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Predictive model of mild neurocognitive disorder due to Alzheimer's disease in Cuban adults

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Abstract

Objective: *Develop a predictive model for mild neurocognitive disorder (NCD) based on the risk factors for Alzheimer's disease (AD). The diagnosis of NCD associated with the presence of risk factors for AD is still incipient and requires greater diagnostic precision.* **Methods:** *A cross-sectional, analytical, observational case-control study was carried out in 100 subjects classified as mild NCD due to possible AD according to Diagnostic and Statistical Manual of Mental Disorders-5 criteria and twice controls with normal cognitive functions, aged 50-64 years and both sexes, selected by simple random sampling, during the period from January 1 to December 31, 2024. The variables that constituted prognostic factors were determined by multivariate binary logistic regression.* **Results:** *Low educational attainment, low skill level, physical inactivity, smoking, diabetes mellitus, hypertension, obesity, weight loss and COVID-19 were included in a model that explained 82.5% of the dependent variable (Nagelkerke's R^2); with 83% sensitivity and 95% specificity; calibration was good (Hosmer-Lemeshow test = 0.940) with an area under the receiver operating curve (AUROC) of 0.976 (95% confidence interval [CI]: 0.961-0.990). A risk score was calculated from the model, defining two categories: low risk (< 33) and high risk (≥ 33), with an AUROC of 0.918 (95% CI: 0.877-0.958).* **Conclusions:** *The predictive model included nine variables that were easy to determine and interpret; therefore, it can constitute a useful tool in decision-making aimed at early and probably more effective interventions.*

Keywords: *Alzheimer's disease. Cognitive dysfunction. Risk factors.*

Modelo predictivo de trastorno neurocognitivo leve debido a la enfermedad de Alzheimer en adultos cubanos

Resumen

Objetivo: *Desarrollar un modelo predictivo de trastorno neurocognitivo leve basado en los factores de riesgo de la enfermedad de Alzheimer (EA) . El diagnóstico de trastorno neurocognitivo asociado a factores de riesgo de la EA es incipiente y requiere gran precisión.* **Métodos:** *Se realizó un estudio observacional, analítico, transversal de casos y controles en 100 sujetos clasificados de deterioro neurocognitivo leve debido a la EA posible de acuerdo con criterios del Manual Diagnóstico y Estadístico de Trastornos Mentales (DSM-5) y 200 controles con funciones cognitivas normales, de 50 a 64 años y ambos sexos, seleccionados por muestreo aleatorio simple, durante el período del 1 de enero al 31 de diciembre de 2024. Las variables pronósticas se determinaron por regresión logística binaria.* **Resultados:** *Bajo nivel escolar, bajo nivel de*

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competencias, inactividad física, tabaquismo, diabetes mellitus, hipertensión arterial, obesidad, pérdida de peso y COVID-19 fueron incluidos en un modelo que explicó el 82.5% de la variable dependiente (R^2 de Nagelkerke), con 83% de sensibilidad y 95% de especificidad, buena calibración (prueba de Hosmer-Lemeshow = 0.940) y área bajo la curva operativa del receptor (ABCOR) de 0.976 (95% CI: 0.961-0.990). Se calculó un puntaje de riesgo a partir del modelo, definiendo dos categorías: bajo (< 33) y alto (≥ 33), con ABCOR de 0.918 (95% IC: 0.877-0.958). **Conclusiones:** *El modelo predictivo incluyó 9 variables de fácil determinación e interpretación; por eso, puede constituir una herramienta útil en la toma de decisiones orientadas a intervenciones tempranas y probablemente más efectivas.*

Palabras clave: *Disfunción cognitiva. Enfermedad de Alzheimer. Factores de riesgo.*

Introduction

Alzheimer's disease (AD) is the most common form of dementia and represents 60-70% of all cases, characterized by cognitive impairment of degenerative nature and progressive evolution[1]. Although the prevalence of AD and other causes of dementia has increased in recent years[2], it presents a global underdiagnoses[3]. Cuban researchers locate the genesis of underdiagnosis in primary health care (PHC) to low prevalence of dementia (10.2% in people aged 65 years or older) and low incidence rate (21.7/1000)[4]. Diagnosis in the PHC is usually late (on average, 2 years before death), compared to hospital records[5].

