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ORIGINAL ARTICLE

Glycated hemoglobin A1c and cognitive impairment in complex chronic patients: A cross-sectional study.

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Abstract

OBJECTIVE: This study examines the relationship between Glycated hemoglobin A1c (HbA1c) levels and cognitive impairment in elderly patients with complex chronic conditions, a link previously unclear.

DESIGN: This is a cross-sectional study.

MATERIAL AND METHODS: The data from 2,366 patients in Catalonia (2013-2017) from the Dryad database. HbA1c levels were taken from clinical records, and cognitive function was assessed with ICD-10 criteria and the Pfeiffer test. We included demographic details, comorbidities, medications, and clinical data as covariates. Multivariate logistic regression was used, with subgroup analyses by age and other factors.

RESULTS: The cohort had an average age of 84.1 ± 10 years; 46.4% were male, with an average HbA1c of 6.5 ± 1.4%. Cognitive impairment was present in 20.2% of participants. The association between HbA1c and cognitive impairment was not significant after adjusting for all variables (OR = 0.99, 95% CI: 0.91-1.08, $p > 0.05$). Ischemic cardiomyopathy ($p = 0.008$) and Barthel scores > 40 ($p = 0.032$) demonstrate an interaction effect on their relationship.

CONCLUSION: In the population of patients with complex chronic conditions, HbA1c did not show a statistically significant correlation with cognitive impairment, indicating that HbA1c might not be an independent predictor of cognitive decline in this group, though further research is needed to confirm this.

Abbreviations:

HbA1c	- Glycated hemoglobin A1c
CCP	- complex chronic patients
STROBE	- Strengthening the Reporting of Observational Studies in Epidemiology
ICD-10	- the 10th edition of the International Classification of Diseases
NSAIDs	- non-steroidal anti-inflammatory drugs
SSRIs	- selective serotonin reuptake inhibitors
HAS-BLED	- Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly
Mean ± SD	- mean ± standard deviation
IQR	- interquartile range
Q1	- Quartile 1
Q2	- Quartile 2
OR	- odds ratios
95% CI	- 95% confidence intervals

INTRODUCTION

Cognitive impairment refers to varying degrees of dysfunction in one or more cognitive domains, affecting memory, orientation, attention, and other higher cortical functions (Xing *et al.,* 2024). It is common in the elderly and significantly impacts their social functioning and quality of life due to its severity and complex causes (Luo *et al.* 2024). The World Health Organization indicates that cognitive impairment ranges from mild cognitive impairment to dementia and is among the top 10 causes of death globally. It often coexists with various diseases, and many studies have found that diabetic patients exhibit different levels of cognitive impairment (Srikanth *et al.* 2020). Glycated hemoglobin A1c (HbA1c), a marker reflecting average blood glucose levels over 2-4 months, is crucial for predicting and diagnosing diabetes and has been widely studied as a potential risk factor for cognitive impairment (Gomez-Peralta *et al.* 2022). However, most studies on the relationship between HbA1c and cognitive impairment focus on diabetic or specific populations (Casagrande *et al.* 2021), leaving this relationship unclear in complex chronic patients (CCP) .

The concept of CCP emerged in primary care in Spain due to the prevalent chronic diseases and complex health needs among the elderly. To better manage the health of these individuals and provide medical services, conditions such as multimorbidity, frailty, and aging were classified together, characterized by clinical vulnerability. According to the Catalonian Terminology Resource Tremcat online dictionary, CCP are defined as chronic patients facing severe clinical conditions. Studies in Catalonia, Spain, show that approximately 4% to 5% of those identified as CCP consume 65% of healthcare resources (Lorman *et al.* 2021). These individuals have more frequent and complex interactions with healthcare services, increasing the likelihood of medical errors, such as poor medication adherence and adverse drug events (Hernansanz *et al.* 2021).

Caring for patients with complex chronic conditions is highly challenging due to their extensive needs, providing opportunities to explore clinical risk assessments and key risk factor predictions. Some studies suggest HbA1c as a potential risk factor for cognitive impairment (Sun *et al.* 2020). However, conflicting results have emerged, some studies indicate a correlation, while others do not (Feinkohl *et al.* 2019). As a result, the impact of HbA1c on cognitive impairment remains controversial. Therefore, it is crucial to investigate whether there is an independent association between HbA1c and cognitive impairment in this population.

