**Title**

**Research Priorities to Reduce the Global Burden of Dementia by 2025**

**Authors**

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**Abstract**

At the March 2015 WHO First Ministerial Conference on Global Action Against Dementia, 160 delegates including representatives from 80 Member States and four UN Agencies adopted a Call for Action to reduce the global burden of dementia by fostering a collective effort to advance research. WHO has conducted a globally representative research prioritization exercise adapting the Child Health and Nutrition Research Initiative (CHNRI) methodology. We elicited (N=863) and consolidated research questions (N=59), which were scored anonymously by 162 researchers and stakeholders from 39 countries according to five criteria. Six of the top 10 research priorities were focused on prevention, identification and reduction of dementia risk, and delivery and quality of care for people with dementia and their caregivers. Other questions related to diagnosis, biomarkers and treatment development and basic research into disease mechanisms. Research priorities identified by this systematic international process should be mapped onto the global dementia research landscape to identify critical gaps and inform and motivate policymakers, funders and researchers to support and conduct research to reduce the global burden of dementia. Efforts are required by all stakeholders including WHO, Member States and civil society to continuously monitor research investments and progresses, through international platforms such as a Global Dementia Observatory. WHO and Member States should collaborate to continuously monitor research investments and progress, and to translate the ‘call for action’ into a ‘Global Dementia Action Plan’ to reduce the global burden of dementia.

***Funding*** *The UK Department of Health provided financial support for the study.*

**Introduction**

Population aging will likely lead to a dramatic increase in dementia prevalence across all world regions, and by 2050, more than 130 million people are expected to be affected. Today, there is already considerable impact on those living with dementia, their families, and society at large. The current burden and global annual costs of 818 billion USD are expected to increase significantly in the next few decades.(1)

An unprecedented coordinated global response is imperative to effectively address the burden and challenges of dementia. The public health approach to dementia called for by WHO in 2012 has rapidly gained widespread support among leaders, researchers and stakeholders.(2) At the historic ‘G8 Dementia Summit’ held in London in December 2013, and led by the UK government, the then G8 countries launched a Global Action Against Dementia. The agreed twelve specific commitments included the identification of strategic research priority areas and the development of a coordinated international research action plan,(3) and culminated in the significant First WHO Ministerial Conference in March 2015 to bring together stakeholders and experts from research, clinical and NGO communities.

As resources are limited even if recently increasing, there is a need to set research priorities to guide policymakers and funding organizations as they work to advance the dementia research agenda. A number of efforts including the ‘Grand Challenges initiatives’ have been successfully conducted in the past decade to identify research priorities in various fields from global health,(1) to chronic non-communicable diseases,(4) and mental health.(5) These initiatives have had great merit in spurring research progress because the identification of research priorities is crucial to inform governments, funding agencies and the private sector on how to prioritize investments in a systematic way. A fully transparent, systematic, rigorous, replicable and fair prioritization process, that is globally representative and involves all relevant stakeholders, is required to guide a coordinated international response to the existing complex and sizable challenges in the field of dementia research. The Child Health and Nutrition Research Initiative (CHNRI) method was developed to respond to this need for methodological rigor and has been successfully used as a tool to assist decision making and consensus development in child health and nutrition,(6) and subsequently in numerous other priority setting exercises(7) including research on disability,(8) and global mental health.(9)

Past research prioritization exercises conducted in the field of dementia have been insightful, have used a variety of approaches and methods, but have not been conducted on a global scale. For example, in both the US and Europe unmet needs and research priorities for neurodegenerative diseases or Alzheimer’s disease have been identified by non-systematic consultations with selected groups of experts,(10-12) or involving health and social care professionals and patients and carers’ representatives.(13)

In this Policy View, we report the research priorities that need to be addressed in the next 10 years to substantially reduce the impact of dementia on patients, their families and society at large. These priorities were identified through an adapted CHNRI exercise conducted under the auspices of the World Health Organization in preparation for the First Ministerial Conference on Global Action Against Dementia. In panel 1 we list the aims of this Policy View. In panel 2 we describe the context, purpose and remit of the present CHNRI exercise adapted to the field of dementia.

**Current Landscape of Dementia Research**

Though currently there is no systematic analysis of global data detailing the full scope of ongoing dementia research projects, research expenditures, and the number of individuals with dementia and/ or their carers participating in research, there have been a number of individual national and international efforts to map assets devoted to dementia research. For example, the International Alzheimer’s Disease Research Portfolio (IADRP) was launched in 2010 by the United States National Institute on Aging and the United States Alzheimer’s Association to categorize research supported by public and private organizations both in the US and internationally using the Common Alzheimer’s Disease Research Ontology or CADRO(14, 15). The EU Joint Program on Neurodegenerative Disease (JPND) Research Strategy seeks to gather researchers, existing research evidence and national funding bodies to align national programs identifying common goals and establish a framework for future investment. The Canadian Consortium on Neurodegeneration in Aging (CCNA) was established by the Canadian Institutes for Health Research to bring together premier Canadian researchers in the field of neurodegenerative diseases to promote inter-institutional and interdisciplinary collaborative work across Canada and internationally. Further, OECD has conducted an Analysis of G7 Dementia Research Funding and identified key objectives of dementia policy for countries to consider. Additional notable examples include the UK National Institute for Health Research (NIHR) Analysis of Dementia Research Participation in G7 countries. Similar to previous research prioritization exercises, most existing research portfolio analyses have been limited in scope and stakeholder involvement.

