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Featured Article

Associations of hemoglobin A1c with cognition reduced for long diabetes duration

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Abstract

Introduction: Associations of some risk factors with poor cognition, identified prior to age 75, are reduced or reversed in very old age. The Protected Survivor Model predicts this interaction due to enhanced survival of those with extended risk factor duration. In a younger sample, this study examines the association of cognition with the mean hemoglobin A1c risk factor over the time at risk, according to its duration.

Methods: The interaction of mean hemoglobin A1c (average = 9.8%), evaluated over duration (average = 116.8 months), was examined for overall cognition and three cognitive domains in a sample of 150 "young-old" veterans (mean age = 70) with type 2 diabetes.

Results: The predicted interactions were significant for overall cognition and attention, but not executive functions/language and memory.

Discussion: Findings extend the Protected Survivor Model to a "young-old" sample, from the very old. This model suggests focusing on individuals with good cognition despite prolonged high risk when seeking protective factors.

Keywords: Type 2 diabetes; Diabetes duration; Hemoglobin A1c; Cognitive function; Risk factors; Protective factors; Protected survivor

1. Introduction

Type 2 diabetes (T2D) affects more than 25% of the adults aged 65 years or older [1], associated with nearly twice the risk of developing cognitive impairment, dementia, and Alzheimer's dementia. Previous studies have found that while aging is one of the major risk factors for dementia, among patients with T2D, hyperglycemia, and hypoglycemia, and duration of the diabetes is an additional risk factor for cognitive impairment [2–5]. In a few studies of very old age (>75 years) patients with T2D, the risk of a bad cognitive outcome was diminished [6] or even reversed [7–10], in contrast to "young-old" (average age <75) samples [11].

The Protected Survivor Model [12] was developed to explain these changes in outcomes measured at different points in late life [10,13–15]. This model assumes that a large majority of a birth cohort are vulnerable to the presence of a risk factor, but a minority have protection against the bad outcome despite the presence of the risk factor. With increasing age, "survivors" are those cohort

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members who are still alive and have not yet demonstrated the bad outcome. Unprotected individuals with high levels of risk factor are less likely to survive. Over time, an increasing proportion of survivors are either protected individuals—regardless of the risk factor level—or unprotected individuals with low risk factor levels. Moreover, those with high risk factor levels are increasingly likely to be protected, so that the observed association of high risk with bad outcome is diminished or even reversed with increasing age. In addition, if the risk factor is associated with higher mortality, this increasing proportion of protection is further accelerated.

According to the Protected Survivor Model, diminished or even reversed risk association is clearest in "oldest-old" (at least age 85) survivors. In addition to late old age as a measure of extended survival, the model can also be applied to duration of risk regardless of age. This extension of the model—from age to duration of high risk as a measure of survival—is the focus of the present study of a relatively young sample. It examines how the association of cognitive performance with hemoglobin A1c (HbA1c; a measure of average blood glucose over 3 months) changes according to duration of diabetes. In individuals with T2D, medication and/or lifestyle may reduce HbA1c down to nondiabetic levels (<6.5%). Many studies of individuals without [16,17] as well as those with T2D [18] have implicated relatively high levels of HbA1c as a risk factor for dementia, including Alzheimer's disease, or cognitive impairment and decline.

The present study of a young-old sample with diabetes investigates how the association of cognitive performance with mean HbA1c over time differs according to survivorship indexed by T2D duration. Its participants (aged 55+ years) were enrolled in a clinical trial, "Computerized Cognitive Training to Improve Cognition in Diabetic Elderly Veterans" [19] and assessed at baseline. Based on the Protected Survivor Model, we hypothesized an interaction of T2D duration and HbA1c for cognitive performance: relatively good cognition among those with high levels of both risk factors, after taking account of the separate effects of T2D duration and HbA1c.

2. Methods

2.1. Participants in the clinical trial

The clinical trial—conducted at Bronx, NY and Ann Arbor, MI Veterans Affairs Medical Centers (VAMC)—enrolled US military veterans aged at least 55 years with a diagnosis of T2D identified in their VA medical records [19]. Participants were required to be free of dementia; any major medical, psychiatric, or neurological conditions that affect cognitive performance; and severe impairment in vision or hearing. The clinical trial focuses on efficacy for better T2D self-care, so the Diabetes Self-Management Questionnaire [20] screened for self-reported deficits in self-care; a score of ≤18, reflecting deficits below the maximum of 20, was required. Women were not excluded but were rare (3%). The VA's Central Institutional Review Board approved the study as did the Research and Development committees of both VAMCs, and all participants provided signed informed consent.