MATERIAL AND METHODS

This cross-sectional study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Date Sources

Dryad is an open data publishing platform and community dedicated to data openness and accessibility. In this study, we utilized publicly available data from Dryad to analyze a multicenter, retrospective, community-based cohort study. This research focused on CCP cases in primary healthcare centers in the Catalonia region of Spain over a five-year period, from January 1, 2013 to December 31, 2017. All participants were managed by the Catalonian Health Institute. The study data were sourced from the electronic health record database of the Catalonian Health Institute, which includes data from primary care, specialist outpatient clinics, and hospital treatments. The cases in the database were coded according to the 10th edition of the International Classification of Diseases (ICD-10) to create clinical records, which were de-identified by the information technology department before being provided to researchers (González-Henares *et al.* 2020).

Study Design and Population

Our analysis is based on data from the Dryad database, collected from primary healthcare centers in the Catalonia region between January 1, 2013, and December 31, 2017. All residents within the study area with medical records from any of the participating centers were considered for inclusion, except those diagnosed with terminal, progressive, and irreversible chronic diseases, those unlikely to benefit significantly from specific treatments, and those with limited life expectancy. Additionally, transient populations, cases with incomplete clinical records, and displaced individuals were excluded from the study.

Individuals with complex chronic conditions typically meet at least four of the following criteria: aged 65 or older; having four or more active comorbidities; showing functional limitations, such as a Barthel index below 60, living in long-term care facilities, receiving home care assistance, or being prone to frequent falls; facing psychosocial challenges, characterized by cognitive or psychological impairments; having undergone active treatment with more than four medications in the past six months; living alone or with a caregiver at age 75 or older; and having had unplanned hospitalizations in the past year (two hospital admissions due to chronic disease exacerbations or three visits to the emergency room).

Ethical Considerations

The data were processed by the information technology department and then provided to the researchers in a fully anonymized format, strictly adhering to local

data protection laws. According to Dryad's Terms of Service, we are authorized to conduct secondary data analysis on this dataset, exploring different hypotheses while respecting the rights of the original authors. As this study was retrospective, ethical approval was not required for secondary analyses. The study followed the principles of the Declaration of Helsinki, ensuring ethical considerations throughout. All methods used in the study complied with relevant guidelines and regulations.

Assessment of HbA1c and Cognitive Impairment

In this study, HbA1c and cognitive impairment were the primary variables. HbA1c was treated as a continuous variable, while cognitive impairment was a binary variable. Data for both HbA1c and cognitive impairment were directly sourced from electronic health record database. Cognitive function was assessed using ICD-10 criteria and the Pfeiffer test (González-Henares *et al.* 2017; González-Henares *et al.* 2020). The Pfeiffer test consists of 10 questions (Pfeiffer E, 1975), with a score of 0 to 2 errors indicating intact cognitive function, coded as 0, and a score of 3 or more errors indicating mild to severe cognitive impairment, coded as 1.

Covariates

Considering the relevant variables identified in previous literature and the available data, this study included variables such as demographics, comorbidities, medications, and clinical data. These variables were assessed based on home visit evaluations and records from hospitals, general practitioners, and institutional care facilities. The continuous variables included age and Barthel score (used to assess functional status in basic activities of daily living). The binary variables (0 = no, 1 = yes) included gender (1 = male, 0 = female), arterial hypertension (average measurement over the past six months), diabetes, atrial fibrillation, hypercholesterolemia, ischemic cardiopathy, ischemic stroke/transient ischemic accident, peripheral vascular disease, heart failure, thromboembolism, chronic kidney disease, chronic liver disease, neoplasia, intracerebral hemorrhage, institutionalization (long-term stay in a care facility), oral anticoagulants, falls (recurrent falls or increased risk of falls), statins, non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs) (current medications recorded during home visits and verified against medical records), and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile International Normalized Ratio, Elderly, Drugs/alcohol concomitantly) score (< 3, ≥ 3, used to assess the bleeding risk in patients with atrial fibrillation receiving anticoagulation therapy).

Statistical analysis

The baseline characteristics of the study participants were compared using t-tests and chi-square tests. Continuous variables were presented as mean ± standard deviation (Mean ± SD) or median (interquartile range, IQR), and categorical variables were expressed as frequency or percentage. We used two-tailed significance tests, setting the statistical significance threshold at $p < 0.05$. HbA1c was categorized based on a 6.5% cutoff, following the guidelines of the International Diabetes Federation, into Quartile 1 (Q1) and Quartile 2 (Q2). Logistic regression models were employed to calculate the odds ratios (OR) and 95% confidence intervals (95% CI) for the association between HbA1c and cognitive impairment.

