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Glycated hemoglobin, type 2 diabetes, and poor diabetes control are positively associated with impulsivity changes in aged individuals with overweight or obesity and metabolic syndrome

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Abstract

Impulsivity has been proposed to have an impact on glycemic dysregulation. However, it remains uncertain whether an unfavorable glycemic status could also contribute to

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an increase in impulsivity levels. This study aims to analyze associations of baseline and time-varying glycemic status with 3-year time-varying impulsivity in older adults at high risk of cardiovascular disease. A 3-year prospective cohort design was conducted within the PREDIMED-Plus-Cognition substudy. The total population includes 487 participants (mean age = 65.2 years; female = 50.5%) with overweight or obesity and metabolic syndrome. Insulin resistance (HOMA-IR), glycated hemoglobin (HbA1c), presence of type 2 diabetes mellitus, and type 2 diabetes control were evaluated. Impulsivity was measured using the Impulsive Behavior Scale questionnaire and various cognitive measurements. Impulsivity z-scores were generated to obtain Global, Trait, and Behavioral Impulsivity domains. Linear mixed models were used to study the longitudinal associations across baseline, 1-year, and 3-year follow-up visits. HOMA-IR was not significantly related to impulsivity. Participants with higher HbA1c levels, type 2 diabetes, and poor control of diabetes showed positive associations with the Global Impulsivity domain over time, and those with higher HbA1c levels were further related to increases in the Trait and Behavioral Impulsivity domains over the follow-up visits. These results suggest a potential positive feedback loop between impulsivity and glycemic-related dysregulation.

KEYWORDS
glycated hemoglobin (HbA1c), impulsivity, insulin resistance (HOMA-IR), type 2 diabetes control, type 2 diabetes mellitus

INTRODUCTION

Personality traits have been identified as stable characteristics that modulate individual responses to various types of environmental stressors.[1] They play a crucial role in enabling individuals to show a spectrum of potential behaviors,[2] and have been recognized as relevant predictors of various health outcomes.[3] Impulsivity is defined as "a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others."[4] Impulsivity is a personality trait which has been shown to be more modifiable across the lifespan than other personality traits.[5] The development of impulsivity can be influenced by genetic background and ontogenetic processes,[5,6] and impulsive behaviors are manifested when individuals ultimately engage in unplanned and rash actions.

This personality predisposition is associated with maladaptive impulsive behaviors that increase the risk for highly prevalent disorders and diseases with significant public health burdens, such as overeating and obesity,[7,8] cardiovascular disease,[9,10] eating disorders,[11,12] and substance-related disorders,[13,14] among others. With regard to glycemic dysregulation, high glucose levels in healthy participants have been shown to be positively associated with inattention, poor inhibitory control, and risky decision-making.[15,16] Along this line, it has been reported that participants with prediabetes or type 2 diabetes mellitus have higher levels of trait impulsivity compared to healthy individuals.[17,18] These findings suggest that both high trait and behavioral impulsivity may drive the establishment of glycemic impairment and may lead to a poor glycemic prognosis. Indeed, behavioral impulsivity, as assessed by higher reward sensitivity, has been associated with poor adherence to diabetes medications and

uncontrolled levels of glycated hemoglobin (HbA1c) levels in studies of adolescents with type 1 diabetes and adults with type 2 diabetes.[19,20] Moreover, trait impulsivity has been positively associated with poor management of type 2 diabetes and self-care in adults.[21,22]

Conversely, it has been suggested that glycemic dysregulation, such as higher glucose levels, may modulate impulsivity.[23] For example, in individuals with type 1 diabetes, the neural reward system—which is related to impulsivity[14]—was found to play a key role in the observed associations between metabolic trajectories and cognitive impulsivity.[24] Along this line, the association between higher insulin resistance and poor performance on behavioral impulsivity tasks is mediated by the activation of impulsivity-related neural areas in individuals with type 2 diabetes and obesity.[25] However, no associations have been found between trait impulsivity and fluctuations in glucose levels[26,27] or changes in HbA1c levels,[28] or between behavioral impulsivity and blood glucose levels.[27]

Therefore, the directionality of these potential associations is controversial, and new research in this field is needed using prospective studies and clinical trials that simultaneously assess both trait and behavioral measures of impulsivity.

The aim of the present study was to assess the associations between insulin resistance, glycated hemoglobin, presence of type 2 diabetes mellitus, and type 2 diabetes control with several assessments of impulsivity across 3 years of follow-up in an older Mediterranean population at high risk of cardiovascular disease. A positive longitudinal association between poorer glycemic status and impulsivity was hypothesized.

MATERIALS AND METHODS

Study design

An observational prospective study was conducted with the PREDIMED-Plus-Cognition cohort, a substudy conducted within the PREDIMED-plus cohort. The baseline visit of the PREDIMED-Plus study is the same as for the PREDIMED-Plus-Cognition study. PREDIMED-Plus is a 6-year multicenter, randomized, parallel-group clinical trial conducted in Spain with the primary aim of evaluating the effect of lifestyle intervention on the primary prevention of cardiovascular disease and mortality. Participants in the intervention group received recommendations to increase their adherence to an energy-reduced Mediterranean diet and physical activity promotion. In contrast, participants in the control group only received general usual care recommendations to follow an energy-unrestricted Mediterranean diet. Participants were recruited between September 2013 and December 2016. The study protocol has been described elsewhere[29,30] and is available at http://www.predimedplus.com. The trial was registered in the International Standard Randomized Controlled Trial registry, and details can be found at http://www.isrctn.com/ISRCTN89898870.