The late diagnosis of cognitive impairment is related to a low diagnostic capacity in adulthood[6]. It is favorable to diagnose AD in subclinical stages, even before mild cognitive impairment (MCI)[7,8]. Early diagnosis allows the evaluation of reversible causes, improves the care of comorbidities, guides the selection of appropriate treatments, and identifies the need for social support, planning for the family, and the person themselves[5].

Predictive models of the progression of MCI to AD[9,10], in patients with some degree of cognitive impairment aged over 65 years, could be too late for effective interventions due to the long subclinical progression of the disease. Other models describe MCI's prediction, which, despite their great sensitivity and specificity, present real limitations in low-income countries because some of their variables cannot be easily measured, such as eye tracking technology, concentration of amyloid protein in magnetic resonance scans, and ε4 allele of apolipoprotein E[11-13]. Therefore, the development of new predictive tools with easy variables to determine and interpret is necessary, even in adults with normal cognitive functioning. The present investigation was carried out with the objective of developing a predictive model for mild neurocognitive disorder (NCD) based on the risk factors for AD.

Methods

Type of study

A cross-sectional, analytical, observational case-control study was carried out in patients of Manuel Fajardo Rivero Polyclinic, in the Cuban municipality of Las Tunas and province of the same name, during the period from January 1 to December 31, 2024.

Population

The population included 11,037 patients aged between 50 and 64 years old of the PHC Area, determined by dispensarization in 2023. The age range is under 65 years according to the average age of onset of AD suggested in the literature[1,2,4-8], to provide early diagnosis of the tool.

A random population sample of 97 subjects was estimated, using the GRANMO sample size calculator version 7.12[14], from a population of 11,037 subjects, with an alpha risk of 0.95, precision of ± 0.1 in two-sided contrast for an estimated proportion of 0.5 and a replacement rate of 0%.

Those subjects who expressed their willingness to participate, with one or more AD's risk factors[1,2,4-13] and other factors at the criteria of the authors according to their own systematic review, were included[15]. Included cases presented evidence of modest cognitive decline from a previous level based on: concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and a modest impairment in cognitive performance, documented by standardized neuropsychological testing. The cognitive deficits do not interfere with the capacity for independence in everyday activities[16].

Subjects who did not cooperate with the neurological/neuropsychological examination and with evidence of mixed etiology (neurodegenerative or cerebrovascular disease, other neurological, mental or systemic disease,

or any other condition with a high probability of contributing to cognitive decline) were excluded[16].

These inclusion and exclusion criteria were based on the diagnostic criteria for mild NCD due to possible AD, as described in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders[16].

Finally, from a group of subjects of the population with one or more AD's risk factors, 100 subjects with MCI were detected and twice as many normal cognitive functions controls were included from the rest, through simple random sampling (Fig. 1), with a median age of 58 years and male predominance (172/57.3%).

Variables

To describe the sample, 16 variables were studied.

Dependent variable: cognitive impairment. MCI was defined by a score of 70 and under in the neurocognitive evaluation, using the Cuban Addenbrooke's Cognitive Examination Revised (CACE-R), with reliable internal consistency (Cronbach's coefficient $\alpha = 0.879$) and optimal cutoff score of 84/85[17]. For the regression analysis, two categories were considered: (0) no and (1) yes.

Independent variables:

