A blueprint for dementia research

World Health Organization

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Foreword

Addressing dementia is one of the greatest health challenges of our generation.

In the years ahead, societies and health systems will have to cope with a staggering increase in the number of people with dementia, which is set to reach 78 million by the end of this decade, with most of these people living in low- and-middle-income countries.

Now, more than ever, we need to work together as a global community, leveraging the unique knowledge and expertise that each of us has to offer. During the COVID-19 pandemic, we have learned how fast we can advance research and development if we act in a coordinated manner. It is now time to translate these learnings to address another global health challenge that we've been confronted with for years: dementia. It is therefore timely for WHO to publish this blueprint for dementia research, the first WHO initiative of this kind in the context of non-infectious diseases.

This blueprint builds on and applies key lessons learned from previous WHO efforts to prioritize and coordinate research for infectious diseases, and considers the entire dementia research spectrum, incorporating diagnostics and therapeutics, as well as emerging scientific and technological advances such as artificial intelligence, multiomics, and biomarkers. It also encompasses epidemiology, health economics, care and carer research, risk reduction, and brain health across the life course. The blueprint emphasizes that advances in these areas will only be fully accomplished if appropriate and sustainable funding is allocated, diversity and equity become the norm, and people with lived experience are included throughout the entire research process.

Achieving these goals means reaching beyond our traditional ways of doing research and finding better strategies to coordinate between sectors and stakeholders. As a key component to support the implementation of the global action plan on the public health response to dementia 2017–2025, the blueprint for dementia research identifies knowledge gaps and defines actions and milestones to achieve strategic research goals. This blueprint is designed to provide guidance to policy makers, funders, and the research community on dementia research, making it more efficient, equitable, and impactful.

We must come together globally, and in a coordinated manner, to tackle dementia and halt the debilitating impact it has on people and communities.

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Abbreviations

AD	Alzheimer disease
CT	Computed tomography
DALYs	Disability-adjusted life-years
DLB	Dementia with Lewy bodies
GBD	Global Burden of Diseases Study
HIC	High-income countries
LMIC	Low- and middle-income countries
MCI	Mild cognitive impairment
MRI	Magnetic resonance imaging
NCDs	Noncommunicable diseases
PET	Positron emission tomography
PPC	Preferred product characteristics
SCD	Subjective cognitive decline
TPP	Target product profile
TDP-43	TAR DNA-binding protein-43
VaD	Vascular dementia

1. Introduction

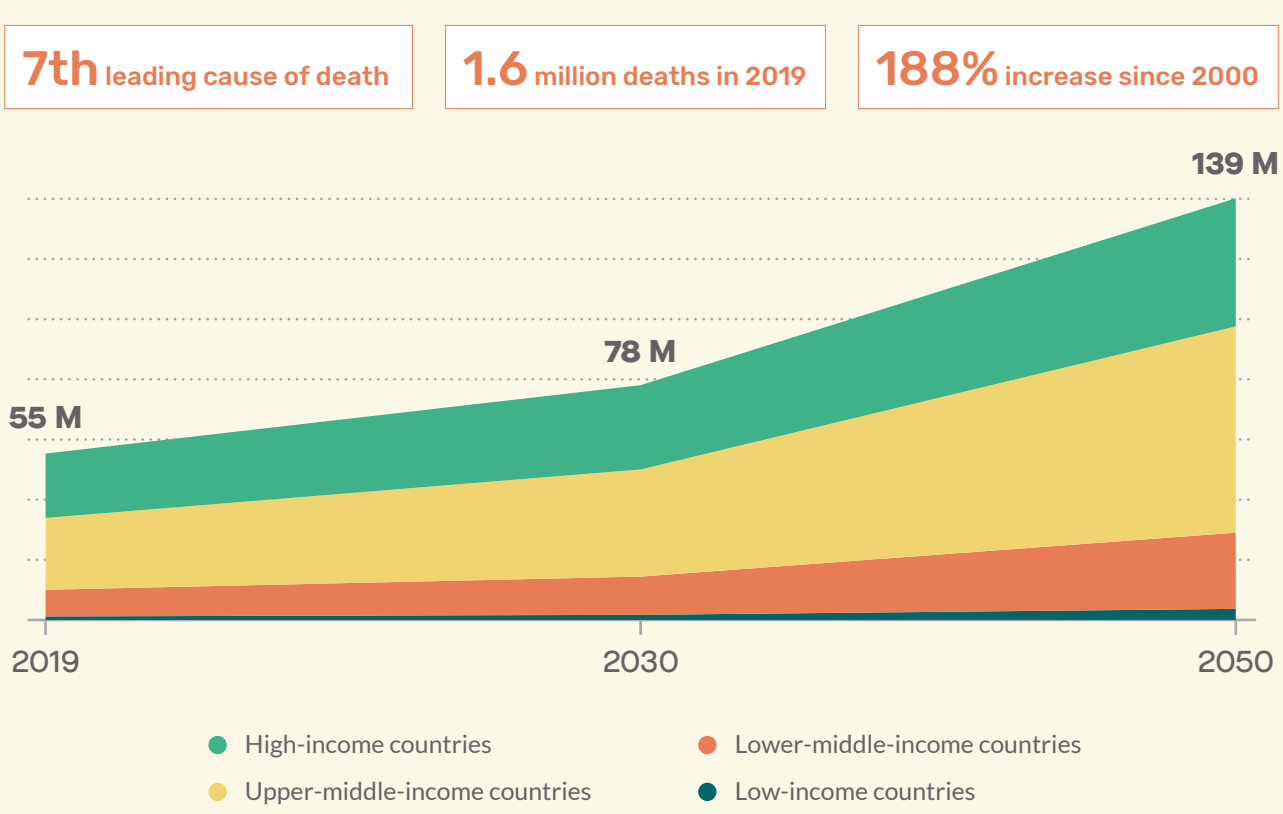
1.1 Rationale for this blueprint

Dementia is a major cause of disability and dependence in older adults worldwide. It affects memory and other cognitive functions, leads to changes in mood and behaviours, and interferes with the ability to perform daily activities and participate independently in society. Dementia causes significant burden on individuals and their families as well as on health, social welfare, and financial systems in all countries.

Approximately 55.2 million people have dementia worldwide, over 60% of whom live in low- and middle-income countries (LMIC) *(1, 2)*. With life expectancy increasing in almost every country and older age being the strongest independent risk factor for dementia, the number of people living with dementia is expected to rise to 78 million by 2030 *(2)* (Fig. 1). In 2019, dementia was the seventh leading cause of death worldwide, accounting for 1.6 million deaths (Fig. 1), and 28.3 million disability-adjusted life-years *(1)*. The global cost of medical, social, and informal care associated with dementia in 2019 was estimated to be more than US$ 1.3 trillion and this cost is expected to exceed US$ 2.8 trillion by 2030 *(1)*.

Despite the recognition that dementia research should be accelerated, it remains fragmented, with wide variation in the types and levels of investment, as well as research quality. Moreover, research into dementia risk factors and effective interventions to reduce risk must be carried out over long time periods as dementia risk accumulates over the life

Fig. 1. Worldwide impact of dementia in 2019



Source: Global status report on the public health response to dementia *(1)*.

course and the lag time between exposure to risks and/or interventions and the onset of dementia may be very long. Similarly, research into novel therapies tends to have lower success rates, take longer to conduct, and face difficulties in patient recruitment *(3)*. Consequently, market incentives, public investment, and research outputs remain lower than for other disorders *(4)*. Research on dementia is also inequitable, as the vast majority of studies are conducted in high-income countries (HIC), despite most people with dementia living in LMIC. Data for 2019 indicate that, although funding for dementia has increased, it is primarily directed towards research in HIC. Of the 50 organizations and institutions that received the most grants for dementia research in 2019, 41 were in the USA, six in the United Kingdom, and three in Canada *(1)*. Additionally, despite dementia being caused by several diseases, most research is on Alzheimer disease (AD). Therefore, global dementia research must be strengthened to include other underlying causes of dementia, all potential risk and protective factors, as well as care and support for those living with dementia and their carers. Moreover, while the global scale of the dementia challenge needs to be reflected in research efforts, regional differences and the heterogeneity of populations deserve much more attention.

During the G8 dementia summit in 2013, countries collectively pledged to enhance coordination for more innovation in therapeutic approaches, and to increase structured funding for dementia research by setting the ambitious goal of identifying a cure or disease-modifying therapy by 2025. Similarly, in 2017, all 194 WHO Member States adopted the global action plan on the public health response to dementia 2017–2025 *(4)* and committed to strengthening their response to dementia, supporting people with dementia and their families, as well as achieving the targets set in the action plan by 2025. Commitment to the global dementia action plan was reinforced by the G20 countries in 2019, as they recognized the impact of dementia and urged countries to develop ambitious national responses and adopt integrated approaches aligned with the global dementia action plan. Notwithstanding such commitments, the targets set by the global dementia action plan are unlikely to be reached by 2025 *(1)*. Similarly, the lack of progress in all dementia action areas compromises the efforts towards achieving other global commitments including the Sustainable Development Goals targets, such as universal health coverage, and the action areas of the United Nations Decade of Healthy Ageing.

In the face of this challenge, urgent action is needed in making research an integral part of the response to dementia. To ensure that all aspects of research (including basic science, clinical research and implementation science) as well as critical areas across the dementia care pathway (ranging from risk reduction, diagnosis, treatment, care, and rehabilitation to ultimately finding a cure) are adequately addressed, dementia research must be recognized as a global priority. At the same time, investigative approaches need to be harmonized and redundancies reduced. Moreover, research must be rooted in equity, diversity and inclusiveness, be person-centred, include families and reflect the reality of dementia in different contexts. This will require strengthening research capacity in low-income settings and developing mechanisms to ensure the inclusion of people from diverse cultural and ethnic backgrounds, as well as of people living with dementia, their families, and carers in research.

1.2 Objectives of this blueprint

Building on previous efforts to prioritize and coordinate research for infectious diseases, WHO set out to develop a blueprint for dementia research (hereafter referred to as “blueprint”) in 2021. This blueprint is the first of its kind in the context of non-infectious diseases and aims to support the global prioritisation of dementia research and provide a coordination mechanism among stakeholders.

The specific objectives of this blueprint are to:

- facilitate timely and high-quality evidence generation to address research gaps
- fast-track innovation and increase intervention success-rates
- enhance and encourage collaboration in dementia research
- build research capacity, especially in LMIC
- guide actions for mobilizing adequate resources
- promote the empowerment and engagement of people with lived experience and
- ensure the successful and timely implementation of research evidence.

Through these objectives, the blueprint directly supports the implementation of the global action plan and accelerates efforts to achieve targets that will make research more equitable, efficient and impactful, ultimately contributing to the provision of better care and support for people living with dementia, their families, and carers.

1.3 About this blueprint

Development

The blueprint was informed by a comprehensive literature review, a survey of experts, and a consultation workshop with international dementia experts (i.e., researchers, academics, people living with dementia, representatives of civil society organizations and policy-makers). Overall, more than 100 dementia experts from around the world and colleagues from relevant WHO departments and units were involved in the development and peer-review of the blueprint. Declaration of interest forms were obtained from all external contributors prior to their involvement in the blueprint development and any conflicts were managed as per WHO policy.

Content

The blueprint summarizes the current state of dementia research across six broad research themes, identifies existing research gaps, and outlines 15 strategic goals with actions and timebound milestones to address those gaps. The six research themes consider the entire dementia research spectrum, incorporating diagnostics and therapeutics, as well as emerging scientific and technological advances such as artificial intelligence, multiomics, and biomarkers to increase our understanding of underlying disease mechanisms and to foster early diagnosis and treatment. It also encompasses epidemiology, health economics, care and carer research, risk reduction, and brain health across the life course.

Addressing these complex issues and existing gaps will require an enabling research environment. The blueprint therefore outlines eight drivers of research that are considered to be essential in accelerating dementia research across the six identified themes. For instance, the strategic goals can only be accomplished if appropriate and sustainable funding is allocated and research capacity is built, especially in LMIC. More emphasis needs to be put on promoting diversity and equity in dementia research and including people with lived experience throughout the entire research process. The blueprint also highlights that research progress will be driven by better coordination and increased collaboration among research sectors, including data-sharing to ensure better use of data, avoid redundancy, and promote a more inclusive research environment. Finally, encouraging the use of new technologies will be also vital to drive innovation in the field.

Target audience and implementation

The primary target audience for this blueprint are national and international research agencies, funding bodies (including governmental, private, and philanthropic organizations), regulation authorities, civil society, and the broader research community working on dementia and related areas. These stakeholder groups are encouraged to work collaborative to address current challenges and create a structured plan of action to promote scientific advances in all the necessary research areas to ease the impact of dementia everywhere.