Study population

Eligible participants were men aged 55–75 years and women aged 60–75 years with overweight or obesity (27 kg/m^2 ≥ body mass index [BMI] < 40 kg/m^2) and meeting at least three criteria for metabolic syndrome[31] at baseline. Exclusion criteria have been reported elsewhere.[30] As part of the initial PREDIMED-Plus population (n = 6874), the current study included participants from the PREDIMED-Plus-Cognition substudy (n = 487) recruited in four Spanish centers: Institut Hospital del Mar d'Investigacions Mèdiques, Bellvitge University Hospital, Universitat Rovira i Virgili, and Universidad de Valencia. As the latter center did not perform the computerized cognitive tests, only 417 participants were analyzed for cognitive assessments. The participants' flowchart and data availability are shown in Figure S1.

Ethical standards

All participants provided written informed consent. According to the ethical standards of the Declaration of Helsinki by the Research Ethics Committees, all the participating institutions approved the study protocol and procedures (CEIC del Hospital de Bellvitge—University Hospital Bellvitge-IDIBELL: PR240/13; CEIC Parc de Salut Mar y IDIAP Jordi Gol—IMIM: PI13/130; CEIC Corporativo de Atención Primaria de la Comunitat Valenciana—University of Valencia: CEIC del Hospital Universitari Sant Joan de Reus y IDIAB Jordi Gol—Universitat Rovira i Virgili: 2011-005398-22; 13-07-25/7proj2).

Glycemic status

Exposures were assessed at baseline or as a time-varying variable across the 3 years of follow-up, depending on their availability. Blood samples were collected at baseline, 1-year, and 3-year follow-up under fasting conditions, and biochemical analyses were performed to determine glycated hemoglobin (HbA1c) using standard laboratory methods at baseline and across follow-up. Insulin was measured by an electrochemiluminescence immunoassay using an Elecsys immunoanalyzer (Roche Diagnostics), and the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index was calculated[32] at baseline and at 1-year follow-up. Participants with a previous diagnosis of diabetes or use of antidiabetic medication were identified as positive cases of type 2 diabetes mellitus at baseline, as well as according to the American Diabetes Association criteria: HbA1c ≥6.5% (48 mmol/mol) or having fasting plasma glucose ≥136 mg/dL at both the screening and baseline visits. Type 2 diabetes control was assessed at baseline and as time-varying exposure across the follow-up by categorizing participants into those having good glycemic control (HbA1c <7% or <53 mmol/mol) and poor glycemic control (HbA1c ≥7% or ≥53 mmol/mol).[33]

Covariates

Sex, age, intervention group, educational level, marital status, smoking status, and presence of hypertension and hypercholesterolemia were obtained from self-reported questionnaires administered by trained PREDIMED-Plus personnel and were assessed at baseline. Physical activity, Mediterranean diet adherence, alcohol consumption, and presence of obesity and depressive symptomatology were assessed as time-varying variables across time points. Weight and height were measured to determine BMI, and the presence of obesity was defined as BMI >30 kg/m^2. Physical activity was estimated using the validated Regicor Short Physical Activity Questionnaire.[34] Adherence to the Mediterranean diet was assessed using the validated 17-point Mediterranean diet adherence screener questionnaire.[35] Risk for depressive symptomatology was assessed using the Beck Depression Inventory-II questionnaire.[36]

Impulsivity

Trait and behavioral impulsivity were assessed at the baseline, 1-year, and 3-year follow-up visits.

Trait impulsivity was evaluated using the Impulsive Behavior Scale (UPPS-P),[37] validated for the Spanish population.[38] The UPPS-P assesses five personality subfactors related to impulsivity pathways: negative urgency, (lack of) perseverance, (lack of) premeditation, sensation seeking, and positive urgency. Scores for each dimension and a total score of the UPPS-P were calculated by adding the unweighted respective items, with higher scores indicating higher levels of impulsivity. Cronbach's α values for the total score were 0.92, 0.93, and 0.93 at baseline, 1-year, and 3-year of follow-up, respectively.

Behavioral impulsivity was evaluated using the commissions and perseverations scores of the Conners' Continuous Performance Test (CPT) third edition,[39] the Iowa Gambling Task (IGT),[40] and the Stroop Color and Word Test (SWCT).[41] Further description of behavioral impulsivity assessments can be found in the Supplementary Material.

Statistical analysis

The PREDIMED-Plus-Cognition database, updated in September 2021, was used for the present analyses.

To facilitate comparisons across impulsivity assessments, z-scores were generated for each impulsivity measurement, and z-score domains of Global, Trait, and Behavioral Impulsivity were further obtained following specified methods.[42,43] More detailed information about impulsivity z-scores can be found in the Supplementary Methods.

Baseline participant characteristics are presented as numbers and percentages and mean ± standard deviation (SD) for qualitative and quantitative variables, respectively. Linear mixed models were performed to assess longitudinal relationships between glycemic-related measures and impulsivity z-scores. Linear mixed models address missing data by assuming that repeated measures for each participant are intracorrelated. These models maximize the use of all available data, even if the data were collected at a single point in time during the follow-up visits. Specifically, analyses were performed to assess the associations of: (a) baseline levels of HOMA-IR and HbA1c, presence of type 2 diabetes (no/yes), and diabetes control in participants having type 2 diabetes (no/yes) with impulsivity z-scores as time-varying outcomes; and (b) time-varying HOMA-IR, HbA1c, and type 2 diabetes control with time-varying impulsivity z-scores. The time variable was introduced as a categorical variable in the models with an interaction with the respective glycemic status exposure, along with the respective glycemic exposure and the time variables. The results were interpreted using the baseline visit as the reference. Additionally, a *p*-value for trend was estimated by conducting the same models using the time variable as a continuous variable. Three models were fitted, and covariates were specified in figure and table footnotes and in the Supplementary Methods. Random effects were hierarchically established by center, members sharing the same household unit, and each participant's response. The random slope was defined considering follow-up periods.