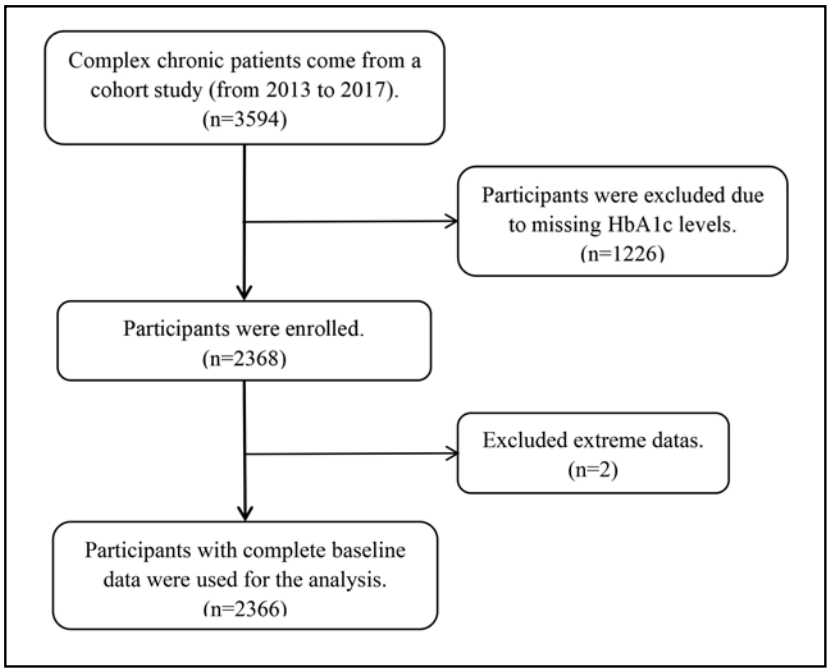

Fig. 1. Flowchart of patient enrollment in the study

Based on previous literature, variables strongly associated with the relationship between HbA1c and cognitive function were identified for model adjustments. Model 1 adjusted for demographic factors, including age and sex. Building on Model 1, Model 2 incorporated adjustments for Barthel score, falls, institutionalized. Model 3 further included adjustments for complicated variables (diabetes, hypercholesterolemia, ischemic cardiomyopathy, heart failure, chronic liver disease, chronic kidney disease, neoplasia, peripheral vascular disease) on top of Model 2. Finally, Model 4 expanded Model 3 by accounting for medications (oral anticoagulant, NSAIDs, SSRIs, statins).

Next, stratified binary logistic regression models were used for subgroup analysis. We transformed continuous variables into categorical variables, including age

Tab. 1. Characteristics of participants at primary healthcare centers in the Catalonia region from 2013 to 2017