WHO will work side by side with all stakeholders to ensure research prioritization for dementia, the promotion of research across all identified areas and capacity building in all countries. This blueprint represents a first step towards supporting these efforts by encouraging more evenly distributed research and innovation in both HIC and LMIC to address regional gaps and challenges.

Fig. 2

Objectives of the blueprint for dementia research

- Timely and high-quality evidence
- Fast track innovation
- Enhanced collaboration
- Increased research capacity
- Adequate resources
- Engagement of people with lived experience
- Successful and timely implementation of research

Research themes

Summarizing current state and research gaps

Dementia epidemiology and economics

Dementia disease mechanisms and models

Dementia diagnosis

Drug development and clinical trials for dementia

Dementia care and support

Dementia risk reduction

15 strategic goals

Actions and timebound milestones address research gaps

1. High-quality epidemiological data
2. Economic impact of dementia
3. Understanding underlying diseases
4. Models of diseases
5. Development of biomarkers
6. Development of clinical assessment of cognition and function
7. Diagnosis during prodromal stages
8. Development of novel therapies
9. Improving clinical trials
10. Legislative and regulatory environments
11. Tools and methodologies for interventions
12. Models across the continuum of care
13. Methodologies and approaches for risk reduction research
14. Understanding risk factors
15. Risk reduction interventions

Drivers of dementia research

Empowerment and engagement of people with lived experience

Diversity and equity

Funding

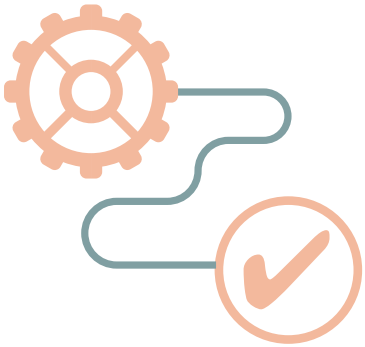
Access to science, data and material

Capacity building for research

Technology

Knowledge translation and exchange

Regulatory environments



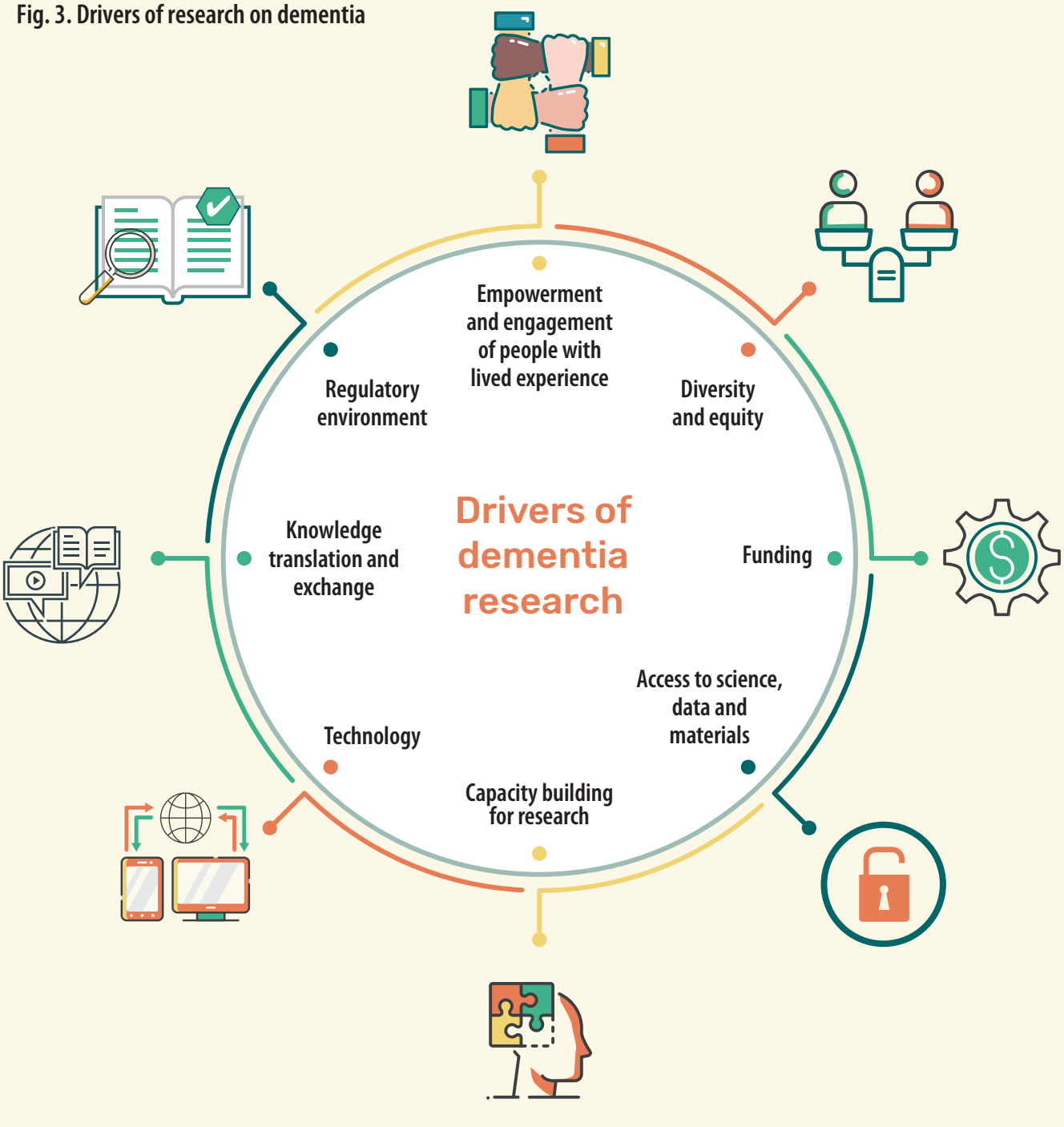
Implementing the blueprint

Successfully implementing the blueprint requires empowering and engaging people with lived experience in all aspects of research. WHO encourages national and international research agencies, together with other funding bodies, to use this blueprint to inform upcoming funding streams and operationalize the outlined drivers of research. Civil society can ensure that advocacy efforts are likewise aligned, supporting the drive for a more equitable, efficient, and collaborative research landscape. Researchers can support the achievement of milestones and strategic goals of this blueprint by addressing the research gaps identified.

2. Drivers of dementia research

The blueprint is a global coordination mechanism for transformative change, fast-tracking of innovation and addressing long-standing barriers in dementia research. To achieve this vision, research must take place within an enabling environment. The eight drivers of dementia research (Fig. 3) identified in this chapter are considered essential to create such an environment and support the realization of significant progress in the field.

Fig. 3. Drivers of research on dementia



2.1 Empowerment and engagement of people with lived experience

People with lived experience of dementia (including those living with dementia, their families and communities and formal and informal carers) have the greatest direct interest in the outcomes of research. It is therefore essential that they remain central to and are directly involved in all aspects of dementia research. This is not the norm in many parts of the world, and its introduction will require a major shift in perspectives and approaches.

People with lived experience should be involved in all stages of research, including setting priorities, devising procedures, selecting outcome measures, implementing the research strategy, disseminating results and turning recommendations into practice and policy. The objectives of including them are to ensure that research is directly relevant to their needs, designed to maximize real-world benefits and minimize or eliminate harm and is fully consistent with the United Nations Convention on the Rights of Persons with Disabilities and other international and regional human rights instruments. For example, the ethical and psychological implications of disclosing the results of cognitive tests, information on biomarkers and genetic risk profiles are not well understood and should be a priority for further investigation, with the involvement of people with lived experience.

People with lived experience should also be involved in committees that oversee dementia research and be on the boards of public and private agencies that award research funds.

Their involvement in research should take into consideration their diversity. Many will not have a background in science or skills in research methods. Many will have cognitive, sensory and/or physical impairments that may affect their ability to engage, so that research teams will have to adopt inclusive approaches to engagement. Research training courses could enable people with lived experience to contribute effectively to research, and researchers could provide opportunities for people with lived experience with whom they work. It is also important to engage people who may not have dementia but are interested in being actively involved, for example to reduce their risk of developing dementia. Direct involvement of people with lived experience will ultimately benefit research, as it is likely to encourage greater participation.

2.2 Diversity and equity

The principles of equity and diversity in, e.g., gender, race, ethnicity, gender identity, sexual orientation, religion, disability, socioeconomic status, marginalization and Indigenous status must be upheld in all aspects of dementia research. This includes equal participation, outcomes, benefits, resources, funding and coverage. Some populations and communities are less willing or able to participate in dementia research; therefore, the research community and sectors should seek to understand the reasons by engaging with them and designing research and associated processes that make participation more feasible and acceptable. Better understanding of the prevalence and incidence of dementia, the costs of illness and the prevalence and impact of risk factors is required in LMIC and other ethnic and regional groups. Research into the mechanisms of dementia, such as biomarkers, genetic and epigenetic markers, should include and account for differences in these groups.

Equity must also be assured for researchers working in under-represented countries and regions, such as their inclusion in decision-making, ownership and fair recognition and reward for research outcomes.

Sex and gender equity must also be considered in all components of dementia research. Efforts should be made to correct the substantial underrepresentation of women in research studies and leadership positions, with creation of research environments that offer a fair career–life balance for women.

2.3 Funding

Even in HIC, dementia research has been chronically underfunded, despite the high health and social burden associated with dementia. Increasing dementia research funding, in absolute terms and relative to that for other comparably impactful diseases, is essential. Given the chronic, slowly progressive nature of most diseases causing dementia, continuous funding must be assured for comprehensive, longitudinal research, which is often costly. Secure long-term funding is necessary for all areas of dementia research but especially for research into novel treatments and risk reduction. After three decades and several hundred failed trials, many large pharmaceutical companies have abandoned efforts around dementia therapeutics *(6)*, as the cost of bringing a new drug to market approval is prohibitively high, one estimate in 2013 being about US$ 2.6 billion *(7)*. Nonetheless, the potential societal and economic benefits of a successful treatment would be enormous. There is renewed interest in the field, in part due to a collaborative approach among industry, academia and government and also greater attention to drug repositioning and repurposing as possible alternative, more cost–effective treatments. Public investment could reduce private risk and thereby reinvigorate research and development. Work on therapeutics should therefore be renewed, facilitated by public–private partnerships.

More funding is also necessary for research on prevention, diagnosis, treatment (including non-pharmacological treatments) and for high-quality care. Clinical translation and implementation should also be studied further and appropriately funded.

Increased funding for dementia research should be provided by public, private and philanthropic funding organizations. Funding should be better balanced, including for under-researched aspects of dementia, such as conditions other than AD and dementia in highly vulnerable or marginalized populations, including Indigenous peoples. Allocation of funding to LMIC by international bodies should be targeted for building research capacity and infrastructure and ensuring perennial development and training of a research workforce. Funders should demand that a portion of their awards be allocated to collaboration between HIC and LMIC in the design and execution of studies. Appropriate funding of researchers in LMIC and fostering real, transparent research collaboration will decrease the power imbalance and the dependence on HIC institutions, increase output and representation of LMIC in data and result in substantial, inclusive global dementia research.

Many countries do not prioritize dementia research at all, and they should be encouraged and helped to change their approach. As dementia is a global problem, research should be global and include flows of funds and materials from higher- to lower-resource settings. Incentives to undertake "cutting-edge", innovative research should include government grants and tax breaks. The use of research funds should be monitored and a network of international and inter-agency collaboration be created to reduce duplication of research and thereby reduce waste. This does not refer to replication, which is usually necessary to establish the validity of research findings and their applicability to other settings.

Finally, funding should be equitably allocated to female researchers in order to reduce the gender gap and counter the relatively fewer grants and professorships awarded to female researchers.

2.4 Access to science, data and materials

Global dementia research could be improved by increasing access to scientific knowledge and by sharing protocols, procedures, data and other research materials, including biological samples. Scientific sharing has many potential benefits.

Access to science

During the past decade, substantial efforts have been undertaken to make knowledge more accessible to the scientific community, including researchers in LMIC. This is vital and must be sustained in order to make research publications widely available, contribute to the democratization of science and overcome the financial barriers often faced by LMIC researchers and institutions. Open access publishing has made research more accessible, although publication costs are often high. Publications that can be accessed by paid subscription only are generally expensive and out of reach in low-resource settings. Global action is necessary to address such inequity.

Data-sharing

Addressing challenges associated with dementia research requires collaborative efforts among stakeholders from all parts of the world. Naturally, the ability to share data, or lack thereof, significantly impacts the progress in the dementia research field. With recent scientific progress, substantial data is routinely collected in many research areas, including epidemiology, biomarker and drug development and clinical trials.

