Received: 15 May 2023 | Accepted: 23 June 2023

DOI: 10.1002/gps.5965

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Research evaluating the effectiveness of dementia interventions in low- and middle-income countries: A systematic mapping of 340 randomised controlled trials

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Funding information
UK Research and Innovation Global Challenges Research Fund, Grant/Award Number: ES/P010938/1

Abstract

Objectives: More people with dementia live in low- and middle-income countries (LMICs) than in high-income countries, but best-practice care recommendations are often based on studies from high-income countries. We aimed to map the available evidence on dementia interventions in LMICs.

Methods: We systematically mapped available evidence on interventions that aimed to improve the lives of people with dementia or mild cognitive impairment (MCI) and/or their carers in LMICs (registered on PROSPERO: CRD42018106206). We included randomised controlled trials (RCTs) published between 2008 and 2018. We searched 11 electronic academic and grey literature databases (MEDLINE, EMBASE, PsycINFO, CINAHL Plus, Global Health, World Health Organization Global Index Medicus, Virtual Health Library, Cochrane CENTRAL, Social Care Online, BASE, MODEM Toolkit) and examined the number and characteristics of RCTs according to intervention type. We used the Cochrane risk of bias 2.0 tool to assess the risk of bias.

Results: We included 340 RCTs with 29,882 (median, 68) participants, published 2008–2018. Over two-thirds of the studies were conducted in China (n = 237, 69.7%). Ten LMICs accounted for 95.9% of included RCTs. The largest category of interventions was Traditional Chinese Medicine (n = 149, 43.8%), followed by Western medicine pharmaceuticals (n = 109, 32.1%), supplements (n = 43, 12.6%), and structured therapeutic psychosocial interventions (n = 37, 10.9%). Overall risk

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of bias was judged to be high for 201 RCTs (59.1%), moderate for 136 (40.0%), and low for 3 (0.9%).

Conclusions: Evidence-generation on interventions for people with dementia or MCI and/or their carers in LMICs is concentrated in just a few countries, with no RCTs reported in the vast majority of LMICs. The body of evidence is skewed towards selected interventions and overall subject to high risk of bias. There is a need for a more coordinated approach to robust evidence-generation for LMICs.

KEYWORDS
dementia, evidence, global south, health policy, LMIC, low- and middle-income, psychosocial interventions, systematic review, traditional Chinese medicine

Key points

- While the majority of people with dementia reside in low- and middle-income countries (LMICs), it is not known what types of interventions have been studied in these settings and how effective they are.
- We conducted the first comprehensive mapping study of interventions for people with dementia or mild cognitive impairment (MCI) and/or their carers in LMICs.
- This high-level overview of dementia intervention research in LMICs identified the following gaps: dementia intervention research is highly concentrated in just a few LMICs, and skewed towards Traditional Chinese Medicine, Western pharmaceuticals, and supplements, with comparatively little evidence generated on interventions for carers.
- Lack of robust and locally relevant evidence on effective interventions presents a substantial challenge to designing evidence-based treatment and care systems that help people with dementia or MCI and their carers to live better lives.

1 | INTRODUCTION

Dementia will be one of the biggest global health challenges of the 21st Century. Tremendous successes in public health and healthcare over recent decades have made it possible for more people to live into old age. In consequence, there are rapidly more people at risk of age-related conditions, of which dementia is one of the most challenging through its effects on disability, quality of life, and costs.[1] Moreover, dementia can also affect younger people.[2] Causing life-changing disability and dependency for millions of people, as well as impacting on the lives of family carers, dementia is seen as a public health priority by the World Health Organization (WHO).[3] A silver bullet to target this global issue is not in sight; even if effective disease-modifying treatments are developed, their availability and affordability in low-resource settings must be in serious doubt.

Most people with dementia reside in LMICs.[4] With high prevalence of some risk factors, dementia prevalence in LMICs is expected to increase more rapidly than in high-income countries.[5,6] Need for support in everyday activities means that dementia affects not only the person with the condition but also family members and other close contacts who provide care and support. Consequently, informal care is the largest economic cost of dementia in LMICs.[4] These impacts provide a clear rationale for creating care and support systems in LMICs for people with dementia that improve the quality of life for affected individuals and their carers.

