



Cognitive Function and the Risk for Diabetes Among Young Men

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OBJECTIVE

Diabetes is a risk factor for an accelerated rate of cognitive decline and dementia. However, the relationship between cognitive function and the subsequent development of diabetes is unclear.

RESEARCH DESIGN AND METHODS

We conducted a historical-prospective cohort study merging data collected at premilitary recruitment assessment with information collected at the Staff Periodic Examination Center of the Israeli Army Medical Corps. Included were men aged 25 years or older without a history of diabetes at the beginning of follow-up with available data regarding their general intelligence score (GIS), a comprehensive measure of cognitive function, at age 17 years.

RESULTS

Among 35,500 men followed for a median of 5.5 years, 770 new cases of diabetes were diagnosed. After adjustment for age, participants in the lowest GIS category had a 2.6-fold greater risk for developing diabetes compared with those in the highest GIS category. In multivariable analysis adjusted for age, BMI, fasting plasma glucose, sociogenetic variables, and lifestyle risk factors, those in the lowest GIS category had a twofold greater risk for incident diabetes when compared with the highest GIS category (hazard ratio 2.1 [95% CI 1.5–3.1]; $P < 0.001$). Additionally, participants in the lowest GIS category developed diabetes at a mean age of 39.5 ± 4.7 years and those in the highest GIS group at a mean age of 41.5 ± 5.1 years (P for comparison 0.042).

CONCLUSIONS

This study demonstrates that in addition to a potential causal link between diabetes and enhanced cognitive decline, lower cognitive function at late adolescence is independently associated with an elevated risk for future diabetes.

Evidence from the last several years suggests that dysglycemia accelerates the rate of cognitive decline and increases the risk for dementia. Indeed, people with diabetes are about 1.5-fold more likely to experience an accelerated rate of cognitive decline and are twice as likely to develop dementia (1–4). It also has been shown that dysglycemia per se is associated with an increased risk for dementia (5). This relationship is partially explained by cardiovascular risk factors, education, socioeconomic status (SES), and lifestyle factors. However, common mechanistic pathways such as inflammation, microvascular disease, and the effects of insulin sensitivity on the brain and in the periphery have also been hypothesized as an explanation for this relationship.

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Despite the extensive amount of data regarding diabetes as a cause of cognitive dysfunction, there is a paucity of information regarding a potential association between cognitive function and the subsequent development of diabetes.

The Metabolic, Lifestyle and Nutrition Assessment in Young Adults (MELANY) cohort of the Israel Defense Forces (IDF) has been used to assess risk factors for coronary artery disease and diabetes among young men (6–11). This cohort also contains extensive cognitive performance data that are routinely collected at military recruitment (age 17 years) together with periodic medical assessments up to late adulthood. Here, we used the MELANY cohort to assess the relationship between cognitive function in late adolescence and the risk for subsequent development of diabetes during young adulthood.

RESEARCH DESIGN AND METHODS

Study Population

The MELANY cohort is part of an ongoing investigation of the IDF Medical Corps (6–11). Army personnel that remain in military service beyond 2–3 years of mandatory service and are older than 25 years of age are referred every 3–5 years for a routine health examination and screening tests at the Staff Periodic Examination Center (SPEC). At each visit to the SPEC, participants complete a detailed questionnaire assessing demographic, nutritional, lifestyle, and medical factors. Blood samples are drawn following a 14-h fast and analyzed immediately. Height and weight are measured, and a physician at the center performs a complete physical examination. All medical information is recorded in the same central database (independent of SPEC visits), thereby facilitating ongoing, uniform follow-up as described

previously (7,8,10). All participants in MELANY, independent of their rank and position, have similar access to medical services, which are provided free of charge. Additionally, prior to enlistment in the military at age 17 years, MELANY participants undergo a mandatory general intelligence test (general intelligence score [GIS], detailed below).