- Sex[8,15]: (0) male, (1) female.
- Educational attainment[8,15]: is the highest level of education that the person has completed, according to the levels of education in Cuba. For the regression analysis, two categories were considered: (0) for high educational attainment in the case of high school and university, and (1) for low educational attainment in the case of primary and middle levels.
- Family history of dementia[8,15]: (0) no, (1) yes.
- Smoking[8,15]: (0) no, (1) yes.
- Physical activity[8,15]: (0) sufficiently active: 4 points and over, (1) insufficiently active: under 4 points, according to the Abbreviated Physical Activity Assessment Questionnaire for Primary Care (BPAAT) with a concordance coefficient k of 0.774 and high statistical significance and power ($p < 0.000$; 95% confidence interval [CI]: 0.69–0.85) with the International Physical Activity Questionnaire[18].
- Social isolation[8,15]: (0) not isolated: over 12 points, (1) isolated: 12 points and under, according to the criteria of the validated Spanish version of the six-item Lubben Social Network Scale[19].
- Diabetes mellitus[8,15]: (0) no, (1) yes.
- Hypertension[8,15]: (0) no, (1) yes.
- Chronic kidney disease[20]: (0) no, (1) yes.
- Obesity[8,15]: BMI > 30 kg/m^2: (0) no, (1) yes.
- Hypercholesterolemia[21]: (0) no, (1) yes.
- Weight loss[22]: decrease in body weight of 2 kg and over or 5% and over in the previous 12-month period, not due to change in diet, physical exercise, bariatric surgery, or proven disease or cause: (0) no, (1) yes.
- Ischemic heart disease[23]: (0) no, (1) yes.
- Skill level: it was defined as a function of the complexity and range of tasks and duties to be performed in an occupation according to criteria of the International Standard Classification of Occupations (ISCO-08)[24,25]. Two categories were considered: (0) for high skill level in the case of 3 and 4 levels of the ISCO-08, with greater intellectual requirements, and (1) for low skill level: in the case of 1 and 2 levels of the ISCO-08, with a predominantly manual work activity.
- COVID-19[26,27]: history of biomolecular diagnosis by polymerase chain reaction: (0) no, (1) yes.

Data processing and analysis

The data were obtained from the interrogation, physical examination, and clinical history. It was processed in Statistical Package for the Social Sciences, version 25 for Windows. The Chi-square statistical test was used based on its homogeneity hypothesis to determine the differences between the groups established according to qualitative variables.

A multivariate binary logistic regression analysis was implemented to determine the variables that constituted prognostic factors, which included those that had statistical significance in the univariate analysis. Variables with collinearity problems were not included in the model. For each independent variable in the model, more than 10 frequencies of the dependent variable were taken into account. Analysis was done with a reliability of 95%.

The omnibus test of the model was evaluated, and Nagelkerke's R^2 was analyzed for explaining the variance. The goodness of fit of the model was determined through the Hosmer-Lemeshow test. The variables whose coefficients were significantly different from 0 ($p < 0.05$) were identified using the Wald test. The discriminatory capacity was evaluated using the sensitivity and specificity values, positive predictive value (PPV), negative predictive value (NPV), receiver operating curve, and area under the curve (AUC).

From the results of the logistic regression, the odds ratios (OR) rounded to a whole number were taken as weights for each variable, OR = Exp (B); in this way, the resulting predictive model was composed of a