Sharing of fully de-identified data on participants among research groups allows mega-data analyses and meta-analyses, providing greater statistical power and answering many novel questions without collecting new data. Data-sharing thus prevents unnecessary duplication of research and is essential for testing the reproducibility of findings. Sharing also encourages better quality control, openness, greater scrutiny, research integrity and collaboration.

Data-sharing can be promoted and made possible through the creation or engagement with existing national dementia registries, national and international databases of dementia research, an international drug development platform, an international database of epidemiological data and a network of biobanks. This will require resources, infrastructure and policies to promote safe, equitable and accessible sharing of high-quality data.

Internationally recognized policies should be developed for the quality, integrity, sharing, privacy and security of data. Potential conflicts between open, accessible data and requirements for governance and ethical frameworks for the security and privacy of research participants should be resolved. Robust policies on data privacy should be in place to sustain current and future data acquisition and sharing. Regional work in this regard should be made global. Funding agencies should actively promote data-sharing by providing incentives and making it mandatory, when possible, while acknowledging the intellectual and practical work of the primary researchers and the importance of responsible, ethical use of data.

WHO has published policy and implementation guidance *(5)* on how to develop a data management and sharing plan for creating digital datasets that are in line with WHO's policy on the sharing and reuse of health-related data for research purposes, and ensure an equitable, ethical, efficient and fair approach.

Sharing of materials, protocols and procedures

International regulations should be adapted or created to facilitate sharing of biological samples, imaging and other materials among countries, while ensuring the safety, intellectual protection and privacy of people. Protocols for epidemiological studies and trials, measures for assessment and outcomes of interventions, diagnostic criteria and guidelines for several topics (e.g., cognitive assessments, neuroimaging, fluid biomarkers and neuropathological assessments) must be developed and agreed by consensus across experts from different parts of the world, input from people with lived experience, and shared with the research community to support research capacity and standardisation of methods.

Pre-registration of research protocols with journals may reduce publication bias and ensure greater transparency and reproducibility of findings. Sharing of protocols and procedures should respect local conditions, culture, language and legislative requirements to ensure that research in dementia is consistent globally and adheres to the best international standards. For example, countries and regions should develop, validate and adopt economically and culturally appropriate clinical assessment instruments that are culturally and linguistically fair and readily accessible. This will require qualitative research to understand local concepts of dementia-related variables and avoid de-facto translations of instruments developed in other contexts.

2.5 Capacity-building for research

Training programmes (e.g., fellowships, workshops, postgraduate courses) to increase the capacity and capability of researchers in all disciplines relevant to dementia research, particularly in LMIC, would improve the quality of all dementia research. Gaps in research (e.g., in understanding non-AD dementias in LMIC) should be filled by training more personnel in the relevant disciplines or establishing collaborations. National and international exchange programmes, research-sharing platforms and collaborative networks may be useful. The involvement of people with lived experience organizations that support and represent them are critical in such work.

All researchers involved in dementia research, particularly those who work directly with people with cognitive impairment, should receive training in dementia and ageing and in identifying early signs and symptoms of cognitive decline. Training could be increased strategically in areas in which skills are lacking, such as in basic science, epidemiology, cognitive assessment, ethical research practice and dementia care. Non-dementia researchers who work with older people with conditions such as diabetes or heart disease could be trained in dementia research to increase the possibility of collaborations. Likewise, engaging with mental health researchers and workforce can help to build capacity of researchers in understanding stigma and complex interventions. A cross-disciplinary approach to research in which basic scientists work with medical and allied health and related disciplines will maximize the potential of dementia research. As such requirements may be more challenging to meet in LMIC than in HIC, funding should be provided to increase the research workforce in regions. Enabling sustainable and fair collaboration between HIC and LMIC institutions will also support capacity building of researchers globally.

The career paths of junior researchers should be considered. Research careers are generally insecure, and the transitions from doctorate to early career researcher and then to an established researcher are challenging. Many promising junior researchers that are unsupported and underfunded may seek alternative careers, causing "brain drain" and a reduction in research capacity. Better funding models and support systems are necessary to address this problem internationally.

2.6 Technology

Technological advances present both opportunities and challenges. Developments in areas such as computing and wearable technologies, imaging hardware, intelligent design and architecture, artificial intelligence and deep learning offer opportunities to advance dementia research. For example, wearable devices and smartphones, which are readily available in both HIC and LMIC, can passively collect large amounts of continuous real-time data that can be integrated and harmonized by big data technology in a variety of sources and scales.

Global cooperation in the development and sharing of digital biomarker technologies is essential. They include the technologies used to acquire data (e.g., smart devices), store data (e.g., digital infrastructures) and share data (e.g., robust ethical guidelines) internationally. Another important application of technological advances is for the development of tools and devices that support activities of daily living and ensure security and safety of people living with dementia. These must be developed taking into account the specific needs of people living with dementia and their potential cognitive impairments.

The "digital divide" both within and between HIC and LMIC must be reduced. As technology is more likely to be used to collect data in HIC, they disproportionately contribute to digital biobanks and skew findings. Funding for research on digital biomarkers in LMIC is imperative.

Researchers in HIC have taken advantage of big data technologies and have developed data-driven approaches to dementia prevention. They can process and manage such data quickly and efficiently. Data-driven approaches like machine learning algorithms and deep-learning frameworks are often not available in LMIC because of their high cost. Access to digital health tools and increased literacy in digital epidemiology in digitally disadvantaged groups are therefore essential. Alternative solutions should be found in regions where digital infrastructure is not yet well established while an increase in investment into digital infrastructure takes place.

Technology such as encryption and block chain can preserve privacy. The development and application of machine learning and artificial intelligence can enhance understanding of the mechanisms, diagnosis and biomarkers of dementia. Digital models may reduce animal experimentation and make intervention trials more accessible. Technology can resolve many issues of diversity and inequity in dementia research, but only if a concerted effort is made to include all ethnic, regional and socioeconomic groups.

2.7 Knowledge translation and exchange

To best help people living with dementia and their families and carers, beneficial research findings must be applied as quickly as possible in health practice and public health policy. There are, however, considerable barriers (e.g., lack of awareness) to translating even robust research. Moreover, implementation can reveal unsuspected challenges; their resolution feeds into knowledge creation, thereby providing bidirectional exchange of information. Increasing the awareness, presence and standard of implementation science is therefore critical to bringing the benefits of research rapidly to the people who need it.

Building capacity and infrastructure for translating research findings into practice for people living with dementia is necessary in public, research and private settings and in both HIC and LMIC. Investment in capacity and infrastructure must come from all these settings in direct international collaboration, including sharing of resources and the benefits of implementation. This is important for every country and region but particularly for LMIC and subnational regions that may lack the necessary resources.

Dementia research is usually multidisciplinary, and the necessary expertise in all areas may not be found in some settings. International sharing of expertise can facilitate multi-component research and collaboration. This will require formation of networks to link diverse researchers and setting up databases and platforms for sharing at local, national and international levels.

2.8 Regulatory environment

A strong, well-formulated and transparent regulatory environment is a key driver of research and an important enabler of collaborations and successful research implementation. Complexity and lack of transparency in regulatory environments, however, and divergent international norms and standards may create barriers that will hinder the establishment of collaborations and slow down the implementation of innovations. Creation of ethically and morally sound guidelines that anticipate the evidence and requirements necessary for regulatory review and policy development would fast-track life-changing scientific advances. Moreover, international harmonization of norms and standards and international agreements can facilitate establishment of worldwide collaborations, increase access to resources and avoid future hurdles in regulatory and policy decisions.

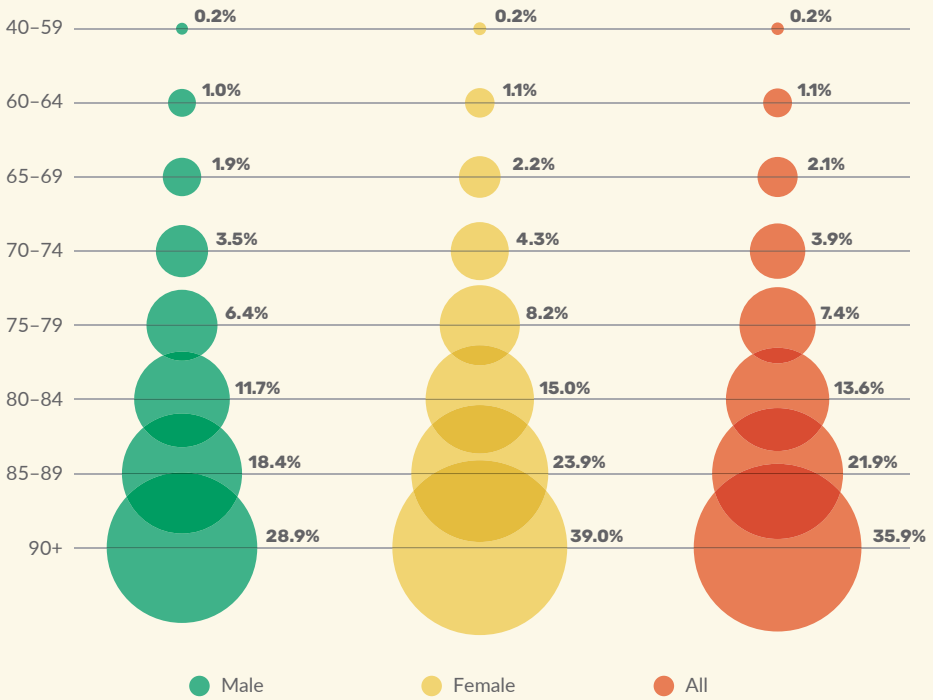
3. Dementia epidemiology and economics

3.1 Context

In 2019, an estimated 55.2 million people were living with dementia *(1)*. Dementia was the seventh leading cause of death worldwide, accounting for 1.6 million deaths in that year and contributed to 28.3 million disability-adjusted life-years *(8)*. Figures like these are the basis for policy-making, allow resource planning for the health and social care sector (both public and private) and support the monitoring of secular trends in dementia, identifying and understanding risk and protective factors and research for new interventions. Counting cases of dementia is complex, and estimates of prevalence and incidence may depend on the study design, sampling strategy, the age range included, representation of minority groups, the quality of population demographic data and the method used for case ascertainment *(9)*. Determining the number of cases is further complicated by stigmatization of dementia *(10)* and by changes in the diagnostic criteria for dementia and its disease subtypes over time.

In the *Global status report on the public health response to dementia (1)*, it was estimated that the prevalence of dementia in people aged ≥ 60 years ranged from 2.9% in the South-East Asia Region to 6.5% in the European Region; other regional estimates ranged from 3.1% to 5.7%. Fig. 4 shows the global dementia prevalence, stratified by age group and sex. Women are disproportionately affected by dementia, as reflected by a greater prevalence among women than men in all age groups, 60% more disability-adjusted life-years due to dementia in women than in men and a higher proportion of deaths from dementia among women *(1)*.

Fig. 4. Global prevalence of dementia by sex and age group, 2019



Source: Global status report on the public health response to dementia *(1)*.

Current projections of the numbers of cases of dementia are based on the assumption that age-specific prevalence rates are stable *(11)*, consistent with various estimates based on global data *(12–14)*. Evidence from HIC, however, suggests that dementia incidence may be decreasing *(15)*. This is not a global phenomenon, and, in some countries, the incidence appears to be increasing among more recent birth cohorts *(16)*. Globally, the number of people living with dementia is likely to triple by the middle of the century *(13)*.

Various determinants of health influence the incidence of neurological disorders, including dementia, during the life course *(17)*. For instance, the incidence of dementia is affected by the prevalence of risk and protective factors at population-level and the strength of their association with dementia during the life course as well as the timing of exposure to those factors. Some risk factors are more prevalent than others and account for more cases of dementia in LMIC than in the rest of the world *(18)*. While the risk and incidence of dementia may ultimately decrease as concerted efforts are made to address individual and population risk and protective factors, persistent inequality may prevail, with implications for the projected prevalence in those populations *(1)*. For more details on risk and protective factors, see chapter 8.

The global societal cost of dementia can be calculated from current prevalence rates. For instance, in 2019, the annual global cost associated with dementia was estimated to be US$ 1.3 trillion. On the basis of population projections and corrections for inflation, the cost is expected to reach US$ 2.8 trillion by 2030 *(1)*. Approximately 20% of the cost of dementia is attributable to direct medical costs, irrespective of national income; however, the proportion of the costs attributable to informal care in each country is much higher in low-income countries (approximately 70%) than in HIC (approximately 40%) *(1)*. While the economic benefits of preventing or slowing the progression of dementia are obvious, methods to ensure cost–effectiveness have been applied to dementia only recently. The limited evidence suggests that reducing exposure to risk factors *(19)*, psychosocial interventions *(20)* and medications *(21)* is cost-effective. In addition, there is some evidence that psychosocial interventions for carers are cost–effective *(22, 23)*. Developments in the field of dementia economics are important in terms of planning health interventions and care and resource development and for incentivizing governments, funders and service providers to invest in effective approaches to reduce the risk of dementia and for treatment and care for current and future populations *(20)*.

