BMJ Open Study protocol for a prediction model for mild cognitive impairment in older adults with diabetes mellitus and construction of a nurse-led screening system: a prospective observational study

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ABSTRACT

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Professor Guiling Geng; sxl1105421943@163.com, Xiangyun Qian; qxy03062020@126.com and Jianqun Chen; 1153464524@qq.com **Introduction** With an increasing number of older adults in China, the number of people with cognitive impairment is also increasing. To decrease the risk of dementia, it is necessary to timely detect mild cognitive impairment (MCI), which is the preliminary stage of dementia. The prevalence of MCI is relatively high among older adults with diabetes mellitus (DM); however, no effective screening strategy has been designed for this population. This study will construct a nurse-led screening system to detect MCI in community-dwelling older adults with DM in a timely manner.

Methods and analysis A total of 642 participants with DM will be recruited (n=449 for development, n=193 for validation). The participants will be divided into MCI and none-MCI groups. The candidate predictors will include demographic variables, lifestyle factors, history of diseases, physical examinations, laboratory tests and neuropsychological tests. Univariate analysis, least absolute shrinkage and selection operator regression screening, and multivariate logistic regression analysis will be conducted to identify the outcome indicators. Based on the multivariate logistic regression equation, we will develop a traditional model as a comparison criterion for the machine learning models. The Hosmer-Lemeshow goodness-of-fit test and calibration curve will be used to evaluate the calibration. Sensitivity, specificity, area under the curves and clinical decision curve analysis will be performed for all models. We will report the sensitivity, specificity, area under the curve and decision curve analysis of the validation dataset. A prediction model with better performance will be adopted to form the nurse-led screening system.

Ethics and dissemination This prospective study has received institutional approval of the Medical Ethics Committee of Qidong Hospital of TCM (QDSZYY-LL-20220621). Study results will be disseminated through conference presentations, Chinese Clinical Trial Registry and publication.

Trial registration number ChiCTR2200062855.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will construct a nurse-led screening system using a prediction model for the timely detection of mild cognitive impairment in older adults with diabetes mellitus in communities.
- ⇒ The design of this study strictly follows the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statements to improve our methodology.
- ⇒ This study will include variables available in primary care for predictor selection, such as demographic variables, lifestyle factors, history of diseases, physical examinations, laboratory tests and neuropsychological tests.
- ⇒ After comparing the traditional model established by multilogistic regression and different models established by machine learning algorithms, the model with the best differentiation performance will be adopted as the final model in the nurse-led screening system.
- $\Rightarrow\,$ Data on lifestyle factors from self-reports may lead to recall bias, which is unavoidable in this study.

INTRODUCTION

Mild cognitive impairment (MCI) refers to a mild decline in memory and other thought processes but not functional decline.^{1 2} A recent study estimated that the overall prevalence of MCI in China is 15.5%.³ MCI is a transitional stage between normal cognitive function and dementia.^{4 5} Approximately 10%–15% of older adults with MCI would develop dementia.⁶ Meanwhile, 10%–40% of MCI cases can revert to normal cognition for more than 4–5 years.⁷ Hence, people with MCI are the key population for secondary prevention of dementia.



Diabetes mellitus (DM) is an important risk factor for dementia. DM may increase the risk of progression from MCI to dementia, in addition to increasing the risk of progression from intact cognition to dementia.⁸ Researchers have also found that diabetes and prediabetes inhibit MCI reversion.9 Current theories indicate that hyperglycaemia, cerebral microvascular injury, insulin resistance, altered insulin signalling, neuroinflammation and build-up of cerebral amyloid and tau proteins may contribute to the pathophysiology underlying cognitive decline and DM.¹⁰ Globally, the prevalence of MCI in patients with type 2DM (T2DM) is 45.0%.¹¹ Among patients aged ≥ 60 years, up to 20% of those with T2DM may eventually develop dementia.¹² The number of older adults with DM in China was approximately 35500000 in 2021,¹³ suggesting that a large population with DM may have MCI or dementia. Therefore, it is essential to promote early detection of MCI in older adults with DM.