Figure 1 shows a schematic illustration of the study design. Included in this study were men with complete GIS assessment (conducted at age 17 years) who attended the SPEC at least once between 1 January 1995 and 8 March 2011. Data regarding participants who developed diabetes (type 1 or 2) prior to their first visit at the SPEC ($n = 62$) and those with a follow-up of <3 months from enrollment to the diagnosis of diabetes ($n = 815$) were censored from the analysis (Fig. 1). The institutional review board of the IDF Medical Corps

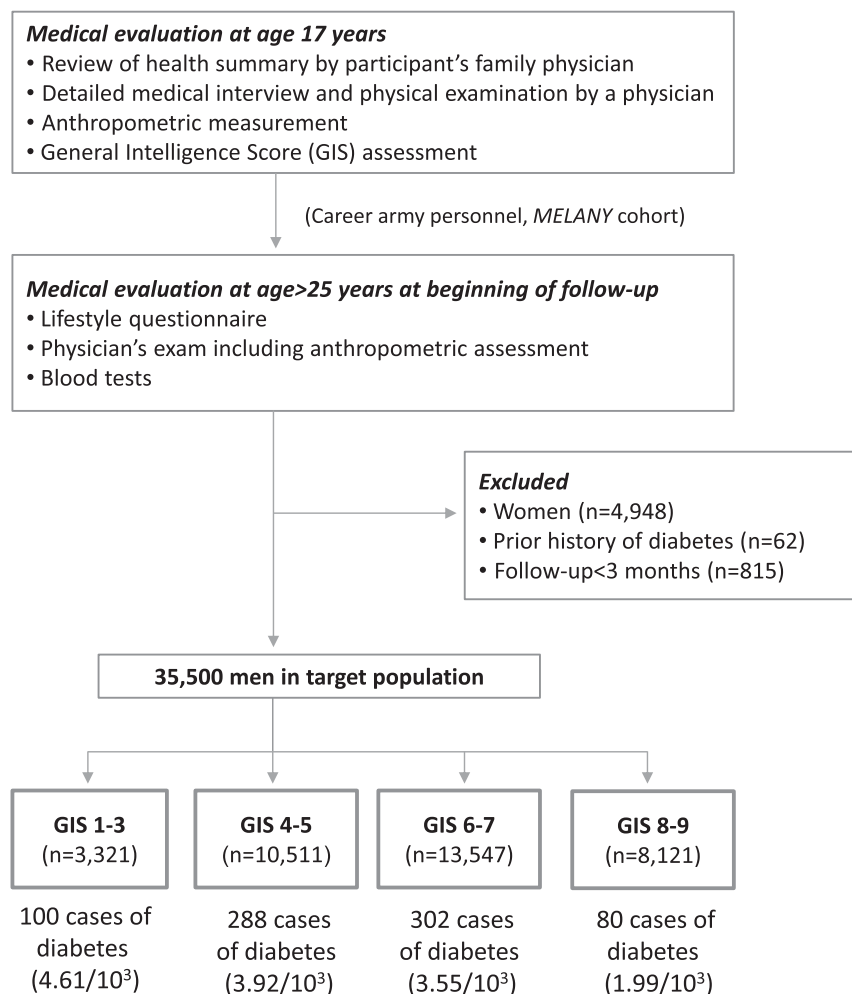


Figure 1—Study flow diagram: participant assessment, designation, and outcomes. Rates of diabetes incidence (in person-years of follow-up) are given in parentheses for different GIS subgroups.

approved this study on the basis of strict maintenance of participant anonymity during data analyses. Our data set included 4,948 women, 31 of whom developed diabetes. This small number of incident cases precluded meaningful statistical analyses; thus, this study included only men.

Assessing GIS

The general intelligence test is conducted as part of the military recruitment assessments. The validity of the GIS as a measure of general intelligence has been previously demonstrated to exhibit a correlation >0.8 with the Wechsler Adult Intelligence Scale total IQ (12–17). The lowest GIS group in our study (GIS 1–3) corresponds to an approximate IQ score range of 70–85. A GIS value of 5 reflects the mean score of the population (an IQ score of 100), whereas a GIS value of 9 refers to an IQ score of 130 points or higher. It includes evaluation of language ability and intellectual performance. The intelligence assessment includes four subtests: the Otis-R, which is a measure of the ability to understand and carry out verbal instructions; Similarities-R, which assesses verbal abstraction and categorization; Arithmetic-R, which assesses mathematical reasoning, concentration, and concept manipulation; and Raven's Progressive Matrices-R, which measures nonverbal abstract reasoning and visual-spatial problem-solving abilities (12). The sum of the scores of the four tests form a validated measure of general intelligence (IQ) scored on a 9-point scale (13). The GIS is administered by personnel who undergo a 4-month training course.