Variables		HbA1c,%			
		Total	Q1 (< 6.5)	Q2 (≥ 6.5)	*p*
Number of participants		2366	1417	949	
Age, Mean ± SD (years)		84.1 ± 10.0	85.3 ± 9.6	82.3 ± 10.4	< 0.001
Age, n (%)					< 0.001
	≤44 years	8 (0.3)	4 (0.3)	4 (0.4)	
	45-59 years	52 (2.2)	25 (1.8)	27 (2.8)	
	60-74 years	306 (12.9)	152 (10.7)	154 (16.2)	
	75-89 years	1217 (51.4)	699 (49.3)	518 (54.6)	
	≥90 years	783 (33.1)	537 (37.9)	246 (25.9)	
Sex, n (%)					0.737
	Female	1269 (53.6)	764 (53.9)	505 (53.2)	
	Male	1097 (46.4)	653 (46.1)	444 (46.8)	
Cardiovascular risk factors					
Arterial hypertension, n (%)					0.312
	No	455 (19.2)	282 (19.9)	173 (18.2)	
	Yes	1911 (80.8)	1135 (80.1)	776 (81.8)	
Diabetes, n (%)					< 0.001
	No	874 (36.9)	784 (55.3)	90 (9.5)	
	Yes	1492 (63.1)	633 (44.7)	859 (90.5)	
Hypercholesterolemia, n (%)					< 0.001
	No	1116 (47.2)	710 (50.1)	406 (42.8)	
	Yes	1250 (52.8)	707 (49.9)	543 (57.2)	
Comorbidities					
Ischemic cardiopathy, n (%)					0.107
	No	1886 (79.7)	1145 (80.8)	741 (78.1)	
	Yes	480 (20.3)	272 (19.2)	208 (21.9)	
Ischemic stroke/Transient ischemic accident, n (%)					0.54
	No	2174 (91.9)	1306 (92.2)	868 (91.5)	
	Yes	192 (8.1)	111 (7.8)	81 (8.5)	
Peripheral vascular disease, n (%)					0.017
	No	2111 (89.2)	1282 (90.5)	829 (87.4)	
	Yes	255 (10.8)	135 (9.5)	120 (12.6)	
Atrial fibrillation, n (%)					0.088
	No	1664 (70.3)	978 (69)	686 (72.3)	
	Yes	702 (29.7)	439 (31)	263 (27.7)	
Heart Failure, n (%)					0.13
	No	1669 (70.5)	1016 (71.7)	653 (68.8)	
	Yes	697 (29.5)	401 (28.3)	296 (31.2)	
Thromboembolism, n (%)					0.066
	No	2167 (91.6)	1310 (92.4)	857 (90.3)	
	Yes	199 (8.4)	107 (7.6)	92 (9.7)	
Chronic kidney disease, n (%)					0.176
	No	1677 (70.9)	1019 (71.9)	658 (69.3)	
	Yes	689 (29.1)	398 (28.1)	291 (30.7)	

(grouped by cutoffs of 45, 60, 75, and 90 years) and Barthel scores (grouped by cutoffs of 41 and 61 points). Interaction tests were performed to assess the interaction effects between these converted variables and other study factors. Additionally, effect modification tests were performed for the grouped indicators, including likelihood ratio tests to compare models with and without interaction terms, determining whether the impact of the primary predictor variables varied with different levels of another variable. To ensure robustness and reliability, sensitivity analyses were conducted, including categorizing HbA1c and calculating the *p* for trend. Data analysis was performed using R software version 3.3.2 and Free Statistics software version 1.9, available at http://www.R-project.org, provided by the R Foundation.

Variables		HbA1c,%			
		Total	Q1 (< 6.5)	Q2 (≥ 6.5)	*p*
Chronic liver disease, n (%)					0.432
	No	2325 (98.3)	1390 (98.1)	935 (98.5)	
	Yes	41 (1.7)	27 (1.9)	14 (1.5)	
Neoplasia, n (%)					0.026
	No	1796 (75.9)	1053 (74.3)	743 (78.3)	
	Yes	570 (24.1)	364 (25.7)	206 (21.7)	
Intracerebral haemorrhage, n (%)					0.222
	No	2264 (95.7)	1350 (95.3)	914 (96.3)	
	Yes	102 (4.3)	67 (4.7)	35 (3.7)	
Other conditioning factors					
Institutionalized, n (%)					0.642
	No	2207 (93.3)	1319 (93.1)	888 (93.6)	
	Yes	159 (6.7)	98 (6.9)	61 (6.4)	
Cognitive impairment or dementia, n (%)					0.064
	No	1888 (79.8)	1113 (78.5)	775 (81.7)	
	Yes	478 (20.2)	304 (21.5)	174 (18.3)	
Falls, n (%)					0.018
	No	2038 (86.1)	1201 (84.8)	837 (88.2)	
	Yes	328 (13.9)	216 (15.2)	112 (11.8)	
Clinical data					
Barthel score, Mean ± SD (scores)		51.3 ± 40.4	48.9 ± 40.2	55.0 ± 40.4	< 0.001
Barthel, n (%)					0.003
	≤40 scores	968 (40.9)	613 (43.3)	355 (37.4)	
	41~60 scores	263 (11.1)	165 (11.6)	98 (10.3)	
	≥61 scores	1135 (48.0)	639 (45.1)	496 (52.3)	
HAS_BLED score, n (%)					0.484
	<3 scores	337 (14.2)	196 (13.8)	141 (14.9)	
	≥3 scores	2029 (85.8)	1221 (86.2)	808 (85.1)	
Medication					
Oral anticoagulant, n (%)					0.022
	No	1622 (68.6)	946 (66.8)	676 (71.2)	
	Yes	744 (31.4)	471 (33.2)	273 (28.8)	
Non-steroidal anti-inflammatory drugs, n (%)					0.101
	No	537 (22.7)	338 (23.9)	199 (21)	
	Yes	1829 (77.3)	1079 (76.1)	750 (79)	
Statines, n (%)					< 0.001
	No	823 (34.8)	587 (41.4)	236 (24.9)	
	Yes	1543 (65.2)	830 (58.6)	713 (75.1)	
Selective serotonin reuptake inhibitors, n (%)					0.304
	No	1529 (64.6)	904 (63.8)	625 (65.9)	
	Yes	837 (35.4)	513 (36.2)	324 (34.1)	