We tested interactions for sex, age (<65 or ≥65 years; based on the median of the population), intervention group, and presence of obesity (no/yes) and depressive symptomatology (no/yes) in the associations between glycemic status and the Global Impulsivity z-score by comparing the model with and without the interaction product using the likelihood ratio test.

The Stata-18 software program (StataCorp) was used to perform the statistical analyses, and significance was defined as $p < 0.05$.

RESULTS

Descriptive results

Table 1 shows the sociodemographic, lifestyle, and medical history of disease characteristics of the study population at baseline (n = 487). The mean age was 65.2 ± 4.7 years, and 49.5% of participants were men. Approximately half of the population had completed primary school level education, three-quarters were married, and half had never smoked. Almost 75% of the study population had obesity or hypercholesterolemia, while 84.4% had hypertension and 19.9% had depressive symptomatology. Baseline scores for trait and behavioral measures of impulsivity are shown in Table 1. The mean and SD for the total UPPS-P score at baseline and 1- and 3-year follow-up visits were 108.7 ± 22.7, 109.1 ± 24.1, and 106.9 ± 23.9, respectively. Table S1 shows the baseline population characteristics by intervention and control group, with no statistical differences between groups for any assessed variable.

TABLE 1 Baseline participant characteristics ($n = 487$).

Characteristics	Values
General characteristics	
Age (years)	65.2 ± 4.71
Sex (female)	246 (50.5)
Intervention group	240 (49.3)
Education level	
Primary school or less	260 (53.4)
High school	142 (29.2)
College	85 (17.4)
Marital status	
Single, divorced, separated	54 (11.1)
Married	382 (78.4)
Widowed	51 (10.5)
Smoking status	
Never smoked	239 (49.1)
Former smoker	189 (38.8)
Current smoker	59 (12.1)
Physical activity (MET min/week)	2361 ± 2036
Alcohol intake (g/day)	8.98 (11.8)
Adherence to Mediterranean diet (0–17 points)	7.77 (2.47)
Body mass index (kg/m^2)	32.5 ± 3.41
Obesity (BMI ≥ 30 kg/m^2)	354 (72.7)
Hypercholesterolemia	357 (73.3)
Hypertension	411 (84.4)
Medication for diabetes[a]	121 (24.85)
Depressive symptomatology (BDI-II score)	8.52 ± 6.91
Depressive symptomatology	97 (19.9)
Glycemic assessments[b]	
HOMA-IR	5.59 ± 4.01
HbA1c (%)	6.14 ± 0.84
HbA1c (mmol/mol)	43.6 ± 9.15
Type 2 diabetes prevalence	148 (30.4)
Good type 2 diabetes control[c]	78 (52.7)
HbA1c (%)	6.29 ± 0.36
HbA1c (mmol/mol)	45.3 ± 3.94
Poor type 2 diabetes control[d]	70 (47.3)
HbA1c (%)	7.84 ± 0.96
HbA1c (mmol/mol)	62.1 ± 10.4
Impulsivity assessments[b]	
UPPS-P total score (0–236 points)	108.7 ± 22.7
UPPS-P Negative Urgency (0–48 points)	24.5 ± 7.38
UPPS-P Premeditation (0–44 points)	19.8 ± 5.60
UPPS-P Perseverance (0–40 points)	18.9 ± 4.96
UPPS-P Sensation Seeking (0–48 points)	22.3 ± 6.05
UPPS-P Positive Urgency (0–56 points)	23.0 ± 8.24
CPT Commissions	19.5 ± 11.9
CPT Perseverations	0.48 ± 0.98
Iowa Gambling Test	1.25 ± 16.2
Stroop Color Word Test	−1.25 ± 8.12

Note: Data are expressed as *n* (%) for categorical variables and mean ± SD for quantitative variables.

Abbreviations: BDI-II, Beck's Depression Inventory-II; BMI, body mass index; CPT, Conner's Performance Test; HbA1c, glycated hemoglobin; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; UPPS-P, Impulsive Behavior Scale.

[a]Medication for diabetes included participants taking insulin, insulin secretagogues, other noninsulin hypoglycemics, thiazolidinediones, metformin, other biguanides, sulfonylureas, alpha-glucosidase inhibitors, GLP-1 analogues, DPP-4 inhibitors, or SGLT2 inhibitors.

[b]See Figure S1 for data availability over time.

[c]Good type 2 diabetes control defined as HbA1c <7% or <53 mmol/mol.

[d]Poor type 2 diabetes control defined as HbA1c ≥7% or ≥53 mmol/mol.

Glycemic-related assessments and impulsivity

As shown in Table 2, no associations of baseline and 1-year time-varying HOMA-IR with 3-year time-varying impulsivity domains were found.