In the absence of an effective disease-modifying treatment, other interventions (pharmacological and non-pharmacological) can improve cognition and quality of life, and are recommended by WHO and in clinical practice guidelines.[7–10] However, evidence on what interventions work seems to mostly come from high-income countries. Indeed, previously proposed packages of dementia care for LMICs were largely based on evidence from high-income countries.[11,12] Findings from studies in high-income settings may not be applicable in low-resource settings with different cultures, social environments, diagnosis rates, and less well-resourced health and care systems.[3] It is unclear what dementia interventions have been studied in LMICs, and how extensively.

A comprehensive map of dementia intervention research in LMICs is missing. We therefore systematically reviewed studies of interventions aimed at improving the lives of people with dementia or MCI and their families in LMICs.

2 | MATERIALS and METHODS

We conducted a systematic mapping study to describe which interventions for people with dementia or MCI and for their carers have been studied using randomised controlled trials (RCTs) in LMICs between 2008 and 2018. Studies involving people with MCI were included due to their high propensity to develop dementia.[13] This

mapping study forms part of a systematic review and meta-analysis on the effectiveness of dementia interventions in LMICs, registered on PROSPERO (CRD42018106206).[14]

2.1 | Search strategy and selection criteria

We searched 11 electronic peer-reviewed and grey literature databases (MEDLINE, EMBASE, PsycINFO, CINAHL Plus, Global Health, WHO Global Index Medicus, Virtual Health Library, Cochrane CENTRAL, Social Care Online, BASE, MODEM Toolkit) to identify studies published between 1 January 2008 and 31 December 2018. The search syntax for each database was developed in collaboration with a library information specialist (AF) and tested for sensitivity against a set of 10 previously identified records. Searches were structured around four search blocks ("dementia"; "intervention"; "study design"; "LMIC"), combining, as available, free text with variants, controlled vocabularies, and filters. The full search strategies for four databases are available in the supplementary material (Tables S1-S4).

Database searches were conducted throughout October 2018 and updated through 9 January 2019. To complement database searches, we manually reviewed lists of studies included in 75 previous systematic reviews (Table S5) and all dementia intervention reviews indexed in the Cochrane Database of Systematic Reviews as of September 2018.

We included RCTs, including cluster-RCTs, published 2008–2018 of any intervention aiming to improve the lives of people with dementia or MCI, or their carers, in any LMIC (as defined by the Organisation for Economic Co-operation and Development at the time the RCT was conducted).[15] We followed study authors' definitions of dementia and MCI to identify eligible participants in each study. We imposed no restrictions on interventions to capture all previously studied interventions. Similarly, we did not specify any outcomes or imposed sample size restrictions. Inclusion criteria in the PICOS (Participants, Intervention, Comparator, Outcomes, Study design) format are in Table 1. Detailed exclusion criteria are in our published protocol.[14] Briefly, we excluded studies that were either not conducted in LMICs, not focussing on people with dementia or MCI or their carers (i.e., non-dementia-specific interventions or primary prevention interventions), not assessing an intervention, as well as non-original reports (reviews), or studies not published in a language spoken by a member of our global team (51 researchers covering 15 languages).

TABLE 1 Inclusion criteria.

Participants	Adults with dementia or MCI in LMICs and their carers (including family members, other unpaid carers, as well as professional carers)
Intervention	All interventions aiming to improve lives of people with dementia or MCI and their carers
Comparator	Any
Outcomes	Any
Study design	Randomised controlled trials

Records identified from database searches and previous reviews were collated and de-duplicated. We applied a combination of semi-automated and manual screening of abstracts and titles.[16] We first uploaded all records to the Rayyan platform for systematic reviews to obtain prediction scores for probability of a record matching inclusion criteria.[17] The prediction algorithm was trained using a set of 4000 inclusion/exclusion decisions made by hand. After assessing performance of the algorithm for 1000 records around a conservative cut-off prediction score (1.5 out of 5 stars, where 1 indicated minimal and 5 maximal relevance), all records below that score were screened by one reviewer while remaining records were screened independently by two reviewers. Full text review was performed independently by two reviewers. For full texts in languages other than English, at least one reviewer was a native speaker of that language. Conflicting decisions were arbitrated by a member of the core review team (DM, MS-K, GW, CS).