Finally, we conducted post-hoc power analysis using G*Power software, setting a medium effect size (ρ = 0.3), significance level (α = 0.05), and one-tailed test. The results indicated an actual power of 1.0, meaning the probability of detecting a true effect with a sample size of 2,366 was 100%. This ensures high sensitivity and reliability of the analysis, effectively controlling for Type I and Type II errors.

RESULTS

Baseline characteristics of enrolled participants

Between 2013 and 2017, a total of 3,594 CCP participants were involved in primary healthcare centers across Catalonia. We excluded individuals with missing HbA1c data (n = 1,226) and those with extreme HbA1c values (n = 2), resulting in a final study population of 2,366 participants. Figure 1 provided a detailed outline of the participant inclusion process. Table 1 summarizes the baseline characteristics of the included participants. According to the American Diabetes Association (ADA), HbA1c levels ≥6.5% were diagnostic for diabetes. Participants were divided into two groups based on their HbA1c levels: Q1 (<6.5%) and Q2 (≥6.5%). The average age of the participants was 84.1 ± 10.0 years, with 1,217 individuals (51.4%) aged between 75 and 89 years. There were 1,097 male participants (46.4%), the mean HbA1c level was 6.5 ± 1.4%, and 478 participants (20.2%) were classified as having cognitive impairment. Compared to individuals with lower HbA1c levels, those with higher HbA1c levels were significantly more likely to be relatively younger ($p < 0.001$), have a higher prevalence of diabetes ($p < 0.001$), hypercholesterolemia ($p < 0.001$), and peripheral vascular disease ($p < 0.05$). They also tended to have a relatively lower incidence of neoplasia ($p < 0.05$) and a lower risk of falls ($p < 0.05$). Additionally, these individuals demonstrated better daily living activity capacity, as indicated by higher Barthel scores ($p < 0.001$), lower usage rates of oral anticoagulants ($p < 0.05$), and higher usage rates of statins ($p < 0.001$).

Univariate Analysis of Factors Associated with Cognitive Impairment

Table 2 summarized the results of the univariate analysis. Using logistic regression, we identified age, sex, hypercholesterolemia, ischemic cardiopathy, ischemic stroke/transient ischemic accident, heart failure, chronic kidney disease, chronic liver disease, neoplasia, institutionalized, falls, HbA1c, Barthel score, oral anticoagulants, NSAIDs, statins, and SSRIs as factors associated with cognitive impairment. Among these, sex, ischemic cardiopathy, heart failure, chronic kidney disease, chronic liver disease, neoplasia, HbA1c, Barthel score, oral anticoagulants, NSAIDs, and statins were negatively associated with cognitive impairment. Conversely, factors positively associated with cognitive impairment included age, ischemic stroke/transient ischemic accident, institutionalized, falls, and the use of SSRIs.

Multivariable Regression Analysis of the Association between HbA1c and Cognitive Impairment

Table 3 presented the results of a multivariable logistic regression analysis examining the relationship between HbA1c levels and cognitive impairment. When HbA1c was treated as a continuous variable, Models 1, 2, 3and 4 show no significant association between HbA1c and cognitive impairment. When HbA1c was converted to a binary variable with a cutoff of 6.5, none of the models showed a significant association with cognitive impairment ($p > 0.05$). In the quartile analysis of HbA1c, compared to the first quartile, the second quartiles, third quartile, and fourth quartile were showed no significant association with cognitive impairment across all models ($p > 0.05$). Table 3 could be observed that all p-values are greater than 0.05, and the 95%Cl cross 1. This indicates that the results are statistically non-significant, suggesting a negative outcome.