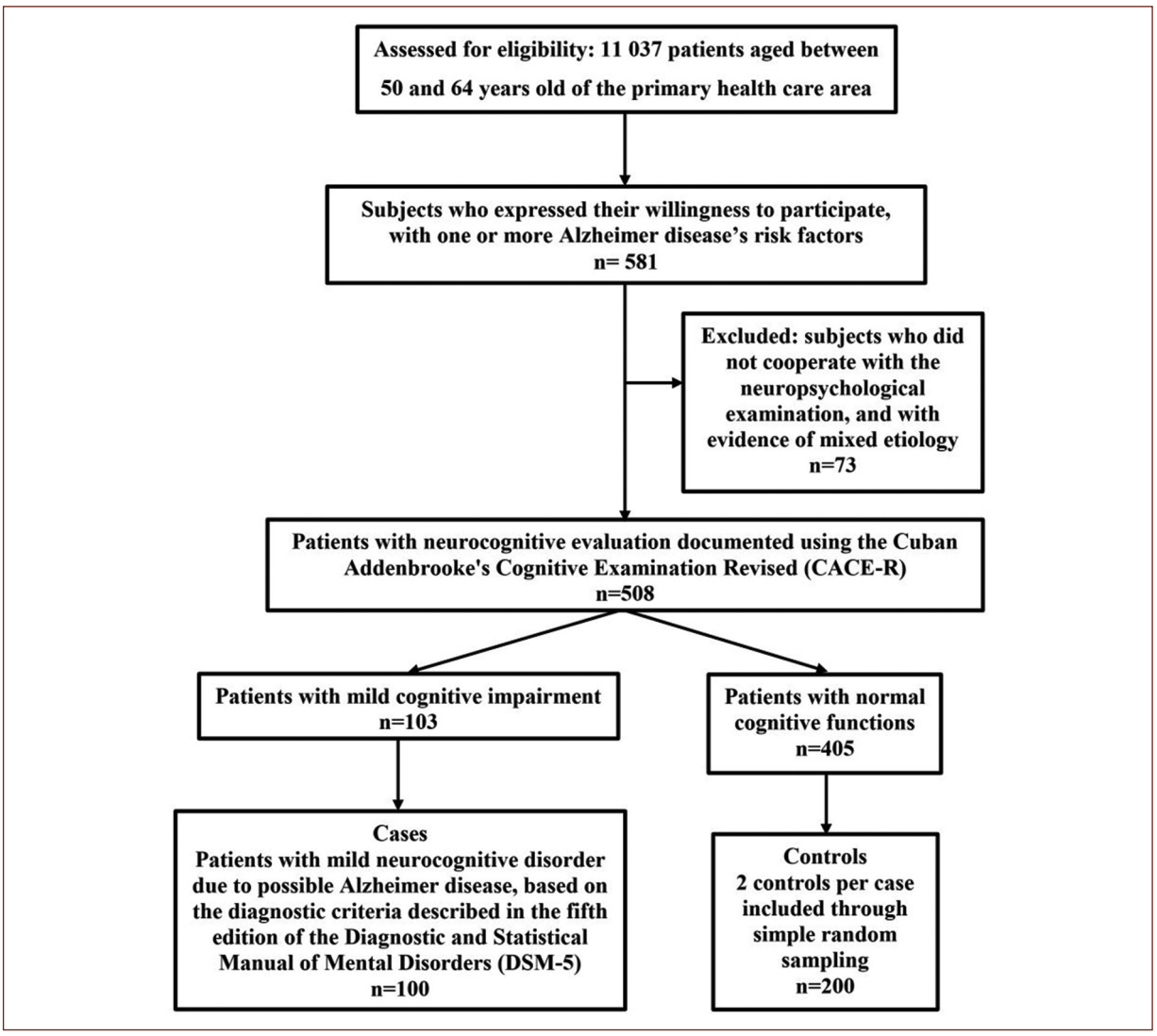

Figure 1. Flow diagram of participant selection.

global index in form of a linear combination: I = x1w1 + x2w2+…+xkwk, where I constitutes the proposed model; k, the number of variables, xk is the predictive variable; and wk, the weight chosen for said variable in the model.

A risk score was calculated for each subject, with the 70th percentile of empirical values defining two categories: low risk and high risk, and its discriminatory capacity was evaluated similarly to the model.

Bioethical considerations

The investigation was carried out under the approval of the scientific council and the ethics committee of Manuel Fajardo Rivero Polyclinic. Participation in the study was carried out under the principle of voluntariness, obtained through informed consent. It was accepted that the ethical principles for research in human beings, under the Declaration of Helsinki[28].

Results

Table 1 shows the distribution of clinical epidemiological variables in the two study groups. The group classified with MCI showed a significant predominance of low educational attainment, low skill level, physical inactivity, non-communicable chronic diseases (diabetes mellitus, hypertension, obesity), smoking, weight loss, and history of COVID-19 infection. Factors such as female sex, family history of dementia,

Table 1. Distribution of subjects according to clinical and epidemiological variables versus neurocognitive evaluation in univariate analysis