We deviated from the published review protocol by focussing on RCTs only and excluding non-randomised studies. This decision was taken after inclusion and exclusion decisions had been made for the full set of studies meeting our initial eligibility criteria, revealing an unexpectedly large number of eligible studies (approximately two-thirds randomised and one-third non-randomised). Extracting information from and appraising all studies was not feasible and we therefore focussed on eligible RCTs as they would be expected to provide the most internally valid evidence.

Data extraction was performed independently by two reviewers using a standardised data extraction form. At least one of the two reviewers was a native speaker of the language of the main study paper/report. We extracted information on study characteristics (location, funding, care setting), design (including outcomes measured), participants (baseline characteristics), interventions, results, and risk of bias. Conflicting data extractions were resolved by a senior researcher (DM, MS-K, CS).

Risk of bias assessment was conducted independently by two reviewers using the Cochrane risk of bias 2.0 tool.[18] For each study, risk of bias was judged as low, moderate ("some concerns") or high in five domains according to a series of signalling questions. As recommended by Cochrane, high risk of bias for any of the domains resulted in an overall study-level "high risk" judgement. Conflicting judgements were resolved by a member of the core review team (DM, MS-K, CS). For all included studies, arbitration by a senior reviewer also served as an additional quality assurance mechanism.

Study inclusion decisions, data extraction, and risk of bias assessment were managed using Covidence systematic review software (Veritas Health Innovation, Melbourne, VIC, Australia). Researchers based in 13 countries contributed to the review.

2.2 | Data analysis

We grouped interventions in mutually exclusive and exhaustive categories. A draft list of intervention types based on previous reviews[19–21] was iteratively discussed and refined among the senior project team with expertise in evidence synthesis and international dementia research. Our final mapping aimed to minimise heterogeneity of interventions within categories. Studies were categorised according to "experimental" intervention arm (or arms, if several interventions were studied). Where no clear control group could be identified, all study arms were considered experimental.

We report total number and proportion of included studies by country and category of intervention. Inclusion of multi-country trials and studies investigating more than one experimental intervention means that reported proportions may add up to >100%.

2.3 | Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

2.4 | Patient and public involvement

People with dementia/MCI, their carers, or the public were not directly involved in this research. Representatives from associations advocating for people with dementia and their carers were actively involved in the research and are named as members of the STRiDE Evidence Review Group.

3 | RESULTS

A total of 63,585 records were identified through database searches (Figure 1). After screening of titles and abstracts, 192 additional potentially relevant studies were added from lists of included studies in Cochrane and other systematic reviews. In total, 1360 studies were assessed at the full-text screening stage and 340 studies with 29,882 participants were ultimately included. The most common reasons for exclusion were studies not being conducted in LMICs (n = 447), non-RCTs (n = 235), and review articles (n = 149).

Included studies and their main characteristics are listed in supplementary material (Table S6). 237 RCTs (69.7%) were conducted in mainland China, 27 (7.9%) in Iran, 26 (7.6%) in Brazil, 9 (2.6%) in Turkey, and 8 (2.4%) in India. Jointly, these five countries accounted for 90.6% of included RCTs, and a total of 10 LMICs accounted for 95.9% of RCTs. Included studies were conducted in 21 LMICs, and there were no RCTs identified for most LMICs (Figure 2).

Approximately two-thirds (65.0%) of all RCTs (n = 221) included one experimental intervention and 119 RCTs included two or more experimental arms (35.0%). The largest category of interventions was Traditional Chinese Medicine (n = 149 RCTs, or 43.8%; Figure 3, Panel A). Western pharmaceuticals (both established and investigational dementia drugs) were studied in 109 RCTs (32.1%), supplements (including dietary supplements and any based on non-Chinese traditional medicines) in 43 RCTs (12.6%), and structured therapeutic psychosocial interventions in 37 RCTs (10.9%). The latter included different forms of psychosocial interventions, including cognitive stimulation therapy, cognitive training, rehabilitation, reminiscence therapy, occupational therapy, and combinations of different psychosocial interventions. Other intervention categories each accounted for 7% or less of included studies. Categories are described, with examples, in supplementary material (Table S7).

Interventions focussing on carers of people with dementia were studied in 17 RCTs: 11 of group or individual support programmes, and six of training and education interventions to provide carers with knowledge and tools to support people with dementia to live better lives.