Follow-up and Outcomes

Follow-up began at participants' first visit to the SPEC and ended at the time of diabetes diagnosis, death, retirement from military service, or 8 March 2011, whichever came first. The median age for army discharge was 37.4 years with $<10\%$ of the participants remaining in service after the age of 45 years. Screening for diabetes was performed at each visit to the SPEC based on fasting plasma glucose (FPG) levels. Incident cases of diabetes were based on a physician diagnosis of diabetes according to American Diabetes Association criteria by documenting either two FPG levels ≥ 126 mg/dL (7.0 mmol/L) or a glucose level ≥ 200 mg/dL 2 h after ingestion of

75 g of glucose (conducted in individuals in which the examining physician deemed the test necessary). All laboratory studies were performed on fresh samples in an ISO-9002 quality-assured core facility laboratory. In order to strengthen the odds that most diagnosed diabetes cases were type 2 and not type 1 diabetes, additional analysis on the number of participants who used insulin was imputed. As computerized documentation of the pharmacological therapy in the medical record was available only from 1 January 2004, this was done in only a subset.

Definition of Variables

SES data based on place of residence were obtained from records of the Israeli Ministry of Interior, which stratifies all municipalities according to a 1–10 scale devised by the Israeli Central Bureau of Statistics. Variables that might affect SES, such as age distribution, available workforce, level of unemployment, level of education (fraction of undergraduate students and those entitled to a high school diploma), average income per capita, and fraction of income support recipients are considered. As reported previously (14,15), SES was coded into three groups: low (SES 1–4), medium (SES 5–7), and high (SES 8–10). Education was modeled as a categorical variable of low or high level at a threshold of 11 complete years of school education. This cutoff was chosen because it represents the maximum potential school instruction at the time of GIS assessment. Country of origin (classified by the father's or grandfather's country of birth) was categorized into five geographical areas: former USSR countries, Asia (non-USSR), Africa (excluding South Africa), Western (comprised of non-USSR Europe, North and South America, South Africa, Australia, and New Zealand), and Israel. Country of birth was classified in a similar manner. BMI, triglyceride level, fasting glucose level, and white blood cell (WBC) count at enrollment were treated as continuous variables. Smoking status (current smoker, ex-smoker, or never smoked), physical activity (≥ 150 min/week, <150 min/week, or inactivity), breakfast consumption (16) (frequent, sometimes, or none), and family history of diabetes (yes or no) were treated as categorical variables.

Statistical Analysis

Continuous variables were summarized using mean and SD and/or medians with intraquartile ranges. Counts with percentages were used for binary variables. GIS was analyzed as a continuous as well as a categorical variable comprised of four groups of scores, 1–3, 4–5, 6–7, and 8–9, as reported previously (13, 17–21). Linear regression models were used to delineate the relationship between differences of 1 unit in GIS at age 17 years and the risk for incident diabetes. Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% CIs for developing diabetes among the four GIS categories. Several models were used to assess these relationships after adjusting for possible confounders (age, sex, education, SES, etc.) and mediators (FPG, physical activity, etc.) of the diabetes–cognitive dysfunction relationship. Possible confounders and mediators of the diabetes–cognitive dysfunction relationship are as follows: model 1, age; model 2, age, BMI, and FPG; model 3, model 2 variables and sociogenetic risk factors (family history of diabetes, country of birth, country of origin, SES, and education); model 4, model 2 variables and lifestyle risk factors (physical activity, smoking status, triglyceride level, and breakfast consumption); and model 5, model 2 variables, sociogenetic and lifestyle risk factors, and WBC count. Log minus log plots for each variable were inspected to verify the assumption of proportionality of the hazards. As part of a sensitivity analysis, the analysis was repeated for subpopulations with 5 and 10 years of follow-up for several subgroups and utilizing a limited definition of diabetes (a follow-up FPG value ≥ 126 mg/dL at scheduled SPEC visits). One-way ANOVA was used to compare mean age at diagnosis among GIS subgroups. Analyses were performed with SPSS statistical software, version 19.0 (SPSS, Inc., Chicago, IL).

