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Glycemic control, inflammation, and cognitive function in older patients with type 2 diabetes

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Abstract

Objective—Glycated hemoglobin (HbA1c) and C-reactive protein (CRP) have been associated with cognitive impairment independently. However, it is unclear if their combination exacerbates poor cognitive function. We assessed whether long-term glycemic level and glycemic variability modulate the association of systemic inflammation with cognitive function, in a sample of cognitively normal older people with type 2 diabetes.

Methods—A retrospective cohort study of 777 randomly selected participants from ~11,000 patients in the Maccabi Healthcare Services Diabetes Registry, as part of the Israel Diabetes and Cognitive Decline study. Subjects averaged 18 (±9.4) HbA1c measures in the Maccabi Healthcare Services Registry, which were used to calculate long-term glycemic level (HbA1c-mean) and glycemic variability (HbA1c-standard deviation (SD)). Linear regression models assessed the interactions of CRP, a marker of systemic inflammation, with HbA1c-mean and HbA1c-SD on

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Conflict of interest

None declared.

Author contributions

All authors critically revised the manuscript and approved the final version for publication. Jimmy Akrivos conducted the literature review, performed statistical analyses, interpreted the results, and wrote the manuscript. Ramit Ravona-Springer contributed to the planning and design of the study, the data collection and research, and the interpretation of the results. James Schmeidler performed statistical analyses, interpreted the results, and contributed to the writing of the manuscript. Anthony Heymann collaborated in planning the study design, data collection, and data research. Rachel Preiss contributed to the planning of the study design and data collection. Hadas Hoffman searched the data. Keren Koifmann contributed to the planning of the study design and data collection. Derek LeRoith contributed to critical revisions of the manuscript. Jeremy M. Silverman contributed to the conception of the study design and to the interpretation of results. Michal Schnaider Beeri led the development of the study design, data collection, interpretation of results, and contributed to the writing of the manuscript. Jimmy Akrivos 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.

subjects' performance in tests of Memory, Executive Functions, Attention, and Semantic Categorization.

Results—Quadratic interactions of CRP with HbA1c-SD approached significance for executive functions and overall cognition. However, after Bonferroni adjustment, none of the interactions of CRP with HbA1c were statistically significant. In partial correlations according to HbA1c-SD tertiles, CRP was weakly correlated in the middle tertile with decreased performance in the domains of semantic categorization ($r = -0.166$, $p = 0.011$), executive functions ($r = -0.136$, $p = 0.038$), and overall cognition ($r = -0.157$, $p = 0.016$).

Conclusions—Glycated hemoglobin does not substantially modulate the association of CRP with cognition in a sample of cognitively normal, community dwelling older people with relatively well-managed type 2 diabetes.

Keywords

HbA1c; C-reactive protein; cognitive function; type 2 diabetes; older people

Introduction

The upregulation of complement, cytokines, acute-phase proteins, and other inflammatory biomarkers has been widely reported in animal models and human studies of Alzheimer's disease (Akiyama *et al.*, 2000). C-reactive protein (CRP), in particular, is a marker of subclinical systemic inflammation that has been associated with poor cognitive function (Jefferson *et al.*, 2011), cognitive decline (Jenny *et al.*, 2012), and higher risk of cognitive impairment (Noble *et al.*, 2010) in older people. Moreover, elevated plasma CRP at midlife has been found to predict dementia and Alzheimer's disease 25 years later (Schmidt *et al.*, 2002), and findings from the Rotterdam Study indicate that CRP may also predict vascular dementia (Engelhart *et al.*, 2004). However, not all findings have been consistent suggesting that the role of CRP in cognitive impairment requires further investigation (Mooijaart *et al.*, 2011).

Various lines of research indicate that the relationship of inflammation with cognition in older people is complex and may involve interactions with underlying metabolic and cardiovascular pathophysiological mechanisms. Type 2 diabetes in particular, may share common biological pathways with systemic inflammation (de Jager *et al.*, 2006) and their combination may have a synergistic effect on the pathogenesis of neurocognitive impairment in older people. The combination of metabolic syndrome and higher levels of CRP increases the risk of cognitive impairment (Yaffe *et al.*, 2004) and cardiovascular disease (Ridker *et al.*, 2003). Type 2 diabetes-related risk factors including, insulin resistance, hypertension, hypercholesterolemia, and obesity have all been linked to a higher degree of inflammation (Festa *et al.*, 2000) and an increased risk of cognitive impairment and dementia (Beeri *et al.*, 2009).