Variables	No cognitive impairment, n (%)	Mild cognitive impairment, n (%)	Total, n (%)	Sig.
Female sex	86 (43)	42 (42)	128 (42.7%)	0.869
Low educational attainment	50 (25)	75 (75)	125 (41.7)	0.000
Low skill level	54 (27)	91 (91)	145 (48.3)	0.000
Family history of dementia	11 (5.5)	6 (6)	17 (5.7)	0.860
Hypercholesterolemia	100 (50)	60 (60)	160 (53.3)	0.102
Physical inactivity	49 (24.5)	80 (80)	129 (43)	0.000
Social isolation	32 (16)	18 (18)	50 (16.7)	0.661
Diabetes mellitus	56 (28)	82 (82)	138 (46)	0.000
Hypertension	54 (27)	79 (79)	136 (44.3)	0.000
Chronic kidney disease	25 (12.5)	14 (14)	39 (13)	0.716
Obesity	25 (12.5)	52 (52)	77 (25.7)	0.000
Smoking	33 (16.5)	63 (63)	96 (32)	0.000
Weight loss	44 (22)	65 (65)	109 (36.3)	0.000
Ischemic heart disease	19 (9.5)	11 (11)	30 (10)	0.683
COVID-19	58 (29)	88 (88)	146 (48.7)	0.000

Sig: significance level from Chi-square statistical test.

hypercholesterolemia, social isolation, chronic kidney disease, and ischemic heart disease did not show significantly different frequencies between the control group and MCI patients.

Table 2 lists variables included in the binary logistic regression with OR > 1 ($p < 0.05$): low educational attainment ($p = 0.000$; OR = 6.767), low skill level ($p = 0.000$; OR = 11.364), physical inactivity ($p = 0.007$; OR = 4.209), smoking ($p = 0.040$; OR = 3.330), diabetes mellitus ($p = 0.004$; OR = 4.641), hypertension ($p = 0.000$; OR = 10.011), obesity ($p = 0.002$; OR = 7.103), weight loss ($p = 0.011$; OR = 4.485), and COVID-19 ($p = 0.000$; OR = 8.099).

Among the variables in the model, a low skill level (score = 11) had the highest impact, followed by hypertension (10), COVID-19 history (8), and low educational attainment and obesity (both score = 7). Other variables scored 3-5.

The model (omnibus test $p = 0.000$) explained 82.5% of the dependent variable (Nagelkerke's R^2), correctly classified 91% of cases with 89.25% PPV, 91.79% NPV, 83% sensitivity, and 95% specificity. Calibration was good (Hosmer-Lemeshow test = 0.940) with an AUC of 0.976 (95% CI: 0.961-0.990; Fig. 2).

The resulting predictive model was composed of a global index in the form of a linear combination: I = 11*x1 + 10*x2 + 8*x3 + 7*x4 + 7*x5 + 5*x6 + 4*x7 + 4*x8 + 3*x9, where I constitutes the proposed model; x1 is low level of skill, x2 is hypertension, x3 is COVID-19, x4 is low educational attainment, x5 is obesity, x6 is diabetes mellitus, x7 is weight loss, x8 is physical inactivity, and x9 is smoking.

A risk score was calculated from the model for each subject, with the 70th percentile of the empirical values distribution defining two categories: low risk (under 33) and high risk (33 and over). The AUC of the scale was 0.918 (95% IC: 0.877-0.958; Fig. 3), with 90.72% PPV, 94.08% NPV, 88% sensitivity, and 95.5% specificity, indicating significant predictive value.

Discussion

The results of this investigation demonstrated that the predictive model can distinguish subjects with risk factors for AD who are at higher risk of mild NCD, using easily identifiable clinical and epidemiological variables, including COVID-19 history.

Table 2. Summary of multivariate binary logistic regression analysis

Variables	B coefficient	S.E.	Wald	Sig.	Exp (B)	95% CI	
						Lower limit	Upper limit
Low educational attainment	1.912	0.541	12.513	0.000	6.767	2.346	19.520
Low skill level	2.430	0.602	16.307	0.000	11.364	3.493	36.967
Physical inactivity	1.437	0.530	7.342	0.007	4.209	1.488	11.905
Smoking	1.203	0.584	4.237	0.040	3.330	1.059	10.469
Diabetes mellitus	1.535	0.527	8.472	0.004	4.641	1.651	13.048
Hypertension	2.304	0.537	18.427	0.000	10.011	3.497	28.659
Obesity	1.961	0.633	9.579	0.002	7.103	2.052	24.583
Weight loss	1.501	0.633	6.515	0.011	4.485	1.417	14.196
COVID-19	2.092	0.569	13.494	0.000	8.099	2.653	24.724

B: estimated logit coefficient; S.E.: standard error; Sig.: significance level; Exp (B): odds ratio; CI: confidence interval.