RESULTS

Characteristics of Study Participants

Data from 35,500 young men who were followed as part of the MELANY cohort met the inclusion criteria. During a mean follow-up period of 6.2 ± 4.3 years (median 5.5 years), 78 and 54% completed at least 3 or 5 years of follow-up, respectively. Seven hundred

seventy incident cases of diabetes were diagnosed during 220,265 person-years of follow-up. Among the 553 cases of incident diabetes diagnosed after January 2004, there were 37 participants who were treated with insulin throughout the study period. In four cases (0.7%), the prescription of insulin was immediate (within the month of diagnosis); 9 (1.6%) and 11 cases (2.0%) were treated with insulin 6 and 12 months after diabetes diagnosis, respectively. Table 1 presents the baseline characteristics of the cohort across four GIS

categories. The distribution of the GIS among the study participants is available as supplementary material (Supplementary Fig. 1). Table 1 presents the distribution for variables collected before beginning follow-up (age 17 years at the time of GIS assessment) and variables collected at the first SPEC assessment (beginning of follow-up) across the four GIS categories. Participants who were born in Israel or were at least a second generation in the country constituted 82.8 and 8.3% of the cohort, respectively, with a

higher proportion in the lower GIS group. As expected, the GIS was associated with several parameters reflecting level of education and SES. Additionally, more individuals in the lower versus higher GIS categories reported a family history of diabetes. Finally, mean FPG levels were higher in the lowest (89.6 ± 9.2 mg/dL) versus highest GIS category (88.6 ± 8.7 mg/dL; $P < 0.001$) and there was a higher proportion of participants with impaired fasting glucose in the lowest (12.5%) versus highest GIS category (9.8%; $P < 0.001$).

Table 1—Characteristics of the cohort according to GIS at the first SPEC visit (beginning of follow-up) and at the age of 17 years

	GIS category				Total or average \pm SD
	1–3	4–5	6–7	8–9	
<i>n</i>	3,321	10,511	13,547	8,121	35,500
Age (years)	29.81 ± 5.08	31.42 ± 5.87	31.93 ± 5.95	30.20 ± 5.29	31.19 ± 5.76
Country of birth					
Israel	86.9	84.8	81.5	80.7	82.8
USSR	2.9	4.5	8.2	12.0	7.5
Asia	1.4	2.0	1.7	0.7	1.5
Africa	8.4	7.1	5.5	1.0	5.2
West	0.4	1.5	3.1	5.5	2.9
Country of origin					
Israel	16.8	8.8	7.3	6.0	8.3
USSR	4.4	6.5	12.8	20.5	11.9
Asia	23.0	29.0	24.9	15.3	23.7
Africa	48.6	42.5	27.9	11.9	30.5
West	7.2	13.1	27.2	46.2	25.5
Education >10 years	73.9	85.5	95.2	99.3	91.3
SES					
Low	50.4	40.4	29.1	18.1	31.9
Intermediate	45.0	51.5	55.2	55.3	53.2
High	4.6	8.1	15.6	26.5	14.9
BMI at age 17 years (kg/m^2)	21.37 ± 3.31	21.32 ± 3.14	21.41 ± 2.96	21.40 ± 2.86	21.38 ± 3.03
Height at age 17 years (cm)	171.8 ± 6.6	172.4 ± 6.6	173.9 ± 6.8	175.5 ± 6.6	173.6 ± 6.8
BMI (kg/m^2)	25.64 ± 4.37	25.70 ± 4.12	25.59 ± 3.86	24.87 ± 3.71	25.46 ± 3.97
BMI <25 kg/m^2	48.2	47.0	48.3	56.9	49.9
25 \leq BMI <30 kg/m^2	36.6	38.5	39.1	34.3	37.6
BMI \geq 30 kg/m^2	15.2	14.3	12.4	8.6	12.4
BP _{Systolic} /BP _{Diastolic} (mmHg)	117.3 ± 12.7 / 74.4 ± 9.5	117.5 ± 12.0 / 74.9 ± 9.8	117.8 ± 12.6 / 75.1 ± 9.6	117.7 ± 12.0 / 74.0 ± 9.5	117.7 ± 12.0 / 74.7 ± 9.7
FPG (mg/dL)	89.6 ± 9.2	90.0 ± 9.2	89.8 ± 8.9	88.6 ± 8.7	89.7 ± 9.0
IFG	12.5	13.5	12.7	9.8	12.2
HDL (mg/dL)	45.2 ± 10.5	45.5 ± 10.6	46.2 ± 10.8	48.0 ± 10.9	46.3 ± 10.8
LDL (mg/dL)	116.6 ± 33.0	118.3 ± 33.8	118.4 ± 33.4	114.1 ± 32.3	117.1 ± 33.3
Triglycerides (mg/dL), median (25th; 75th)	125.7 (73; 155)	128.0 (74; 154)	125.1 (73; 151)	110.6 (66; 133)	
Physical inactivity	62.2	67.3	65.3	61.6	64.7
Family history of diabetes	15.4	15.6	13.7	11.0	13.8
Smoking status					
Never	46.0	50.0	59.2	74.8	58.8
Ex-smoker	12.6	13.8	15.1	10.4	13.4
Current smoker	41.3	36.3	25.8	14.8	27.9
Frequent breakfast consumption	15.7	15.3	18.5	27.6	19.4