Table 3 displays the relationships of baseline and 3-year time-varying HbA1c with impulsivity domains across the 3 years of follow-up. In the fully adjusted model, baseline HbA1c levels were associated with increases in Global Impulsivity and Trait Impulsivity at 1-year follow-up, and with increases in Behavioral Impulsivity at the 3-year follow-up. When HbA1c was assessed as a time-varying exposure, positive associations were observed at all the follow-up time points for Global Impulsivity (1-year follow-up: $\beta = 0.23$; 95% CI [0.05, 0.42]; 3-year follow-up: $\beta = 0.25$; 95% CI [0.07, 0.43]) and Trait Impulsivity (1-year follow-up: $\beta = 0.23$, 95% CI [0.08, 0.38]; 3-year follow-up: $\beta = 0.20$, 95% CI [0.06, 0.38]). For the Behavioral Impulsivity domain, the association was shown only at the 3-year follow-up ($\beta = 0.20$; 95% CI [0.02, 0.38]), although a significant positive trend across visits was found for all impulsivity domains.

Table 4 presents the associations between type 2 diabetes at baseline and impulsivity domains across 3 years of follow-up, with participants without diabetes as the reference. In all models, the presence of type 2 diabetes was only significantly associated with high Global Impulsivity at 1-year follow-up (fully adjusted model: $\beta = 0.36$; 95% CI [0.05, 0.67]). No relationships were found for the Trait and Behavioral Impulsivity domains, nor were significant trends observed over time.

Table 5 shows the relationships of baseline and time-varying type 2 diabetes control with time-varying impulsivity domains over 3 years, considering participants with good type 2 diabetes control as the reference. In all models, poor type 2 diabetes control at baseline was positively associated with Global Impulsivity at 1-year follow-up. In the fully adjusted model when type 2 diabetes control was assessed considering the three time points, poor diabetes control was associ-

TABLE 2 Associations of baseline and time-varying HOMA-IR with time-varying impulsivity domains.

HOMA-IR	Model	Time point	Baseline			Time-varying		
Impulsivity		Time point	*n*	β (95% CI)	*p*	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.012 (−0.025, 0.049)	0.531	267	0.012 (−0.025, 0.049)	0.517
	1	Year 3	287	0.008 (−0.031, 0.048)	0.681	–	–	–
Trait Impulsivity	1	Year 1		0.018 (−0.012, 0.048)	0.234	379	0.019 (−0.011, 0.049)	0.205
	1	Year 3	390	−0.008 (−0.040, 0.024)	0.630	–	–	–
Behavioral Impulsivity	1	Year 1		−0.008 (−0.042, 0.026)	0.659	309	−0.006 (−0.040, 0.028)	0.734
	1	Year 3	321	0.014 (−0.027, 0.054)	0.505	–	–	–
Global Impulsivity	2	Year 1		0.008 (−0.028, 0.045)	0.650	267	0.010 (−0.026, 0.046)	0.588
	2	Year 3	287	0.015 (−0.024, 0.054)	0.456	–	–	–
Trait Impulsivity	2	Year 1		0.014 (−0.015, 0.044)	0.343	379	0.015 (−0.015, 0.045)	0.337
	2	Year 3	390	−0.010 (−0.042, 0.022)	0.553	–	–	–
Behavioral Impulsivity	2	Year 1		−0.011 (−0.044, 0.023)	0.539	309	−0.009 (−0.042, 0.025)	0.611
	2	Year 3	321	0.018 (−0.023, 0.058)	0.386	–	–	–
Global Impulsivity	3	Year 1		0.001 (−0.038, 0.041)	0.945	263	0.007 (−0.033, 0.046)	0.744
	3	Year 3	284	0.011 (−0.029, 0.050)	0.590	–	–	–
Trait Impulsivity	3	Year 1		0.011 (−0.020, 0.043)	0.477	374	0.013 (−0.019, 0.044)	0.437
	3	Year 3	386	−0.012 (−0.044, 0.020)	0.450	–	–	–
Behavioral Impulsivity	3	Year 1		−0.020 (−0.057, 0.016)	0.274	308	−0.017 (−0.052, 0.019)	0.368
	3	Year 3	320	0.017 (−0.024, 0.058)	0.407	–	–	–

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline and time-varying linear HOMA-IR levels with time-varying linear impulsivity domains. Time-varying assessments only include data between baseline and 1-year follow-up due to HOMA-IR data not being available at the 3-year follow-up. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline and 1-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable. Participants taking an insulin treatment were excluded for HOMA-IR analysis ($n = 10$).

ated with higher Global Impulsivity levels at each time point (1-year follow-up: $\beta = 0.95$, 95% CI [0.27, 1.62]; 3-year follow-up: $\beta = 0.61$, 95% CI [0.05, 1.17]) and higher Trait Impulsivity at the third year of follow-up ($\beta = 0.49$; 95% CI [0.01, 0.97]), and a positive trend was also observed for the Trait Impulsivity domain ($p = 0.041$). No other associations were found between type 2 diabetes control and impulsivity domains.

Figure 1 shows graphically the association of baseline HOMA-IR, baseline presence of type 2 diabetes mellitus, 3-year time-varying HbA1c, and 3-year time-varying diabetes control with Global Impulsivity across the 3-year follow-up period.

Specific relationships of HOMA-IR, HbA1c, presence of type 2 diabetes, and control of type 2 diabetes with trait impulsivity subfactors and each impulsivity-related behavioral assessment are shown in Table S2, Table S3, Table S4, and Table S5, respectively.

No interactions with age, sex, intervention group, and presence of obesity or depressive symptomatology were found in the analyses performed for HOMA-IR, HbA1c, and type 2 diabetes with the Global Impulsivity z-score in any of the models evaluated.