Health and cost estimate models are only as accurate as their input data and are presently seriously limited.

It should be noted that these estimates are only as accurate as the data used in the models and are seriously limited by the lack of data on prevalence, disability, mortality and cost in certain parts of the world. Improved datasets are necessary to increase the accuracy and representativeness of the data.

3.2 Research gaps

Epidemiology

Lack of good-quality data

Many countries, both HIC and LMIC, do not have up-to-date, high-quality, nationally representative data on the prevalence or incidence of dementia derived from epidemiological studies or administrative data *(24, 25)*. Data on young-onset dementia are very limited.

Insufficient diversity

Reliable data on differences in dementia rates among people in, e.g., different ethnic and racial groups *(9)* and in sexual minorities *(26)*, are lacking, and the rates in Indigenous peoples have rarely been measured *(27)*.

Methodological issues

Many epidemiological studies are of poor quality, with suboptimal implementation of multiphase design (i.e., screening of all participants in the first phase and diagnostic assessment of subsamples

in subsequent phases), small samples, suboptimal recruitment of individuals with dementia, especially those at moderate–severe stages, and/or lack of a comprehensive diagnostic assessment for dementia.

Disease representation

Most of the available epidemiological studies do not include data on biomarkers for subtyping dementia and do not take into consideration that dementia is often of mixed etiology.

Lack of standardization

Coding of dementia as the underlying cause of death in registration of vital statistics is widely inconsistent among countries and over time. Furthermore, recording of dementia as a cause of death has increased *(28)*. These factors complicate estimation of global mortality from dementia.

Economics

Lack of representative data

Few data are available from many parts of the world, particularly LMIC. Even in countries with data, few population-based cohort studies have been conducted that represent diverse communities and include data on resource use and costs. Consequently, most costing studies have been based on clinical or convenience samples and not on known populations. Many of the studies that provide data were conducted only in a limited geographical area where research capacity is sufficient; however, the findings are often extrapolated to whole countries and even regions.

Dependence on poor-quality prevalence data

The validity of global studies of the costs of dementia relies directly on the quality of estimates of prevalence and data on service contacts in each country. Variations in the way in which dementia is diagnosed lead to highly variable estimates of prevalence that affect estimates of the cost of illness. Data on cost of illness are rarely nationally representative and are particularly sparse in LMIC *(29)*.

Variation in the definition of informal care

Variation in the definition of informal care raises several methodological challenges to estimating the time spent caring, impacts on carers and how their time is valued *(30)*.

Lack of data on cost–effectiveness

While use of economic evaluation in dementia is increasing, few studies of dementia risk reduction and intervention have included cost–effectiveness in their design *(21, 31)*. Lack of such evidence is a considerable barrier to wide-scale approaches to more effective risk reduction and treatment. Cost–effectiveness data are also necessary to incentivize investment in effective interventions. Outcomes that matter to many populations of interest are not well described, and this is an important area of research.

3.3 Strategic goals, actions and milestones

STRATEGIC GOAL 1

High-quality epidemiological data

Ensure availability of high-quality epidemiological data from widely representative geographical, ethnic and socioeconomic groups with appropriate disaggregation by gender and sex, age, disease severity and subtypes and relevant measures of inequity.

Actions:

- **Obtain high-quality, up-to-date, representative data.** Conduct epidemiological studies of dementia both in countries with no data and in those for which data are outdated or unrepresentative. Studies should be representative of the populations in which they are conducted and should ensure sufficient sampling and characterization of socially marginalized groups, where applicable. Both cross-sectional and longitudinal studies are necessary to obtain prevalence and incidence data. Epidemiological studies should be repeated and/or revised periodically to include changing trends in both rates and risk factors.

- **Apply international standards.** Follow international benchmarks for methodological rigour in epidemiological studies for dementia. The method and instruments used must be adapted appropriately to the setting of the study, which should include translation, cultural and contextual adaptation and validation of instruments when necessary. WHO's GATHER guidelines *(32)* should be applied for accurate, transparent reporting of health estimates.

- **Analyse risk and protective factors and burden of dementia.** Include analyses of associations with risk and protective factors and their interactions throughout the life course in all populations. Studies should accurately capture rates of morbidity and mortality associated with dementia *(33)*. Data should be collected specifically in world regions for which there are few data.

- **Include disease subtypes in epidemiology studies.** Address cognitive decline and dementia in all disease subtypes, and include data on biomarkers when possible and if resources permit.

- **Use other data sources.** Use other sources of data to complement epidemiological data in order to arrive at true prevalence figures. These may include data on hospital admissions for dementia, data from surveys in primary care settings, records of prescription for anti-dementia medications and data from surveys of long-term care facilities and aged care services. Some such data may be obtained from national administrative datasets collected routinely in many countries. This can be considerably facilitated by establishment of dementia registries *(34)*.

- **Improve the quality of administrative data.** Improve the quality of data derived from administrative health systems and the linkage between systems such as health and social care data, for example by creating clearer guidelines for death certification and unique patient identifiers and increasing awareness of the mortality associated with dementia. New methods could be used that do not rely on vital registration data for calculating excess mortality *(14)*.

- **Promote data-sharing.** Promote the development and coordination of sustainable international platforms for sharing data, with appropriate standardization and privacy (e.g., Alzheimer's Disease Neuroimaging Initiative, the Global Alzheimer's Association Interactive Network, the Alzheimer's Disease Data Initiative, Dementias Platform UK and Dementias Platform Australia).

Milestone 1.1: By 2027, to have international benchmarks for epidemiological studies and use of open-access, inter-operable, international platforms to archive and share epidemiological data from regions around the world.

Milestone 1.2: By 2030, to have a comprehensive dataset from high-quality epidemiological studies that include geographical, ethnic and regional populations for whom there are currently insufficient data to fill major gaps in international data.

Milestone 1.3: By 2030, to have ensured that countries have high-quality health administrative data to monitor dementia and the quality of its assessment and care.

STRATEGIC GOAL 2

Economic impact of dementia

Establish better understanding of the economic impact of dementia on society and generate robust evidence on the cost–effectiveness of risk reduction, treatment and care.

Actions:

- **Build consensus on methods for measuring cost of illness.** To ensure meaningful synthesis of data globally, reach consensus on the conduct of cost-of-illness studies in dementia, with a focus on monetary valuation and definition of informal care.
- **Generate high-quality data on service contacts and costs.** Conduct research to understand and better estimate the cost of dementia, including in regions and countries for which there are no data.
- **Obtain evidence of cost–effectiveness.** Promote research to understand and identify WHO best buys[1] for cost-effective treatment, care and risk reduction. The research should account for the fact that some investments take decades to yield benefits but that they may have positive outcomes for healthy ageing overall. The data should be relevant to all regions and resource settings and different populations.
- **Include dementia as an outcome in other studies.** Ensure that studies on preventive interventions for other noncommunicable diseases (NCDs) include dementia, or at least cognition as a proxy, in modelling cost–effectiveness in view of the similarity of the risk factors and comorbidity.

Milestone 2.1: By 2027, to have established a database on burden of disease and cost estimates for dementia from different geographical, ethnic and regional groupings around the world.

Milestone 2.2: By 2030, to have generated robust evidence on the cost–effectiveness of treatment and care interventions and strategies to reduce the risk of dementia to support establishment of public health interventions throughout the life course.

[1] Similar best buys have been developed for the prevention and control of noncommunicable diseases (NCDs). These WHO Best buys comprise a list of recommended and most cost-effective interventions, including overarching/enabling policy actions. These include, for example, actions to reduce tobacco use and the harmful use of alcohol and the promotion of healthy diet and physical activities.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4. Dementia disease mechanisms and models

4.1 Context

Dementia consists of a group of symptoms (a syndrome) associated with a variety of diseases that share the development of progressive neurodegeneration and cognitive decline (Table 2). The origins of and the mechanisms leading to dementia are complex and multifactorial. During the past three decades, major advances have been made in understanding the pathophysiology of dementia, and yet it remains poorly understood. Bridging this knowledge gap will include identifying biomarkers for timely diagnosis, accurate prognosis and monitoring of progression. Dementia generally develops over many years and is often diagnosed only when significant neurodegeneration has already occurred. Therefore, understanding of the different disease mechanisms during the life course is crucial to identify new therapeutic targets and develop treatments to intervene earlier in the disease course.

A further complication is the frequent concomitant occurrence of several diseases, particularly in older adults, which makes it difficult to isolate the primary causal factors. The overlap of some neuropathological characteristics in different disease subtypes suggests some common basis. For example, accumulation of insoluble fibrillar forms of tau can be present in AD, frontotemporal dementia and other tauopathies. Recently, the importance of cerebrovascular mechanisms has been recognized, some evidence suggesting that vascular dysfunction may occur early in the process of AD *(35)*, although its role in frontotemporal dementia and dementia with Lewy bodies is less clear *(36)*. While the overlap of conditions in several subtypes may be seen as a complication to understanding the underlying mechanisms, it suggests that treatments targeted to those common conditions could be beneficial in treating various

Table 1. The most common dementias and their distinguishing brain pathological features

Dementia	Approximate proportion of all dementias (%)	Distinguishing brain pathological features*	Reference no.
Alzheimer disease	60–80	Amyloid-β plaques and tau neurofibrillary tangles	*37*
Vascular dementia	13	Cerebrovascular pathology	*38*
Dementia with Lewy bodies	3.1–7.1	α-Synuclein protein clusters	*39*
Frontotemporal dementia	3.0	Frontal and temporal lobe atrophy, abnormal tau, TDP-43, fused sarcoma protein	*40*
Dementia due to Parkinson disease	3.6	α-Synuclein deposits	*41*

*Note that several features may be present, and different sources cite different single and multiple features.

diseases causing dementia, including rarer examples such as Creutzfeldt-Jakob disease *(36)*. It might also indicate that a combination of therapies is required according to the molecular signatures of the diseases of each person with dementia.

Most research to date has addressed the most common disease subtype causing dementia, AD, in which causative autosomal dominant gene mutations are found in three genes in some extremely rare cases of familial early-onset disease *(42)*. For the more prevalent clinically diagnosed late-onset AD (which is likely to include various other age-related conditions), in addition to the apolipoprotein E ε4 allele, more than 70 genetic loci have been identified that increase risk *(43, 44)*. In order to use the results of these genetic studies to identify viable targets, the mode of action of genetic risk factors must be understood, with identification of their protein products and/or how they affect molecular processes relevant to the disease. Research on the pathological mechanisms leading to AD has mainly addressed its hallmarks: accumulation of amyloid beta plaques and neurofibrillary tangles in the brain. Population-based neuropathological studies have shown that most older people have these changes in their brains irrespective of whether they express dementia clinically. The amyloid cascade hypothesis has dominated the research field *(45)*, and strategies to reduce amyloid and tau have been tested in many clinical trials. Because of the continued failure of trials of strategies targeting amyloid plaques, however, the amyloid hypothesis has recently come under increased scrutiny. Although the role of amyloid-β accumulation and tau tangles is supported by substantial evidence, it has become apparent that a more holistic approach is required to understand the molecular underpinnings of AD etiology.

Research on the pathological mechanisms of AD mainly addressed its hallmarks: amyloid plaques and neurofibrillary tangles.

Alternative and/or additional pathways leading to disease have been studied, including neuroinflammation, excitotoxicity, oxidative stress, mitochondrial dysfunction, lysosome degradation, immunity, ubiquitination, cholesterol transport, glial activation and neurotrophic factors *(44, 46)*. The contribution of each of these mechanisms and the interactions among disease-related pathways and amyloid or tau are still poorly understood. Furthermore, increasingly, a comprehensive view is being taken to understand the roles of factors such as sleep disruption, the microbiome and infection (e.g., virus, bacteria, prion) in the development and progression of AD *(46)*. As ageing is a common risk factor for dementia and other chronic diseases, it is important to understand ageing and the mechanisms by which it promotes disease. This complex set of factors that affect diseases and cause dementia also make it difficult to develop ecologically valid animal models of the various subtypes of dementia, including AD *(47)*. Furthermore, the findings from animal models and ex-vivo models e.g., stem cells, tissues as well as biofluid analysis must be validated, as these reflect only some aspects of this complex disorder.