Categorical variables are presented by %. For continuous variables, the mean \pm SD is given unless otherwise indicated. BP, blood pressure; IFG, impaired fasting glucose.

GIS and Incident Diabetes

The incidence of diabetes was lower in those with higher GIS (highest GIS group $1.99/10^3$ person-years and lowest GIS group $4.61/10^3$ person-years). Table 2 presents the incidence of diabetes across GIS categories using various models. After adjusting for age, the risk for type 2 diabetes was 2.6-fold higher in the lowest GIS group compared with the highest GIS group (HR 2.57 [95% CI 1.91–3.45]; $P < 0.001$). Further adjustment for age, BMI, FPG, and sociogenetic risk factors (model 3) or lifestyle risk factors (model 4) attenuated the risk but did not eliminate it (Table 2).

Figure 2A depicts the incidence of diabetes over time after adjusting for model 5 variables (age, BMI, FPG, sociogenetic and lifestyle risk factors, and WBC count) across the different GIS categories. As can be seen, the incidence of diabetes increased over time in all GIS subgroups; however, more so in the lower GIS groups. After 6 years, a difference of 1% between the highest and lowest GIS categories was noted in diabetes incidence rates, rising to 3.8

and 5.2% after 10 and 12 years of follow-up, respectively.

Figure 2B shows the relationship between incident diabetes and GIS when treated as a continuous variable and after adjustment for the models described above. In the fully adjusted model (model 5), each decrease of 1 point on the GIS index was associated with a 1.1-fold greater risk for incident diabetes (HR 1.10 [95% CI 1.04–1.17]; $P < 0.001$). Similar results were obtained when the analysis was repeated for individuals according to SES subgroups, education attainment, and country of origin (Supplementary Fig. 2) and also when the definition of diabetes was limited to those with an FPG ≥ 126 mg/dL at scheduled follow-up (SPEC) visits ($n = 359$ cases of diabetes; HR 1.08 [95% CI 1.01–1.16]; $P = 0.037$ for incident diabetes per 1 GIS unit decrease). To minimize the possibility that duration of follow-up may have confounded the relationship between GIS and incident diabetes, the analysis was repeated for those with follow-up of >5 and 10 years. The results obtained were similar to the overall results (Supplementary Figs. 2 and 3).

GIS and Age of Diabetes Diagnosis

Figure 2C depicts age of diabetes diagnosis across the four GIS groups. Subjects in the lowest GIS category were diagnosed at a mean age of 39.5 ± 4.7 years and those in the highest GIS group at a mean age of 41.5 ± 5.1 years (P for comparison 0.042). These results persisted when the analysis was limited to ≥ 5 years of follow-up (data not shown).

CONCLUSIONS

This analysis of 35,500 young healthy men followed for 220,265 person-years demonstrates an inverse relationship between cognitive function in late adolescence and incident diabetes in young adulthood. Men with lower cognitive scores at age 17 years had a higher risk for developing diabetes, with an approximately twofold increase in incidence and a ~ 2 -year earlier age of diagnosis when compared with those in the highest GIS group. When GIS was studied as a continuous variable, every unit decrease in GIS was associated with an $\sim 10\%$ increase in the incidence of diabetes. The fact that this relationship

