Preferences of people with mild cognitive impairment for physical activity interventions in China: protocol for a discrete choice experiment study

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ABSTRACT

Introduction Exercise interventions are important non-pharmacological interventions for patients with mild cognitive impairment (MCI), but patients with MCI have poor compliance and there is no consistent strategy for exercise interventions. Understanding the needs and preferences of MCI patients allows for the development of effective and acceptable exercise intervention programmes that achieve the goals of patient-centred care. This study uses a discrete choice experiment (DCE) to measure and quantify MCI patients’ preferences for exercise interventions, and aims at (1) identifying and exploring which elements of exercise intervention programmes are essential for MCI patients; (2) measuring MCI patients’ preferences for exercise interventions and summarising relevant characteristics that may influence preference choices and (3) determining whether these preferences vary by participant characteristics and classifying the population types based on the sociodemographic characteristics of the participants.

Methods and analysis A DCE will be conducted to explore MCI patients’ preferences for exercise interventions. We conducted a systematic literature review and extensive qualitative work to select the best attributes to develop the design of DCE. A partial factorial survey design was generated through an orthogonal experimental design. We will conduct a questionnaire survey in one city each in the eastern (Nanjing), western (Xining), southern (Zhuhai) and northern (Beijing) parts of China and reach the planned sample size (n=278). Final data will be analysed using a mixed logit model and a latent class model.

Ethics and dissemination This study was approved by the Ethics Committee of Nanjing Medical University (2021-666). All participants will be required to provide informed consent. Our findings will be disseminated and shared with interested patient groups and the general public through online blogs, policy briefs, national and international conferences and peer-reviewed journals.

INTRODUCTION

Along with rapid global population ageing, the number of older adults afflicted with cognitive impairment increases dramatically. Therefore, developing strategies to prevent and manage cognitive decline in older adults has become a priority in aged care. Mild cognitive impairment (MCI) refers to the stage between cognitively normal and dementia.1 The Lancet finds that approximately one-fifth of adults older than 65 years suffer from MCI.2 According to estimates, the prevalence of MCI is 15.54% among Chinese adults over 60 years old,3 given that MCI is considered the preclinical period of dementia and has an exceptionally high risk of developing dementia. Therefore, it is essential to adopt early intervention to improve cognitive health and reduce cognitive decline.

In recent years, a growing number of scholars have attempted to uncover the effectiveness and mechanism of exercise interventions in patients with MCI, and increasing evidence has proven the feasibility of exercise interventions.4 Exercise is believed to have a positive effect on improving cognitive function and alleviating negative emotions. The updated MCI guidelines released by the American Academy of Neurology (AAN) in 2018 also recommended physical exercise as an official recommendation for the first time.5 Existing studies have found that the overall adherence of patients with MCI is poor, with half of the patients having difficulty in completing all of the interventions and less than one-fifth of

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a discrete choice experiment (DCE) method to determine how people with mild cognitive impairment (MCI) prefer to exercise.

⇒ To ensure the scientific validity and authenticity of the findings, we conducted a comprehensive literature review and qualitative studies to determine the attributes and levels of DCE to be included.

⇒ This study will provide an insight into the attributes and levels of attributes that impact MCI patients’ decisions to engage in physical activity.

⇒ The DCE study will take place in China, which may limit its generalisability to other contexts.
the patients adhering to the interventions afterward.\textsuperscript{6,7} It is imperative to design an effective exercise intervention programme for patients with MCI. There are two main ways to set up an exercise intervention programme: one is a mandatory arrangement from the outside, where an exercise intervention programme is set up directly based on the experience and skills of the professional, while the other is an exercise intervention from the patient’s perspective, using relatively well-established behaviour theories by analysing the patient’s emotions, beliefs and other internal behavioural patterns.\textsuperscript{8} The second path tends to yield better intervention durability and effectiveness results than the first one.\textsuperscript{9} Considering that the underlying assumption of most behaviour change theories is that individuals can develop coherent and logical plans in their decision-making process,\textsuperscript{9} yet there are limitations to using behavioural theories designed based on normal cognitive populations to construct exercise intervention programmes because of the specificity of cognitive decline in MCI patients compared with normal populations.