The total number of participants in included RCTs was 29,882. Overall median sample size was 68 participants (range 10–677). Among categories with 10 or more RCTs, median sample size was largest for multicomponent RCTs (85, range 40–241), followed by Traditional Chinese Medicine (80, range 22–520), Western pharmaceuticals (73, range 13–677), supplements (60, range 20–395), support for carers (54, range 20–114), structured therapeutic psychosocial interventions (47, range 10–288), physical exercise (45, range 20–178), and electrical brain stimulation (34, range 19–54).

There were more RCTs involving people with dementia (n = 223) than MCI (n = 120); three studies included both. Among intervention types with more than 10 RCTs, there were considerably more studies of Traditional Chinese Medicine, Western pharmaceuticals, multicomponent interventions, electrical brain stimulation, and support for carers involving people with dementia than with MCI. Similar numbers of RCTs in people with dementia and MCI were identified for supplements, structured therapeutic psychosocial interventions, and physical exercise.

Excluding studies conducted in China, the largest category of interventions was supplements (n = 27, 26.2% of all non-Chinese studies), followed by structured therapeutic psychosocial interventions (n = 23, 22.3%), Western pharmaceuticals (n = 23, 22.3%), physical exercise (n = 11, 10.7%), and support for carers (n = 10, 9.7%; Figure 3, Panel B). Other categories each accounted for less than 7% of non-Chinese studies.

Overall risk of bias was judged as high for 201 RCTs (59.1%), moderate for 136 (40.0%), and low for 3 (0.9%; Figure 4). There was high risk of bias for 25% or more of studies in the domains of deviation from intended interventions, missing outcome data, and outcome measurement. Among 96 studies with high risk of bias due to deviations from intended interventions (including lack of blinding of participants and those delivering the intervention), one-third investigated substances (pharmaceuticals or extracts) where masking of both participants and investigators may have been feasible.