Subgroup Analysis

Figure 2 used various variables to examine the trend of effect size changes. Our analysis showed that, according to our predefined criteria, the number of interactions was limited, particularly for ischemic cardiomyopathy and Barthel scores ($p_{\text{interaction}} < 0.05$). Notably, in this study, the p for interaction for ischemic cardiomyopathy patients and those with Barthel scores over 40 were 0.008 and 0.032, respectively, indicating significant interactions between HbA1c levels and cognitive impairment in these subgroups.

DISCUSSION

Key findings of the study

According to the definition of CCP, if an individual meets four out of the following seven criteria—age, comorbidities, functional limitations, cognitive or psychological impairments, medication usage, living alone or with a caregiver, and unexpected hospitalizations—they can be classified as a CCP. These patients typically suffer from multiple diseases or functional impairments and often undergo extensive treatment and medication, which implies a wide range of influencing factors. This complexity makes it more challenging to explore the relationship between HbA1c and cognitive impairment. Additionally, comorbidities such as atrial fibrillation (Li *et al.* 2024), chronic kidney disease (Li *et al.* 2024), and chronic liver disease (Cushman *et al.* 2023) are included, all of which can affect cognitive impairment and further complicate the investigation. Throughout the model adjustment process, whether adjusting for demographic variables alone, incorporating functional status variables, or further including comorbidities and medication use,

Tab. 2. Univariate analysis of association between factors of HbA1c and cognitive impairment

Variable	OR (95%CI)	*p*-value
Age (year)	1.06 (1.05~1.08)	<0.001
Sex (n%)		<0.001
Females	Ref.	
Males	0.63 (0.51~0.77)	
Arterial hypertension	1.02 (0.79~1.31)	0.905
Diabetes	0.96 (0.78~1.18)	0.716
Hypercholesterolemia	0.76 (0.62~0.93)	0.007
Ischemic cardiopathy	0.75 (0.57~0.97)	0.031
Ischemic stroke	1.62 (1.16~2.25)	0.005
Peripheral vascular disease	0.76 (0.54~1.07)	0.117
Atrial fibrillation	0.89 (0.72~1.12)	0.323
Heart Failure	0.7 (0.56~0.88)	0.003
Thromboembolism	0.96 (0.67~1.38)	0.824
Chronic kidney disease	0.64 (0.5~0.81)	<0.001
Chronic liver disease	0.2 (0.05~0.83)	0.026
Neoplasia	0.71 (0.56~0.92)	0.008
Intracerebral haemorrhage	1.23 (0.77~1.96)	0.393
Institutionalized	3.47 (2.49~4.83)	<0.001
Falls	2.21 (1.71~2.86)	<0.001
HbA1c (%)	0.93 (0.86~1)	0.038
Barthel score	0.99 (0.99~0.99)	<0.001
Oral anticoagulant	0.7 (0.56~0.88)	0.002
Non-steroidal anti-inflammatory drugs	0.76 (0.6~0.95)	0.017
Statins	0.72 (0.58~0.88)	0.001
Selective serotonin reuptake inhibitors	2.23 (1.82~2.73)	<0.001
HAS_BLED score: <3score vs ≥3score	0.9 (0.68~1.19)	0.472

Tab. 3. Multivariable Regression Analysis of the Association between HbA1c and Cognitive Impairment

Variable	Model 1		Model 2		Model 3		Model 4	
	Adjusted OR(95%CI)	*p*-value	Adjusted OR(95%CI)	*p*-value	Adjusted OR(95%CI)	*p*-value	Adjusted OR(95%CI)	*p*-value
HbA1c, %	0.98 (0.91~1.06)	0.653	1 (0.93~1.08)	0.994	0.98 (0.89~1.07)	0.621	0.99 (0.9~1.08)	0.778
HbA1c≥6.5%								
No	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Yes	0.95 (0.77~1.18)	0.654	0.99 (0.8~1.24)	0.955	0.92 (0.72~1.18)	0.523	0.94 (0.73~1.21)	0.606
HbA1c, Quartile								
Quartile 1	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.91 (0.69~1.21)	0.521	1 (0.75~1.33)	0.976	0.97 (0.72~1.3)	0.827	0.99 (0.73~1.34)	0.948
Quartile 3	0.87 (0.65~1.16)	0.333	0.94 (0.7~1.27)	0.679	0.83 (0.59~1.16)	0.275	0.88 (0.62~1.13)	0.447
Quartile 4	0.84 (0.63~1.13)	0.25	0.92 (0.68~1.24)	0.588	0.81 (0.57~1.14)	0.226	0.82 (0.58~1.17)	0.282