The US Preventive Services Task Force statement stated that MCI is most likely to be detected by screening.⁴ Cognitive impairment assessments have frequently been conducted using cognitive screening tools,⁷¹⁴ including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment Scale (MoCA), Clock Drawing Test, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and Self-administered Dementia Screening Questionnaire (p-AD8). However, each of these instruments has advantages and disadvantages for MCI detection.¹⁵ Despite a large body of evidence evaluating cognitive screening tools, the cut-off values for screening tools in older adults with DM need to be further validated. Therefore, a simple screening method with high accuracy and practicality for identifying MCI in older adults with DM is urgently required.

Risk factors are considered to be significantly associated with the onset of MCI in older adults with DM .^{16–18} Identifying risk factors for MCI in older adults could aid in the prevention of dementia.¹⁹ Hence, early identification and control of the risk factors for MCI should be highlighted in DM patient care or diabetes regimens. Prediction models based on clinical predictors have been developed for MCI. Yang *et al*²⁰ used plasma proteins to screen for MCI and evaluated the performance of prediction models for MCI at different educational levels. Wang et al established an effective risk prediction model for MCI among older Chinese adults.²¹ Based on the identification of risk factors for MCI, machine learning methods have been introduced for the development of prediction models. Yang *et al*²² have used a random forest algorithm to examine basic characteristics, serum biomarkers and imaging biomarkers. The model developed by Yim *et al*²³ consisted of MMSE, MoCA, informant interviews and clinical assessments, suggesting that a machine learning algorithm could be a supportive screening tool. However, to our knowledge, few studies have developed models targeting older adults with DM for MCI screening, and the factors contributing to the development of MCI in older adults with DM are not well understood. Moreover,

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whether machine learning algorithms are more appropriate than the existing traditional approaches (eg, logistic regression and the Rothman-Keller model) remains unclear. Therefore, an appropriate model based on an integrated cognitive assessment system should be developed to screen older populations with DM for MCI and related risk factors.

This prospective observational study will construct a nurse-led MCI screening system for older adults with DM who are likely to have MCI simultaneously. A prediction model will be developed and validated to assist nurses in the prompt and accurate detection of MCI by evaluating the contributions of the significant predictors available ŝ in primary care. We hope that the early identification copyright, including for uses related to text of MCI and related predictors can aid in patient care or modification of diabetes regimens in terms of cognitive impairment.

METHODS AND ANALYSIS Design

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis checklists²⁴ will be used to design and implement this protocol. The prediction model in our study will be developed and validated based on a cross-sectional study.

Setting

We will sequentially recruit older adults with DM who visit the Medical Examination Centre of Oidong Hospital and of TCM in China (October 2023 to June 2024) to develop and validate the prediction model and nurse-led screening system. The Medical Examination Centre of a Qidong Hospital of TCM undertakes regular checkups, diabetes complication screening and cognitive examination projects with approximately 300 visits of older adults with DM per month, making them available for our study.

Target population

Inclusion criteria: (a) aged 60 or more and (b) diagnosis of T2DM (reported in electronic health records (EHRs)).

Exclusion criteria: (a) intensive care; (b) terminal diseases; (c) vision problems, hearing impairment or any other disability that hinders the completion of this study; technologies (d) acute or unstable psychiatric disorders (such as major depression, significant head injury, substance abuse, alcoholism and delirium) and (e) dementia diagnosis (reported in EHRs).