**Methods**

The dementia research prioritization exercise was initiated by WHO and entrusted to an Advisory Group (AG) of internationally recognized experts and stakeholders in the field of dementia to lead the development of the scope, methodology and implementation of the exercise. The group was balanced in terms of gender, technical expertise, country and regional representation with inclusion of experts, advocates and patients’ representatives from Low and Middle Income Countries (LMIC), (Supplementary materials).

The AG considered available methodologies to set research priorities including stakeholder interviews, experts’ consultation, and Delphi consensus methods, and ultimately chose the widely used CHNRI method because it could address all the aims of the exercise.(16) Closely working with its key methodologist (IR), the AG adapted the CHNRI method (previously focused on eliciting research questions and conducting scoring of those questions by researchers alone) to this dementia priority setting exercise including the involvement of stakeholders (policymakers, patients’ representatives, funders and advocates), whose viewpoint was felt to be critical to shaping the global dementia research agenda and informing this exercise.

The key steps of the CHNRI method adapted to dementia research prioritization are described in Figure 1. Briefly, we combined a number of structured and unstructured strategies to identify experts in the field of dementia ensuring global representation and the widest possible range of disciplinary expertise and perspectives. We identified the most scientifically productive researchers worldwide in the field of dementia in the previous five years using Web of Science.(17) Other stakeholders were identified through the WHO, OECD, Global Action Against Dementia, Interdem Network, International Alzheimer's Disease Research Funder consortium (IADRFC), G7 Dementia Summit Legacy events participants, Wish participants and Advisory group networks, and others using a snowballing technique. In an effort to reach out as much as possible to LMIC, Chinese databases were systematically searched, Alzheimer Disease International (ADI, the global umbrella organization of all national Alzheimer associations), and the 10/66 network of clinicians, health and care workers and researchers from LMIC were actively involved, both to gather research questions and to score them (below). We contacted the identified experts and stakeholders via email to solicit three to five research questions.

Three researchers (HS, CD and EA) independently categorized all questions received according to pre-defined domains: (i) Basic (discovery research that underpins investigations into the cause, development, detection and treatment of disease), (ii) Clinical-Translational (Patient-oriented work conducted in/on (live) humans), and (iii) Implementation (provision and delivery of health and social care services) research; and four themes (prevention, diagnosis, treatment, and care). The AG, convened in a two-day workshop held in London in January 2015, consolidated the research questions, which were renamed Thematic Research Avenues to avoid confusion, and identified ensuing Overarching Research Domains through iterative discussion while being mindful of consistency in the level of granularity and specificity of the questions (Figure 1).

Scoring of the final list of consolidated Thematic Research Avenues took place over two weeks using an online platform and Excel spreadsheets when internet access was problematic. The scorers were asked to answer ‘Yes’ (=1), ‘No’ (=0), or ‘Not sure/I do not know’ (=0.5) to five queries that defined the five scoring criteria purposely devised for this priority exercise: [(i) potential for success (i.e. “to the best of your knowledge and experience, would you say that the proposed research would likely be successful in reaching the proposed endpoint within the next decade?); (ii) impact on burden reduction (“If successful, Would you say that this research has a potential to markedly reduce the burden of dementia on patients, caregivers and the society as a whole?); (iii) potential for conceptual breakthrough (“If successful, would you say that this research is likely to result in a paradigm shift [“game changer”] that would fundamentally change our thinking or approach to the challenge of dementia?”); (iv) potential for translation (“If successful, would you say that the proposed research would likely lead to practical application, implementation of new knowledge and/or be deliverable at scale?”); and (v) equity (“If successful, Would you say that the proposed research outcome is likely to benefit people living with or at risk of dementia, their carers, and societies as a whole in an equitable manner? Please consider countries, cultures, ethnicities, socio-economic status, gender, age, and any other relevant factors”).](#Panel_3)

**Statistical Analysis**

Consistent with previous CHNRI exercises,(18) intermediate scores were calculated for each Thematic Research Avenue as the sum of the scores (‘Yes’=1, ‘No’=0 and ‘Not sure/I do not know’=0.5) divided by the number of scorers (N=162, below), separately for each of the five scoring criteria. This resulted in five numbers (one for each of the five scoring criteria) ranging between 0 (low) and 1 (high) that represent the “collective wisdom” of the scorers that a given Thematic Research Avenue would fulfill a given scoring criterion. We then computed the overall priority score averaging the five intermediate scores without applying any weights, and ranked the Thematic Research Avenues accordingly. In addition, for each Thematic Research Avenue we calculated the percentage of scorers choosing the most common response between ‘Yes’, ‘No’ and ‘Not sure/I do not know’. We then calculated the mean of these percentages across the five criteria to obtain the average expert agreement (AEA), a measure of cohesiveness or dispersion in the scorers’ opinion around the overall priority score.

**Role of the funding source**

The UK Department of Health provided funding support for the study; they had no role in the study design, collection and analysis of data, or writing of the report. TD had full access to all data and takes final responsibility for submission of the manuscript.

**Global Research Priorities**

We identified a total of 2004 experts (672 researchers and 1332 stakeholders) (for identification criteria, see Supplementary materials). We successfully contacted 1386 (69%) experts, of which 201 (15%) submitted their research ideas. They were from 35 Countries (23 high and 11 middle income from Europe, South-East Asia, Africa, West Pacific and the Americas; for additional information see Supplementary materials), and they proposed a total of 863 individual research questions, four questions on average each (for the complete list see Supplementary materials). The consolidation process led to 59 Thematic Research Avenues (Supplementary materials, Table 2) that were grouped across seven Overarching Research Domains (Figure 2).