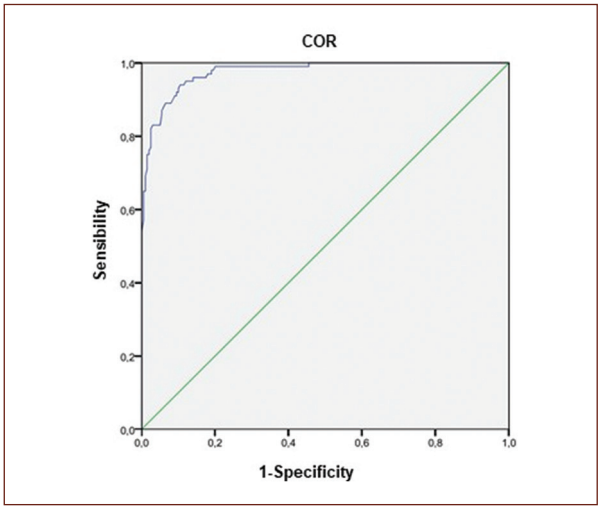

Figure 2. Discriminatory capacity of the model by the receiver operating curve.

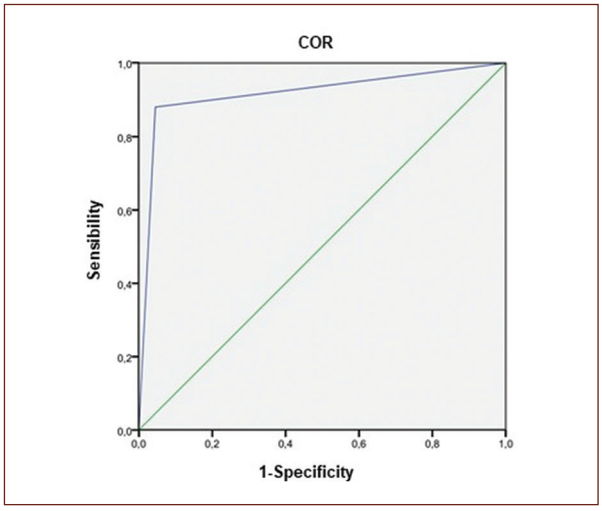

Figure 3. Discriminatory capacity of the scale by receiver operating curve.

No significant differences in sex distribution were observed between the control group and MCI patients in this study, contrasting with findings from Hernández-Ulloa et al.[29], whose observational study reported that women have a higher risk of cognitive decline and subsequent AD development.

In the review by Livingston et al.[8], the percentage reduction in dementia cases was raised if several risk factors of the model of this study were intervened, thus increasing the practical contribution of the proposed model.

In the case of educational attainment, researchers[8] have proposed that a low level should be corrected before the age of 45 to reduce cases by 5%, which represents a late intervention for the sample of this study that included adults aged over 45 years. Another investigation[30] suggested that the prevalence of suspected cognitive impairment presents with a higher OR as the years of education decrease.

In the review by Livingston et al.[8], it was suggested the correction of several factors in middle age (45-65 years) causes varying degrees of reduction in

cases of dementia: physical inactivity (2%), diabetes (2%), hypertension (2%), smoking (2%), obesity (1%), among others. These factors included in the final model were described in the literature for their association with MCI and AD.

One study[31] identified an association between physical inactivity and AD (OR 1.2; 95% CI 1.2-1.3). In a prospective cohort[32], the risk of dementia increased for each 5-year decrease in the age at onset of type 2 diabetes (OR 1.24; 95% CI 1.06-1.46). One study[33] identified the highest risk of dementia in people who started smoking between 33 and 44 years of age (OR 1.42; 95% CI 0.05-3.60).