Model 1: Adjusted for age, sex.
Model 2: Model 1 + Barthel score, falls, institutionalized.
Model 3: Model 2 + diabetes, hypercholesterolemia, ischemic cardiomyopathy, heart failure, chronic liver disease, chronic kidney disease, neoplasia, peripheral vascular disease.
Model 4: Model 3 + oral anticoagulant treatment, non steroidal anti inflammatory drugs, selective serotonin reuptake inhibitors, statins.

the results remained largely unchanged. This consistency highlights the stability of the findings.

Prior research related to the subject

Israa Salih *et al.* observed cognitive decline in individuals with diabetes through a sample of 380 participants but did not report a significant association with HbA1c (Salih *et al.* 2022). Similar findings were reported in studies conducted by Insa Feinkohl (Feinkohl *et al.* 2019) , Garfield V (Garfield *et al.* 2021) and Lindeman RD (Lindeman *et al.* 2001), aligning with our own results. However, there are contrasting findings in studies such as the one by H.B. Maan *et al.* where high HbA1c or uncontrolled diabetes, along with the duration of diabetes, were linked to cognitive function impairment. Furthermore, a significant association

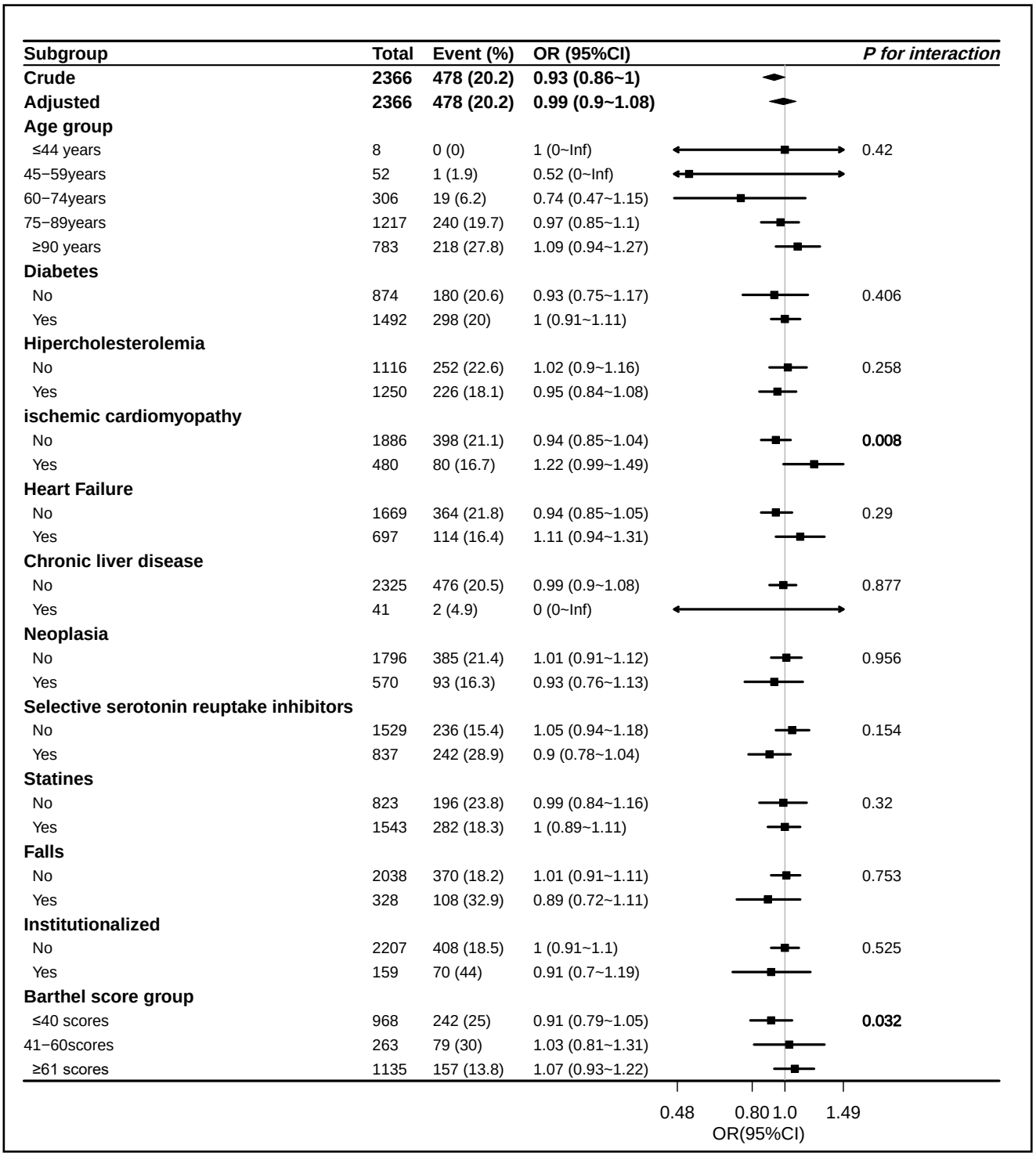

Fig. 2. Stratified analyses assessing the effect of HbA1c on cognitive impairment. Results are presented as adjusted OR (95% CI) of HbA1c, which were adjusted for age, diadetes, hipercholesterolemia, ischemic cardiomyopathy, heart failure, chronic liver disease, neoplasia, selective serotonin reuptake inhibitors, statines, falls, institutionalized, Barthel score. CI, confidence interval, OR, odd ratio.

was found between cognitive decline and both the duration of the disease and high HbA1c (Maan *et al.* 2021).

After analyzing these inconsistent studies, we hypothesize that the differences in results may be due to significant variations in study populations. HbA1c reflects average blood glucose levels, and related literature mainly focuses on type 2 diabetes patients, adjusting for variables like blood sugar, lipids, and BMI (Ganguli *et al.* 2020). In contrast, our study involves a complex chronic population with many additional covariates. Moreover, previous studies might not have adjusted for various factors such as arterial hypertension (Bower *et al.* 2012), atrial fibrillation (Papazoglou *et al.* 2022), hypercholesterolemia (de Oliveira *et al.* 2024), ischemic cardiopathy (Mancini *et al.* 2019), ischemic stroke/transient ischemic accident (Rost *et al.* 2022), peripheral vascular disease (Gardner *et al.