In 2001, the Institute of Medicine (IOM) report ‘Crossing the Quality Gap’ listed patient-centred care as one of the six aims of quality healthcare.\textsuperscript{10} Patient-centred care is defined as ‘care that is respectful and responsive to individual patient’s preferences, needs and values’, where preference refers to the individual’s subjective tendency towards an event or outcome and is also the cause of the behaviour.\textsuperscript{11} It is feasible to increase treatment compliance by first identifying the motivations for behaviour from the patients’ perspective and then incorporating those preferences into therapy programmes. Existing studies have found that MCI patients still have the ability to express and maintain their preferences despite impaired cognitive function.\textsuperscript{12,13} At the same time, studies have found that decreased cognitive ability has no significant impact on the priority level and stability of daily life preferences.\textsuperscript{14} As seen, it is viable to conduct research on MCI patient preferences. Therefore, some scholars have attempted to explore the application of preferences and found that preferences play an important role in decision-making, such as treatment selection for MCI patients. Smith \textit{et al} performed an online survey of intervention modality and treatment outcome preferences of MCI patients and revealed that patients ranked quality of life and memory compensation training as the highest priority, based on which the investigators designed a multicomponent behaviour intervention tool to address this preference.\textsuperscript{15} Chong \textit{et al} have discovered through focus-group discussions that due to memory impairment and peer lack, older MCI patients tend to choose simple, safe, easy and group cooperative exercises.\textsuperscript{16} Based on these findings, Cox \textit{et al} designed and implemented exercise intervention programmes to meet the preferences of ageing MCI patients.\textsuperscript{17} While the preceding studies have delved deeply into the preferences of MCI patients, they are all qualitative studies, and the preferences of MCI patients cannot be quantified to guide intervention programmes objectively. Meanwhile, due to the heterogeneity of preferences across patients, the results of previous studies may be insufficiently comprehensive or exist with some measurement bias.

Discrete choice experiment (DCE), a multiattribute approach, can help identify preferred components crucial to achieving better intervention results. To the best of our knowledge, this study is the first application that uses DCE to measure and quantify the preferences of MCI patients for exercise interventions, hoping to determine the relative importance (RI) of attribute levels and the utility associated with the attributes of exercise intervention approaches for patients with MCI, as well as to determine whether preferences vary by sociodemographic variables. Understanding these preferences and delineating patient populations with similar preferences may help develop exercise interventions for patients with different characteristics. Therefore, the objectives of the study are as follows:

1. To identify and explore which components of exercise intervention programmes for MCI patients are essential.
2. To measure MCI patients’ preferences for exercise interventions and summarise relevant characteristics that may influence preference choices.
3. To determine whether these preferences vary by participant characteristics and to classify population types based on the participants’ sociodemographic characteristics.

\section*{METHODS AND ANALYSIS}

\subsection*{Study setting}

According to a review published in the Lancet Neurology in 2020,\textsuperscript{18} the regions of China with the highest prevalence of cognitive impairment are primarily West China, North China, Central China and South China. As a result, four cities were chosen as sample areas: Xining City, Qinghai Province; Beijing; Nanjing City, Jiangsu Province and Zhuhai City, Guangdong Province, to investigate whether MCI patients in different regions have different preferences. Simultaneously, taking into account the benefits of memory outpatient clinics in conducting systematic and standardised diagnosis and treatment in the cognitive impairment population, as well as the effect of attracting patients from different sources (urban or rural),\textsuperscript{19} we will choose two or three hospitals with memory clinics in each of the four sample areas as study sites.

\subsection*{Design}

Our study employed a DCE to explore MCI patients’ preferences for exercise interventions. The DCE process consists of four phases: attributes and levels identification, experimental design and questionnaire, sample and recruitment, as well as statistics and data analysis. The procedure of DCE is shown in figure 1.