2.2. Cognitive and neuropsychological measurements

Before randomization in the clinical trial, participants were screened for dementia and overall cognitive functioning; a battery of neuropsychological tests assessed overall cognitive function as well as specific cognitive domains.

2.2.1. Clinical dementia rating scale

Severity of cognitive-related functional impairment is assessed from the participant and an informant. "No dementia" (0) or "questionable dementia" (0.5) is required for inclusion—higher scores (1 to 3) indicate severity of a definite dementia [21].

2.2.2. Mini–Mental State Examination

This 30-point screening questionnaire assesses global cognition. A score 25 or above was required [22].

2.2.3. Neuropsychological battery

Nine tests (Word List Memory, Logical Memory (story A), Target Cancellation Tests, Trail Making Test, Digit Symbol Substitution Test, Digit Span, Boston Naming Test, Verbal Fluency Test, Similarities) yielded 16 scores associated with the cognitive domains of executive functions, language, memory, and attention [23].

2.3. Diabetes diagnosis and HbA1c measurements

In 1999, the VA fully implemented its electronic medical record database, the Centralized Patient Record System (CPRS) [24]. Among many other features, for every VA patient, the CPRS includes diagnoses documented by physicians, laboratory values with associated dates, and demographic information. For all participants in the clinical trial, we obtained all HbA1c measurements as performed by the VA clinical laboratory, and diagnoses of medical conditions, including T2D, from the CPRS.

2.4. Required data for the present study

Clinical trial participants were required to have complete baseline data on demographics (self-reported age, sex, years of education), clinical dementia rating (CDR) and Mini–Mental State Examination scores, and all 16 neuropsychological test scores. Duration of T2D was estimated as the number of days from the date of the first recorded CPRS measurement of HbA1c to the date of the last HbA1c measure at or before the cognitive assessment. A minimum of three HbA1c measures were required. At least one HbA1c measurement had to be at least 91 days and one-sixth of the T2D duration from both the first and the last

measurement. This excluded any participant for whom all intermediate measurements were very near the first or last measurement, almost as if only two times were assessed. The primary analyses used the mean HbA1c, called here simply HbA1c, as the summary for each participant.

2.5. Statistical methods

The first principal component of a factor analysis of the neuropsychological tests was used as the estimate of overall cognition, the primary cognitive outcome. Scree plot comparison of the eigenvalues and interpretation of orthogonal Varimax factors were used to define two to four uncorrelated secondary cognitive outcomes—cognitive domain scores possibly combining memory, executive functions, language, and attention. For each of the cognitive scores, hierarchical regression analysis entered six predictors: CDR status (step 1), age (step 2), years of education (step 3), T2D duration (in months) (step 4), HbA1c (step 5), and the product of T2D duration and HbA1c (step 6)—which represented their interaction, after controlling for both variables. Step 6 is the test of the hypothesis of this study—an interaction of T2D duration and HbA1c, with relatively good cognition among those with high levels of both risk factors, indicated by a positive partial correlation.

Other risk factors for cardiovascular disease, many substantially intercorrelated with HbA1c, were not included as covariates. Our interest was to investigate cognition of participants with both high HbA1c with long T2D duration. Relatively good cognition would nominate this combination as a possible "marker" for a cognitive protective factor according to the Protected Survivor Model. Thus, we did not seek to limit the effect of the combination of high HbA1c and long T2D duration to its unique contribution to cognition, beyond the effect of other cardiovascular risk factors. The number of women was so small that inclusion of sex as an additional covariate, commonly used in studies of cognition, was not appropriate.

To operationalize the hypothesized "high levels of both risk factors" in an interaction, the entire sample was dichotomized twice into majority "lower risk" and minority "high risk" groups, using the lower limit of the upper third of T2D duration or HbA1c. These two dichotomies created four subgroups: shorter T2D duration/lower HbA1c, shorter T2D duration/high HbA1c, long T2D duration/lower HbA1c, and long T2D duration/high HbA1c. Using dichotomized rather than continuous measures of T2D duration and HbA1c, a 2 × 2 analysis of covariance tested their interaction, controlling for CDR, age, and education.

Statistical significance was defined as $P < .05$. Although the hypothesis was directional, a two-sided test was used to take account of a possible opposite result.