Glycated hemoglobin (HbA1c), which reflects average blood glucose over the past 3 months, is the "gold standard" measure of glycemic control in diabetes treatment and diabetes research. HbA1c is a reliable predictor of macrovascular and microvascular

complications (Holman *et al.*, 2008) and has also been associated with cognitive outcomes (Luchsinger *et al.*, 2011). Besides long-term hyperglycemia, however, additional evidence suggests that glycemic variability may be another key component of the disease process in type 2 diabetes (Monnier and Colette, 2008), although it has been rarely studied in the context of cognition.

Short-term fluctuations of blood glucose, as measured by continuous glucose monitoring or blood glucose clamp, have been associated with the pathogenesis of oxidative stress (Monnier *et al.*, 2006), endothelial dysfunction (Ceriello *et al.*, 2008), and cognitive impairment (Rizzo *et al.*, 2010; Zhong *et al.*, 2012). One study, which examined the effect of postprandial plasma glucose excursions on cognition over a 12-month period, found that tighter control may prevent cognitive decline in older patients with type 2 diabetes (Abbatecola *et al.*, 2006). However, investigations of the effects of long-term glycemic variability are scarce, and we are not aware of any that have reported on its interaction with systemic inflammation. Given the potential contribution of poor glycemic control in the relationship between inflammation and cognition, we assessed the role of long-term level and long-term variability of HbA1c in the association of CRP with cognitive function in a large sample of cognitively normal older people with type 2 diabetes.

Methods

This study was approved by the institutional review board committees at the Icahn School of Medicine at Mount Sinai, Sheba Medical Center, and Maccabi Health Services (MHS).

The methods of the Israel Diabetes and Cognitive Decline (IDCD) study have been described in detail elsewhere (Ravona-Springer *et al.*, 2013). Briefly, the IDCD study is an investigation of the long-term effects of type 2 diabetes-related risk factors, such as inflammation, poor glycemic control, and obesity on cognitive decline. The current investigation is a retrospective cohort study utilizing data from the MHS Diabetes Registry, which contains over 15 years of comprehensive diabetes-related medical records for MHS clients with type 2 diabetes (including, HbA1c, full lipid profile, creatinine, albumin, body mass index (BMI), and medication history). From the approximately 11,000 patients in the MHS Diabetes Registry, 1288 participants were randomly selected, screened for eligibility, and signed consent. To be eligible, participants had to be 65 years or older, have a type 2 diabetes diagnosis, and live in the Tel Aviv area. Participants who were on cholinesterase inhibitors, or had dementia, Mild Cognitive Impairment, or major psychiatric or neurological impairment that could affect cognitive performance were excluded. Moreover, participants who did not have an informant, could not speak Hebrew, or had less than three HbA1c measurements were also excluded. This study includes 777 subjects who met all eligibility criteria and had a CRP measure and complete demographic, biomarker, and cognitive data. Of the subjects who were excluded, 109 refused further participation after consent, 120 had incomplete biomarker or cognitive data, and 282 did not meet eligibility criteria (the vast majority, 84%, because of cognitive impairment).

Inflammation

C-reactive protein (mg/L) was measured from plasma, using the ADVIA 1650 Chemistry System with a CRP latex reagent.

Glycemic control

Subjects had on average 18 (±9.4 SD; range: 3–60) HbA1c (%) measures in the Diabetes Registry. Using these measures, we were able to calculate the within person mean (HbA1c-mean) and standard deviation (HbA1c-SD) for each subject, representing long-term glycemic level and glycemic variability, respectively.

Physician evaluation

All participants who signed consent and who passed the preliminary screening underwent a medical and neurological evaluation by a study physician. During the evaluation, a blood draw was also performed to determine inflammatory markers and Apolipoprotein E genotype (*APOE*).

Apolipoprotein E genotype

Apolipoprotein E genotype status was established using the polymerase chain reaction method from DNA isolated from blood.