\subsection*{Attributes and levels identification}

Identifying appropriate attributes and levels is critical for valid results, and the attributes and levels will be selected in
accordance with ISPOR’s (International Society for Pharmacoeconomics and Outcomes Research) guidance. Qualitative research, including focus group discussions (FGDs) and in-depth interviews (IDIs), is essential in determining attributes and levels. Prior to that, a thorough review of the literature is recommended to identify conceptual attributes and provide a foundation for qualitative research. FGDs allow for data collection in a group setting while capturing as many different attributes and related levels as possible. Meanwhile, the purpose of the IDIs is to prioritise the final attributes and specify the level of each attribute from a personal perspective for data collection. Therefore, we conducted FGDs as well as one-on-one IDIs based on the literature review.

**Literature review**

First, we used the method of evidence summary to review the literature on exercise intervention in MCI patients, taking into account the scientific validity and feasibility of the intervention programme. A comprehensive literature search was conducted in the evidence summary process. On the basis of established evidence-based issues, inclusion and exclusion criteria for literature were constructed. The inclusion criteria included: (1) studies on MCI patients; (2) evidence content including exercise assessment, exercise style, exercise assistance measures, and so on and (3) evidence styles including clinical guidelines, expert consensus/position statements, evidence summaries and systematic reviews. Included among the exclusion criteria were research with poor quality, missing information or multiple publishing. We searched the following electronic bibliographic databases: BMJ Best Practice, UpToDate, JBI, Registered Nurses Association of Ontario (RNAO), The National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), Guidelines International Network (GIN), Medline and the websites of the American Psychological Association (APA), the American Geriatrics Society (AGS) and the Alzheimer’s Association (AA). To ensure the comprehensiveness of the included research, we utilised combinations of Medical Subject Headings and free-text words and searched up to 4 August 2021, with no language constraints. Additionally, we gathered the reference lists of all eligible research and any pertinent studies using alternate methods (eg, Google Scholar). Then, we conducted an expert meeting and several patient interviews to determine whether or not each piece of evidence was valid, feasible, appropriate and clinically significant. Three clinicians, three clinical nurses, one nursing manager, one rehabilitation therapist and one community nurse are among the experts. All of the specialists have over 10 years of experience. Except for the community nurse, all specialists are from the neurology and rehabilitation departments of tertiary hospitals. Two men and three women, ranging in age from 53 to 72 years, made up the five patients. It yielded 27 pieces of evidence in seven dimensions. After screening the evidence, we selected attributes such as exercise modalities, exercise settings, exercise duration and exercise assistance for a broader retrieval of MCI patients. Finally, we developed a list of possible attributes and levels that will serve as the foundation for the discussion of qualitative research. We did not include monetary costs as a relevant attribute but rather the mode of payment due to the Chinese unequal health insurance policy for urban and rural residents and the absence of similar charging items. A complete list of search strategies, evidence summaries and potential attributes and levels is provided in online supplemental materials S1–S3.

**Focus group discussions**

Second, we conducted FGDs to further explore the attributes and levels obtained from the literature review, as well as to obtain other relevant attributes and levels from the perspectives of patients, families and experts (January 2022 to February 2022). Focus groups were chosen because they encouraged participants to reflect and express their subtle thought processes as they discussed their shared experiences. We conducted a targeted sampling based on factors such as gender, age and educational level to ensure adequate representation. Two focus groups were held in two different regions (Nanjing and Beijing), each consisting of five patients and their families. Patients and their families were recruited in memory clinics and wards, and all patients had been clinically diagnosed with MCI. Considering the impact of COVID-19, we convened an online meeting with 10 experts (including four neurology clinical nursing staff, three neurology clinicians, one nursing manager, one community nurse and one motor
In-depth interviews

Third, we conducted qualitative interviews with 15 MCI patients in the form of one-on-one IDIs based on the key attributes obtained from the FGDs to determine the attributes and levels of the final DCE survey according to the prioritisation of the attributes (December 2021 and January 2022). The one-on-one interviews are conducted to ensure the following: (1) the final attribute list included only the most critical attributes; (2) the final included attributes were based on the priority of the patient’s preferences and (3) each attribute and level are understandable and feasible. The patients were recruited from memory clinics (n=4) and neurology wards (n=11) in Nanjing Brain Hospital, all clinically diagnosed with MCI. Detailed information about the interviewed patients is provided in online supplemental materials S4. We collaborated with clinicians and psychometrists to determine patient eligibility during the recruitment process.