A total of 162 scorers (44 % of whom had also previously provided questions for the exercise) took part in the survey to score of the 59 Thematic Research Avenues. They were from 39 countries (20 High income, and 19 Low and Middle Income), more likely to be researchers or clinicians (90%), men (62%), from Western countries (73%) (and as designated by WHO regions, 36% from the Region of the Americas, 37% from the European region, 17% from the Western Pacific region, 7% from the African region, 2% from South-East Asia region and 1 participant from the Eastern Mediterranean region), and between 41 and 60 years of age (56%). However, of the scorers, 11% also designated themselves as carers of someone with dementia, 14% as policymakers, 9% as civil society representatives, and one individual self-identified as a person with dementia.

Overall Research Priority Scores (ORPS) for the 59 Research Avenues ranged from 0.81 (highest) to 0.49 (lowest). The Average Expert Agreement (AEA) revealed that, on average, 53 to 78% of scorers shared their views on the 59 proposed Thematic Research Avenues (see Supplementary Materials, Table 2). The top three research avenues in each research domain are shown in Table 1, ranked according to their ORPS.

The theme of dementia risk reduction was the most prevalent among Thematic Research Avenues that received the highest ORPS, spanning basic research (e.g., "to improve our understanding of the contributions of vascular conditions and of mechanisms of resilience to neurodegenerative diseases causing dementia"), epidemiologic research (on risk and protective factors), clinical trials and/or public health research (e.g., the exploration of the efficacy of evidence-based interventions for primary and secondary prevention of dementia, which was identified as the leading research priority overall), and translational research (to determine the best strategies to translate knowledge of modifiable risk factors into brain health promotion in different cultures and settings).

The six Thematic Research Avenues on quality and delivery of care emphasized that high priority should be given to psychosocial research into models of care in the community and across the disease course, including late- and end of life care. Multi-faceted interventions, including e-health and mobile health technologies for people with dementia were also highlighted, along with the burden reduction, and education, training and support of formal and informal caregivers, and the health and social workforce, also targeting behavioral and psychological symptoms of dementia (Table 1).

In the domain of ‘diagnosis’, highest priority was given to research that would promote a timely and accurate diagnosis of dementia in primary care practices through both the development and validation of genetic, biological and clinical biomarkers, and the longitudinal cognitive surveillance of healthy individuals to detect earliest changes that distinguish normal aging from pre-manifest neurodegenerative diseases that cause dementia.

The top Research priority in the domain of pharmacological and non-pharmacological translational research was the diversification of therapeutic approaches, followed by methodological improvements of clinical trials, including adaptive designs and better outcome measures.

There were significant variations in overall scores by scoring criteria. For instance, when considering ranking by the ‘burden reduction’ criterion, research domains of “quality of care” and “delivery of care” were most often represented, whereas the criterion of ‘potential for conceptual breakthrough’ supported the “physiology and progression of normal ageing and disease pathogenesis” domain, and the ‘equity’ criterion highlighted the “public awareness” and “delivery of care” domains (Figure 3). Further, while the 'likelihood of success' criterion and the 'potential for translation' criterion were both scored highly for most Thematic Research Avenues, the ‘fundamental paradigm shift' criterion was considered less likely (priority score = 0.56), particularly for the Thematic Research Avenues pertaining to quality of care (priority score = 0.31) (Table 1).

Finally, the scorers rated the 'potential impact on burden reduction' as the most important (mean score = 3.7), followed by 'potential for success' (3.4), 'potential for translation' (3.0), 'paradigm shift' (2.8), and 'equity' (2.1) (p < 0.001).

To address the reduction of the burden of dementia globally in the next 10 years, this Policy View presents the priority scores for the 59 Thematic Research Avenues, and the seven Overarching Research Domains identified by the WHO 2015 prioritization exercise. On the basis of potential for success, equity, burden reduction and translation, six of the top 10 overall research priorities were focused on prevention, identification and reduction of dementia risk, and to delivery and quality of care for people with dementia and their caregivers. In the extended top 20 priorities list, seven questions related to diagnosis and biomarkers and to treatment development. Basic research into disease mechanisms was considered to have the greatest potential for conceptual breakthrough. The dementia experts and stakeholders (including policymakers and funders) who took part in this unprecedented, fairly globally representative CHNRI exercise concurred that most of these key research questions may be successfully answered by 2025.

**Summary and Main Strengths and limitations of Current and Previous Priority-Setting Exercises**

To address the reduction of the burden of dementia globally in the next 10 years, this Policy View presents the priority scores for the 59 Thematic Research Avenues, and the seven Overarching Research Domains identified by the WHO 2015 prioritization exercise. On the basis of potential for success, equity, burden reduction and translation, six of the top 10 overall research priorities were focused on prevention, identification and reduction of dementia risk, and to delivery and quality of care for people with dementia and their caregivers. In the extended top 20 priorities list, seven questions related to diagnosis and biomarkers and to treatment development. Basic research into disease mechanisms was considered to have the greatest potential for conceptual breakthrough. The dementia experts and stakeholders (including policymakers and funders) who took part in this unprecedented, fairly globally representative CHNRI exercise concurred that most of these key research questions may be successfully answered by 2025.