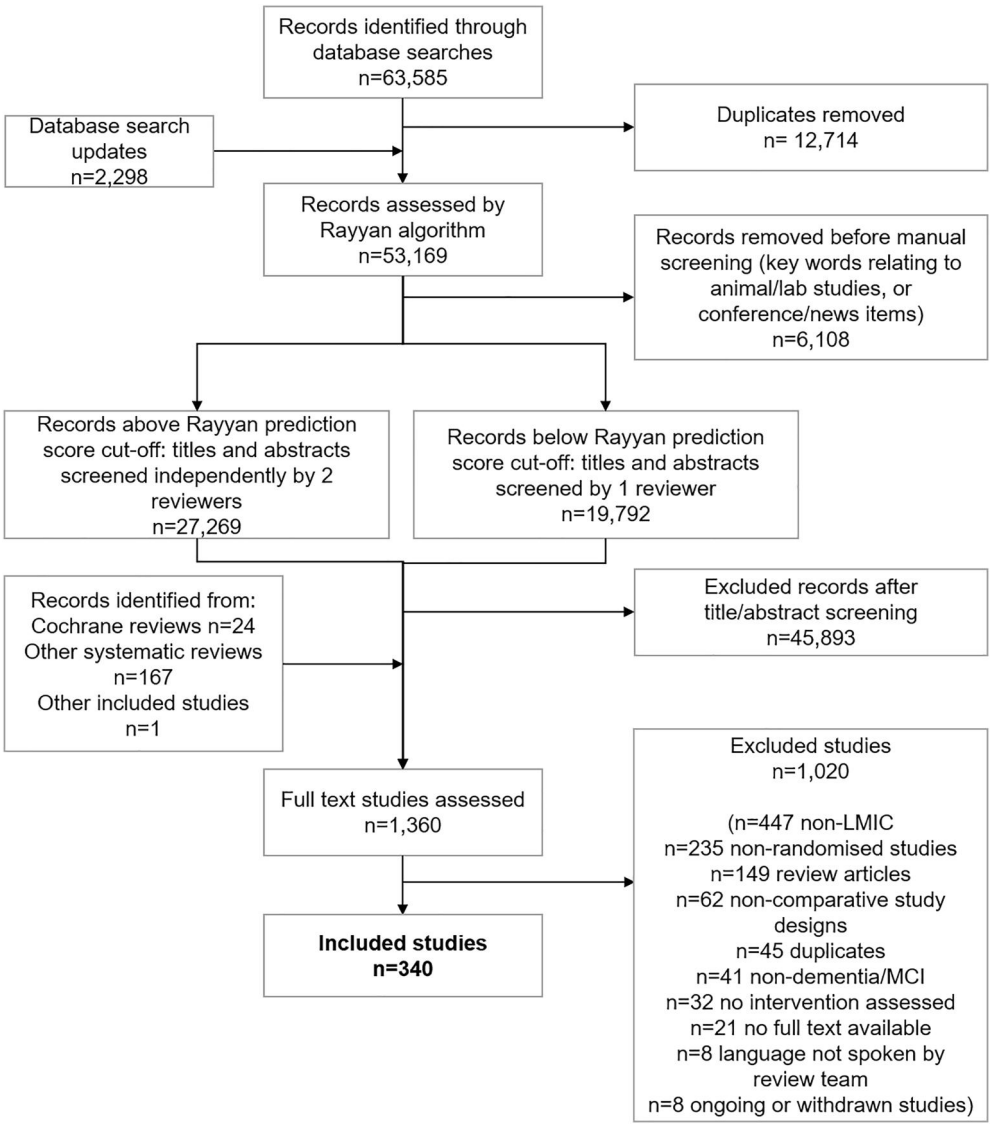

FIGURE 1 PRISMA flow chart.

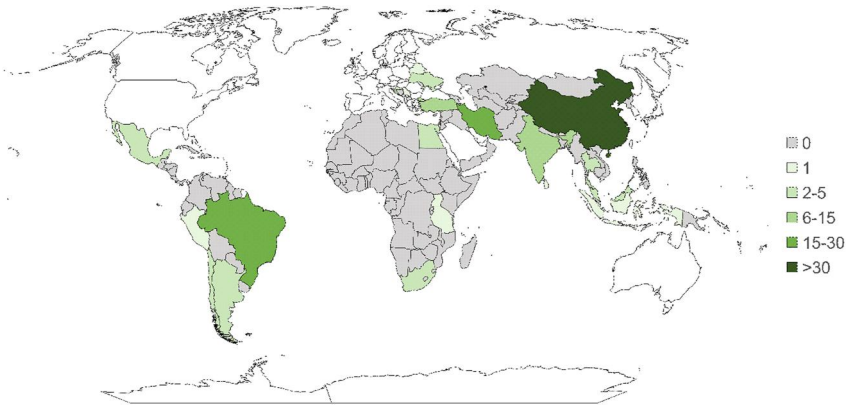

FIGURE 2 Number of randomised controlled trials in LMICs assessing interventions for people with dementia/MCI or their carers, 2008–2018. Darker shades show LMICs with more RCTs. LMICs without any RCT shown in grey. HICs shown in white. *Source*: Author's data collected from published studies. Map created in MS Excel: Powered by Bing. © GeoNames, Microsoft, Navinfo, TomTom, Wikipedia.

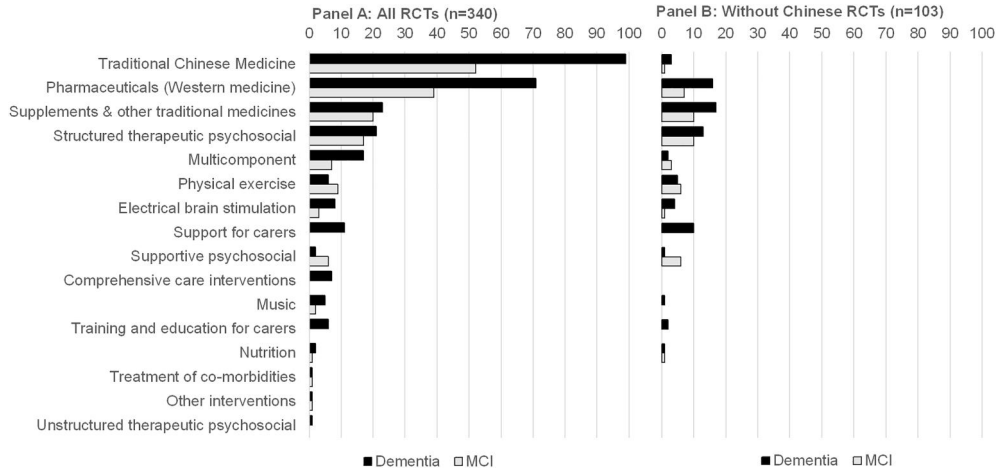

FIGURE 3 Number of randomised controlled trials of different intervention types. Number of RCTs in low- and middle-income countries studying different types of interventions for people with dementia (dark colouring) and mild cognitive impairment (light colouring). Panel A shows all RCTs (n = 340); Panel B shows only RCTs conducted outside mainland China (n = 103).