DISCUSSION

To the best of our knowledge, this is the first study examining the associations of HOMA-IR, HbA1c, type 2 diabetes mellitus, and diabetes control with impulsivity over 3 years of follow-up, further assessing glucose-related exposures at baseline and as time-varying variables and also controlling for several potential confounding factors. The main findings of the present study indicated that a worse glycemic status at baseline (assessed by HbA1c levels, presence of type 2 diabetes, and poor type 2 diabetes control) was associated with increases in the Global Impulsivity domain at 1-year follow-up. In addition, when considering exposures as time-varying factors across the 3 years of follow-up, the progression to a worse glycemic status (assessed by HbA1c and poor type 2 diabetes control) was associated with higher Global Impulsivity at each time point, compared to the baseline visit. Insulin resistance, as measured by HOMA-IR, showed no relationships with impulsivity z-scores.

Impulsivity is considered a personality trait characterized by a predisposition to act quickly and without forethought. It is established

TABLE 3 Associations of baseline and time-varying HbA1c with time-varying impulsivity domains.

HbA1c	Model	Time point	Baseline			Time-varying		
Impulsivity		Time point	*n*	β (95% CI)	*p*	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.275 (0.120, 0.129)	0.001		0.262 (0.075, 0.449)	0.004
	1	Year 3	342	0.082 (−0.087, 0.252)	0.341	344	0.134 (−0.036, 0.303)	0.123
Trait Impulsivity	1	Year 1		0.228 (0.102, 0.354)	<0.001		0.237 (0.092, 0.382)	0.001
	1	Year 3	445	0.054 (−0.082, 0.189)	0.438	461	0.152 (0.013, 0.291)	0.032
Behavioral Impulsivity	1	Year 1		0.028 (−0.111, 0.166)	0.697		0.025 (−0.138, 0.188)	0.761
	1	Year 3	380	0.120 (−0.042, 0.282)	0.146	382	0.104 (−0.062, 0.271)	0.218
Global Impulsivity	2	Year 1		0.272 (0.117, 0.427)	0.001		0.236 (0.050, 0.423)	0.013
	2	Year 3	342	0.089 (−0.079, 0.257)	0.298	344	0.157 (−0.015, 0.238)	0.073
Trait Impulsivity	2	Year 1		0.226 (0.100, 0.352)	<0.001		0.220 (0.074, 0.366)	0.003
	2	Year 3	445	0.054 (−0.081, 0.188)	0.435	461	0.163 (0.023, 0.302)	0.022 *
Behavioral Impulsivity	2	Year 1		0.041 (−0.098, 0.180)	0.563		0.043 (−0.121, 0.207)	0.607
	2	Year 3	380	0.139 (−0.022, 0.300)	0.090	382	0.137 (−0.031, 0.304)	0.110
Global Impulsivity	3	Year 1		0.270 (0.115, 0.425)	0.001		0.231 (0.045, 0.418)	0.015
	3	Year 3	339	0.133 (−0.039, 0.305)	0.131	341	0.253 (0.072, 0.434)	0.006 **
Trait Impulsivity	3	Year 1		0.238 (0.112, 0.365)	<0.001		0.230 (0.082, 0.378)	0.002
	3	Year 3	441	0.073 (−0.062, 0.207)	0.288	457	0.197 (0.056, 0.338)	0.006 **
Behavioral Impulsivity	3	Year 1		0.049 (−0.093, 0.191)	0.496		0.052 (−0.115, 0.218)	0.543
	3	Year 3	379	0.167 (0.003, 0.332)	0.046	381	0.198 (0.021, 0.375)	0.028 *

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline and time-varying linear HbA1c levels with time-varying linear impulsivity domains. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable.
*p for trend <0.05; **p for trend <0.01.

before adulthood, and remains relatively stable over time, though showing more variability compared to other personality traits. Behavioral impulsivity is observed if this predisposition results in actions with a lack of premeditation and is guided by emotional urges.[5,37,44] Therefore, an impulsive predisposition to interact with the environment can result in impulsive behaviors that may lead to the establishment of a worse glycemic status. Indeed, some studies have shown that impulsivity promotes hyperglycemia and poor diabetes control[17–22] as well as increases cardiometabolic risk.[9,10] However, a key aspect that needs to be further explored is whether these metabolic impairments might subsequently also lead to an increase in impulsivity levels, potentially inducing a positive feedback loop between impulsivity and poorer glycemic status.

Impulsivity covers many psychological and cognitive characteristics.[44,45] Therefore, assessing several specific trait and behavioral impulsivity features in order to obtain Global, Trait, and Behavioral Impulsivity domains that average directionalities in composite z-scores provides a new and more comprehensive approach for assessing the extensive nature of impulsivity. In fact, in the meta-analysis of Sharma and colleagues, it was hypothesized that trait and behavioral impulsivity composites would predict important life outcomes much more strongly than either type of measure alone.[44] As no previous studies have reported relationships between glycemic parameters and impulsivity composites, our study addresses this gap in the literature by exploring these associations.

Insulin receptors are widespread throughout the brain.[46] They have been shown to be present in neural regions such as the hypothalamus, the mesolimbic pathway that regulates dopamine release to prefrontal areas, and the ventromedial prefrontal, insular, and orbitofrontal cortices, which are regions that have been identified as having impulsivity-related functions regulating the interpretation of emotions, perceptual integration, decision-making, and motor control.[47–49] Therefore, insulin sensitivity appears to be associated with neural pathways related to impulsivity, but limited research evaluating these associations using questionnaires or cognitive tasks assessing impulsivity in adult or older individuals was found. In our study, both baseline and time-varying HOMA-IR at 1-year follow-up showed no association with Global, Trait, or Behavioral Impulsivity domains over time, neither with specific impulsivity traits nor with behavioral assessments. This

TABLE 4 Associations of baseline type 2 diabetes prevalence with time-varying impulsivity domains.