Understanding the molecular mechanisms of diseases other than AD that cause dementia and the interplay among different conditions is also important. The term "vascular cognitive impairment and dementia" is used to describe vascular dementia and pre-dementia cognitive impairment that is attributed to cerebrovascular pathology *(38)*. Vascular dementia is the second most common type of dementia. Dementia with Lewy bodies is another common form, associated with accumulation of Lewy bodies *(39)*. Likewise, Lewy bodies also occur in Parkinson disease, in which there is a strong likelihood of dementia over time. Frontotemporal dementia is a heterogeneous disorder with diverse clinical symptoms, underlying conditions and genetic architecture. It is rare and is often expressed as early-onset dementia *(48)*. The

pathological mechanisms of less common dementias, such as those caused by Huntington disease, corticobasal degeneration, progressive supranuclear palsy and prion diseases, are also being investigated, including their possible overlaps with each other and with more common diseases causing dementia *(49)*. Finally, sex is a source of disease variation in AD (50), dementia due to Parkinson disease *(51)* and frontotemporal dementia *(52)*.

Altogether, it is paramount to improve our knowledge of the underpinnings of the diseases causing dementia. More studies on the mechanisms underlying these diseases will not only improve understanding about the origins of these neurological disorders but also form the basis for development of diagnostics and therapeutic strategies.

4.2 Research gaps

Pathological mechanisms

Complete understanding of protein-associated pathological mechanisms

While robust evidence has confirmed the association of amyloid-β and tau with AD, their role in disease development and progression and their association in the complex environment of the brain is not completely understood. The degree to which Lewy bodies themselves cause dementia is also unclear, as they frequently occur in AD-type conditions.

Other pathways

The role of other pathogenic pathways, such as neuroinflammation, oxidative stress and other downstream effects, and their consequences and representation in disease models is not fully understood and should be further explored, including their potential role as targets for therapeutics (see chapter 6).

Pathophysiology of AD

While considerable research has been conducted on the amyloid cascade hypothesis in AD, its integration with genetic and environmental risk factors and other diseases during the life course requires more complex models of pathogenicity which are presently lacking.

Pathophysiology of diseases other than AD

Little research is conducted on the pathological mechanisms of non-AD dementias, such as dementia with Lewy bodies and frontotemporal dementia, which are poorly understood.

Molecular contribution of risk factors

Although several comorbid conditions and health determinants have been identified as risk factors for dementia (e.g., cardiovascular disease and obesity), further research is required on the molecular relations among these diseases and their impact on dementia development.

Contribution of vascular aspects

There is currently an incomplete understanding of vascular contributions to dementia and a need to translate findings into the development of effective interventions that are accessible globally.

Biological causes of behaviours and psychological symptoms associated with dementia

Little is known about the biological mechanisms underlying behaviours and psychological symptoms associated with dementia.

Contribution of several conditions

Several pathological elements can coexist in the same individual (e.g., amyloid-β, tau, α-synuclein, TDP-43), but there is limited understanding of how and whether they interact.

Deeply phenotyped cohorts

Inadequate information is available on extensively phenotyped cohorts for studying disease mechanisms in humans. Many of the studies were performed by private entities, and, with very few exceptions, the data are not freely available to the scientific community.

Geriatrics and the contribution of biological ageing

Ageing is the major risk factor for dementia; however, its biological role in disease development is poorly understood. There is a lack of collaboration between geriatricians and other disciplines (e.g., neuroscience and neurology) *(53, 54)*.

Lack of genetic and ethnic diversity

Genetic research has been conducted mainly in HIC and populations of European origin. Studies of diverse populations, particularly life course cohorts, would provide new insights into the origins of diseases causing dementia and the role of genetics in dementia development.

Sex differences

Men and women appear to differ in biomarker patterns and clinically in different forms of dementia. The contribution of the genetic, hormonal and societal roles of sex and gender as risk factors for dementia is not well understood and could provide new insights into the mechanisms of the diseases.

Resilience and compensation mechanisms

The underlying mechanisms of reserve, resilience and compensation (e.g., education, physical exercise) are often not included in investigations of disease mechanisms.

Disease models

Limited experimental models are currently available, and they do not reflect the complexity of neurodegeneration observed in the human brain and body. Models of a single aspect of a disease are usually not ecologically valid. Moreover, animal models have been designed primarily for AD, and there are few models of other dementias or mixed dementia conditions.

4.3 Strategic goals, actions and milestones

STRATEGIC GOAL 3

Understanding underlying diseases

Increase understanding of the origins and mechanisms of the diseases that cause dementia through a life course approach.

Actions:

- **Mechanisms of monogenic diseases causing dementia.** Conduct more research on the disease mechanisms that are the basis of neurodegeneration and symptoms, and that are caused by single-gene mutations (e.g., autosomal dominant AD, some frontotemporal dementias, Huntington disease).
- **Complex multifactorial mechanisms in dementia.** Investigate the contributions of multiple pathogenic pathways to dementia (e.g., protein aggregation and toxicity, neuroinflammation, excitotoxicity, oxidative stress, mitochondrial dysfunction, lysosome degradation, immunity, ubiquitination, cholesterol transport, glial activation and neurotrophic factors) considering ageing, environmental and lifestyle risk factors and genetic background. Longitudinal studies with deep characterization of participants by, e.g., imaging, biomarker profiling and omics technologies (e.g., genomics, transcriptomics, proteomics and metabolomics) are essential.
- **Biological causes of behaviours and psychological symptoms associated with dementia.** The biological causes of behaviours and psychological symptoms associated with dementia should be investigated as background for the design of therapeutic interventions to be incorporated into care models (see chapter 7).
- **Molecular impact of risk factors.** Promote both preclinical and clinical research to understand the molecular influence of risk factors such as comorbid conditions and health determinants on the development of dementia.
- **Sex differences.** Study the role of biological sex differences in the diseases that cause dementia, biological ageing and risk and protective factors throughout the life course.
- **Molecular profiles in the brain:** Map the molecular profiles of different brain cell populations (e.g., neurons, glia) for spatial and chronological characterization of vulnerable brain cell systems affected in dementia.
- **Technological innovations.** Use recent technological innovations in omics technologies, neuroimaging, computational science and artificial intelligence to better understand the mechanisms of dementia, and develop new technologies in partnerships with academia, government and private enterprises.
- **Research collaborations and partnerships.** Provide funding and support for collaborative interdisciplinary research in fundamental neuroscience through to clinical studies to address the complexity of these disorders. Partnerships among researchers, clinicians, consumer bodies, government and private industry should be facilitated.
- **Brain banks.** Create a global coalition of brain banks to facilitate research into the pathology of diseases causing dementia across several countries and ethnic and racial groups and promote equitable access to such resources around the world. Currently, brain bank consortia tend to be national or regional (e.g., BrainNet Europe, US National Institutes of Health NeuroBiobank). Funding should be provided for the establishment of brain banks in LMIC.
- **Longitudinal studies.** Bring together existing international cohorts and establish new cohorts with innovative approaches and appropriate inclusion of under-represented communities. Birth cohorts and multigenerational cohorts are necessary to understand the developmental aspects of diseases causing dementia and potentially different risk profiles according to generation. Deep phenotyping of cohorts should be conducted with the currently available technologies, with exploration of sex and gender differences. Global collaboration, open access, sharing of data and pooling of resources are essential, including data from industry-sponsored trials, which are currently not readily accessible.

Milestone 3.1: By 2027, to have developed an international collaborative network for sharing basic scientific data and techniques, technical innovations and materials that includes both HIC and LMIC, academia, government and industry.

Milestone 3.2: By 2027, to have established new life course cohorts to investigate the development and progression of various diseases causing dementia.

Milestone 3.3: By 2030, to increase understanding of the cellular and molecular mechanisms (e.g., protein aggregation, inflammation, lysosomal dysfunction, oxidative stress) of the different diseases causing dementia and the relevance of determinants and pathways throughout the life course.

STRATEGIC GOAL 4

Models of diseases

Develop models of the diseases that cause dementia that reflect their complex mechanisms and downstream molecular events.

Actions:

- **Behavioural models.** Develop new, standardized, high-throughput, unbiased behavioural platforms.
- **Better ex-vivo and computational models.** Develop novel, diverse, ecologically valid experimental models of diseases that cause dementia to better understand the mechanisms of neurodegeneration. The models could include stem-cell-based, 3D bioprinting, cerebral organoids and computational models.
- **Animal models.** Develop animal models that reflect the complexity of dementia and represent the many molecular events in disease development, including biological ageing, protein aggregation and interaction, inflammation, lysosomal dysfunction and oxidative stress.

Milestone 4.1: By 2030, to have improved ex-vivo and animal models that represent molecular disease characteristics and phenotypes, and are ecologically valid for dementia in humans and underlying diseases.

5. Diagnosis of dementia

5.1 Context

Timely, accurate diagnosis of dementia potentially allows early intervention, action on modifiable risk factors, better management of symptoms, support for people living with dementia and their carer and families, planning for the future, maintenance of independence and postponement of institutionalization *(55, 56)*. From the perspective of research, it is also important for recruitment and stratification of clinical trial participants and accurate assessment of the effectiveness of new therapeutic interventions. The global action plan on the public health response to dementia 2017–2025 *(4)* includes the target of 50% of countries reporting that at least 50% of cases of dementia are diagnosed. Most countries, however, have not reached this target *(1, 57)*; the global rate of undiagnosed dementia is up to 75% and may be as high as 90% in some LMIC *(39)*.

The average time from onset of symptoms to clinical diagnosis is unduly long, at almost 3 years for late-onset dementia and 4.4 years for early-onset dementia *(58)*. The global COVID-19 pandemic has further delayed access to diagnostic assessment, and the full impact is yet to be determined *(39)*. Accurate diagnosis of dementia and the disease subtype requires a trained workforce and dementia-specific clinical guidelines, equipment, standards and protocols; however, fewer than two thirds of the countries included in WHO's Global Dementia Observatory reported having such guidelines and standards *(1)*. Misdiagnosis of the disease subtype is common; it is estimated to be about 30% when confirmed post mortem, and 25% of AD diagnoses must be adjusted after an amyloid PET scan *(39)*.

Although timely and accurate diagnosis of dementia is extremely important, there is an increasing emphasis on recognising neurocognitive disorders at the prodromal stage of dementia including mild cognitive impairment (MCI) and even subjective cognitive decline (SCD) when no cognitive impairment is objectively documented *(59, 60)*. While the identification of people at increased risk of developing dementia raises the possibility of implementing strategies to slow progression and delay the onset of dementia, the sensitivity and specificity of diagnosis during prodromal stages remain poor. Accurate identification of individuals at these stages is increasingly based on evolving biomarker science, which so far has been used mainly to identify clinically applicable biomarkers for AD and not for other disease subtypes. Biomarkers are commonly investigated in cerebrospinal fluid and blood, and the investigations usually consist of the identification and quantification of abnormal amounts of proteins (tau and amyloid) and markers of neurodegeneration and neuroinflammation *(61, 62)*. Likewise, genetic biomarkers for both early- and late-onset dementia could improve diagnosis and prognostication, including identifying individuals at risk of progression from mild cognitive impairment to dementia *(63)*. Given the limited evidence on many biomarkers and their availability only in some high-resource settings, their clinical application at the prodromal stage or even at dementia stages should be further developed and validated.

Diagnosing dementia is extremely complex. Several approaches, including the emerging biomarkers, are being used, although much remains to be done. A standardized neuropsychological assessment is valuable for the diagnosis of mild cognitive impairment and the early stages of dementia and may include subtyping, assessment of progression and planning of treatment and care. Several attempts have been made to harmonize assessments so that the same tests and normative data are used *(64–67)*. Structural imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), is an important component of initial evaluations of early dementia. Significant advances have also been made in functional imaging with positron emission tomography (PET) *(39)*, including the finding of new amyloid and tau ligands, and other tools, such as dopamine transporter imaging and cholinergic PET for identification of underlying diseases such as Parkinson disease and dementia with Lewy bodies *(41, 61, 68–70)*. There is growing interest in

identifying behavioural phenotypes of dementia with ubiquitous, accessible technology (e.g., smart phones, rings) to derive continuous personal data for early diagnosis and subtyping *(71, 72)*.

In view of its complexity, diagnosing dementia requires an integrated, multifactorial approach in which clinical examination is combined with neuropsychological, imaging, fluid biomarker and genetic data sources. By studying the time course of disease and monitoring how different indicators of disease change over time, diagnostic tools could be developed to better understand disease stages, identify tailored interventions and provide more accurate prognoses. Barriers in health systems, such as lack of services and a trained workforce, also affect access to and the quality and sustainability of timely, accurate diagnosis. These barriers are further discussed in chapter 7.

Diagnosing dementia requires combining clinical examination with neuropsychology, imaging, fluid biomarkers and genetic information.