Qualitative data collection and analysis

All respondents participated in the study voluntarily during FGDs and in-depth interviews and provided written informed consent prior to being included in the study. Interviews were conducted by three experienced and pretrained researchers from the School of Nursing, Nanjing Medical University. The interview sites were selected in separate consultation rooms and quiet ward activity rooms. Participants were given a unique identification number, which they used to complete the demographic questionnaire, as well as the FGDs and IDIs. To maintain anonymity, participants used pseudonyms in all discussions. The interview was structured around a list of potential attributes and levels, and the researcher responded, guided and followed up appropriately to stimulate patients to express their opinions more clearly. The attributes that were more significantly salient to the patients were collated and matched to the appropriate levels and descriptions. The average length of the IDIs and FGDs was 43 and 60 min, respectively. All participant interviews were audiorecorded and transcribed.

FGDs are centred on a broad exploration of potential, unincorporated attributes and levels. Therefore, FGDs coded the thematic analysis using an inductive approach, which does not attempt to place the data into a pre-existing theoretical framework, but allows themes to emerge from the data. In-depth interviews are intended to prioritise attributes and expressions of the final incorporated attributes and levels. The in-depth interviews’ data were analysed using qualitative content analysis, aided by coding and aggregation using NVivo V.11.0 software. The results include two parts: one to collate and summarise patients’ ranking of attribute priorities to determine the final attributes and levels for inclusion, and the other to refine the attributes and levels based on asking patients to describe each attribute meant to them. Table 1 shows the finalised list of attributes and levels.

Experimental design and questionnaire

After determining the experimental attributes and corresponding levels, it is necessary to construct choice sets with different combinations of attributes and levels through experimental design. Because the attributes and levels we set (4^2 * 5^3) will generate a large number of choice tasks (ie, full factorial design), it is usually impossible to provide respondents with all hypothetical scenario choices in practical applications. According to Zwerina et al, the most efficient experimental design satisfies four principles: orthogonality, horizontal balance, minimal overlap and utility balance. Therefore, this study conducted a fractional factorial design by SPSS V. 26.0 software to optimise the design of the choice schemes and reduce the choice schemes for the respondents on the basis of making the DCE design meet the statistical efficiency requirements. The following two additional considerations were made during the choice sets design process: (1) to avoid exaggerating the relative weight of each attribute and improve the efficiency of the questionnaire, the Opt-out option was not included in this study, (2) even with the fractional factorial design, there were still 32 choice sets (ie, 16 choice tasks). In order to reduce the cognitive burden on MCI patients, the 16 choice tasks were divided into two versions in this study. Each version has eight tasks, and respondents will randomly select one of the versions to respond. The random number method was used to include the sixth choice task in each version to test the internal consistency of participants’ choices, but the data for this task were not included in the final data analysis, and the final questionnaire for each version contained nine choice tasks. In addition, this study used a combination of pictures and text to present the choice tasks in order to help patients with different education levels better understand the options. An example of the choice task is shown in figure 2.

Four sections comprised the questionnaire: an introduction, selection tasks, a general information sheet and a section on disease status. The introductory section informs participants about the study’s purpose and the requirements for completing the questionnaire and educates them about the importance of exercise intervention. The section on selection tasks provides an overview of the attributes, levels and descriptions to assist patients in better understanding the meaning of each attribute and level prior to selecting a protocol. The general information sheet contains several demographic variables (age, gender, level of education, occupation and marital status) as well as physical activity status that may influence patient preferences. Professional psychometrists or clinicians will complete the disease status section, which includes results from the major cognitive function-related scales, such as Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) and Activities of Daily Living (ADL). The purpose of the pre-experiment
is to determine whether the content of the questionnaire is clearly expressed and easily understood. The questionnaire was pretested on 10 patients, and the length of time patients took to complete the questionnaire was recorded. Participants were also asked to complete the questionnaire in an audio-reflective manner. The content of the questionnaire is further modified through discussion. The average time required to complete the task for the 10 patients was 8.95 min. The majority of patients felt the survey was ‘appropriate in length’ and ‘easy to understand in content’, but some felt the attributes and levels were abstract and required an additional explanation from family members or investigators. As a result, we included examples of partial levels during the investigators’ training.