Presence of type 2 diabetes	Model	Time point	Baseline		
Impulsivity		Time point	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.373 (0.064, 0.682)	0.018
	1	Year 3	344	0.243 (−0.088, 0.574)	0.150
Trait Impulsivity	1	Year 1		0.220 (−0.019, 0.459)	0.072
	1	Year 3	462	−0.025 (−0.276, 0.226)	0.845
Behavioral Impulsivity	1	Year 1		0.183 (−0.086, 0.453)	0.183
	1	Year 3	382	0.264 (−0.054, 0.582)	0.104
Global Impulsivity	2	Year 1		0.384 (0.074, 0.696)	0.015
	2	Year 3	344	0.232 (−0.093, 0.558)	0.162
Trait Impulsivity	2	Year 1		0.213 (−0.028, 0.455)	0.084
	2	Year 3	462	−0.030 (−0.279, 0.219)	0.811
Behavioral Impulsivity	2	Year 1		0.202 (−0.068, 0.473)	0.202
	2	Year 3	382	0.268 (−0.047, 0.583)	0.096
Global Impulsivity	3	Year 1		0.361 (0.051, 0.670)	0.022
	3	Year 3	341	0.260 (−0.070, 0.591)	0.122
Trait Impulsivity	3	Year 1		0.229 (−0.017, 0.174)	0.068
	3	Year 3	458	−0.010 (−0.256, 0.237)	0.940
Behavioral Impulsivity	3	Year 1		0.211 (−0.065, 0.487)	0.136
	3	Year 3	381	0.281 (−0.041, 0.604)	0.087

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline type 2 diabetes prevalence ("no prevalence" as the reference category) with time-varying linear impulsivity domains. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable.

apparent discrepancy in our results relative to previous studies may be explained by the duration of the study and the assessment of impulsivity: in our study, we used a long observational follow-up period to assess specific trait and behavioral measures of impulsivity, whereas previous work had assessed impulsivity using neuroimaging techniques or intranasal insulin administration over immediate or short periods of time.[25,47–49]

In the present study, it was shown that baseline and changes of HbA1c levels were positively associated with changes in the Global Impulsivity domain, suggesting an overall effect of HbA1c on impulsivity. Regarding trait impulsivity, baseline and changes of HbA1c levels were also associated with increases in the Trait Impulsivity domain. Moreover, positive relationships were found between HbA1c levels and all impulsivity-related personality subfactors as assessed by a lack of premeditation and perseveration, sensation seeking, and positive and negative emotional urgency. Glucose impairments may influence trait impulsivity through hypothalamic brain areas. Hypothalamic regions have been identified as a major neural integration center of personality traits, as both are involved in hormonal regulation that affects mental function, shapes the individual's perception and integration of environmental stimuli, and ultimately determines how the individual will behave.[50–52] Specifically, impulsivity has been linked to the ventromedial hypothalamic–melatonin circuit, as upregulation or downregulation of melatonin increases impulsivity in rats,[53,54] and fluctuations in blood glucose levels have been linked to the ventromedial hypothalamic region.[55] Therefore, we hypothesize that high glucose levels may increase trait impulsivity through this hypothalamic–melatonin pathway. However, other potential unknown mechanisms cannot be disregarded. Regarding behavioral impulsivity, higher HbA1c levels were associated with CPT-Commissions and IGT z-scores over time, indicating attention deficits and risky decision-making, respectively. Nevertheless, when attention, decision-making, impulse control (CPT-Perseverance), and cognitive inhibition (SCWT) functions were estimated as a composite of behavioral impulsivity, a convergence of directionalities and magnitudes resulted in a positive association between baseline and changes of HbA1c levels and changes in the Behavioral Impulsivity domain over 3 years of follow-up. Our findings may be explained by previous results showing that increases in HbA1c were associated with poorer cognitive performance over short and long periods of time,[42,56] which may promote higher levels of behavioral impulsivity[16] via deleterious endothelial function and oxidative stress in brain cells.[57,58]

TABLE 5 Associations of baseline and time-varying type 2 diabetes control with time-varying impulsivity domains.

