-related mortality in the current and other European cohorts reported similar consistent point estimates [2]. This further supports the extrapolation of our data to other Western populations.

We found a significant interaction between cognitive function, sex and T2D; however, the observed associations were similar between the sexes. We speculated that the interaction reported is due to the large sample size and does not signify a true biological difference. Sex differences in cognitive functioning have been described over the past decades, but the findings are inconsistent [9, 20–22].

Several explanations are possible for the observed relation between global cognitive and cognitive subdomains scores with inci-dent diabetes. First, the relation may be mediated by better lifestyle behaviors [23,24] including adoption or maintenance of physical activity and healthy diet, avoidance of smoking, moderate alcohol consumption, more persistent adherence to medical treatment and self-management of vascular risk factors among individuals with higher vs lower cognitive ability [8,25]. Second, better cognitive abil-ity can lead to better educational attainment and consequently to better occupational status, and a higher SES. Indeed, a recent meta-analysis demonstrated an association of lower SES with higher risk for incident type 2 diabetes [26]. However, in this analysis we did not find any interaction between SES status, cognitive scores and incident type 2 diabetes. Third, intelligence test scores in childhood and young adulthood might be influenced by pre- and postnatal life factors which may predispose to both lower cognitive test scores and diabetes [2]. In addition, the relation described may be due to a common pathway. Insulin signaling in the brain modulates neu-rotransmitter channel activity, brain cholesterol synthesis and mitochondrial function in neurons. In turn, its disruption plays a prominent role in brain functions that regulate brain metabolism, and leads to impairment of neuronal function and synaptogenesis [27,28]. Thus, variations in insulin signaling in the brain may affect both cognitive function and the development of diabetes. Indeed, recent neuroimaging studies have revealed a significant insulin-induced response in several brain areas such as the hippo-campus, which are responsible for memory functions and spatial navigation; and in the fusiform gyrus, which is responsible for visual attention [28].

This study has limitations. First, we lacked longitudinal sociode-mographic, lifestyle, familial diabetes status and metabolic data (such as BMI) parameters in adulthood. In addition, SES at baseline was defined according to residential area and thus its precision is limited. Second, because we lacked data of antibodies that mark beta cell autoimmunity, we cannot exclude the possibility that individuals with type 1 diabetes were included. However, we previously reported [17] that only 1.2% of those who were classified as having T2D in the INDR were treated initially by insulin only, which makes the contribution of such potential misclassification negligible. Third, the absence of biochemical measures of glucometabolic status at baseline precludes analyses by the degree of baseline dysglycemia. Furthermore, for 12% of the initial population, we did not have data of all subdomain cognitive scores, and thus, they were not included in this analysis. Among the strengths of this study are the systematic data collection including a comprehensive cognitive assessment, sociodemographic and medical data, and the linkage between two nationwide databases.

In conclusion, we observed an inverse relationship in both sexes, of global and subdomain cognitive scores in late adolescence with early onset T2D. These relationships were independent of adolescent sociodemographic background or BMI. The findings support the hypothesis that cognitive abilities at adolescence are a risk marker for future metabolic health.

Author contributions

ML, IZ, GT, CDB, ED, DT, IR, OP-H, OM, AA and TC-Y contributed to the study design. ML, IZ, GT, and TC-Y did the literature search and drafted the manuscript. GT, ED and DT contributed to data collection. ML, ED, DT and DN contributed to data analysis. All authors contrib-uted to data interpretation and to the writing of the report, approved the final submitted version and agreed to the published version of the manuscript.

Funding

Data sharing statement

The data are not publicly available due to privacy and ethical restrictions. Interested parties can contact the corresponding author (GT).

Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted arti-cle. Dr Gerstein reports grants from Sanofi, personal fees from Sanofi, grants from Eli Lilly , personal fees from Eli Lilly, grants from Astra Zeneca, grants from Boehringer Ingelheim, personal fees from Boeh-ringer Ingelheim, personal fees from Abbott, grants from Novo Nor-disk, personal fees from Novo Nordisk, grants from Merck, personal fees from Merck, grants from Abbott, personal fees from Kowa Research Institute , personal fees from Pfizer, personal fees from Zuel-lig, personal fees from DKSH, personal fees from Covance, personal fees from Roche, outside the submitted work. Dr. Raz reports other from AstraZeneca, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Inc, Sanofi, other from AstraZeneca, Insuline Medical, Medial EarlySign Ltd, CamerEyes Ltd, Exscopia, Orgenesis Ltd, BOL, Glucome Ltd, DarioHealth, Diabot, Concenter BioPharma, other from AstraZeneca, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Inc., Sanofi, other from Glucome Ltd, Orgenesis Ltd, Dario-Health, CamerEyes Ltd, Diabot, BOL, outside the submitted work. All the other authors have no conflicts to declare.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101138.

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