Sample size

The sample size is calculated through using the pmsampsize package.²⁵ It requires the prevalence of the binary outcome and the number of candidate predictor parameters. According to a previous study, the prevalence of MCI in older adults with DM in China was 21.8%.²⁶ Therefore, we assume that the prevalence of MCI during the study period would be 21.8%. We expect to include 10 candidate variables. For an outcome proportion of 21.8%, the max R^2 is 0.6496. It is assumed that the new model would explain 20% of the variability; hence, the expected \mathbb{R}^2 is 0.12992 (equal to 0.6496×0.2). Then, the parameters, 'pmsampsize, type(b) rsquared (0.12992) parameters (10) prevalence (0.218)' are used in Stata V.15.1. The output indicates that the sample size required to develop the model is 642. It is expected that 140 events and events per candidate predictor parameter are 14. Random number tables will be used to randomly divide the participants into two groups. A total of 449 (70% of participants) will be assigned to a training dataset for the selection of screening tools, predictor selection and model construction; 193 participants (30%) will be assigned to a validation dataset to evaluate the performance.²⁷

Procedures

During older adults' first visits for regular checkups in the Medical Examination Centre, word-of-mouth will be the main method of recruitment for our study. Individuals will be included in this study if they meet the eligibility criteria and sign consent forms requiring the use of personal data in EHRs. Data on demographic variables, lifestyle factors, history of diseases and laboratory tests will be retrieved from the EHRs generated during their check-ups.

Within a week, when the participants pay their second visit for their check-up results, MCI diagnosis, along with physical examinations and neuropsychological tests, will be conducted by two researchers through face-to-face interviews.

Patient and public involvement

This study was designed, conducted, reported and disseminated without the involvement of patients or the general public.

Outcomes

The primary outcome of the study will be the presence of MCI in patients with DM. The MCI subtypes will not be analysed in this study. The diagnostic criteria of MCI refer to Petersen's Criteria,^{4 28} the International Working Group on MCI²⁹ and Chinese expert consensus on the prevention and treatment of cognitive impairment³⁰: (1) preserved general cognitive function, (2) self and/ or informant reporting impairment of objective cognitive tasks, (3) objective memory impairment demonstrated by neuropsychological testing (MoCA cut-off points: illiterate, ≤ 13 ; 1–6 years of education, ≤ 19 and 7 or more years of education, ≤ 24),³¹ (4) with or without minimal impairment in complex instrumental functions, basic activities of daily living (ADLs) are preserved²⁹ and (5) no diagnosis of dementia. If all five criteria are met, the patients will be categorised into the MCI group; otherwise, they will be categorised into the non-MCI group. The final diagnosis will be confirmed by a senior neurologist.

Variables and measures

The project selection of the model will include risk factors considered to be clinically important in the guidelines

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for MCI. This 10 min tool consists of eight domains: visuospatial, naming, executive function, attention, language, abstract, memory and orientation abilities. The cut-off values for MCI vary among older adults with different levels of education.

The Chinese version of the ADL scale⁴⁶ was developed by Lawton and Brody by combining the Physical Self-Maintenance Scale and Instrumental ADL scale. The Physical Self-Maintenance Scale assesses functional ability using six categories of ADL: toileting, feeding, dressing, grooming, physical ambulation and bathing. The Instrumental ADL scale includes eight items: telephone, shopping, food preparation, housekeeping, laundry, transportation, medication and finances. Each item is scored from 1 (no impairment) to 4 (severe impairment), with a total range of 14-56 points. Higher scores indicate lower ADL ability. If participants have two or more items with a score \geq 3 or a total score \geq 22, it indicates impairment in complex instrumental functions.⁴⁷

Self-administered Dementia Screening Questionnaire (p-AD8) is a participant-rated tool for cognitive impairment developed by Galvin et al.48 The Chinese version was validated by Xie et al.49 For suspected memory dysfunction, a p-AD8 had sensitivity and specificity of 85.7% and 77.6%, respectively. This tool briefly assesses the domains of memory, orientation and judgement.⁴⁸ It takes approximately 3 min to complete the assessment; thus, it appears to be a suitable screening tool for medical examination centres and primary care settings. If the score is ≥ 2 , participants are expected to have a high risk of cognitive impairment.

IQCODE is an informant-based screening tool.⁵⁰ The Chinese version of IOCODE was validated by Li *et al.*⁵¹ with an optimal cut-off score of 3.19 for MCI with a sensitivity of 0.979 and a specificity of 0.714. The IQCODE comprises 16 items scored on a 5-point scale (1=much improved to 5=much worse). The total score is presented as the average of the completed items. If a caregiver or informant is present, IQCODE should be completed.