### Sample and recruitment

In this study, the inclusion criteria for DCE investigation subjects is MCI patients,24 and the exclusion criteria included: (1) serious physical disorders or physical disabilities such as heart, liver and kidney, (2) inability to understand the purpose and content of the experiment after detailed explanation by the investigator. Our sample size calculations are based on Johnson and Orme’s equation \( N > \frac{c}{(t \times a)} \), which states that the minimum number of people to include (N) is determined by the number of choice tasks (t), the number of alternatives within each choice set (a) and the highest number of attribute levels across all attributes (c).25 Combined with the experimental design of this study, c=4, t=9 and a=2. Taking into account the 20% of invalid questionnaires, this study required a minimum of 278 participants.

### Table 1 Attributes and levels

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise effect</td>
<td>Improving cognitive function</td>
<td>Exercise programmes may vary depending on the results you prefer to achieve. Example, improving physical function may have more endurance training, while improving poor mood may add some mind-body training.</td>
</tr>
<tr>
<td></td>
<td>Improving quality of life</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improving negative mood</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improving physical function</td>
<td></td>
</tr>
<tr>
<td>Exercise modality</td>
<td>Exercise independently</td>
<td>Depending on whether you choose group training and what type of group, different exercise programmes will be arranged, such as different exercise content and different personnel arrangements.</td>
</tr>
<tr>
<td></td>
<td>Exercise with family/friends</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercise with strangers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exercise with patients with the same disease</td>
<td></td>
</tr>
<tr>
<td>Exercise duration</td>
<td>160–200 min per week</td>
<td>Exercise duration includes a warm-up period, a workout period and a cool-down period. The total number of exercise hours per week will be divided into 3–5 sessions to complete.</td>
</tr>
<tr>
<td></td>
<td>200–250 min per week</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250–300 min per week</td>
<td></td>
</tr>
<tr>
<td>Exercise setting</td>
<td>Home</td>
<td>The choice of exercise settings will partially limit the content of the exercise, the more professional the exercise setting, the more exercise content will be provided.</td>
</tr>
<tr>
<td></td>
<td>Community fitness place/community service centre/park</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gym/rehabilitation Centre</td>
<td></td>
</tr>
<tr>
<td>Exercise assistance</td>
<td>Smart wristband/cell phone alerts</td>
<td>During the exercise intervention, you will be provided with different types of assistance to help you learn to exercise better as well as to adjust your condition.</td>
</tr>
<tr>
<td></td>
<td>Professional guidance/accompaniment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Video/graphic materials</td>
<td></td>
</tr>
<tr>
<td>Exercise supervision</td>
<td>Supervision by professionals</td>
<td>The more professional the supervisor, the less likely you are to have a bad exercise event (such as a fall).</td>
</tr>
<tr>
<td></td>
<td>Supervision by equipment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-supervision</td>
<td></td>
</tr>
<tr>
<td>Mode of payment</td>
<td>Free</td>
<td>The payment mainly includes personalised instruction by professionals and the cost of related equipment.</td>
</tr>
<tr>
<td></td>
<td>Fully reimbursed by Medicare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partially reimbursed by Medicare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Completely self-funded</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2** Example of the choice task.
Participants will be recruited at memory clinics in four cities: Xining, Qinghai Province, Beijing; Nanjing, Jiangsu Province and Zhuhai, Guangdong Province. Memory clinic is a widely accepted diagnosis-treatment-education-management model designed to provide home care education and caregiver training for early diagnosis, identification and treatment of patients with dementia and related cognitive impairments. It provides the fastest access to those who have been professionally diagnosed with MCI and is an ideal place to recruit. The pre-experiment found that the acceptance rate for recruitment exceeded 50%. During the epidemic, one memory clinic received approximately 5–10 patients per week and at least 20 patients per month, resulting in a minimum of 80 recruited patients per month to the four memory clinics, which would take approximately 7–8 months for this study. During recruitment, everyone who entered the memory clinic with a diagnosis of MCI was informed about the possibility of participation. Interested volunteers will be briefed in detail by a researcher about the purpose of the study and the process. The survey will be conducted in a separate, quiet room within the clinic. A researcher will be present to assist patients and answer all their questions. The survey will be available in both paper and electronic formats, depending on the patient’s wishes and abilities. Electronic questionnaires will be collected electronically and paper questionnaires will be entered independently by two researchers using EpiData V.3.1 software and systematically checked.