The CHNRI methodology is transparent, systematic, rigorous, replicable, democratic, and it has been validated and widely used to set research priorities in numerous fields of global health.(6) The main output is an intuitive list of meaningful research questions provided by a group of more than 200 experts and stakeholders, and organized by defined Overarching Research Domains, and then ranked according to explicit priority criteria by more than 160 experts and stakeholders. This is between two-fold and ten-fold increase on the number of those who were involved in previous CHNRI exercises,(7) and the first time that research experts and stakeholders from all world regions contributed and scored specific research questions in the dementia field.(10-13, 19) Nevertheless, some limitations are worth noting. The application of the CHNRI methodology to the field of dementia required some contextual adaptations including the experts and scorers selection, question classification, consolidation and scoring processes. However, the CHNRI methodology was originally conceived to be adaptive and has been similarly customized before. (7-9, 20) Our adaptations were collectively discussed and agreed under the guidance of the CHNRI key methodologist (IR). Further, despite efforts to include multiple disciplines and represent all geographic regions and resource levels, respondents were predominantly clinicians, researchers and stakeholders, and the South East Asia, African and Eastern Mediterranean regions were relatively underrepresented. Although this may reflect the current low dementia research and advocacy efforts and potential barriers to participation that may exist in these settings, we acknowledge that priorities may vary by culture, region and resource level. This exercise was not able to capture and examine these differences, and culture and system specific research may be required. Nevertheless, participants were from 39 countries and global representation was significantly higher compared to other CHNRI exercises,(7, 21, 22) and not sought in previous dementia research priorities efforts.(10, 11, 13, 19) Further, Delphi consensus and experts consultation methods may be biased by potential circularity because of the restricted number of participants and their potential influence on both selection and ranking of research topics. The CHNRI method does not allow any single person to have any appreciable influence on the outcome. The large number of scorers compared to the number of research questions implies that each participant contributed to the final results by less than 1%. In addition, we used a combination of non-structured and structured strategies to identify the dementia experts (who were only in part researchers), and the groups of those who proposed and who scored the research questions did not coincide. Yet, because participants were mainly clinicians and researchers, we cannot exclude that their perspective may have influenced our results. However, the between-scorers agreement was higher than 70% for most of the top 20 priorities. Moreover, a too broad inclusiveness of non-experts, which is crucial at the research topics elicitation step, may actually be counterproductive at the scoring step in CHNRI exercises, and may dilute the differences in priority scores across research topics through regression to the mean.(23)

‘Equity’ was considered to be the least important amongst the five scoring criteria. Nevertheless, the general concern for translation was grand because our results clearly show that there was a widespread and serious concern amongst the 162 scorers that a number of research avenues may be unlikely to benefit those with or at risk of dementia and their families in an equitable manner. Policy makers are urged to promptly tackle the persistent remarkable imbalance between the allocation of research funding and resources, and the unaddressed needs of the majority of those who live with dementia worldwide, particularly in LMIC where international partnerships should be established to raise awareness of dementia and improve the health and social systems responsiveness.

Although the prevalence of dementia will steeply increase in the coming decades because of population ageing,(1) epidemiological evidence suggests a potential declining trend in dementia incidence in recent years,(24, 25) and the results of the FINGER trial suggest that multi-domain interventions could halt cognitive decline in at-risk older adults.(26) This may uplift and foster the general optimism of the scientific community already expressed in 2011 that the risk of dementia may be decreasing.(27) This is somewhat echoed in our results, which indicate a general confidence that the worldwide burden of dementia can be substantially reduced in the next 10 years particularly through improved prevention and care. However, similarly to a widespread concern expressed by all stakeholders at the time of the launch of the NAPA in 2011,(27) the scorers seemed to have little hope that any of the 59 research questions can lead to a “significant paradigm shift that would fundamentally change our thinking or approach to the challenge of dementia”. This may suggest that the current evidence was considered largely insufficient in this CHNRI exercise to support the ambition to identify a cure for dementia (or disease-modifying therapy) by 2025, which was one of the most emphasized outcomes of the 2013 London G8 summit. The stress put on finding a cure for AD in the next 10 years should probably be de-emphasized, and it was already criticized in a Lancet Editorial that warned that: “The quest for new drugs must not overshadow improving today’s care and patients’ lives”.(28)

Indeed, we would argue that our results suggest a pragmatic optimism in this large group of dementia experts, which calls for a transformative evolution of funding mechanisms toward the implementation of a global dementia research agenda that should encompass increased investments along with improved capacity building and international partnerships development to allow real time sharing of knowledge on an unprecedented global scale. The research priorities identified will inform and assist the balance of this research investment across research domains.

A number of expert consultations and initiatives that have been conducted in recent years in high income countries (HIC) have produced research recommendations for better dementia detection,(29) prevention,(10) and treatment, (30, 31) and to expressly improve the quality of life of people affected by dementia, their families and carers.(13) In these and other exercises that have been conducted in the US,(11, 27) and in Europe,(19),32 research themes were defined through a series of highly structured workshops and the recommendations for research priorities, which were identified through discussion but without formal scoring procedures,(11, 19) were conceived to inform pre-existing plans and agendas (e.g. the US NAPA,(27) and the European JPND research initiative(19)). Comparisons are not straightforward because the scope and methodology used varied. The research domains and priorities identified in this CHNRI exercise have communalities with the broad thematic themes,(19) goals,(11, 27) recommendations(12) previously reported, and the top 10 research priorities identified in a recent James Lind Alliance exercise that encapsulated ‘the views of people affected by dementia, practitioners and clinicians’.(13) However, the CHNRI is the soundest methodology available in global health to identify research priorities, and, as said, its output has the great advantage to provide an intuitive list of meaningful research questions. Because compared to HIC the current and future prevalence and burden of dementia are greater in LMIC, while resources, research and advocacy are scant,(2) in this first instance of application of the CHNRI methodology to the field of dementia, a global and unprecedented representation of the articulated landscape of dementia researchers and stakeholders was deemed to be crucial to achieve the ambitious goal of identifying the top research priorities that have the greatest potential to reduce the burden of dementia on a global scale.