5.2 Research gaps

Cross-cutting gaps

High-quality data

There is a lack of high-quality data on time of diagnosis, accuracy, subtyping and optimal diagnostic tools used in primary care settings.

Standardization of assessments

Assessments for dementia in primary care are not always optimal for the resource setting, are not standardized or do not account for the diverse socioeconomic and cultural backgrounds and literacy of the population. The potential trade-off between adaptation and standardization requires a sophisticated, coordinated approach in order to achieve both.

Neuroimaging

Structural imaging implementation in clinical practice

Structural imaging (CT and MRI) is still used clinically to rule out associated conditions rather than to rule in dementia and its disease subtypes. Most major advances in MRI technology have not been used in clinical practice, and new and emerging MRI techniques such as diffusion, perfusion and functional imaging should be further explored for clinical application. MRI has not been used for prognosis or in clinical trials on various disease subtypes. Few efforts are under way to develop portable, low-field MRI scans to increase access *(73)*.

PET imaging techniques

Molecular PET imaging developed for AD and dopamine transporter imaging are useful for diagnosing dementia with Lewy bodies and dementia due to Parkinson disease, but its use for other disease subtypes and other factors such as neuroinflammation and synaptic integrity should be explored. Insufficient evidence is available on suitable markers and PET radioligands for measuring aspects such as neuroinflammation.

Machine learning in imaging

Reporting of neuroimaging requires experts who evaluate a limited range of the information available from the scans. The use of machine learning and other artificial intelligence techniques is not widespread, and there are few tools that do not require a highly trained workforce.

New techniques

Newer imaging techniques, such as magnetic particle imaging, and novel tracers (e.g., based on nanoparticles) are still being developed for clinical application.

Fluid biomarkers

Cerebrospinal fluid biomarkers

Although significant advances have been made in the development of cerebrospinal fluid biomarkers for AD (Aβ42/Aβ40, pTau, tTau) and neurodegeneration (NfL),

little is known about biomarkers for dementia with Lewy bodies, neurogenerative diseases associated with TAR DNA-binding protein-43 (TDP-43), vascular dementia and others or about markers for neuroinflammation, synaptic loss and other processes.

Blood biomarkers

The validity and reliability of biomarkers in blood plasma (e.g., pTau isoforms, Aβ42/Aβ40, NfL, GFAP) and in cerebrospinal fluid is not yet fully established. The assays used are not standardized, which would minimize inter-laboratory variation and ensure clinical robustness. Little is known about longitudinal changes in these biomarkers and how they are related to disease progression, as well as changes in PET, atrophy and cognition. International consensus should be reached on the methods and reference ranges applicable to diverse populations.

Other fluids

The use of other types of fluids (e.g., nasal swabs) is still not backed by evidence and requires methodological and clinical validation to determine what they might offer over and above cerebrospinal fluid and blood.

New biomarkers

Longitudinal analysis of cohorts is not common; however, this could facilitate the identification of biomarkers for the different diseases that can cause dementia, even in the prodromal stages. Omics technologies could be used to identify other proteins, lipids or RNA as potential biomarkers.

Genetic biomarkers

Diversity

Little research has been undertaken on diverse populations, especially in LMIC.

Non-AD genetics

Diseases other than AD are under-researched, particularly with transcriptomics and epigenomics, and the specificity of genetic biomarkers for different types of diseases causing dementia is unclear.

Genetic variation

How variations in genetics and mutations lead to disease is insufficiently explored in research.

Sex differences

Genetic risks according to sex have been so far inadequately studied.

Ethics

The ethical implications and psychological impact of disclosure of genetic risk profiles are not well understood. This is an important consideration for genetic tests that are available to the general public.

Neuropsychological assessment

Complexity of assessment

Current tools require trained personnel (neuropsychologists), are time-intensive, are not adapted to different cultures and languages and lack appropriate normative data.

Prediction of dementia

Little is known about the role of subjective cognitive complaints or concerns in the prediction of future dementia or of the factors involved in the progression from subjective cognitive decline to mild cognitive impairment to dementia.

Technology

Current technologies such as for remote assessment and computerized testing have not been adequately validated against traditional methods and are not always accessible in low-resource settings, even after validation.

Sex differences

Differences by sex in neuropsychological assessments are not well understood or used to optimize diagnosis.

5.3 Strategic goals, actions and milestones

STRATEGIC GOAL 5

Development of biomarkers

Develop highly sensitive, specific diagnostic biomarkers for dementia that are cost–effective and can distinguish the underlying diseases that cause dementia.

Actions:

- **WHO target product profile (TPP) or preferred product characteristics (PPC).** Develop a TPP or PPC to provide guidance to funders, researchers, product developers and regulatory agencies in the development of diagnostic tools by accounting for access, equity and affordability at all stages of innovation.
- **Imaging biomarkers.** Further validate and standardize imaging biomarkers for diagnosis and monitoring of disease progression. Promote research into new imaging biomarkers, taking into account the molecular mechanisms of the different diseases causing dementia. Ensure that throughout the development process, safety, accessibility, and affordability are considered as well as their implementation in different resource settings.
- **Blood biomarkers.** Promote research on the correlation between blood biomarkers, disease progression and other biomarkers (e.g., imaging). Studies should also be conducted to assess the best combinations of clinically relevant blood biomarkers that yield the greatest benefit for diagnosis, prognosis, treatment and care. The studies must ensure appropriate representation of different populations and account for intra-day, between-day, biological variations, and disease subtypes. Studies of blood biomarkers should also address the use of different protein isoforms and conformations as potential biomarkers of diseases and their correlation with basic primary care assessments, clinical presentation and disease progression.
- **Genetic biomarkers.** Support large-scale studies to identify genetic biomarkers of the different disease subtypes, with appropriate representation of populations for whom data are currently lacking. The studies should include correlation with other clinical assessments and biomarkers, and the methods should account for sex differences.
- **Digital biomarkers.** Increase research on digital biomarkers of early dementia phenotypes, potentially with novel artificial intelligence strategies (e.g., machine and deep learning) and wearables, smart devices, cognitive measures and non-digital biomarkers *(74, 75)*. New digital solutions should not create barriers for implementation and use in clinical practice in different regions.
- **Scalability and diversity.** Conduct studies to determine the feasibility of scaling up work on fluid, blood and genetic biomarkers for clinical use and trials, and design strategies to ensure inclusion of diverse populations, LMIC and populations of low socio-economic status in such studies.
- **Precision medicine approach to biomarkers.** In view of inter-individual variation, all biomarkers used for diagnosis should be studied using a precision medicine approach to facilitate identification of disease subgroups for tailored treatment, as is currently done for certain types of cancer such as breast cancer.
- **New technologies.** Develop new platforms, scanners, assays and other techniques to find new, more accessible diagnostic tools.

Milestone 5.1: By 2027, to have developed an affordable test for diagnosis of AD that is acceptable worldwide.

Milestone 5.2: By 2030, to have developed affordable tests for diagnosis of non-AD dementias such as dementia with Lewy bodies, frontotemporal dementia and neurogenerative diseases associated with TDP-43.

STRATEGIC GOAL 6

Development of clinical assessments of cognition and function

Develop or improve clinical assessments of cognition and function that are applicable to diverse settings and cover the entire disease spectrum.

Actions:

- **Development and validation of tools.** For LMIC and diverse populations, validate evidence-based, culturally appropriate instruments for cognitive and functional assessments that can be used in primary care and provide appropriate normative data while prioritizing non-proprietary diagnostic tools to improve access. Develop screening tools that are sensitive and discriminatory in the prodromal or early phases for use in primary care of older populations and people presenting with cognitive decline.
- **Novel technologies.** Promote research into novel technologies to improve clinical assessment and monitoring of disease progression, including cognition, function and behaviour, and integrate the results with data from wearables, smart devices, cognitive measures and biomarkers. Promote the development of artificial intelligence and data science technology that is culturally fair and adaptable to local conditions.
- **Remote assessments.** Support research to validate remote dementia assessments (e.g., telemedicine via computers and smart devices) that are easy to access and adaptable to various resource and cultural contexts.
- **Global consortium.** Establish a global research consortium for clinical assessment of cognition and function with equitable regional representation to evaluate and monitor emerging evidence, and curate resources for sharing knowledge.

Milestone 6.1: By 2027, to have developed and incorporated into existing digital platforms curated clinical assessment tools for dementia diagnosis that are open access, used in primary care, culturally fair and readily adaptable to different contexts.

STRATEGIC GOAL 7

Diagnosis during prodromal stages

Improve understanding and diagnosis of prodromal stages of diseases causing dementia and of the clinical, legislative and economic implications of such diagnosis.

Actions:

- **Implications of diagnosis during prodromal stages.** Conduct rigorous research to establish the possible benefits and potential harms, including costs and the social, legal and insurance implications, of diagnosing diseases causing dementia in their prodromal stages.
- **Markers during prodromal stages.** Identify readily accessible, scalable markers to anticipate progression (or not) to dementia. Long-term cohort studies may be necessary to establish such markers.
- **Diversity.** Account for the socioeconomic, ethnic, and sex/gender diversity of populations when investigating different disease pathways and consider how these affect the accuracy of diagnosis during the prodromal stages of dementia.

Milestone 7.1: By 2030, to have developed diagnostic benchmarks for diseases causing dementia at the prodromal stages (such as mild cognitive decline and subjective cognitive decline) that are applicable in diverse settings and are identified by accessible markers.

6. Drug development and clinical trials for dementia

6.1 Context

There are few effective drug treatments for dementia. Only four drugs are currently available internationally for AD *(1)*: three acetylcholinesterase inhibitors and one N-methyl-D-aspartate receptor antagonist, and all are symptomatic treatments, with no disease-modifying properties. Since 2002, when memantine was approved for moderate-to-severe AD, no new drug has been approved. The only exception is the accelerated approval of a monoclonal antibody against amyloid β – aducanumab – by the US Food and Drug Administration in 2021 on the basis that it removes amyloid from the brains of people with AD and may have cognitive benefits. The approval is controversial for several reasons, not the least because cognitive benefits have not been conclusively established, adverse effects are significant, and there is no strong evidence in this specific case that the removal of amyloid is associated with clinical benefits *(76)*. Drugs for treating the neuropsychiatric symptoms of dementia, which are often difficult to manage, also remain inadequate.

As mentioned in section 2.3, the cost of bringing a new drug to market approval is prohibitively high, and, although many large pharmaceutical companies have halted their efforts around dementia, interest in the field is being renewed by collaborations among industry, academia and governments. Examples are the Alzheimer's Prevention Initiative, the United Kingdom Dementia Consortium, the Accelerating Medicines Partnership – Alzheimer's Disease, the European Union Joint Programme – Neurodegenerative Disease Research and the Davos Alzheimer's Collaborative. In a recent review *(77)*, 143 agents were identified in 172 clinical trials on AD listed in the www.clinicaltrials.gov database, of which 83.2% were putatively disease-modifying drugs, 9.8% cognitive enhancers and 6.9% for treatment of neuropsychiatric symptoms. Of the different drugs, 31 were in phase-III, 84 in phase-II and 30 in phase-I trials. Of the drugs under investigation, 37% were repurposed. Drug repositioning and repurposing has been recognised as a valuable alternative route for effective treatments. A Delphi consensus in 2018–2019 identified several candidates for repurposing *(78)* and described potential use of transcriptional signatures from cells in various diseases to identify candidate drugs.

Drug development for vascular cognitive impairment and dementia has been limited to treatment or prevention of small- and large-vessel disease or post-stroke interventions and some symptomatic treatment of cognitive impairment *(79)*. Some studies have approached the prevention of dementia by preventing strokes on the basis of the shared risk factors for vascular cognitive impairment, dementia and stroke *(80)*. Fewer drugs have been developed for other diseases that cause dementia. For example, in 2019, www.clinicaltrials.gov listed eight agents in clinical trials for dementia with Lewy bodies, which included some disease-modifying drugs *(81)*. Several disease-modifying drugs for frontotemporal dementia are now in phase-II trials *(82)*, but results will only be available in several years.

The approaches to treatment development have thus far largely focused on single molecules or other treatments with a specific disease focus, such as immunotherapy for specific disorders or targeting specific enzymatic pathways. However, different underlying diseases often contribute to dementia development, progression and disease phenotypes. Even when one, such as AD, is the cause, many pathways are involved. It might therefore be necessary to intervene at several pathways or several points on the same pathway to achieve clinically meaningful benefits *(83)*. Consideration should therefore be given to developing combination treatments delivered simultaneously or sequentially.

More attention should also be paid to the precision medicine approach, whereby a treatment is tailored to a patient's specific condition. Much of the delay in this field is due to pooling patients with different conditions and testing the same drug in all of them (e.g., amyloid-negative individuals in amyloid-lowering trials). Addressing this requires the use of disease-specific biomarkers and their development for other dementia-related conditions is essential.