Depressive symptoms will be evaluated using the 15-item Geriatric Depression Scale, one suitable screening tool for depression symptoms in community-dwelling older adults.⁵² Item scores are simply added up, ranging from 0 to 15. A cut-off score of 5 indicates the presence of depressive symptoms.

The Social Support Self-Rating Scale developed by Xiao is one common instrument for measuring social support in China.⁵³ A total of 10 items included 3 dimensions: subjective support (range: 8-32), objective support (range: 1-22) and support-seeking behaviour (range: 3-12). This total support score (range: 12-66) consists of three categories: low (≤ 22), moderate (23–44) and high (≥ 45) levels of support.⁵⁴

Quality control

All researchers should accept two training sessions (one for clinical data collection and one for the utilisation of neuropsychological tools), provided separately by a senior geriatric doctor and a neuroscientist, and obtain authorisation before screening. All the investigators should strictly follow the protocol. If any problems appear during the trial, the research group should promptly have a focus group discussion and provide solutions.

Missing data

Any variable with over 5% of missing data will be excluded from the main analysis. For complete-case analysis, we will use multiple imputations in the R multiple imputation procedure for missing data.

STATISTICAL ANALYSIS METHODS Model development and validation

Protected by copyright, For model development and validation, participants will be reclassified into two groups, a training dataset and a validation dataset, to test the models' ability to discriminate between the cognitive stages (MCI vs non-MCI). After comparing the traditional model established by g multilogistic regression and different models established ٥u by machine learning algorithms, the prediction model for uses related with the best differentiation performance will be adopted as the final model in the nurse-led screening system. A kappa value of ≥ 0.4 represents moderate²³ when it is used to correct two groups' unbalanced distribution.

Selection of screening tools

6 Screening tools will be selected for both initial and te secondary screening. For the initial assessment, screening and tools with higher sensitivity will be recommended for clinical practice after comparisons between IQCODE, p-AD8 ical practice after comparisons between IQCODE, p-AD8 or a combination of both. The AD8 and IQCODE are selfadministered, friendly screening tools that are suitable Ξ for prescreening to reach the maximum number of older adults with suspected positives.⁵⁵ Unlike other tools, AD8 and IQCODE are not restricted by age, sex and educa-≥ tional level; thus, they are more suitable for older adults screening, assessments with higher specificity are priorishould exclude false positives.¹⁴ The MoCA is considered as the most preferable tool for MCI screening,⁵⁶ but its application among older adults with T2DM in the communities has not been sufficiently validated. Hence, specific screening tools or the combinations (IQCODE, p-AD8, IQCODE+p-AD8, p-AD8+MoCA, IQCODE+MoCA or IQCODE+p-AD8+MoCA) will be evaluated for the preferred screening tools. The receiver operating char- 8 acteristic (ROC) curve analyses will be performed using SigmaPlot V.12.5, which will provide scores for sensitivity, specificity and the area under the curve (AUC) considering education level and age stratification. The cutoff scores for tools that differentiate between different groups (MCI vs non-MCI) will be calculated using the Youden index. The significance level will be set at 5%. The screening tools with better performance will be included in the development of the models.

Predictor selection

The Shapiro-Wilk test will be employed to test normality. Values will be presented as the mean (SD) if quantitative data are normally distributed or the median (quartile) if not normally distributed. Quantitative data will be compared using the Student's t-test or Mann-Whitney U test, according to the appropriate application. Categorical data will be analysed using the χ^2 test or Fisher's exact test. Statistical significance will be set at p<0.05, and parameters with p<0.05 will be analysed using the least absolute shrinkage and selection operator logistic regression approach (LASSO).

LASSO is used to process multicollinearity since a great number of various variables included in this study may present possible collinearity. The LASSO approach can reserve the predictors with the strongest effects and improve the interpretability of the model by shrinking some coefficients to zero.⁵⁷ The optimal parameters will be estimated using a 10-fold cross-validation method.