An analysis of two prospective cohorts[34], reported that the risk of dementia in midlife for women is higher in smokers (OR 2.63; 95% CI 1.14-6.09) and diabetics (OR 1.74; 95% CI 1.08-2.80). For men, it was higher in smokers (OR 3.19; 95% CI 1.37-7.42), diabetics (OR 2.97; 95% CI 1.50-5.89), those with low educational attainment (OR 2.93; 95% CI 1.80-4.78), with hypertension (OR 1.70; 95% CI 1.02-2.84), and low activity physical (OR 1.71; 95% CI 1.03-2.85).

A meta-analysis[35], identified people with untreated hypertension had a higher risk of dementia than healthy controls (OR 1.42; 95% CI 1.15-1.76), and this risk was attenuated or lost with treatment.

A systematic review and meta-analysis[36], identified that midlife obesity was associated with later all-cause dementia (OR 1.31; 95% CI 1.02-1.68).

Weight loss was included in the final model. One study[22] revealed that participants at increased risk of AD had lost an average of 1% of their body weight per year, with no other potential causes of changes in body weight, while participants with lower risk had not experienced weight loss.

Low skill level was also included in the model. A study[25] concluded that people with a predominantly manual work activity have a greater risk of suffering from cognitive impairment than those who have occupations with greater intellectual requirements. Furthermore, the latter could help promote the maintenance of intact cognitive functions for longer and delay the onset of the disease.

In a systematic review and meta-analysis, it was found more than fifth of people presented with MCI (95% CI 0.17-0.28; $p < 0.001$), without meeting clinical criteria for dementia, 12 or more weeks after being diagnosed with COVID-19[27], that was an important factor in the sample of this study and was included in the final model.

In people aged over 65 years, a level of risk reduction was attributed to several factors, among which stands out: social isolation (5%)[8], which in this study did not have statistical significance, but is a repeated risk factor in the literature, as well as the family history of dementia[8], chronic kidney disease[20], hypercholesterolemia[21], and ischemic heart disease[23], which did not have significant differences in this research, but its analysis is recommended in another study sample or different clinical contexts.

The model enables earlier prediction of the cognitive impairment, compared to existing models of the progression of MCI to AD focused on patients aged over 65 years, described in systematic reviews[9,10]. Although it does not incorporate biomarkers (unlike models proposed in prior studies[11-13]), it demonstrates significant predictive value and outperforms other MCI risk factor-based models[37-40].

For instance:

- A Chinese MCI risk prediction system for elderly populations in China, incorporating hypertension, diabetes, educational level, hyperlipidemia, smoking, physical exercise, living alone, stroke, drinking, and heart disease, achieved an AUC of 0.859 (95% CI: 0.812-0.906, $p < 0.05$), with 86.6% sensitivity and 76.5% specificity[37].
- A machine learning model identifying middle-aged and older adults at high MCI risk included 13 factors (gender, education, marital status, residence, diabetes, hypertension, depression, hearing impairment, social isolation, physical activity, drinking status, body mass index, and expenditure). This model achieved an AUC of 0.774 for all incident MCI, with follow-up AUC values of 0.739, 0.747, and 0.750 at 2, 4, and 7 years, respectively[38].
- A risk prediction index for MCI and dementia incorporated age, female sex, years of schooling, hearing loss, depression, life satisfaction, and a number of cardio-metabolic risk factors (wide waist circumference, pre-diabetes/diabetes, hypertension, dyslipidemia). The development showed a progression AUC of 0.73, whereas the validation cohort achieved an AUC of 0.74 for MCI/dementia prevalence and incidence[39].
- A machine learning model for cognitive impairment in Chinese adults aged ≥ 60 years with normal baseline cognition identified four predictive features: age, instrumental activities of daily living, marital status, and baseline cognitive function. Its concordance index was 0.814 (95% CI: 0.781-0.846)[40].

A key limitation of our model is its relatively small sample size compared to the broader population with AD and mild NCD risk factors in the study context, necessitating further validation studies.

Conclusion

The predictive model of 9 variables that were easy to determine and interpret contributes to the stratification of the risk of mild NCD due to possible AD in adulthood. Therefore, it can constitute a useful tool in decision-making aimed at early and probably more effective interventions. It is recommended to validate the predictive model in cohorts with a larger estimation sample.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that artificial intelligence was used in the writing of this manuscript [specify the tool and all sections of the manuscript where it was used].

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