New therapies are necessary to improve the lives of people with dementia and their carers. An appropriate, better coordinated regulatory environment must provide transparent guidance to developers, streamline regulation and identify clear requirements for the approval and release of drugs. The return on investment and cost–effectiveness of therapies must also be investigated, as discussed in chapter 3.

6.2 Research gaps

Multiple underlying diseases

Dementia is associated not with one but with many diseases that may have different causes and potentially an additive effect. Better understanding these associations is essential to develop effective therapies, perhaps with several targets.

The drug development pipeline for AD does not reflect its complex, diverse mechanisms

While major advances have been made around AD, major gaps remain in understanding the pathophysiological process and the relation between pathology and clinical presentation. Although non-amyloid pathways in AD, including tauopathy, neuroinflammation, oxidative stress and synaptic loss, are also being addressed with diverse strategies, the interaction of these pathways and how different treatment strategies should be combined for synergistic effects are not well understood. Better understanding of the mechanisms, including the underlying causes of the diseases, and the biological causes of behaviours and psychological symptoms associated with dementia is required to identify targets and ensure effective treatments (see chapter 4).

Timing of interventions

The diseases that cause dementia often occur many years before the onset of any clinical symptoms and the timing of an intervention is likely to be crucial in determining its success. Although many agree that interventions should be made as early as possible, when and how to introduce interventions and whether they differ according to the underlying disease, the presence of comorbid conditions, genetic background and sex remain to be understood.

Suboptimal clinical trial design

Due to the slow evolution and progression of dementia symptoms, clinical trials for assessing the prevention (see chapter 8), treatment or cure of dementia are natually long. This makes clinical trials very expensive and prone to high rates of attrition. More adaptive clinical trials should be conducted, and clinical trial networks should be established to make trials more feasible, equitable and inclusive. This will require engagement of research beneficiaries and the general public.

Underrepresentation in clinical trials

Research on drug development and clinical trials lack population and geographical diversity (84). Even in HIC, socially marginalized populations are usually under-represented. The pharmacokinetics and pharmacodynamics of drugs in many populations are therefore not well studied, resulting in inequity. Despite being at greater risk of developing dementia, women are under-represented in clinical trials for AD *(85)*.

Insufficient collaboration

Drug development is an intensely collaborative exercise. It requires partnerships among scientists, pharmaceutical companies, clinical trialists, health specialists and service providers. Collaborative networks should include academia, industry and government, and trials should be truly international. Such collaboration and networks are only just starting to be established.

Involvement of people with lived experience

The research beneficiaries, i.e., the people living with or at risk of cognitive disorders and their carers, must be central to any study and be involved in all stages. Consumer involvement is not the norm in many jurisdictions.

6.3 Strategic goals, actions and milestones

STRATEGIC GOAL 8

Development of novel therapies

Develop novel molecules, repurpose drugs currently in use or newly developed and investigate next-generation biotherapeutics for effective treatment of dementia.

Actions:

- **Multiple targets.** Promote research to investigate both amyloid and non-amyloid targets and the biological causes of behaviours and psychological symptoms associated with dementia, and consider diverse populations, different sexes, different genetic backgrounds and comorbid conditions.
- **Investment in non-AD therapeutics.** Increase investment in the development of treatments for diseases causing dementia other than AD, including Lewy body disease and frontotemporal dementia.
- **Novel approaches.** Develop next-generation therapeutics that target the cell, gene or nucleotide and treatments that target brain networks for resilience, maintenance and repair for dementia in general as well as specific pathological processes. Other novel approaches such as antimicrobial treatments, the gut–brain axis (including nutritional interventions), stem cell therapy, brain stimulation and parabiosis should be further investigated.
- **Combination therapy.** Increase research on combination therapies for dementia that target the many pathways involved.
- **Complex disease mechanisms.** Include consideration of the complex mechanisms of diseases underlying dementia in the design of therapeutics and the results of the actions proposed in chapter 4. This is also applicable to the four actions above.
- **Cognition as an outcome.** Include cognition as a secondary outcome of trials for treatments of NCDs (e.g., diabetes, mellitus, hypertension, coronary artery disease, stroke) to explore the potential role of these treatments in cognitive disorders and to identify new drugs and drugs that could be repurposed for the treatment of dementia.
- **Precision medicine.** Apply the principles of precision medicine in dementia research to verify both the efficacy of a treatment and the reliability of specific biomarkers.
- **Access, safety and capacity.** At all stages of treatment development, integrate consideration of access, equity, affordability and health system capacity to provide the treatment.
- **Collaboration.** Strengthen local and national networks that link researchers "from the bench to the bedside", and create adequate infrastructure for progress from preclinical research to phase-III trials.
- **Integration of databases.** Support countries in creating research databases for dementia therapeutics that are harmonized internationally to streamline efforts and funding for the development of dementia therapeutics, promote collaboration and avoid unnecessary duplication. Databases should include efforts by private industry and not-for-profit actors.
- **International platforms.** Building on national databases, promote the establishment of an international drug development platform to connect expertise in medicinal chemistry, pharmacokinetics, toxicology, animal models and trial design in order to fill any gaps in particular regions or countries, thereby encouraging true collaboration while taking into consideration sharing of intellectual property.

Milestone 8.1: By 2027, to have established therapeutics development networks and national research databases for dementia treatment, with support from governments, academia, industry and philanthropic organizations, and to have integrated national databases into international platforms.

Milestone 8.2: By 2027, to have ensured that new trials on treatment of diseases such as diabetes mellitus, hypertension, stroke and coronary artery disease include cognitive assessment as a secondary outcome and make the data available to researchers for analysis and consideration for repurposing of therapies.

Milestone 8.3: By 2030, to have developed disease-modifying therapy for AD that is safe and affordable and has a clear clinical benefit.

STRATEGIC GOAL 9

Improving clinical trials

Facilitate the translation of preclinical findings into human trials in all phases up to approval and introduction of treatments, with hallmarks of the trials being efficiency, consistency and equity.

Actions:

- **Adaptive, efficient trial designs.** Design more adaptive trials of two or more treatments for use in combination.
- **Recruitment of patients and timing of interventions.** As the pathological processes that cause dementia often predate the onset of clinical symptoms by many years, design trials to recruit patients as early as possible when relevant to the therapeutic strategy.
- **Harmonized international outcome measures.** Improve international collaboration for identifying and validating outcome measures for clinical trials, including cognitive and functional outcomes and biomarkers. Global consensus should be sought on the acceptable safety of drugs, with consumer involvement.
- **International guidance for trials:** Based on the three actions above, develop expert guidance on the design of clinical trials for drug development to ensure global harmonization, equity and safety to all.
- **Partnerships and collaboration for trials.** Foster collaboration among triallists, including researchers, clinicians, pharmacologists and statisticians, and involve academia, clinical medicine, industry and consumer organizations to agree on the designs and outcome measures of efficient, adaptive trials.
- **International trial infrastructure.** To ensure equity and develop infrastructure for trials in both HIC and LMIC, so that trials are international, gender-balanced, include all populations, are fully transparent and provide equal access to the data and results by researchers in all settings. A national registry and a database of people who are interested in trial participation should be established, and the research workforce should be trained to ensure that they have the required skills and competence. Triallists should ensure that trial participants are appropriately supported after conclusion of the trials.

Milestone 9.1: By 2027, to have developed standardized expert guidance on the design of clinical trials for drug development.

Milestone 9.2: By 2027, to have developed capacity in countries to conduct clinical intervention trials for dementia, especially in LMIC, including basic infrastructure and workforce and ensuring appropriate involvement and recruitment of people living with dementia.

STRATEGIC GOAL 10

Legislative and regulatory environments

Develop legislative frameworks and appropriate regulatory environments in countries for the execution of trials, approval of drugs and devices, cost–benefit analyses and post-marketing surveillance.

Actions:

- **National ethical and regulatory frameworks.** Strengthen national ethical and regulatory frameworks for clinical trials to ensure international consistency, and reduce legal, regulatory and administrative obstacles when possible. Efforts should be made to harmonize such frameworks globally to avoid obstacles to international collaboration.
- **Treatment development frameworks.** Develop regulatory frameworks for trials of new treatments, their approval for clinical use and their post-approval surveillance, in line with international standards.
- **Health economics frameworks.** Develop health economics frameworks to evaluate the cost–benefit of a new treatment before its approval, to be repeated subsequently as required in the context of national health budgets and health priorities.
- **Guidance on approval requirements for new drugs.** Develop clear guidance for drug developers, highlighting the requirements and milestones that need to be achieved for approval.

Milestone 10.1: By 2027, countries to have strengthened their national ethical and regulatory frameworks for the conduct of trials, approval of drugs and devices, their cost–benefit analysis and post-marketing surveillance, that are internationally harmonized.

7. Dementia care and support

7.1 Context

Dementia requires complex care, and research into dementia care must be based on both sound evidence from health systems and robust clinical and interventional science. Both aspects of dementia care research are covered in this chapter, with cross-links to relevant topics such as economics and pathophysiology that are covered in other chapters.

Dementia services and support range from diagnosis and treatment to secondary prevention of cognitive and non-cognitive symptoms of dementia to long-term care, rehabilitation, end-of-life support and services for carers and families *(4)*. Ideally, these services are provided in the community or in primary care to allow people with dementia to live at home as long as possible and continue to be part of their communities. Coordinated home care models *(87)* and, when necessary, person-centred institutional care models *(88)* have been shown to be effective. There is, however, increasing recognition that health and social care systems worldwide are unable to meet these complex needs *(89, 90)*, and most low- and some middle-income countries have limited dementia or long-term care services *(1, 57, 91)*. Even in HIC, the quality of dementia care in the community and institutional long-term care settings varies, and the services often do not meet the needs of people with dementia *(92, 93)*. Globally, dementia care pathways are often fragmented, are not person-centred *(94)* and often do not reflect the research evidence.

Access to a well-trained dementia workforce also varies by country. For instance, in almost one in five LMIC, basic training in dementia is not provided to relevant health-care cadres (e.g., doctors, nurses, nurse aids, pharmaceutical personnel, social workers); such a lack is seen in only 1 in 10 HIC *(1, 57)*. Similarly, specialists with expertise in diagnosing and treating dementia, such as neurologists, geriatricians and psychogeriatricians, are more common in HIC than LMIC, with median numbers of psychogeriatricians per 100 000 population of 2.2 and 0.02, respectively *(1)*. Insufficient numbers and an under-skilled workforce are barriers to the provision of good-quality dementia care *(95, 96)*.

Important pillars of dementia care provision are family members and close friends, who provide most of the care for people with dementia, particularly in LMIC. The bulk of the burden is borne by women: wives, daughters and daughters-in-law *(1)*. While there are positive aspects to caregiving, it can negatively affect the physical and mental health of carers. General lack of knowledge on how to provide care for people living with dementia also negatively impacts the prognosis. Family carers should be given information, education, support and access to formal care *(97)*. Carer education and support programmes have been shown to be effective as well as cost–effective *(98, 99)*.

While the world is searching for a cure or disease-modifying treatments (see chapter 6), research on dementia care has shifted from a predominant focus on improving or maintaining cognition or decreasing behavioural changes to outcomes such as a better quality of life, positive living with dementia, "reablement", compensation for disability and improving daily function, mood, social health, community participation and social and emotional communication.

Non-cognitive symptoms of dementia such as changes in behaviour, often referred to as behaviours and psychological symptoms associated with dementia, are common, distressing and require additional care *(20)*. Growing evidence suggests that non-pharmacological interventions, such as psychosocial interventions, are effective in preventing, reducing or treating non-cognitive symptoms *(100)*. Similarly, evidence suggests that rehabilitative interventions such as cognitive stimulation therapy, cognitive rehabilitation, physical exercise and gait/balance training can improve cognition, function, stability and/or the quality of life of people with dementia *(101)*. Evidence is emerging that some psychosocial

interventions are effective when delivered remotely on websites, apps and telehealth, and that assistive products are valuable to promote and maintain optimal levels of functioning and independence *(102, 103)*.

7.2 Research gaps

Methodological issues in clinical research

Harmonized methodologies and outcome measures

For evaluating interventions, there is a lack of appropriate methodologies and outcome measures that reflect the priorities of people living with dementia and their carers and that are suitable for different cultural, language and regional contexts in both formal and informal care settings. Approaches are also required to measure and harmonize the outcomes of interventions for under-researched aspects, including social health, stigmatization and self-efficacy.

Non-pharmacological interventions

There is a lack of research on the cost–effectiveness and acceptability of family-based psychosocial support that harnesses the value systems of families that are taking care of older family members, as for other chronic mental and physical conditions *(104)*. Similarly, scalable, cost-effective interventions are necessary to support carers of people living with dementia, reduce the negative impact of caregiving on carers' health and improve the care of people with dementia.