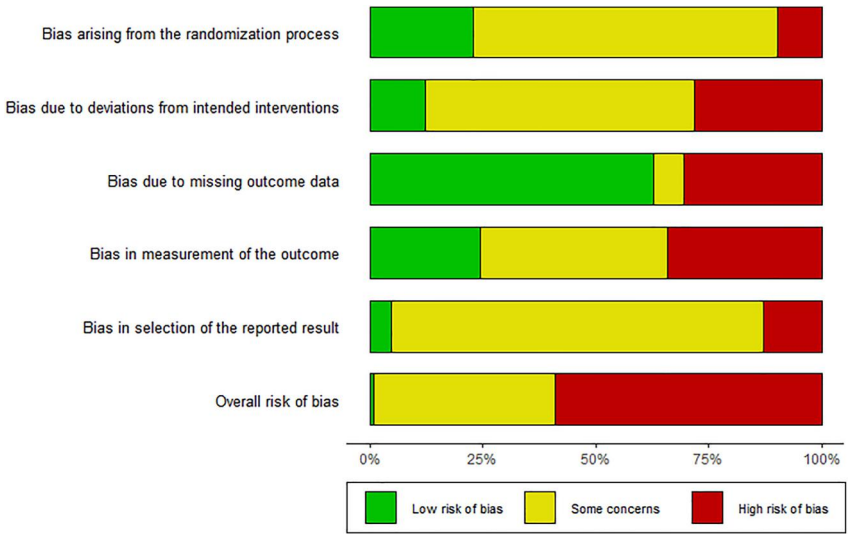

FIGURE 4 Summary plot of risk of bias assessments. Plot shows the proportion of all included randomised controlled trials with "low risk of bias", "some concerns", or "high risk of bias" judgements for five risk of bias domains and the overall judgement.

4 | DISCUSSION

We identified 340 RCTs of interventions for people with dementia or MCI and their carers conducted in LMICs and published 2008–2018. Trials were concentrated in a few countries. On average, they included relatively few participants. The most frequently studied interventions were Western pharmaceuticals, traditional medicines, and supplements, although included RCTs also assessed a range of non-pharmaceutical interventions. We found little evidence on interventions for carers, such as support groups and training programmes. More than half of all included studies were judged to be at high risk of bias, indicating scope for improving the methodological quality of evidence on dementia interventions in LMICs.

This is the first study to comprehensively map evidence in multiple languages on interventions for people with dementia or MCI and/or their carers in LMICs. Previous efforts to map global dementia research have focussed on high-income countries and funding bodies located in them.[22] Similarly, existing systematic reviews have not assessed interventions from a LMIC perspective.[20,21,23–35] Our study drew on the expertise of a global research team across 13 countries (including nine LMICs) to document the breadth of interventions studied in LMICs and categorise them into distinct groups. We therefore provide a high-level overview of the state of dementia intervention research in LMICs, allowing us to identify gaps in the evidence landscape.

A key finding is that evidence on what interventions work in LMICs is heavily concentrated in a few countries. One country (China) accounted for more than two-thirds of included RCTs, and 10 countries accounted for 96% of studies. It is unlikely that a single factor can explain the geographical distribution of dementia RCTs. In absolute numbers, we might expect more trials to be conducted in large countries, but (with the exception of China) there was not a positive association between population size and number of trials. Similarly, richer countries might be expected to invest more money in

research, yet we found that dementia intervention RCTs were also conducted in low-income countries. When accounting for population size, there was a trend of more trials conducted in countries with higher GDP per capita and higher share of over 65-year-olds in total population. While this may indicate some alignment between research priorities and ageing populations among countries already active in dementia research, it is notable that we did not identify a single published RCT for the vast majority of LMICs. This absence of evidence may suggest that dementia is not considered a priority in many countries.