Multivariate logistic regression analysis will include the variables selected from the LASSO regression in order to determine the independent factors predicting MCI. In this study, the multiple logistic regression analysis adopts Wald backward selection to effectively control for confounders.

Model development

The traditional model

The traditional model will be used as a comparison criterion for machine learning models. Clinical data, including demographic variables, lifestyle factors, history of diseases, physical examinations, laboratory tests and neuropsychological tests, will be evaluated. The R package of 'rms' will be applied to establish the traditional model. In this study, 1000 bootstraps will be adopted for internal verification and determination of the predicted cut-off value to prevent overfitting. We will assess the sensitivity, specificity and AUC for the differentiation performance. To evaluate the calibration, the Hosmer-Lemeshow goodness-of-fit test and calibration curve will be performed, and a p>0.05 will be acceptable.⁵⁸ The precision of the traditional model will be evaluated by the Brier score, which is 0-1 points, and the higher the score, the worse the calibration degree. Clinical decision curve analysis (DCA) will be used to measure the clinical applicability of the prediction model with 'rmda' R package.⁵⁹

Machine learning algorithms

Machine learning models will evaluate data from neuropsychological tools, demographic variables, lifestyle factors, medical history, physical examinations and laboratory tests. Machine learning models will be applied using several algorithms, including binary logistic regression, penalised binary logistic regression, naïve Bayesian classification model, decision tree and random forest. The R software (http://www.r-project.org) will be used to measure the performance of the machine learning models. Repeated iterative cross-validation will be applied

to all algorithms to determine the hyperparameters affecting the efficiency of the learning process with the minimal error. Using two stratifications (healthy participants and those with MCI), we will calculate the sensitivity, specificity, ROC curves and DCA of each machine learning model. Statistical significance will be set at p<0.05.

Validation

The validation dataset, comprising 20% of the participants, will be used for external validation of the perfortected mance. ROCs and AUCs of the validation dataset will be assessed. We will also calculate DCA to evaluate its clinical applicability.

DISCUSSION

by copyright, inc Screening for MCI is not routinely performed in primary care settings. The special plan of exploration of Alzheimer's prevention and treatment⁶⁰ mentioned that 'the rate of older adults in the community screened for cognitive function should reach 80%'. Hence, we will develop a nurse-led screening system for older adults with DM, particularly those living in the community. For the initial screening, this system could avoid unnecessary compre-hensive cognitive tests for older adults with DM who are at low risk of cognitive impairment. Furthermore, the high sensitivity of secondary screening may lead to an effective 5 cognitive screening using the machine learning models. Thus, older adults with DM who are at high risk of cognitive impairment can be transferred to a general physician or psychiatrist for diagnosis in a more effective way.

In this study, we consider as many important factors as possible, including democratic as possible, including demographic variables, lifestyle factors, history of diseases, physical examinations, laboratory tests and neuropsychological results, which can be extracted in primary care settings. Machine learning methods applied to screen for MCI in communities could accelerate MCI screening process. As claimed by the Healthy China initiative (2019–2030),⁶¹ 'early identification and control of the risk factors of cognitive impairment, and routine intervention of cognitive impairment are the main methods of the management of cognitive impairment'. The application of machine learning models is conducive to successfully interpreting data with a high degree of accuracy for classification.²³ We hope that the nurse-led screening system using the prediction model will provide an accurate detection of MCI in communities and that the identification of predictors could aid in DM patient care for cognitive impairment.