3. Results

The initial sample of 182 included 176 participants with complete demographic and neuropsychological data, of whom 150 had the required HbA1c measures before the baseline cognitive assessment.

Principal components analysis of the 16 test scores associated with the 9 neuropsychological tests yielded a large first principal component (33% of total variance); the first three principal components accounted for 53%. The three cognitive domains were labelled executive functions/language (with highest magnitudes of loadings on Letter Fluency, Digit Symbol, Trails A, Digit Backwards, Trails B, Digit Forward, Similarities, Category Fluency), memory (Word List: Immediate Recall, Delayed Recall, Recognition; Logical Memory: Immediate Recall, Delayed Recall), and attention (Target Cancellation: TMX, Diamond; Boston Naming).

Table 1 presents the demographic, HbA1c, and cognitive characteristics of the total sample and compares the shorter (N = 100) and long (N = 50) T2D duration subsamples dichotomized at 157.72 months (about 13 years). The T2D duration group difference in HbA1c assesses the association between dichotomized duration group and the continuous HbA1c. This difference reflected a significant association between continuous measures of T2D duration and HbA1c ($r = 0.329$, $P < .001$). It also reflected a significant association between dichotomized measures of T2D duration and HbA1c (phi coefficient = 0.28, $P < .001$). These associations reflect higher values of HbA1c for longer duration.

For the full sample, Table 2 shows the regression models for the overall cognition score and each of the three cognitive domain scores. After controlling, a priori, for CDR status, age, and education (steps 1, 2, and 3), worse overall cognition was significantly associated with risk factors of longer T2D duration (step 4) and higher HbA1c (step 5). These associations were consistent with previous studies of HbA1c and T2D duration as distinct risk factors but were not the primary focus of the present study. The significant positive interaction of T2D duration and HbA1c (Step 6; $P = .01$) confirms the hypothesis of the study—high levels of both risk factors were associated with relatively good overall cognition. Not controlling for CDR, age, and education, the interaction remained significant ($P = .037$).

Of the three cognitive domains, only attention had a significant interaction of T2D duration with HbA1c ($P = .03$). None of the three cognitive domains was significantly associated with both risk factors: worse executive functions/language was significantly associated only with longer T2D duration; worse memory and attention were significantly associated only with higher HbA1c.

To visualize the interaction for overall cognition, Fig. 1 shows separate plots of overall cognition by HbA1c for the shorter and long T2D duration groups, in simple raw data, not controlling for CDR, age, and education. Within the entire shorter T2D duration group (lower panel), overall cognition decreases as HbA1c increases (solid line: $r = -0.364$, $P < .001$). By contrast, within the entire long T2D duration group (upper panel), overall cognition increases as HbA1c increases (solid line: $r = 0.281$, $P = .04$).

Table 1
Characteristics of veterans with diabetes sample: Total and dichotomized T2D duration group

Characteristic	T2D duration: Total sample (7.41–215.15 mo.)	Shorter T2D duration (7.41–157.70 mo.)	Long T2D duration (157.74–215.15 mo.)	Statistic*	*P* value
N	150	100	50		
Age (SD)	69.8 (6.3)	69.4 (5.3)	70.7 (8.0)	t = −1.21	.228
Males (%)	146 (97)	97 (97%)	49 (98%)	χ^2 = 0.13	.72
Education y (SD)	14 (3)	14 (2)	14 (3)	t = −0.59	.56
Mean HbA1c (SD)	9.78 (1.42)	9.39 (1.46)	10.57 (0.94)	t = −5.19	<.001
High HbA1c group (%)	50 (33%)	24 (24%)	26 (52%)	χ^2 = 11.76	<.001
T2D duration mo (SD)	116.79 (59.61)	82.96 (41.68)	184.56 (16.98)	NA	
# HbA1c measures (SD)	40 (41)	23 (18)	72 (53)	t = −8.31	<.001
CDR = 0 (%)	125 (83%)	86 (86%)	39 (78%)	χ^2 = 1.54	.22
MMSE (SD)	28 (1)	28 (1)	28 (1)	t = 1.25	.21
Overall cognition	0.00 (1.00)	0.17 (1.03)	−0.34 (0.85)	t = 3.03	.003
Executive functions/language	0.00 (1.00)	0.18 (0.99)	−0.36 (0.93)	t = 3.23	.002
Memory	0.00 (1.00)	0.05 (0.99)	−0.10 (1.02)	t = 0.91	.37
Attention	0.00 (1.00)	0.003 (0.995)	−0.007 (1.020)	t = −0.57	.96

Abbreviations: CDR, Clinical dementia rating; HbA1c, hemoglobin A1c; MMSE, Mini–Mental State Examination; T2D, type 2 diabetes; NA, not applicable.
*Degrees of freedom: t, 148; χ^2, 1.