**Policy Implications**

The 59 Thematic Research Avenues and the seven Overarching Research Domains presented in this Policy View cover comprehensively the action points of the WHO ‘call for action’ document that was adopted by more than 160 representatives, including 80 member states, on March 17th 2015 at the ‘First WHO Ministerial Conference on Global Action Against Dementia’ held in Geneva. Indeed, the identified priorities provide a sound, balanced research agenda that spans significantly beyond the G7 (then G8) initial very ambitious goal to identify a disease-modifying therapy for dementia by 2025.(3, 28, 32) These research priorities can inform policymakers and funders’ decision-making process globally. However, in order to promote a harmonized strategic global dementia research agenda, further steps are needed, including a comprehensive landscape analysis of countries worldwide, a “Global Asset Map”. This effort should include the assessment of existing funded research projects and expenditures by governments and other funding organizations, and the quantification of patient participation in clinical research. Such an analysis requires a harmonized set of terminology and framework to describe research domains to allow for meaningful cross-national comparisons, such as the Common Alzheimer Disease Research Ontology (CADRO), a collaborative effort between the U.S. National Institute on Aging and the Alzheimer’s Association.(14, 15) Open data-sharing and strategies centered on improving platforms to encourage collaboration will facilitate this effort. When such a harmonized “map” is compared with the research priorities identified, gaps and needs could be recognized to effectively inform the Agenda for Global Action Against Dementia.Nevertheless, the successful implementation of such a global dementia research agenda requires concomitant increases in investment, infrastructure development, capacity building, and international partnerships. Any such collective efforts will require a rigorous and continuous monitoring of the expected progress. WHO is currently working on a Global Dementia Observatory that will function as an international surveillance platform to support evidence-based service planning and strengthening of policies, as well as health and social care systems, across various major strategic domains including research. The 139th Executive Board of WHO in May 2016 “requested the Director-General to develop with the full participation of Member States and in cooperation with other relevant stakeholders a draft global action plan on public health response to dementia, with clear goals and targets” [available at: <http://apps.who.int/gb/ebwha/pdf_files/EB139/B139_DIV2-en.pdf>, accessed August 1, 2016]. Such a plan would facilitate the implementation, and monitoring of progress and benefits of preventive, diagnostic, treatment and care strategies for dementia, and their coverage across and within countries

In conclusion, even though some of the challenges highlighted herein may not be attained by year 2025, there is a historic opportunity to answer research questions in an unprecedented harmonized and coordinated manner and on a global scale. This justifies the pragmatic optimism expressed by the hundreds of experts and stakeholders from all world regions who took part in this exercise that a substantial reduction of the worldwide burden of dementia can be achieved primarily through improved prevention and care.

**Contributors**

SS and TD developed the conceptualization of the study. The survey design and data analysis was done by TD, HS, EA, CD, IR and KL. HS and EA wrote jointly the manuscript and contributed equally to its development and revision. All authors contributed to the data collection, data interpretation, and review and editing of the manuscript.

**Declaration of Interests**

All authors report no competing financial interests. Kenneth M. Langa reports grants from National Institute on Aging. Martin Rossor is NIHR National Director for Dementia Research and receives funding from the NIHR Queen Square Dementia Biomedical Research Unit and Servier. Reisa Sperling is a member of the NIH National Institute of Aging Advisory Council. She has served as a consultant for Abbvie, Biogen, Bracket, Lundbeck, and Sanofi, and has research support from Eli Lilly and Co and Janssen Pharmaceuticals.

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**Figures, Panels and Tables titles and captions**

**Panel 1** Aims of this Policy View

**Panel 2** Search strategy and selection criteria

**Panel 3** Context, purpose and remit of the Dementia Research Priority Setting exercise

**Panel 4** Synoptic Table of Priority Setting Exercises

**Panel 5** Overview of and Policy implications of this Policy View

**Figure 1** The steps of the adapted CHNRI methodology and relevant political and policy events

**Figure 2** Number (%) of Thematic Research Avenues by Overarching Research Domain

**Figure 3** Mean of the top 20 Thematic Research Avenues’ priority scores for each of the seven overarching research goals across the five scoring criteria.