Statistics and data analysis
The final data obtained will be analysed by SPSS V.26.0 software and Stata V.16.0. The choice data will be encoded using dummy variables. Subsequently, a discrete selection model will be constructed to analyse the following: (1) what is the preference of MCI patients for exercise interventions, (2) whether there is heterogeneity in MCI patients’ choice of exercise intervention options because each patient’s own characteristics are different, (3) heterogeneous preferences of MCI patients with different characteristics and (4) the role of each attribute in influencing overall exercise preferences.

In this study, a mixed logit model and a latent class model (LCM) based on random utility theory will be developed respectively to analyse experimental data. The mixed logit model will answer questions (1) and (2), examine the preference for choice and intensity of exercise interventions among MCI patients and will use regressions in which each parameter interacts with each sociodemographic characteristic in turn to explore differences in preferences between groups. Based on the construction of a mixed logit model, this study explores the role of each attribute on the overall exercise preference by analysing the RI of the attributes, that is, the fourth question. RI is to measure the size of the difference generated by each attribute in the total attribute preference, and this difference is the preference weight range of the attributes. The attribute importance is calculated in terms of the horizontal relative weight range, and a set of attribute RI values is obtained, which sums to 100%. The higher the score, the more critical the attribute is to the respondent. Calculating RI requires effect coding for the attributes and levels, and the RI of each attribute can be derived by dividing the difference between the lowest and the highest level utility of the attribute by the sum of the differences of all attribute levels.

LCM can be analysed on the special assumption of individual categorisation, dividing respondents into categories according to their choice preferences, thus explaining the preferences of different categories of respondents. Therefore, it is used to answer the third question. Although the LCM does not require any assumptions about parameter distribution, it requires the researcher to extract the ‘best’ class from the sample. Three criteria will be used to determine the optimal number of classes for model optimality, including the minimum Akaike Information Criterion (AIC), the minimum Bayesian Information Criterion and the ‘Consistent’ AIC. The model automatically calculates the probability that each individual belongs to a certain category, reflecting the model’s ‘potential’ feature and then estimates the probability of choosing an alternative based on the preferences within each class.

Patient and public involvement
Patients were involved in two phases of DCE development, including qualitative interviews and pilot testing. Patient involvement was intended to ensure that what we obtained would be the actual preferences of MCI patients for the exercise intervention.

ETHICS AND DISSEMINATION
This study has been approved by the Ethics Committee of Nanjing Medical University (registration number 2021-066, registration date 12 January 2022). Patient recruitment for this study began in May 2022 and is expected to end around December 2022. Based on the principles of voluntariness and confidentiality, the investigator will explain the background, purpose and possible risks of the study to the patients or specialists participating in the interview and survey, and participants will be required to sign a written informed consent form before study participation. All interview materials and questionnaires will be used only for this study and are provided to researchers in an anonymous manner for ensuring confidentiality. Patients can withdraw from this research at any time. Data analysis will be performed according to the principles of good scientific research on DCEs developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Our findings will be disseminated and shared with interested patient groups and the general public through online blogs, policy briefs, national and international conferences and peer-reviewed journals. Data are available in a public, open access repository.
Contributors CL and YJ conceptualised the study. CL and YJ were involved in the discrete choice experiment’s experimental design. CL conducted the review of the literature. The qualitative data analysis of group discussions and one-on-one interviews was conducted by CL, HY, YJiao, YL and JC. CL drafted the manuscript; all authors contributed to its revision and approval.

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