* 2021), heart failure (Mordi *et al.* 2021), thromboembolism (Yang *et al.* 2024), chronic kidney disease (Heo *et al.* 2023), chronic liver disease (Chen *et al.* 2020), neoplasia (Zheng, J *et al.* 2022), intracerebral hemorrhage (Sawyer *et al.* 2021), institutionalization (Camacho-Conde *et al.* 2020), falls (Ge *et al.* 2023), oral anticoagulants (Lee *et al.* 2024), NSAIDs (Morris *et al.* 2020), statins (Sattar *et al.* 2023), SSRIs ((Liu, L *et al.* 2021), and Barthel scores (Palacios-Navarro *et al.* 2022). These adjustments in our study might explain the differing outcomes.

Clinical Implications

Firstly, few studies have explored the relationship between HbA1c and cognitive impairment in CCP. Existing studies primarily focus on individuals over 65 with Parkinson's disease, diabetes, and hypertension, who do not meet the CCP criteria (Dhikav, V *et al.* 2022; 2021; 2015). Secondly, our findings provide valuable insights for developing diagnostic or predictive models for cognitive impairment.

Advantages and Limitations

Our study has several key strengths. We have a significantly larger sample size compared to previous similar studies. Despite the risk of confounding factors in observational studies, we used rigorous statistical techniques to mitigate their impact. We analyzed the primary variable both as a continuous and a categorical variable, reducing data dependency and enhancing the robustness of our results. By considering modifying factors in our analysis, we increased the validity of our data, leading to more consistent and reliable conclusions across different groups.

However, our study has several limitations. Firstly, due to its cross-sectional nature, we cannot establish a temporal relationship between HbA1c and cognitive impairment, necessitating more well-designed cohort studies. Secondly, our subjects were primarily complex chronic disease patients, limiting the generalizability and external validity of our findings. Thirdly, the sample size of CCP patients in our study was limited. Therefore, caution should be exercised when interpreting these results, and more well-designed prospective studies are needed in this area.

CONCLUSION

In the population of patients with complex chronic conditions, HbA1c did not show a statistically significant correlation with cognitive impairment, indicating that HbA1c might not be an independent predictor of cognitive decline in this group, though further research is needed to confirm this.

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