**Table 1** Top three research questions per each of the seven Overarching Research Domains

**Table 2 (Supplementary Materials)** AllResearch Avenues by Overall Priority Score

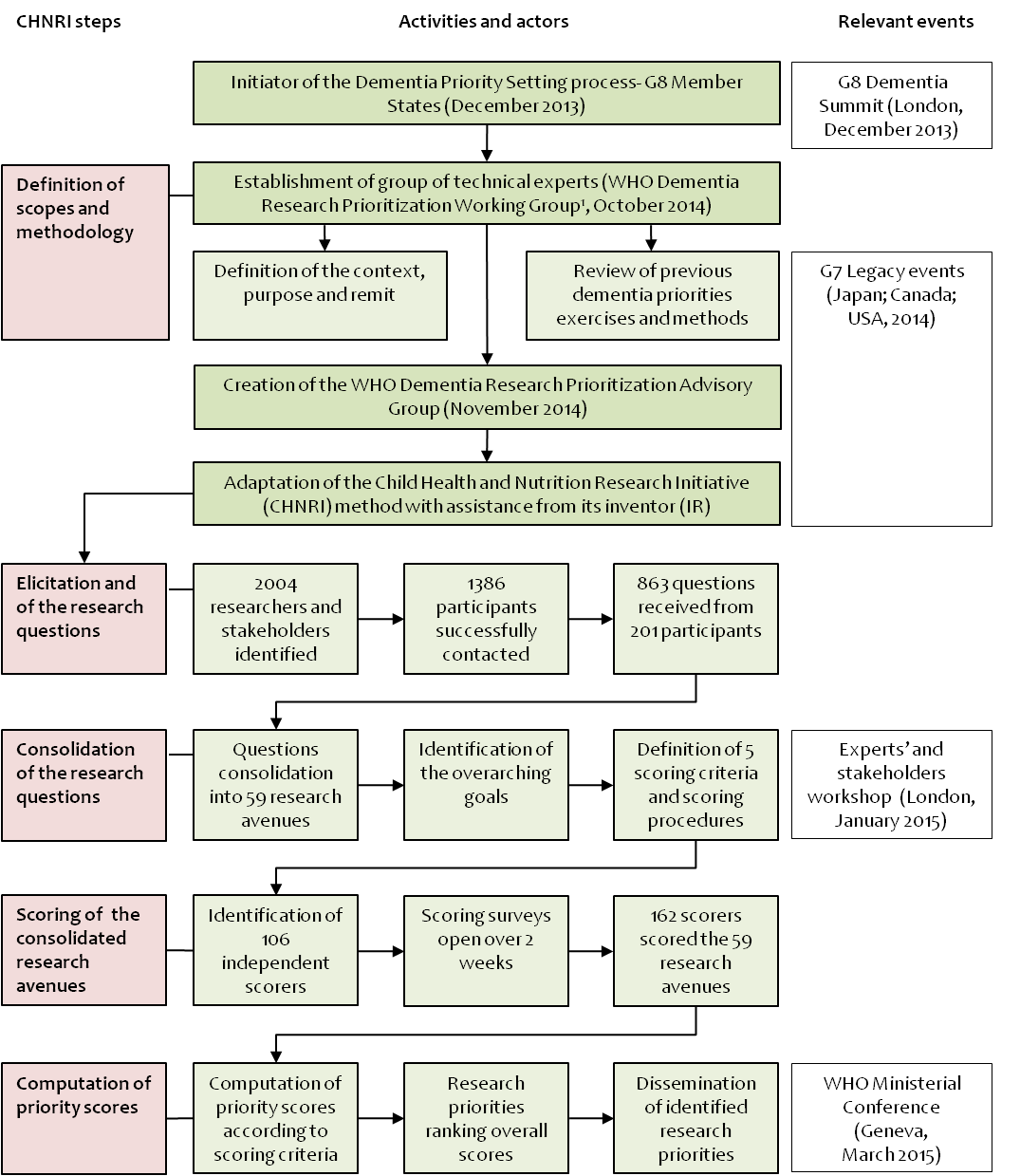
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| ***Panel 1*: Aims of this Policy View** |
| * To describe the adapted CHNRI methodology used to identify the global dementia research priorities for the next 10 years. * To present our results on the top research priorities across research domains and discuss the limitations of our study. * To compare our findings with those of previous dementia prioritization exercises. * To suggest implications for and to provide recommendations to policy makers, funding agencies and stakeholders for future research investments |

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| ***Panel 2*: Search strategy and selection criteria** |
| We searched relevant databases (Medline, Embase, Google Scholar and the Cochrane library) and the Internet (using Google and other search engines) for reports of dementia research priorities/ challenges published between January 2000 and December 2014 applying no language restrictions. We developed and adapted our search strategies combining PubMed MeSh and free-text terms (i.e. ‘Dementia’, ‘Cognitive disorders’, ‘Alzheimer’s disease’, ‘Vascular dementia’, ‘Levy body disease’, ‘Mild Cognitive Impairment’, and ‘challenges’, ‘goals’, ‘priorities’, ‘milestones’, ‘roadmap’, ‘recommendations’, ‘national strategy and plan’) with PubMed clinical queries for aetiologic, diagnostic, prognostic, health and social care, and treatment algorithms. We concentrated on nationwide representative and international reports, from high, middle, middle-low, and low income countries. In addition, we hand-searched the bibliographies of relevant publications and consulted with experts in the field and relevant stakeholders and patients’ organizations representatives to complement the electronic searches. |

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| ***Panel 3*: Context, purpose and remit of the Dementia Research Priority Setting Exercise** |
| **Motivation**  Dementia is seriously disabling and impacts patients, caregivers, families and society at large. The estimated number of people living with dementia is expected to nearly triple to 130 million by 2050. There is a mandate from the ‘G8 Dementia Summit’ to develop a coordinated international action plan for research to better understand and track the full societal impact of dementia, and to identify a cure or significant disease-modifying therapy by 2025. |
| **Long Term Goal**  To enhance dementia prevention and care to avoid or delay the clinical manifestations of the disease, and to improve the quality of life and social well-being of those affected, in order to prepare for and reduce the social and economic burden on families and nations globally. |
| **Population of Interest**  Those with or at risk of dementia, their caregivers and families, the community in which they live, health and social workers, and society at large, worldwide. |
| **Timeframe**  The time frame of 10 years (2015-2025) was defined consistently with the political will expressed at the ‘G8 Dementia Summit’, and was deemed appropriate for all key dementia research domains. |
| **Research Domains & Themes**  Three research domains: Basic, Clinical-Translational, and Implementation Science  Four research themes: Dementia Prevention, Diagnosis, Treatment, and Care |
| **Audience**  Governments, International Funding Agencies, Research Community, Society and relevant Stakeholders at large. |