Proposal of a two-step strategy for MCI screening

In contrast to previous models,^{21 22 62} we aim to form a screening system led by nurses in communities or primary care for the purpose of timely detection of MCI among older adults with T2DM using simple and accurate predictors and screening tools. Hence, we propose a two-step method to detect the early stages of cognitive

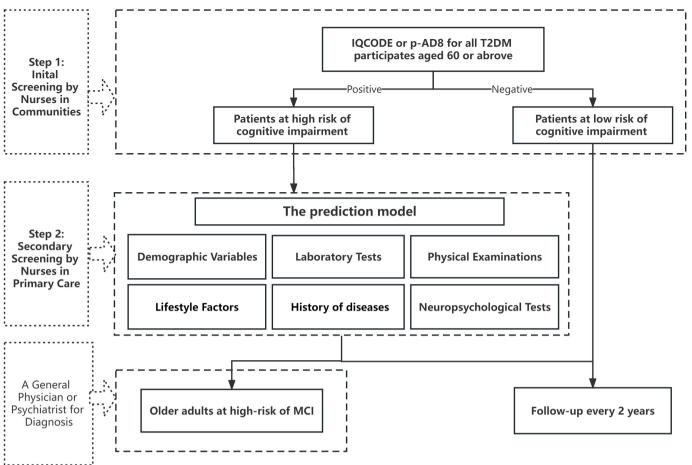


Figure 1 Proposal of a two-step strategy for MCI screening. DM, diabetes mellitus; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MCI, mild cognitive impairment; p-AD8, Self-administered Dementia Screening Questionnaire;

impairment, as shown in figure 1. Initial MCI screening with self-reported screening tools, such as p-AD8 or IOCODE, can be performed in community-dwelling older adults under the guidance of nurses because MCI is often under-recognised within communities.⁶³ Participants with T2DM will be classified into the high-risk and low-risk groups. Individuals with T2DM who are predicted to be at high risk of cognitive impairment will be transferred to primary care settings. Subsequently, a prediction model for secondary screening will be implemented.¹⁴ Then, older adults whose results are positive in the secondary period will be transferred to a general physician or psychiatrist for a final diagnosis. The low-risk group in the first period and the negative group in the secondary screening will be followed up by nurses every 2 years.³³ We hope to promote this two-step strategy to effectively screen for MCI in communities and primary care centres in the future.

Limitations

This study will be conducted as a single-centre trial. Although we will use a large number of methods to validate the models and construct the screening system, the scope of this study may be limited because of the lack of data from different medical centres in China. Second, to improve the feasibility, the proposed model will contain

data min clinical information and assessments commonly available in primary care. In addition, the data on lifestyle factors from self-reports may lead to recall bias. Some indicators with potential effectiveness reported in the previous studies,^{64–66} such as imaging indicators, nerve electrophysiological examination or cerebrospinal fluid examinations, will not be incorporated into the evaluation system because they are less accessible in the primary care. Third, the screening system is only applicable for differentiating cognitive status but not for predicting prognosis, owing to its cross-sectional design for the purpose of early detection of MCI.

CONCLUSIONS This study will develop a nurse-led screening system for the timely detection of MCI in community-dwelling all adults with DUI. adults with DM. Potential predictors will be identified through a comprehensive evaluation of demographic variables, lifestyle factors, history of diseases, physical examinations, laboratory tests and neuropsychological tests. This may assist nurses or health workers in modifying diabetes regimens or providing support for patient care in terms of cognitive impairment. The application of the model with the best performance in this study may

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help improve the efficiency of MCI detection in primary care and offer opportunities for early interventions for dementia prevention.

Ethics and dissemination

Written informed consents are required for older adults' participation. Before enrolment, individuals will be given sufficient time to ask questions and clarify issues regarding the commitment, benefits and risks of the study. Ethical approval was obtained from Medical Ethics Committee of Qidong Hospital of TCM (QDSZYY-LL-20220621). Study results will be disseminated through conference presentations, Chinese Clinical Trial Registry and publication. We will deidentify and store all acquired data electronically with password protected.

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Contributors WM and YL conceptualised the study. WM, HX and WY were involved in study design. CZ conducted the review of the literature. XQ and JC calculated sample size. YL, GG and XQ obtained funding. WM and YL drafted and critical revised the manuscript. JC and GG supervised the protocol; all authors contributed to its revision and approval.

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Competing interests None declared.

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