The dashed vertical lines distinguish between the observations in the lower and high HbA1c subgroups within each T2D duration group. Within each of the four subgroups, the star and associated vertical bars indicate, respectively, the means of HbA1c and cognition, and the standard deviation of cognition. The four subgroups also have separate dotted regression lines. Within the shorter T2D duration group, overall cognition decreases as HbA1c increases within both HbA1c subgroups (lower: HbA1c, r = −0.26, $P < .02$; high: HbA1c, r = −0.24, $P = .25$). By contrast, within the long T2D duration group, although overall cognition also decreases within lower HbA1c (r = −22, $P = .31$), it increases within high HbA1c (r = 0.36, $P = .07$).

Analysis of covariance, controlling for CDR, age, and education, found a strongly significant interaction of dichotomized T2D duration and HbA1c for overall cognition (F [1, 143] = 11.55, $P < .001$), confirming the result for the continuous measures. Because the shorter T2D duration/lower HbA1c subgroup was favorable on both risk factors, it was not surprising that it had the highest estimated overall cognition score (0.291, N = 76). The long T2D duration/high HbA1c subgroup had the next best cognition score (−0.058, N = 26). The other two subgroups had worse cognition scores: shorter T2D duration/high HbA1c (−0.296, N = 24) and long T2D duration/lower HbA1c (−0.563, N = 24). Thus, the long T2D duration/high HbA1c subgroup had better cognition than the subgroups with one favorable and one unfavorable risk factor, although both risk factors were unfavorable.

For the attention domain, for which the interaction of continuous T2D duration and Hb1c was also significant, analysis of covariance using dichotomized measures of T2D duration and HbA1c had a nonsignificant interaction (F [1, 143] = 2.67, $P = .104$). Again, the shorter T2D duration/lower HbA1c subgroup had the highest estimated overall attention score (0.163, N = 76). The long T2D duration/high HbA1c subgroup (−0.039, N = 26) did not have the next best attention score, but it was substantially better than the combined results for the other two subgroups: long T2D duration/lower HbA1c (0.052, N = 24) and shorter T2D duration/high HbA1c (−0.527, N = 24). These descriptive results suggest that attention for patients with high levels of both risk factors was—overall—better than for those with only one, so the regression analysis interaction was in the hypothesized direction.

Table 2
Stepwise multiple regression analyses of overall cognition and cognitive domain scores

	Overall cognition		Executive functions/ language		Memory		Attention	
Stepwise entry	Partial r	*P*-value	Partial r	*P*-value	Partial r	*P*-value	Partial r	*P*-value
1. CDR status	−0.37	<.001	−0.23	.004	−0.35	<.001	0.02	.82
2. Age	−0.09	.27	−0.04	.60	−0.08	.33	−0.03	.68
3. Education (yr)	0.17	.04	0.20	.02	−0.02	.82	0.06	.48
4. T2D duration (mo)	−0.18	.03	−0.24	.004	0.03	.76	0.003	.98
5. Mean HbA1c	−0.28	<.001	−0.14	.09	−0.18	.03	−10.20	.01
6. HbA1c × T2D duration	0.21	.01	0.13	.12	0.08	.33	0.18	.03

Abbreviations: CDR, Clinical dementia rating; HbA1c, hemoglobin A1c; T2D, type 2 diabetes.