Cognitive outcomes

Within 2 weeks from the medical evaluation and blood draw, subjects underwent a battery of cognitive tests that assesses different areas of cognitive functioning, which are typically affected in dementia. A principal component analysis of the tests indicated four factors corresponding to the cognitive domains of episodic memory, executive function, attention/working memory, and semantic categorization. Summary variables for the domains were created as the sums of Z scores of tests loading highly on the factors (with reversal as necessary). An overall cognitive outcome was computed by adding the four summary variables. A detailed description of the IDCD neuropsychological battery has been published previously (Guerrero-Berroa *et al.*, 2014). Briefly, tests of episodic memory consisted of the word list immediate and delayed recall and word list recognition from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery; executive functions tests included the Trail Making Test parts A and B; the attention/working memory domain consisted of the diamond cancelation, digit symbol, and the digit span forward and backward tests; and tests of semantic categorization included the Boston Naming, animal and letter fluency, and similarities. Table 1 describes the cognitive tests that were included in each domain.

Diagnostic consensus conference

All available patient data obtained during the physician and cognitive evaluations were reviewed at a diagnostic clinical consensus meeting, which included a dementia expert (psychiatrist, neurologist, or geriatrician) and a neuropsychologist. Only subjects classified as cognitively normal were eligible to participate in the IDCD study.

Confounding variables

To control for the influence of confounders, the sociodemographic factors of sex, years of education, and age were used as covariates, along with the cardiovascular factors of BMI (kg/m^2), creatinine (mg/dL), total cholesterol (mg/dL), triglycerides (mg/dL), and systolic and diastolic blood pressure (mmHg) (calculated as the average of ~18 measurements per participant). Moreover, we adjusted for important type 2 diabetes-related characteristics, including, duration of diabetes (using length of follow-up in the MHS Diabetes Registry as a surrogate) and type 2 diabetes medications at the time of IDCD assessment. With respect to medications, because over 80% of patients in our sample were on metformin (either alone or in combination with another therapy) and prior literature suggests that, compared with monotherapy, the combination of insulin and oral hypoglycemic medication (insulin+) may provide differential therapeutic effects (Beeri *et al.*, 2008), we created two dichotomous variables that were included in our model: monotherapy versus control by diet and insulin+ versus monotherapy. Lastly, to adjust for the influence of *APOE* genotype, the dichotomy of *APOE*-4 carriers versus non-carriers was also included as a covariate.

Statistical analyses

In order to assess whether HbA1c-mean or HbA1c-SD modulate the association of CRP with each of the five cognitive outcomes, we conducted multiple linear regression analyses, using the predictors as continuous variables, and controlling for the confounding variables described earlier. Model 1 controlled for the effect of age; model 2 included model 1 and the additional sociodemographic confounders of sex and education, which we have previously found to be strongly associated with cognitive performance in this cohort (Guerrero-Berroa *et al.*, 2014); model 3 included model 2 plus all of the cardiovascular, *APOE* genotype, and type 2 diabetes-related confounders described earlier, which have been associated with dementia (Imtiaz *et al.*, 2014; West *et al.*, 2014). Nine families of hypotheses of effects on five cognitive outcomes were defined: CRP; linear and quadratic interactions between CRP and HbA1c-mean; and linear and quadratic interactions between CRP and HbA1c-SD; each for three models. There were five tests of significance for CRP and 10 tests of significance in each family of interaction hypotheses, introducing a problem of increased probability of type I error. In order to account for this, we used a Bonferroni corrected *p*-value of 0.01 (0.05/5) to determine statistical significance for CRP and 0.005 (0.05/10) for each linear or quadratic interaction term.

Influential observations and model assumptions were assessed graphically and through residual analysis and leverage statistics. Variance inflation factors and condition numbers were used to assess multicollinearity.

Results

Sample characteristics

Our overall sample of 777 participants had a mean HbA1c of 6.7%, mean HbA1c-SD of 0.55%, and mean CRP of 1.3 mg/L. Subjects averaged 72 years of age and 13.1 years of education; 40% of the subjects had 12 years of education or less; and 38% were women. Because, as detailed in the succeeding text, interactions of CRP with HbA1c-SD approached

statistical significance, we also present characteristics of the cohort according to tertiles of HbA1c-SD. The ranges of HbA1c-SD for its tertiles were 0.063–0.319%, 0.321–0.576%, and 0.577–3.164%. Table 2 presents the overall sample characteristics and compares HbA1c-SD tertiles on the covariates and the cognitive measures. The high glycemic variability tertile tended to have fewer women, lower cholesterol, higher triglycerides, higher HbA1c-mean, and the lowest cognitive scores.