Given the trajectory of ageing populations, it is essential to develop and test interventions that can affordably be implemented at scale. Efforts to develop effective disease-modifying treatments for dementia are apace, but even if available, there must be questions about access and affordability in many countries. For example, aducanumab, approved in the US, was initially priced at US$56,000 per patient annually.[36] Identifying effective, less costly non-pharmaceutical interventions that improve the lives of people with dementia and their carers is therefore essential.

There is a need for targeted research investment to generate robust evidence to inform future care pathways. Methodologically, RCTs are usually the most powerful tools for assessing intervention effectiveness,[37] and they can inform the selection of interventions to be recommended as part of evidence-based, improved care pathways. Evidence on what interventions work should be juxtaposed with considerations about local settings, including workforce availability. Randomised controlled trials are often associated with the stringent approval process for pharmaceuticals, with trials conducted in controlled environments, focussing on narrowly defined patient populations. Indeed, a bias in generating evidence on both effectiveness and cost-effectiveness towards pharmaceuticals has been shown in other disease areas.[38,39] Western pharmaceuticals, along with traditional medicines and supplements, also accounted for the majority of RCTs in our study. Yet, the robust evidence generation standards of RCTs need not be restricted to the approval of drugs. Our study demonstrates that some RCT evidence already exists for non-pharmaceutical dementia interventions. This is potentially good news for the increasing number of LMICs planning to implement or already implementing national dementia plans.[40] There are likely other promising, potentially affordable and cost-effective interventions for which no RCT has yet been conducted. Such interventions should not be neglected by policymakers when reforming the dementia care landscape in their countries. However, implementing changes to dementia care pathways should also be seen as an opportunity to generate new and robust evidence to inform future policy and practice discussions, for example, through pragmatic, low-cost trials conducted within the context of routine care.[41] National dementia plans that promote robust evidence-generation through such trials can play an important role in creating a learning health and long-term care system that generates the evidence it needs to focus on the most effective, cost-effective and equitable interventions.[42] Implementing RCTs can also strengthen local dementia research capacity through training and international exchange.

In theory, RCTs have high internal validity, but this can be jeopardised by poor study design, implementation, and reporting. In our study, more than half of RCTs were assessed as being at high risk of bias overall, resulting from a "high risk of bias" rating in at least one of the five domains of the Cochrane tool for RCTs. Compared to risk of bias judgements in Cochrane reviews across other disease areas, trials included in our study were more often judged at unclear risk of bias for individual domains, less frequently at low risk of bias, and as high risk of bias at a broadly similar rate.[43] Studies published in non-English language journals were previously shown to be rated at lower methodological standards.[43] While we used published protocols of included studies in our risk of bias assessments, these were often not available. This, along with often poor reporting standards in published papers, makes it difficult to judge whether *risk* of bias identified in our assessment reflected actual bias.[44] Nevertheless, our findings indicate that dementia intervention RCTs should be scrutinised closely before implementing wide-reaching changes on the basis of their findings.

Our study has limitations. It is possible that we missed studies meeting inclusion criteria that were not indexed in the international bibliographic databases searched. However, at least one of these databases included literature published mostly in Spanish and Portuguese and we were also able to capture a substantial amount of the Chinese literature through a comprehensive search strategy that included reviewing previous systematic reviews, including several that searched widely used Chinese bibliographic databases. We excluded studies where full texts were not available in a language spoken by our review team, but because our team (51 reviewers) covered at least 15 languages, this only accounted for eight studies, compared with 340 included studies. Small sample sizes (median 68) across most intervention types indicate that many trials in LMICs were pilot studies—this was also the case for therapeutic substances, which are typically studied in trials with substantially larger sample sizes in high-income countries.[45,46] Evidence generated by each individual trial is therefore likely subject to uncertainty. We excluded non-randomised studies. Included studies therefore represent the most methodologically robust body of evidence, but additional insights on the implementation of interventions in real-world settings may, of course, be drawn from non-randomised studies.