Poor type 2 diabetes control	Model	Time point	Baseline			Time-varying		
Impulsivity		Time point	*n*	β (95% CI)	*p*	*n*	β (95% CI)	*p*
Global Impulsivity	1	Year 1		0.601 (0.059, 1.143)	0.030		0.850 (0.179, 1.521)	0.013
	1	Year 3	84	−0.329 (−0.904, 0.247)	0.263	85	0.228 (−0.425, 0.881)	0.494
Trait Impulsivity	1	Year 1		0.418 (−0.070, 0.907)	0.093		0.064 (−0.490, 0.617)	0.822
	1	Year 3	129	0.088 (−0.328, 0.503)	0.679	139	0.287 (−0.192, 0.766)	0.240
Behavioral Impulsivity	1	Year 1		0.127 (−0.335, 0.590)	0.589		0.250 (−0.298, 0.798)	0.371
	1	Year 3	97	0.103 (−0.480, 0.687)	0.728	98	0.122 (−0.496, 0.740)	0.699
Global Impulsivity	2	Year 1		0.776 (0.241, 1.310)	0.004		1.029 (0.353, 1.705)	0.003
	2	Year 3	84	−0.014 (−0.252, 0.496)	0.956	85	0.436 (−0.154, 1.026)	0.148
Trait Impulsivity	2	Year 1		0.475 (−0.001, 0.952)	0.051		0.218 (−0.327, 0.763)	0.433
	2	Year 3	129	0.134 (−0.280, 0.548)	0.525	139	0.398 (−0.083, 0.880)	0.105
Behavioral Impulsivity	2	Year 1		0.211 (−0.252, 0.675)	0.352		0.369 (−0.191, 0.928)	0.183
	2	Year 3	97	0.186 (−0.355, 0.727)	0.501	98	0.207 (−0.374, 0.788)	0.484
Global Impulsivity	3	Year 1		0.754 (0.229, 1.278)	0.010		0.947 (0.274, 1.620)	0.011
	3	Year 3	84	0.089 (−0.409, 0.587)	0.727	85	0.611 (0.047, 1.174)	0.034
Trait Impulsivity	3	Year 1		0.464 (−0.011, 0.940)	0.056		0.190 (−0.360, 0.740)	0.679
	3	Year 3	129	0.178 (−0.239, 0.596)	0.403	139	0.488 (0.009, 0.966)	0.046 *
Behavioral Impulsivity	3	Year 1		0.200 (−0.265, 0.665)	0.399		0.356 (−0.208, 0.919)	0.216
	3	Year 3	97	0.257 (−0.308, 0.822)	0.373	98	0.298 (−0.302, 0.899)	0.330

Note: Linear mixed models were performed using beta coefficients and 95% CI to assess the associations of baseline and time-varying type 2 diabetes control ("good control" as the reference category and defined as HbA1c <7% and "poor control" defined as HbA1c ≥7%) with time-varying linear impulsivity domains. Model 1: adjusted by sex, age (years), and intervention group at baseline. Model 2: further adjusted by educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes) and hypercholesterolemia (no/yes) at baseline, and physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), and use of diabetes medication (no, yes) as time-varying variables. Model 3: further adjusted by depressive symptomatology (no/yes) as time-varying variable. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up. The *p* for trend was estimated using the time variable as a linear variable instead of a categorical variable.

*p for trend <0.05.

In the current study, participants with type 2 diabetes or with a poor control of this chronic disease at baseline presented with higher Global Impulsivity levels at 1-year follow-up. When type 2 diabetes control was assessed using information across visits, participants with poor control had significant increases in Global Impulsivity at all time points, and in Trait Impulsivity at the third year of follow-up as well as a positive trend in this domain over the 3 years of follow-up. In an earlier cross-sectional study, 18 participants with type 2 diabetes showed poorer decision-making and decreased activation in the prefrontal areas related to this cognitive impulsivity function compared to healthy controls.[59] Other cross-sectional studies found elevated trait and behavioral impulsivity-related features in individuals with type 2 diabetes,[28] as well as inverse cross-sectional associations between trait impulsivity and diabetes self-care behaviors[21] and diabetes control (as assessed by HbA1c levels).[22] In line with this, relationships between poor diabetes control and higher behavioral impulsivity have also been reported.[18,19] Nevertheless, a lack of studies evaluating associations between type 2 diabetes (compared to healthy controls) and impulsivity exists, and to the best of our understanding, the current work is the first in evaluating longitudinal associations between type 2 diabetes or its control with impulsivity assessments. In addition, our results showed that the unique impulsivity domain associated with both conditions, the presence of type 2 diabetes and a poor control of this disease, was the Global Impulsivity domain. These results suggest that type 2 diabetes and a poor control of this metabolic condition are associated with a broader construct of impulsivity-related functions, also extending the scientific evidence in this field from cross-sectional to longitudinal findings in a Mediterranean population at high risk of cardiovascular disease.

The present study also showed that when glycemic status was assessed using baseline data only, there were more significant results for impulsivity at the 1-year follow-up compared with the 3-year follow-up. This may be partially explained by the active interventions in both arms of the PREDIMED-Plus clinical trial, which attempted to improve the health status of participants with the assistance of healthcare professionals. The effect of the interventions is usually greater in the early stages of clinical trials than in the subsequent years,[60] as was also found for body composition in the