Table 2—HR for developing diabetes across four GIS categories for various models

	GIS category				Total
	1–3	4–5	6–7	8–9	
<i>n</i>	3,321	10,511	13,547	8,121	35,500
New cases of diabetes	100	288	302	80	770
Mean follow-up (years)	6.53 ± 4.33	6.98 ± 4.29	6.27 ± 4.20	4.94 ± 4.03	6.20 ± 4.27
Person-years of follow-up	21,690	73,427	85,026	40,122	220,265
Rate (1/1,000 person-years)	4.61	3.92	3.55	1.99	3.49
Mean age of diabetes onset (years)	39.49 ± 4.74	39.81 ± 5.04	40.46 ± 5.09	41.53 ± 5.06	40.20 ± 5.05
Model 1: age					
HR	2.573	1.778	1.577	1	
95% CI	1.915–3.457	1.388–2.278	1.232–2.017		
<i>P</i>	<0.001	<0.001	<0.001		
Model 2: age, BMI, FPG					
HR	2.171	1.684	1.539	1	
95% CI	1.606–2.934	1.308–2.167	1.198–1.978		
<i>P</i>	<0.001	<0.001	<0.001		
Model 3: age, BMI, FPG, family history, birth country, country of origin, SES, education					
HR	1.918	1.549	1.522	1	
95% CI	1.376–2.676	1.178–2.037	1.172–1.976		
<i>P</i>	<0.001	0.002	0.002		
Model 4: age, BMI, FPG, physical activity, smoke status, triglyceride level, breakfast consumption					
HR	2.340	1.810	1.614	1	
95% CI	1.652–3.314	1.350–2.426	1.350–2.426		
<i>P</i>	<0.001	<0.001	0.001		
Model 5: age, BMI, FPG, family history, birth country, country of origin, SES, education, physical activity, smoking status, triglyceride level, breakfast consumption, WBC count					
HR	2.139	1.694	1.608	1	
95% CI	1.461–3.131	1.235–2.323	1.189–2.175		
<i>P</i>	<0.001	0.001	0.002		

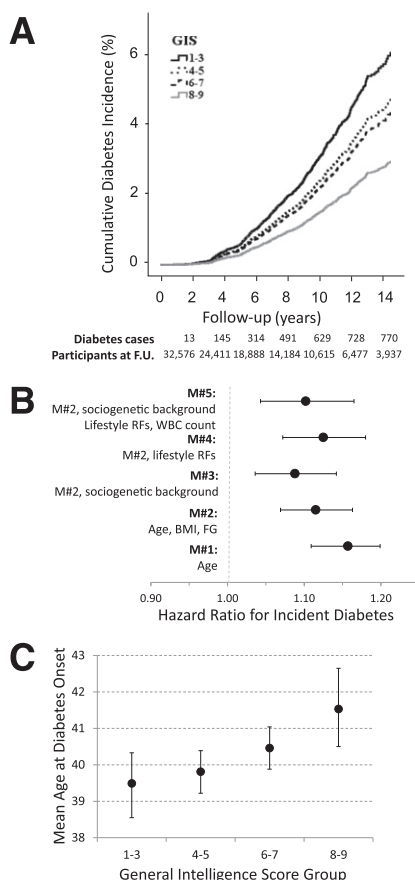


Figure 2—Incidence of diabetes over time depends on GIS. **A:** Incidence of diabetes over time across different GIS categories. Incidence (person-years) was adjusted for age, BMI, FPG, family history of diabetes, countries of birth and origin, SES, education, physical activity, smoking status, triglyceride level, breakfast consumption, and WBC count (model 5 in Table 2). **B:** HR for the development of diabetes per 1-point decrease in GIS in different models. Model 1, age; model 2, age, BMI, and FPG; model 3, model 2 variables and sociogenetic risk factors (family history of diabetes, birth country, country of origin, SES, and education); model 4, model 2 variables and lifestyle risk factors (physical activity, smoking status, triglyceride level, and breakfast consumption); model 5, model 2 variables, sociogenetic and lifestyle risk factors, and WBC count. FG, fasting glucose; F.U., follow-up; M, model; RFs, risk factors. **C:** The age of diabetes onset across the different GIS categories. Mean age (years) of onset of diabetes ($\pm 95\%$ CI) is shown for each category.

persisted after adjusting for multiple confounders and independent risk factors for diabetes in this cohort, including age, family history of diabetes, education, SES, country of origin and birth, BMI, smoking, and physical activity, supports the hypothesis of an independent relationship between premorbid

cognitive function and incident diabetes at young adulthood.