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| **Panel 4 – Synoptic Table of Priority Setting Exercises** | | | | |
| **Initiatives** | **Goal** | **Preset research domains (Setting)** | **Methodology (*Participants)*** | **Main output format** |
| **Leon Thal Symposia (2008 – 2009)** | To determine a process of crafting a roadmap for policy change to encourage development of treatments to prevent dementia | Process of drug discovery, development and clinical trials, and therapy development for the treatment and prevention of AD/dementia.  (National, USA) | Three think-tank meetings with participants divided into four groups. Priorities determined by consensus (70 international leaders in dementia research, loyal friends and colleagues of Dr. Leon Thal). | Wide ranging, agency specific, scientific and public policy recommendations, with a focus on the development of therapies to delay or prevent the onset of disabling symptoms of AD. |
| **JPND** **EU Joint Programme - Neurodegenerative Disease Research (2012)** | To address the challenges of neurodegenerative disorders and establish a framework for future research investments. | Etiopathogenesis, mechanisms and models of neurodegenerative disease; diagnosis; therapies development, preventive strategies and interventions; health and social care  (International; EU, Switzerland, Canada, Norway, and Israel). | The JPND Scientific Advisory Board (SAB) provided recommendations based on a series of thematic workshops and consultations (unspecified number of research opinion leaders and stakeholders from industry, patients representatives, health and social care professionals, and carers). | Nine enabling activities (from research capability and infrastructures, public private partnerships, to education and training), across the preset five thematic research priorities. |
| **Workgroup on NAPA,** **National Alzheimer’s Project Act (2012)** | To delineate a comprehensive 10-year scientific agenda for early detection and develop a broad range of interventions for AD/ dementia. | Etiopathogenesis, early detection and biomarkers, interventions and health service research.  (National, USA) | The Workgroup drafted a scientific agenda as a “living document”, incorporated feedback, and shared it with an NAPA Advisory Council (unspecified number of AD researchers across the US) | An articulated scientific agenda, with a focus on early detection and interventions to prevent dementia or maintain independency in those affected, encompassing scientific and infrastructural challenges, and possible organizational solutions. |
| **Ware Invitational Summit (2012)** | To develop dementia research recommendations for the scientific community, policy makers, legislators, advocacy groups and clinicians | Biomarkers; Clinical Care and Health Services Research; Drug Development; Health Economics, Policy and Ethics  (National, USA, but included international experts) | Preliminary recommendations, based on the work of four workgroups, were discussed and integrated into a set of priorities, recommendations and action plans. | Four main goals and various related recommendations for their implementation through research, regulations and funding. |
| **James Lind Alliance and UK Alzheimer’s Society Dementia Priority Setting Partnership (2013)** | To inform funding allocation on the top research priorities and gaps in dementia prevention, diagnosis, treatment and care, from the perspectives of people with dementia, carers, and health and social care professionals. | Prevention; diagnosis; treatment; care  (National, UK) | Questions (n=4,000) elicited through a national survey, and consolidated into a list (n= 146), which was submitted to 36 partner organizations that ranked their top 10 priorities through internal consultation. At a final workshop, the final top 10 list was agreed upon through discussion and nominal group techniques (1,500 people completed the survey; 18 representatives from partner organizations elaborated the final top 10 list). | Top 10 priorities for dementia research (purposely limited to prevention, diagnosis, treatment and care). |
| **New York Academy of Sciences Alzheimer’s Disease and Dementia Research Roadmap (2014)** | To examine the challenges of and explore solutions to improve productivity of biomedical research and accelerate development of new diagnostics and therapeutics | Basic research; Early development/translational research; Prevention trials; Public/private interface  (National, USA) | Developed recommendations using consensus. | 17 recommendations on collaboration infrastructures and methods and specific research topics. |
| **WHO Dementia Research Prioritization Project (2015)** | To identify the top research priorities that have the greatest potential to reduce the burden of dementia on a global scale | Three research domains (Basic, Clinical-Translational, and Implementation Science), and four research themes (Dementia prevention, Diagnosis, Treatment, and Care)  (International/ global) | Adapted CHNRI methodology to elicit (n=863), consolidate, score and rank research priorities (n=59) (363 experts in the field of dementia including health and social workers, policymakers, funders, advocates, provided and/or scored research questions) . | Top 10 and top 20 research priorities across 7 thematic Overarching Goals identified. |

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| **Panel 5: Overview of and policy implications of this Policy View** |
| **Dementia**  A syndrome characterized by cognitive and functional decline and behavioral and psychological symptoms, which has an enormous impact on those affected, their families and society at large, and which is now a recognized global health priority. |
| **Global Response**   * No nation states in isolation can realistically respond to the impact and challenges posed by dementia. * A fully transparent, systematic, rigorous, replicable and fair process that is globally representative and involves all relevant stakeholders is needed to identify the research priorities, which will inform the global dementia research agenda to effectively respond to the dementia crisis. |
| **Dementia research priorities**   * The global burden of dementia can be reduced by year 2025 prioritizing 59 dementia research topics across seven overarching research goals. * Specific research questions span from prevention, identification and reduction of dementia risk, through delivery and quality of care for people with dementia and their caregivers, to improved diagnosis and treatment development. * Basic research into disease mechanisms may have the greatest potential for conceptual breakthrough. |
| **Strengths and Limitations**   * Dementia research priorities have been identified and ranked by hundreds of participants from 39 Countries (20 High income, and 19 Low and Middle Income) according to explicit priority criteria, applying a sound and unbiased methodology. * Response rates were highest amongst clinicians, researchers and stakeholders and lowest in South East Asia, African and Eastern Mediterranean regions. Cultural, regional and system level differences in dementia priorities are not known. |
| **Policy Implications**   * Funders and policy makers should make use of the 59 research priorities identified in this exercise to allocate resources and investments on a global scale. This upscaling of research investment should be optimized accounting for existing funded research projects and expenditures classified according to a common terminology and framework to describe research domains and methods. Established priorities should be mapped onto the dementia research landscape to identify critical gaps. * Efforts are required by all stakeholders including WHO, Member States and civil society to continuously monitor research investments and progresses, as well as temporal and geographical trends in dementia incidence, prevalence and burden, through international platforms such as a Global Dementia Observatory. * A ‘Global Dementia Action Plan’ should be developed with clear goals and targets, in consultation with all stakeholders and informed by sound public health evidence. Such a plan would facilitate the implementation, and monitoring of progress and benefits of preventive, diagnostic, treatment and care strategies for dementia, and their coverage across and within countries |