Relationship of C-reactive protein with cognitive outcomes

We observed a statistically significant age adjusted association between CRP and reduced performance in the executive functions domain ($p = 0.008$). However, this association was attenuated after further adjustment in models 2 and 3 ($p = 0.044$, for both). No statistically significant associations were observed between CRP and any of the other cognitive outcomes.

Interactions of C-reactive protein with glycated hemoglobin

After centering the variables of HbA1c-mean, HbA1c-SD, and CRP, there was little evidence of multi-collinearity, as all variance inflation factors were less than five. A collinearity diagnostics analysis without the intercept in the model indicated a near collinearity between age and the cardiovascular covariates. When we centered these variables, all conditional numbers became less than 30.

We used leverage values, Cook's distance (d_i), and deleted residuals to examine influential observations and identified 37 cases with outliers. When we repeated our analyses excluding these cases, the model fit with respect to some of the cognitive outcomes did improve modestly, resulting in decreased p-values. However, because all of the identified outliers were plausible, and all d_i values were <1, we included these cases in our final models.

None of the interactions of CRP with HbA1c-mean were significant with respect to the cognitive outcomes in any of the models, without Bonferroni correction. Likewise, none of the linear interactions of CRP with HbA1c-SD were significant. For the quadratic interaction of CRP with HbA1c-SD, significant and nearly significant interactions were observed in all three models with respect to the executive functions domain ($p = 0.012$–0.065); and in models 2 and 3 for the attention/working memory domain and overall cognition ($p = 0.069$–0.078 and $p = 0.023$–0.025, respectively). None of these results maintained significance using the Bonferroni corrected p-value for multiple comparisons. Table 3 presents multiple linear regression tests of the quadratic interactions of CRP with HbA1c-SD for all three models.

To better understand the pattern of these interactions, we conducted partial correlations of CRP with each of the cognitive outcomes according to tertiles of HbA1c-SD, controlling for all confounding variables. For subjects in tertiles 1 and 3, that is, those with stable or very unstable glycemic control, CRP was not associated with cognitive function in any of the neuro-psychological domains. For subjects in the middle tertile, that is, those with intermediate glycemic variability, CRP was weakly correlated with decreased performance across all of the domains. Most notably, in semantic categorization ($r = -0.166$; $p = 0.011$); executive functions ($r = -0.136$; $p = 0.038$); and overall cognition ($r = -0.157$; $p = 0.016$).

Discussion

In this analysis of a large sample of cognitively normal older people with a confirmed diagnosis of type 2 diabetes, we used a comprehensive neuropsychological battery, which allowed for the evaluation of specific cognitive domains, in addition to an overall cognition measure. Our overall findings indicate that long-term glycemic level and long-term glycemic variability do not substantially modulate the relationship of CRP with cognition, as none of our interaction terms in multiple linear regression models reached statistical significance after adjusting for multiple comparisons. In partial correlations, as hypothesized, we found that for those with stable HbA1c, CRP was not associated with cognition suggesting that, if glycemia is well controlled, inflammation does not affect cognition deleteriously. Among those with intermediate instability of glycemic control, we observed borderline significant associations between CRP and poorer cognitive function in the domains of semantic categorization, executive functions, and overall cognition. This distinction between the first and second tertiles is consistent with findings from two prospective observational studies by Yaffe and colleagues who found that the risk of cognitive decline was greatest in those with a combination of the metabolic syndrome and above median serum CRP levels (Yaffe *et al.*, 2004; Yaffe *et al.*, 2007). Results from the Longitudinal Aging Study in Amsterdam have also confirmed this interaction with respect to poor cognitive performance (Dik *et al.*, 2007). However, in contrast to these previous studies, we did not find an association of CRP with cognitive performance in those with highest level of HbA1c or highest instability of glycemic control.

Our study is unique in that all of our subjects had type 2 diabetes. Thus, we were able to assess the interaction of inflammation with glycemic control in participants who were exposed to substantially higher levels of HbA1c—and presumably greater risk for cognitive impairment—compared with previous studies that have reported on the interaction of the metabolic syndrome and inflammation. It is possible that in the context of a sample of older people with type 2 diabetes, other risk factors such as vascular disease and diabetes complications may mask associations with CRP. However, we found that controlling for a number of potential confounders and diabetes-related risk factors such as BMI, hypertension, and dyslipidemia did not affect the results.