This mapping study of dementia intervention research in LMICs identified a number of gaps to be addressed in future research. First and foremost, robust evidence on intervention effectiveness and cost-effectiveness is missing for most LMICs. Due to differences in how interventions are implemented and situated in the local context, high-quality, pragmatic RCTs conducted in the same country are likely to generate the most relevant evidence required to persuade policymakers to take action to support people with dementia and their carers to enjoy better health and quality of life. Second, given the impact of dementia on the lives of family members and others close to the person with the condition, more efforts should be made to develop and evaluate interventions to support carers. Variation in attitudes to dementia between and within countries (including lack of awareness and stigma) means that such interventions should be tailored to local contexts,[47] and their effectiveness rigorously

evaluated in those settings. Finally, assessment is needed of the effectiveness of a wide range of different interventions, and combinations of interventions, to guide policy and practice decisions in LMICs to develop better care pathways and care experiences for people with dementia or MCI. A network meta-analysis to answer questions about the comparative effectiveness of interventions identified in this mapping study is currently underway.[14]

5 | CONCLUSION

In conclusion, in this mapping study of dementia intervention RCTs in LMICs, we found that evidence-generation is concentrated in few countries, the body of evidence is skewed towards selected interventions, and overall it is subject to high risk of bias. Given expected demographic trajectories in LMICs, more and better studies are needed, and a more coordinated approach to evidence-generation—both within and across countries—would improve the likelihood of robust, relevant and impactful findings.

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AUTHOR CONTRIBUTIONS

Maximilian Salcher-Konrad, Adelina Comas-Herrera, Martin Knapp, David McDaid, and Huseyin Naci conceived and planned the study. Maximilian Salcher-Konrad, Adelina Comas-Herrera, Andra Fry, Martin Knapp, Mariana Lopez-Ortega, David McDaid, Christine Musyimi, David Ndetei, Deborah Oliveira, and Huseyin Naci developed the protocol. Maximilian Salcher-Konrad oversaw database searches, study selection, data extraction, and risk of bias assessment. Cheng Shi coordinated study selection, data extraction, and risk of bias assessment for Chinese studies. Maximilian Salcher-Konrad, Cheng Shi, Claudia Iveth Astudillo-García, Kirsten Bobrow, Jacky Choy, Adelina Comas-Herrera, Dara Kiu Yi Leung, Mariana Lopez-Ortega, Klara Lorenz-Dant, David McDaid, Christine Musyimi, David Ndetei, Tuan Anh Nguyen, Deborah Oliveira, Aditya Putra, Alisha Vara, Gloria Wong, Huseyin Naci, as well as other members of the STRiDE Evidence Review Group (see supplementary material S1) contributed to study selection, data extraction, and risk of bias assessment. Disha Patel reviewed data extractions and prepared data for analysis. Maximilian Salcher-Konrad conducted data analysis and wrote the first draft of the manuscript. All authors revised the manuscript. All authors had full access to the data and had final responsibility to submit the manuscript for publication.

ACKNOWLEDGEMENTS

In addition to named members of the STRiDE Evidence Review Group, we are grateful to all other researchers who contributed to individual stages of this review. This research was conducted as part of the STRiDE project, supported by UK Research and Innovation Global Challenges Research Fund (ES/P010938/1).

CONFLICT OF INTEREST STATEMENT

Bobrow reports a research grant from GBHI/Alzheimer's Association, for research outside the submitted work. Naci reports a grant from the National Institute for Health Research and payments from the Health Foundation and the Pharmaceutical Group of the European Union for research outside the submitted work, and is a paid advisor to The BMJ. Nguyen report funding from the Australian National Health and Medical Research Council (NHMRC), the Australian Research Council (ARC), and the National Foundation for Science and Technology Development of Vietnam (NAFOSTED) for work contributing to the submitted work, and a travel grant from the STRiDE project (UK Research and Innovation Global Challenges Research Fund (ES/P010938/1)). Salcher-Konrad reports unpaid membership in a trial steering committee for a dementia caregiver

intervention (iSupport), outside the submitted work. Sani reports an unpaid role as Research Coordinator for Alzheimer Indonesia. All other authors report no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

All data analysed are available in the supplementary material.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Salcher-Konrad M, Shi C, Patel D, et al. Research evaluating the effectiveness of dementia interventions in low- and middle-income countries: A systematic mapping of 340 randomised controlled trials. *Int J Geriatr Psychiatry*. 2023;e5965. https://doi.org/10.1002/gps.5965