***Figure 1*: The steps of the adapted CHNRI methodology and relevant political and policy events**.

Steps are: gather the working and advisory groups who define the context and remit and identification of dementia experts (researchers, health and social workers, and stakeholders); elicitation of research options; classification and consolidation of the research options received by to pre-defined themes and domains into research avenues and identification of ensuing overarching research goals; independent scoring of the competing research avenues in a highly structured way, and according to five purposely devised criteria; computation of priority scores, level of between-scorers agreement, and ranking of research priorities by overarching research goals.

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***Figure 2*** Number (%) of Thematic Research Avenues by Overarching Research Domain

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***Figure 3*** Mean of the top 20 Thematic Research Avenues’ priority scores for each of the seven overarching research goals across the five scoring criteria.

**Table 1** – Top three research questions per each of the seven Overarching Research Domains

|  |  |  |
| --- | --- | --- |
| **Overarching**  **Research Domains** | **Top Three Research Questions for Each Domain** | **Overall**  **Score**  **(Agreement)** |
| Prevention, identification and reduction of risk | *Explore single and multi-domain approaches for primary and secondary prevention of dementias based on evidence on risk/protective factors and the relationship with other chronic diseases.* | 0.81 (76%) |
| *Understand the influence and interactions of non-modifiable (e.g. gender, genetics, age) and modifiable (e.g. physical activity, diet, and cognitive stimulation) risk and protective factors for dementia in population-based samples.* | 0.76 (70%) |
| *Determine the feasibility, optimal mode of administration, and effectiveness of interventions to address risk factors for dementia (including physical activity, cognitive activity, education, nutritional factors and others).* | 0.75 (69%) |
| Quality of care for people with dementia and their caregivers | *Determine the most effective interventions for educating, training and supporting formal and informal carer(s) of people with dementia.* | 0.74 (76%) |
| *Determine and ensure optimal use of psychological and pharmacological treatments for Behavioral and Psychological symptoms of dementia (BPSD) to maximize patients’ quality of life and caregiver burden reduction.* | 0.73 (69%) |
| *Develop and evaluate policies, investments and plans for increasing the capacity, knowledge, skills and interest of the health and social care workforce in the field of dementia.* | 0.69 (71%) |
| Delivery of care and services for people with dementia and their caregivers | *Evaluate the relative effectiveness and identify the optimal models of care and support for people with dementia and their carers in the community (e.g. collaborative care, integrated health and social care, case management) across the disease course.* | 0.75 (74%) |
| *Identify strategies to anticipate and deliver effective and cost-effective late life and end of life care for people with dementia, including advance care planning.* | 0.74 (74%) |
| *Understand the role of assistive and technological devices, including e-health and mobile health technology strategies, for people with dementia and/or their carer(s).* | 0.71 (66%) |
| Diagnosis, biomarker development and disease monitoring | *Identify clinical practice and health system-based interventions that would promote a timely and accurate diagnosis of dementia in primary health care practices.* | 0.79 (78%) |
| *Establish longitudinal cognitive surveillance of healthy individuals to detect earliest changes that distinguish pre-manifest neurodegenerative diseases causing dementia from normal aging, and which may be used as endpoints in primary prevention clinical trials.* | 0.73 (65%) |
| *Develop and validate biomarkers --- including biological, genetic, behavioral and cognitive markers --- for neurodegenerative brain diseases causing dementia, to identify similarities and differences between diseases and dementia subtypes, and assess progression from pre-manifest (pre-symptomatic) to late stage diseases.* | 0.71 (67%) |
| Pharmacological and non-pharmacological clinical-translational research | *Diversify therapeutic approaches (e.g., pharmacologic and non-pharmacologic interventions) for discovery and development in clinical trials for neurodegenerative and other brain diseases that cause dementia.* | 0.77 (70%) |
| *Promote collaborations to explore more efficient trials, adaptive trials, and combination therapy for dementia.* | 0.73 (64%) |
| *Identify, validate and apply better outcome measures for clinical trials of cognition, function and other biomarkers for neurodegenerative diseases causing dementia.* | 0.70 (64%) |
| Public awareness and understanding | *Determine how knowledge of modifiable risk factors for dementia can be translated into effective brain health promotion and dementia prevention messages, and coupled with communication strategies to effect behavioral change in different cultures and countries.* | 0.77 (71%) |
| *Determine the effectiveness and cost-effectiveness of dementia-friendly communities, and other population strategies that target stigma and discrimination, and promote inclusion and quality of life.* | 0.67 ((63%) |
| *Understand cultural differences in attitudes towards people with dementia to determine culturally appropriate ways to promote carer support and reduce stigma* | 0.66 ((64%) |
| Physiology and progression of normal ageing and disease pathogenesis | *Understand the contributions of vascular conditions to neurodegenerative diseases causing dementia.* | 0.77 (70%) |
| *Identify underlying mechanisms of resilience to neurodegenerative diseases causing dementia at all stages (such as cognitive reserve, protective genotypes, and neuroprotection).* | 0.73 (66%) |
| *Understand the role of inflammation and of the immune system in the initiation/onset and progression of neurodegenerative diseases that lead to dementia.* | 0.68 ((64%) |
| *Investigate biological processes of neurodegenerative diseases to understand their contributions to dementia to optimize individualized therapeutic strategies.* | 0.68 ((60%) |

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