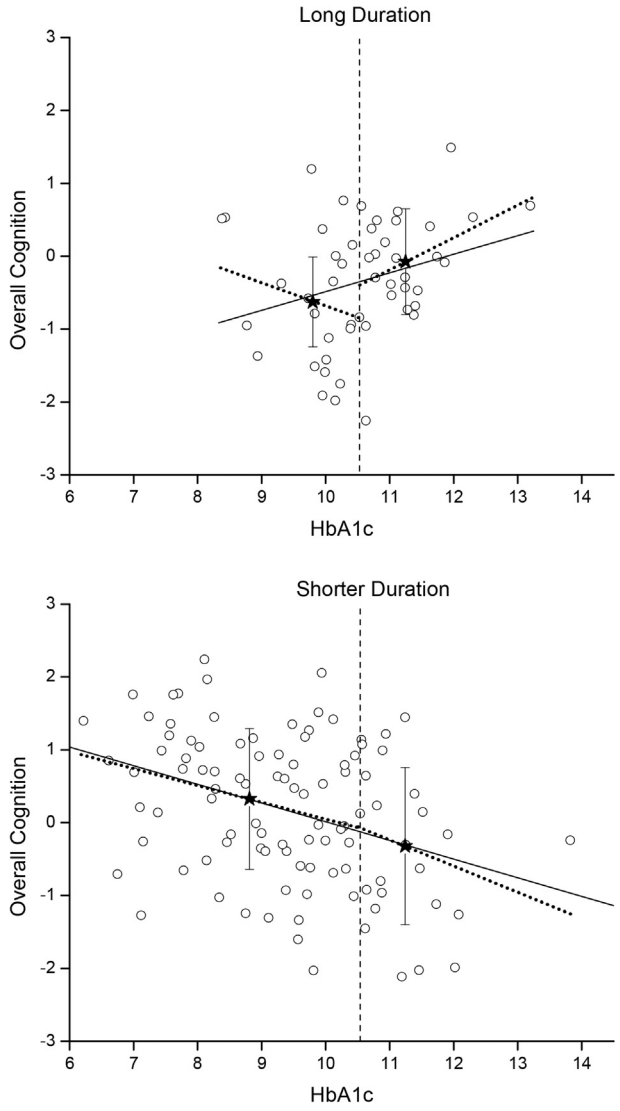

Fig. 1. HbA1c by overall cognition scores divided by duration groups. Mean HbA1c by overall cognition scores in veterans with T2D dichotomized at the low end of the upper third (157.72 months), creating a long T2D duration group (157.74–215.15 months; upper panel) and shorter T2D duration group (7.41–157.70 months; lower panel). In each plot, the dashed vertical line from the x-axis is the dichotomization cut point at the low end of the upper third for HbA1c (10.535%). Solid line in each panel is the regression line for all participants in the T2D duration group. Dotted lines in each panel are the regression lines for participants in the lower and high HbA1c subgroups. For each subgroup, means and standard deviations of HbA1c and overall cognition scores are black stars with vertical bars. Abbreviations: HbA1c, hemoglobin A1c; T2D, type 2 diabetes.

4. Discussion

For the primary outcome, overall cognitive performance, and one of three cognitive domains, attention, there was a significant interaction between T2D duration and HbA1c. For both interactions, relatively good cognition was associated with the combination of longer T2D duration and higher mean HbA1c—as hypothesized. This supplements studies where higher HbA1c alone [16–18], or longer T2DM duration alone [4,5], was found to be associated with greater cognitive impairment. The seemingly paradoxical finding that having both risk factors mitigated rather than exacerbated their separate deleterious effects on cognition is hypothesized by the Protected Survivor Model. Individuals who have maintained good cognition into very old age are said to have successful cognitive aging (SCA). The model proposes that a larger proportion of those with SCA have high risk than do young-old with good cognition. Maintaining good cognition into very old age despite high risk is called resistant SCA (rSCA) [12].

The model was developed to explain unexpected findings in studies of SCA, especially those beyond age 85 years. Many risk factors for cardiovascular disease were consistently identified in samples of young-old as also associated with bad cognition [11]. In samples of very old individuals, some risk factors—including HbA1c [7,14]—were rarely associated with bad cognition and sometimes significantly associated with good cognition: cholesterol [8,25,26], C-reactive protein [9,15,27], blood pressure [10], apolipoprotein E-e4 [28,29].

In the present study, we measured survival by T2D duration rather than age. Thus, a novel feature is testing the model in a young-old sample (mean = 70 years), in contrast to the earlier studies of the very old. The "resistant" aspect of rSCA can be generalized to young-old who nevertheless have lived for a long time at high risk without the bad outcome, comparable to individuals having SCA despite high risk—rSCA.