Patients who have higher HbA1c levels are more likely to be aggressively treated to return to good glycemic control compared with patients with normal glycemia, or intermediate hyperglycemia. In our study, nearly all of our participants (~90%) were on oral hypoglycemic medications, or insulin alone, or in combination. Both oral diabetes medications and insulin are known to have anti-inflammatory properties, while their combination may augment this property. Our analyses accounted for potential confounding effects by type 2 diabetes medication use; however, it is possible that subjects in the highest HbA1c tertiles were also treated more intensively with statins, drugs used to treat high low-density lipoprotein cholesterol, which may decrease CRP (Nissen *et al.*, 2005).

We also assessed the potential contribution of hypoglycemia to our findings by examining the health status of all subjects in our cohort with HbA1c of <5%. There were only three such subjects in our study. None of them had a history of hospitalizations due to

hypoglycemia (although hypoglycemic episodes without hospitalizations cannot be ruled out). Overall, there were 14 subjects in our study with a history of hospitalization due to hypoglycemia, and their HbA1c-mean values ranged from 5.9% to 8.1%. Excluding these 14 subjects from the analyses did not alter our findings.

Another unique aspect of our investigation is that we studied long-term HbA1c variability, a relatively little studied risk factor in type 2 diabetes. As an index of long-term glycemic exposure, HbA1c is less susceptible to biologic and intra-individual variability (Derr *et al.*, 2003). However, as an indicator of glycemic variability, HbA1c must be distinguished from measures of short-term glycemic variability, which quantify acute fluctuations in daily blood glucose levels. We found only weak associations of CRP with cognition and only in the middle tertile of long-term glycemic variability. It is possible that short-term glycemic fluctuations are far more deleterious to cognition, as compared with long-term glycemic variability (Monnier *et al.*, 2006; Ceriello *et al.*, 2008).

Although our findings may weaken the hypothesis that the combination of high inflammation and poor glycemic control exacerbates cognitive compromise, they should be viewed in the context of the limitations of our study. CRP is a non-specific marker of inflammation and may only be a limited indicator of inflammation as it relates to neuropathologic changes (Singh-Manoux *et al.*, 2014). Moreover, although HbA1c was averaged from ~18 measurements over 10 years of follow-up in the MHS diabetes registry, CRP was measured only at the end of this period. It is possible that this resulted in a mismatch of the biological synergy of the two parameters, which may at least in part, account for the null results. Finally, our findings were based only on cross-sectional cognitive data. The longitudinal component of the IDCD study should be able to shed more light on how the combination of chronically elevated inflammation and poor glycemic control impacts cognitive decline and dementia in the context of diabetes.

To our knowledge, this is the first study to report on the combined effect of long-term glycemic variability and inflammation on cognitive function. Our findings are largely negative, and they suggest that glycemic control plays only a limited role in the association of inflammation with cognition in a sample of cognitively normal, community dwelling older people with relatively well-controlled type 2 diabetes.

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Key points

- In a sample of cognitively normal, community dwelling older people with relatively well-controlled type 2 diabetes, glycemic control plays only a limited role in modulating the association of inflammation with cognition.
- Our findings contrast with those of previous studies that have reported greater cognitive impairment in subjects with a combination of metabolic syndrome and high inflammation.

Table 1

Neuropsychological battery by cognitive domain

Memory	**Executive function**
CERAD word list immediate recall	Trail Making A (s)
CERAD word list delayed recall	Trail Making B (s)
Word List Recognition	
Attention	**Semantic categorization**
Shape (diamond) cancelation (s)	Boston Naming
Digit symbol	Animal fluency
Digit span forwards	Letter fluency
Digit span backwards	Similarities

CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

Table 2

Sample characteristics and comparison by HbA1c-SD tertiles

Covariate	Low (*N* = 264)	Medium (*N* = 258)	High (*N* = 255)	Total (*N* = 777)	*F*[a]	*P*
Age (years)	72.2 ± 4.6	72.1 ± 4.6	71.8 ± 5.0	72.0 ± 4.7	0.723	0.486
Education (years)	13.2 ± 3.5	12.9 ± 3.5	13.0 ± 3.1	13.1 ± 3.3	0.309	0.734
Women (%)	37.9	46.9	30.2	38.4	15.17[b]	0.001
APOE-4 (%)	16.7	12.8	11.8	13.8	2.93[b]	0.230
Any T2D medications (%)	77.7	88.0	96.9	87.4	43.55[b]	<0.001
Insulin+ (%)	0.8	5.4	20.4	8.8	67.96[b]	<0.001
T2D duration (years)	10.4 ± 1.5	10.5 ± 1.1	10.5 ± 1.0	10.5 ± 1.2	0.340	0.712
Systolic BP (mmHg)	166 ± 9.2	164 ± 9.1	166 ± 10.1	166 ± 9.5	4.402	0.013
Diastolic BP (mmHg)	83 ± 15.6	82 ± 15.2	85 ± 15.1	84 ± 15.3	3.592	0.028
BMI (kg/m^2)	28 ± 4.2	28 ± 4.7	28 ± 4.2	28 ± 4.4	1.496	0.225
Creatinine (mg/dL)	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.3	1.0 ± 0.2	2.052	0.129
Cholesterol (mg/dL)	182 ± 23	182 ± 23	174 ± 23	178 ± 23	7.211	0.001
Triglycerides (mg/dL)	149 ± 0.57	156 ± 57	171 ± 80	158 ± 64	9.659	<0.001
CRP (mg/L)	1.1 ± 1.9	1.2 ± 1.8	1.4 ± 3.2	1.3 ± 2.4	1.418	0.243
HbA1c-SD (%)	0.22 ± 0.06	0.43 ± 0.07	1.0 ± 0.42	0.55 ± 0.42	742.98	<0.001
HbA1c (%)	6.2 ± 0.4	6.7 ± 0.5	7.3 ± 0.8	6.7 ± 0.7	226.45	<0.001
Cognitive Outcome						
Overall	0.86 ± 7.5	0.13 ± 6.9	−0.73 ± 7.4	0.09 ± 7.3	3.078	0.047
Semantic categorization	0.16 ± 2.3	0.05 ± 2.3	−0.07 ± 2.4	0.04 ± 2.3	0.682	0.506
Attention	0.11 ± 2.1	0.02 ± 2.0	−0.05 ± 2.1	0.02 ± 2.1	0.401	0.670
Executive function	0.36 ± 3.0	0.08 ± 2.6	−0.45 ± 3.1	0.002 ± 2.9	5.086	0.006
Memory	0.21 ± 2.3	−0.02 ± 2.2	−0.15 ± 2.2	0.01 ± 2.2	1.814	0.164

CRP, C-reactive protein; BMI, body mass index; BP, blood pressure; T2D, type 2 diabetes; insulin+, insulin and hypoglycemic medication; *APOE*-4, at least one Apolipoprotein E4 allele; HbA1c, glycated hemoglobin; SD, standard deviation.

Data are mean ± SD or %.

[a] *F* statistic for ANOVA.

[b] Pearson's X^2.

Table 3

Multiple linear regression tests of the quadratic interaction of CRP with HbA1c-SD

	Model 1		Model 2		Model 3	
Cognition	***t***	***p****	***t***	***p****	***t***	***p****
Overall	1.643	0.101	2.285	0.023	2.252	0.025
Semantic	0.088	0.930	0.374	0.708	0.422	0.673
Attention	1.270	0.204	1.823	0.069	1.767	0.078
Executive	1.847	0.065	2.498	0.013	2.531	0.012
Memory	1.546	0.122	1.561	0.119	1.425	0.154

CRP, C-reactive protein; HbA1c, glycated hemoglobin; SD, standard deviation; BMI, body mass index; T2D, type 2 diabetes; *APOE*-4, at least one Apolipoprotein E4 allele.

All models include CRP, HbA1c-SD, HbA1c-SD^2, and the linear and quadratic interactions of CRP with HbA1c-SD. Model 1 is adjusted for age; model 2 includes model 1 and sex and education; model 3 includes model 2 and BMI, creatinine, cholesterol, triglycerides, systolic and diastolic blood pressure, duration of T2D, any T2D medications, insulin+, *APOE*-4, and HbA1c-mean.

*None of the results maintained significance after Bonferroni adjustment.