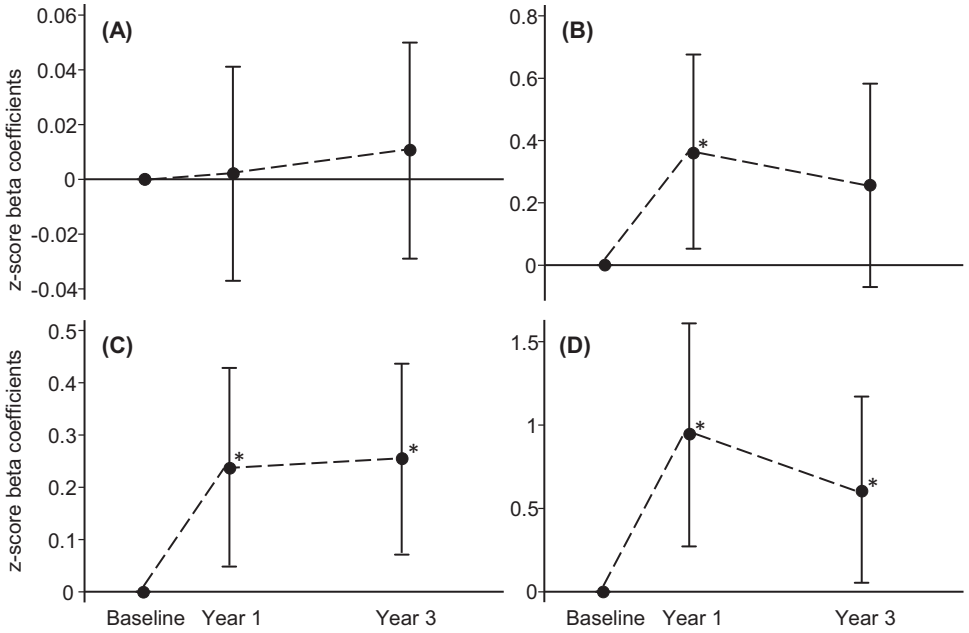

FIGURE 1 Longitudinal associations of baseline HOMA-IR, baseline type 2 diabetes, time-varying HbA1c, and time-varying diabetes control with Global Impulsivity. (A) Insulin resistance measured by HOMA-IR levels. (B) Presence of type 2 diabetes mellitus (no/yes). (C) Glycated hemoglobin (HbA1c) levels. (D) Type 2 diabetes control (good [as the reference category and defined as HbA1c <7%]/poor [defined as HbA1c ≥7%]). Linear mixed models were performed using beta coefficients and 95% CI to assess the longitudinal associations between glycemic-related factors and the Global Impulsivity domain over the 3 years of follow-up. The model was adjusted by sex, age (years), intervention group, educational level (primary school; secondary school; college), marital status (single, divorced, or separated; married; widowed), smoking status (smoker; former smoker; never smoked), hypertension (no/yes), and hypercholesterolemia (no/yes) at baseline, while physical activity (MET min/week), 17-point Mediterranean diet (score), alcohol intake (g/day), obesity (no/yes), diabetes medications (no/yes), and depressive symptomatology (no/yes) as time-varying variables. Random effects were hierarchically established by center, members sharing the same household unit, and participants' responses. The random slope was determined at baseline, 1-year follow-up, and 3-year follow-up.

PREDIMED-Plus study,[61] suggesting that important psychosocial and motivational characteristics associated with the interventions may play a crucial role. For these reasons, the present analyses were conducted assessing exposures, outcomes, and relevant intervention-related components (Mediterranean diet adherence, physical activity, and obesity) and psychological (depressive symptomatology) covariates as time-varying variables. This approach attempted to mitigate these potential confounding effects of the intervention in the studied associations and strengthen the validity of the results examined. It is important to highlight that compared to the first linear mixed model that included only minimally adjusted confounders, the model with the addition of depressive symptomatology had a greater impact on the coefficients in many of the associations examined than the model that included a greater number of covariates such as sociodemographics, lifestyle, and history of disease. This finding may highlight the importance of assessing psychological status as a possible bias factor in future research investigating the relationship between glycemic status and impulsivity, as has been noted in previous studies without an intervention.[21,22]

Our study has some limitations and strengths. First, the observational design of our study does not allow to establish cause–effect relationships. Nevertheless, the present study discusses possible mechanisms for a potential positive feedback loop between impulsivity and a worse glycemic status, also based on the bidirectional mind–heart–body framework.[62] Second, as our study was conducted in a senior Mediterranean population with metabolic syndrome, our results cannot directly be extrapolated to other populations. As strengths, the current study was conducted in a relatively large cohort and presents the first longitudinal results assessing the relationships between glycemic status (assessed by biomarkers) and impulsivity. Finally, we broadly measured the various facets of impulsivity, covering its comprehensive nature.

CONCLUSION

In conclusion, participants with higher HbA1c levels, presence of type 2 diabetes, and with poor type 2 diabetes control were longitudinally associated with increases in overall impulsivity, as assessed by a composite of trait and behavioral impulsivity-related measures. Furthermore, this study contributes to the existing literature on the relationship between impulsivity and glycemic status by suggesting a novel perspective: the existence of a positive feedback loop between impulsivity and glycemic dysregulation. This new perspective allows for a better understanding of the aforementioned relationships and not only emphasizes the need to assess impulsivity for type 2 diabetes prevention, but also highlights that the onset of metabolic dysregulation

promotes new problems driven by additional increases in impulsivity. Nevertheless, additional longitudinal prospective cohort studies and clinical trials are warranted in the future to better understand cause–effect relationships and to explore whether interventions aimed at improving glycemic status could reduce impulsivity levels, thereby further promoting positive health benefits.

AUTHOR CONTRIBUTIONS

The principal PREDIMED-Plus-Cognition investigators R.T., F.F.-A., D.C., and J.S.-S. contributed to study concept and design and to data extraction from the participants. C.G.-M. performed the statistical analyses and C.G.-M., N.B., and J.S.-S. the interpretation of the results. C.G.-M., N.B., S.K.N., and J.S.-S. drafted the manuscript. All authors reviewed the manuscript for important intellectual content and approved the final version to be published.

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COMPETING INTERESTS

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DATA AVAILABILITY STATEMENT

There are restrictions on the availability of data for the PREDIMED-Plus trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Requestors wishing to access the PREDIMED-Plus trial data used in this study can make a request to the PREDIMED-Plus trial Steering Committee chair: predimed_plus_scommitte@googlegroups.com. The request will then be passed to members of the PREDIMED-Plus Steering Committee for deliberation.

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PEER REVIEW

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