An earlier study from our group, examining an Israeli sample of nondemented patients with T2D (N = 897), found worse cognitive performance associated with longer T2D duration specifically in the third of the sample with the highest mean HbA1c measures taken over an average of 8.7 years. There was a substantial discrepancy in the samples between the HbA1c levels of the two samples, at least partly attributable to the eligibility requirements of the clinical trial from which the present sample was derived. It focused specifically on those in need of better T2D self-care. The high HbA1c group in the Israeli study ranged from 7.0% to 10.1%, which did not even overlap with the high HbA1c group in the present sample (10.5% to 13.8%); on the contrary, it was comparable to the lower HbA1c group in the present sample (range: 6.2% to 10.5%). The associations between T2D duration and overall cognition were similar between their high group and the lower group in the present sample (partial r = −0.19 in both groups, indicating worse cognition for longer duration), and statistically significant (Israeli group, $P = .002$; present study group, $P = .027$). Despite the appearance of inconsistency in the directions of interactions in the two studies, the studies are not in conflict. This explanation for the discrepancy also applies to the ACCORD-MIND baseline sample [30]. The negative association between HbA1c level and cognition was found in a sample similar to the lower group of the present study and the high group in the Israeli study; the mean ± standard

deviation HbA1c was 8.3% ± 1.1% and individuals with levels >11% were excluded.

Our finding is an exception to the generality that high risk is associated with impaired cognition, and it is so in the context of an extreme subpopulation—long-term exposure to high risk. The ACCORD study found a different exception—intensive intervention to reduce HbA1c levels was not beneficial [31]. It illustrates the caution that association does not imply a simple causal explanation.

There were limitations on this sample of veterans in treatment who had T2D. The very small proportion of women is representative of their rarity among veterans of this age. The participants were enrolled in a clinical trial that required difficulties in disease management to permit improvements. Those excluded due to very good disease management were likely to have low levels of risk, thus their exclusion in the present study limited the range and reduced power. Although the risk factor measure was derived longitudinally, the outcome cognition was measured cross-sectionally, excluding inferences about causality.

The evaluation of T2D duration started with the date of the first recorded CPRS measurement of HbA1c, which for 17 (11%) of the sample was below the threshold of 6.5%. For them, T2D may have started later, but 11 of the 17 had HbA1c levels indicating borderline diabetes, >5.7% (7 of the 11 had HbA1c greater than 6.5% at their next assessment, as did the remaining 6 of the 17 with HbA1c <5.7%). On the other hand, 26 (17%) of the sample (including three with first HbA1c <6.5%) had HbA1c measurements in the first year of CPRS implementation, so it is plausible that they had been measured earlier with T2D-level values.

A pitfall built into the Protected Survivor Model is the seeming benefit misleadingly associated with long-term high risk. An association of high risk with good cognition depends on the high proportion of protection in survivors with high risk. Even if applicable, the Protected Survivor Model does not identify which high risk survivors are truly protected. Nor does the model assume that the risk factor in protected survivors is beneficial, only that it is not as harmful as in unprotected survivors. Moreover, the focus on cognitive performance does not reflect other dangers of T2D. Thus, the present findings must not be clinically interpreted for a given individual to suggest that control of HbA1c levels becomes less important after an extended period.

Clinical trials for protection against cognitive decline have used a variety of potential protective factors, such as physical activity, dietary, or cognitive engagement factors, but without definitive results [32]. Because resistance to disease is not readily distinguished from nondiseased normality, efforts to identify protective factors pose more challenges than identifying risk factors. Many people may remain free of disease owing to lack of exposure to the factors that increase disease risk, rather than resistance. Affirmative protection is more likely in those who have remained healthy despite their high exposure to risk factors. This strategy identified the protective mutation in the CCR5 gene against HIV [33]—focusing on individuals at high risk of infection who nevertheless remained free of it. According to the Protected Survivor Model, a relatively high proportion of the very old individuals with rSCA have a protective factor against cognitive decline and subsequent dementia, suggesting focusing on them for genetic and other studies seeking protective factors. The present findings generalize this strategy to protection against cognitive decline in the young-old by focusing on individuals with good cognition despite high risk over an extended T2D duration.

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RESEARCH IN CONTEXT

1. Systematic review: Associations between risk factors and cognition vary by age at outcome. The Protected Survivor Model posits the existence of protective factors in a minority of the population to explain diminished or reversed associations in the very old.
2. Interpretation: The present results show how this model can be successfully applied to the young-old by indexing exposure to high risk by duration of illness rather than by very old age.
3. Future directions: The validity of the model can be tested by focusing on individuals with good cognition despite prolonged high risk, as suggested by the results of this study.

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