The inverse relationship between cognitive function in young adulthood and subsequent development of diabetes has several possible explanations. First, as cognitive function is associated with education and SES, it is possible that the relationship observed is a reflection of the already recognized relationship between these two variables and the subsequent risk for diabetes. The fact that the relationship persisted in subgroup analysis (Supplementary Fig. 2), and after adjusting for these factors (Fig. 2), and that the cohort, career army personnel, was exposed during follow-up to similar health care services and ambient conditions makes this less likely the sole explanation but does not eliminate it. Alternatively, differences in GIS might be associated with different lifestyle patterns in adulthood, childhood, and in utero, which our analyses did not account for. Thus, it could be that physical activity and diet in childhood or even in utero could have affected intelligence scores and the subsequent risk for diabetes independently. Analyses were conducted after adjusting for measurable lifestyle risk factors and factors known to be strongly associated with physical activity, such as plasma triglyceride levels (6,8). The fact that the relationship persisted after these adjustments could imply the existence of lifestyle factors that were not measured, or alternatively could suggest an independent relationship between cognitive function and incident diabetes. Finally, it is possible that the relationship observed suggests an origin(s) or pathway(s) common to decreased cognitive function and increased incidence of diabetes (22). These might include, among others, mitochondrial (dys)function (23,24), the sortilin pathway (25), activation of the HPA axis, inflammation, dysglycemia per se, or brain and systemic insulin signaling (26–29). There are many insulin receptors in the brain and some have a role in glucose transport, whereas others are considered to have a function in cognitive processes (30–32). Therefore, variability in cognitive abilities may mirror variability in brain insulin sensitivity; supporting this hypothesis are studies on the cognitive improving capacity of a form of insulin that enters the brain selectively (33,34).

This study had several limitations. First, the analysis was conducted only in men, thereby limiting extrapolation of the results to women. Second, it is not possible to entirely exclude the possibility that duration of follow-up may have confounded the relationship between cognitive function and incident diabetes. However, the similar results obtained for subgroup analyses at 5 and 10 years of follow-up, as well as the earlier age of diabetes onset among those with the lower GIS, minimizes this possibility. Third, a limited number of variables that might be associated with diabetes and cognitive function (confounders) were collected at baseline (SES, education, country of birth and origin, and BMI), and for some of these measures (SES), only crude measures were available. As such, it might be that some confounders were not measured, or were not measured precisely, and thus were not appropriately adjusted for. However, the fact that similar results were obtained in subgroups with different SES and education attainment, the minimal change in point estimates when the measured confounders were added to the model, as well as the fact that all participants in the MELANY, independent of rank and position, had equal access to free medical services minimize the possible effect of this limitation. Fourth, Israel is a “young” country with a relatively high rate of immigration. This analysis pertains to people from a wide range of different backgrounds and origins. The strong relationship observed despite this limitation and after adjustment for country of origin and birth strengthens the robustness of the results. Fifth, the mean age of incident diabetes in our cohort was around 40 years; thus it is not clear if our results are valid for other cohorts with an older age of diabetes onset. However, in several recent studies from U.S. and European cohorts, similar incident rates and a similar age of onset were reported (35–38), thereby likely making our results applicable to a wide population of young adults. Finally, the use of a general intelligence test cannot be used to assess the relationship between specific cognitive domains and diabetes.

To conclude, this analysis of 35,500 young healthy men followed for 220,265 person-years demonstrates a clear inverse relationship between cognitive

function in late adolescence and risk for diabetes during young adulthood. On a clinical level, along with a family history of diabetes, FPG and triglyceride levels, WBC count, and BMI, these results might help identify those at increased risk for diabetes. Moreover, our study lays the logical groundwork for basic research aimed at unraveling mechanisms that connect cognitive function with metabolic dysregulation.

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Author Contributions. G.T. and T.C.-Y. conceived and designed the study, acquired and interpreted data, performed statistical analysis, and drafted the manuscript. I.G. conceived and designed the study and critically revised the manuscript. A.T. conceived and designed the study, interpreted data, and critically revised the manuscript. H.C.G. and G.Y. interpreted the data and critically revised the manuscript. A.A., A.K., B.G., E.F., and G.L. critically revised the manuscript. E.D. conceived and designed the study, performed statistical analysis, and critically revised the manuscript. D.T. acquired data. A.R. provided intellectual input on interpretation of the data and critically read the manuscript. G.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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