Psychosocial and biological basis of behaviours and psychological symptoms associated with dementia

Current interventions targeting behavioural changes and psychological symptoms often focus only on the manifesting symptoms and are not designed to address their causes (see chapters 4 and 6).

Remote monitoring technologies

There is insufficient research into technologies that combine sensors and smart home devices with clinical monitoring. Such combination may allow home monitoring and early intervention and thus represent a potential means to reduce hospital admissions, improve person-centred care and promote independence. Evidence is also lacking on how members of the community (e.g., police, transport workers) could be involved in the identification and safety of people with dementia who are lost and in tracing their carers.

Delivery of care, the continuum of care and health systems research

Models of care delivery and low-cost care

There is a lack of well-studied strategies for improving dementia care throughout the care continuum, from diagnosis to end-of-life care in primary or community care, long-term care, hospitals and specialist settings. Research on low-resource, low-cost but effective models of care is essential, particularly for LMIC.

Implementation research

Insufficient implementation research is conducted to understand barriers to care and to identify the best ways to apply current evidence throughout the care continuum, at all levels of health and social care systems.

Inequities in dementia care

Dementia care is often inequitable, especially for people in rural areas, ethnic minorities, people with disabilities, people living alone and other groups that have poorer access to and quality of care *(105)*. These inequities are poorly described and accounted for, and mitigating strategies are lacking to provide optimal care for all.

Training and retention of the workforce

There is scarce evidence on how best to recruit, train and then retain dementia specialists and generalists and the long-term care workforce.

Telehealth

Robust evidence is required on the cost–effectiveness of telemedicine approaches and their adaptability to ensure their acceptability and implementation. Approaches to overcome low levels of technological literacy and enabling of populations without Internet access are also lacking.

Health administrative data

Administrative data are not collected in many countries and for subnational regions, or such systems are in their early stages of development. More research is necessary to reduce the barriers to collecting data. Even in countries that do collect data, they have often not been used in population-based research on dementia care, especially in models of long-term care suitable for low-resource settings.

7.3 Strategic goals, actions and milestones

STRATEGIC GOAL 11

Tools and methodologies for interventions

Have high-quality tools and methodologies for the design, adaptation and evaluation of dementia care interventions that are applicable internationally and can be adapted locally.

Actions:

- **Collaboration in care interventions.** Convene potential collaborators (countries, philanthropic organizations, civil society, private sector) and experts in evidence-based interventions to study and implement care interventions that target specific gaps in care provision, including support and training of family carers in a sustainable manner and for different settings and contexts.
- **Representative research designs.** Design research that includes person-centred, value-based outcome measures, recruitment and data collection methods to ensure equitable participation of underrepresented populations including cultural and language adaptation for interventions. Conduct research in environments as close to real-life settings as possible, for example, in the home or in "living laboratories".
- **Harmonized methods and frameworks.** Develop and disseminate health service research methods such as interrupted time series, mixed methods case series, policy reviews and health economics. Develop a harmonized framework for contextualized, inclusive research design and outcome measurement. Promote research on implementation design and evaluation of interventions.
- **Interventions for the causes of behaviours and psychological symptoms associated with dementia.** Investigate how to better incorporate the understanding of the biological, psychosocial and environmental causes of behaviours and psychological symptoms associated with dementia, into effective care interventions that target both its causes and symptoms. These interventions should also be developed for community settings outside institutional long-term care.
- **New technologies.** Develop affordable, scalable, adaptable technologies and collect high-quality data on the use of innovative care solutions, including electronic health records, medication trackers and reminders, sensors for dementia-related measures (e.g., urinary tract infection, sleep disturbances, behaviour change), fall and motion sensors and personal emergency systems. This will require multidisciplinary collaboration among experts in disciplines such as engineering, data science and clinical medicine and people living with dementia and carers.
- **Administrative data.** Support research based on health administration data, and support strengthening of such systems in LMIC.

Milestone 11.1: By 2027, to have created a toolkit for implementation of care interventions that can be tailored to various areas of care provision and easily adapted in different resource settings.

Milestone 11.2: By 2027, to have developed internationally applicable guidance on the ethics, practicality, capture, storage and use of health administrative data on dementia.

STRATEGIC GOAL 12

Models across the continuum of care

Develop affordable and cost-effective care models across the continuum of care from diagnosis to the end of life for primary care/community, long-term care, rehabilitation, hospital and specialist settings that are appropriate for ethnic, regional, economic and cultural contexts.

Actions:

- **Culturally appropriate models.** Invest in research into models for delivery of high-quality care that is accessible in low-income settings and to non-specialist personnel, including community interventions for people living with dementia and their carers. Promote research on the integration of different care models.
- **Specialist care models.** Conduct research to evaluate specialist care models of care for people with severe dementia and/or severe behaviours and psychological symptoms associated with dementia throughout the health and social care systems.
- **Telemedicine models.** Research and develop new telemedicine models that are easy to implement and adaptable to local contexts, accounting for populations with restricted internet access and low technological literacy.
- **Implementation in diverse contexts.** Undertake research on how models of care can be adapted to different cultures and contexts, in particular in LMIC.
- **Barriers to access to care.** Conduct research to improve understanding of the barriers to access to care, particularly in LMIC and marginalized communities, and identify health system gaps, synergies and opportunities.
- **Workforce capacity.** Promote research to understand the training requirements for the dementia care workforce, particularly in LMIC, and how they can be met with effective, affordable, sustainable education and training. Research should also be conducted to determine how the workforce can be recruited and retained in the numbers required.

Milestone 12.1: By 2030, to have evidence-based, effective, sustainable models of community and institutional long-term care and rehabilitation programmes that are tailored to populations, culturally appropriate, financially viable, account for diversity in the population and prioritize the needs of people with dementia and their carers.

8. Dementia risk reduction

8.1 Context

Twelve potentially modifiable risk factors across the lifespan account for up to 40% of dementia cases worldwide *(106)* (Fig. 5). As many of the risk factors for dementia are also those for NCDs, effective integration of dementia risk reduction into programmes such as for tobacco cessation, cardiovascular disease prevention and nutrition is an important public health strategy.

The WHO Guidelines on risk reduction of cognitive decline and dementia *(107)* provide support for countries in designing public health interventions to reduce the risks of cognitive decline and dementia (Fig. 5).

Apart from the risk factors already identified, others are being investigated and may emerge as important targets for reducing the risk of dementia, such as use of certain medications, insufficient sleep and infections. Risk and protective factors also differ by ethnic group and geographical location, and their prevalence is changing in most regions. As average educational attainment increases and other modifiable risk factors are better addressed in some countries, inequalities during the life course, such as in access to care, treatments and healthy diets, may become more marked and create barriers to preventive measures.

Fig. 5. Modifiable risk factors for dementia and recommendations for interventions to reduce risk from WHO guidelines

Evidence-based risk factors from the Lancet commission on dementia prevention, intervention and care (2020):

1. less education
2. hypertension
3. hearing impairment
4. smoking
5. obesity
6. depression
7. physical inactivity
8. diabetes
9. low social contact
10. excessive alcohol consumption
11. traumatic brain injury
12. air pollution.

Evidence-based recommendations for interventions to reduce the risk of dementia from WHO guidelines (2019):

1. physical activity interventions
2. tobacco cessation interventions
3. nutritional interventions
4. interventions for alcohol use disorders
5. cognitive interventions
6. weight management
7. management of hypertension
8. management of diabetes mellitus
9. management of dyslipidaemia.

More evidence required for:
- management of depression
- management of hearing loss
- interventions to increase social activity.

Sources: Dementia prevention, intervention, and care: 2020 report of the Lancet Commission *(106)* and Risk reduction of cognitive decline and dementia: WHO guidelines *(107)*.

While many risk factors are the same as those for other NCDs, such as cardiovascular disease and diabetes, some are specific to dementia and are attracting more research. For example, social health *(108)*, which includes consideration of a person's social context (such as living situation, relationship status, social network size), its function (such as social support) and its quality (such as satisfaction with relationships, loneliness) *(109)*. The association between poor social health (i.e., a small social network, infrequent social interactions, little social support) and the risk of cognitive decline or incident dementia is now well established *(106, 110–112)*. Furthermore, the risk of cognitive impairment or dementia has been linked to the built environment, which comprises the physical environment in which people live, work, travel and socialize *(113)*. Research suggests an association between exposure to neighbourhood resources such as green spaces and positive cognitive outcomes *(114)* while an increased risk of dementia is observed with exposure to air pollution and pesticides *(115, 116)*.

In view of projected worldwide demographic ageing and the lack of a cure or widely accepted disease-modifying treatment for dementia, it is important to reduce the individual and population risks of dementia. Evidence suggests that modification of lifestyle and other risk factors can slow cognitive decline and delay the onset of dementia or prevent it altogether *(117)*.

People are exposed to dementia risk factors throughout their lives, with the basis of brain health established in utero *(17)*. Maternal malnutrition, prenatal exposures to toxins and perinatal morbidity directly affect brain health. Childhood malnutrition, less education and adverse childhood experiences also impact brain health in early life, while other risk factors, including comorbid conditions and social adversity affect brain health in mid- and later life *(17)*. Many of these risk factors (e.g., air pollution) are beyond the control of individuals or even a subset of the population (e.g., being unable to afford healthy diets or living in areas that are unsafe for outdoor exercise). Work on dementia prevention has comprised mainly individual behaviour change rather than approaches for whole populations *(118)*. Observational studies supplemented by a small but growing number of controlled trials now make a persuasive case for action to reduce the risk of dementia at both policy and population levels and for individual-level interventions *(106)*.

While treating individual risk factors is important, the evidence is strongest for lifelong accumulation of multiple risk factors for dementia *(119)*. Primordial prevention programmes can have strong positive effects on society by establishing conditions and opportunities for healthy communities and healthy lifestyles before birth and throughout the life course. Therefore, multimodal individual and population interventions targeting several risk factors concurrently over time have been proposed and used. The best known is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER trial) *(120)*, which showed a 25% greater improvement in global cognition in the intervention group than in the control group that received only general health advice. Building on these promising findings, the World-wide FINGERS network involves research teams in over 40 countries and is an example of adaptation of a multidomain intervention for diverse geographical and cultural settings *(121)*. While there is some evidence that multidomain interventions have benefits in terms of cognitive decline, they have not yet been shown to be effective in reducing incident dementia or mild cognitive impairment *(119)*.

8.2 Research gaps

Methodology

Strength and representativeness of evidence

The strength of evidence differs for different modifiable risk factors and interventions for reducing the risk of dementia *(106, 107)*. Some interventions to modify certain risk factors such as use of hearing aids and antidepressant medications and interventions for increasing social activity require more robust, high-quality evidence. Little evidence is available on modifiable risk factors in LMIC or in culturally, sexually and linguistically diverse sub-populations in both HIC and LMIC *(106, 122)*.

Methodology for interventions

Given the many risk factors associated with dementia, approaches to reduce risks are likely to be more effective in combination. There is currently a lack of robust methodologies for evaluating the impact and efficacy of combined individual and population approaches.

Harmonization of measures

Inconsistencies in conceptual definitions, methodologies and measures of risk factors and outcomes limit the ability to compare data from different sources *(123)*. More precise measures of interindividual variation and longitudinal change are also lacking *(124, 125)*.

Lifespan approach

Most of the evidence on risk factors and interventions is for cohorts of older adults *(125)* exposed in mid-life *(106)*, with limited long-term data *(107, 124)*. There is a lack of evidence on exposure throughout the lifespan, from prenatal to early and mid-life, on mitigation of risk factors and on the use and effectiveness of such interventions for people aged ≥ 85 years (a rapidly growing segment of the population) and for people already living with dementia.

Risk factors and interventions

Biological mechanisms

The biological mechanisms underpinning the relation between modifiable risk factors and brain health are poorly understood *(124)*. There are also few robust data on sex-specific risk factors such as early menopause and complications during pregnancy and on the differential effect of risk factors in men and women, as recently shown for cardiovascular events *(125)*.

Social health

Social connections, comprising social structure, function and quality, has often been addressed only partly in cohort studies, from single-item measures instead of validated scales *(111)*. Furthermore, they often address social connections in late life rather than in mid-life, and data on social connections in LMIC *(127)* and from culturally, linguistically and gender-diverse subpopulations are lacking. There are no measures of social adaptation in the face of chronic illness. More theoretical and psychometric work is needed to extend knowledge of social health as a risk factor for dementia. Moreover, few prospective studies have been conducted, which would reduce potential bias due to reverse causality (i.e., cognitive decline causing poor social health).

Contemporary cohorts

More data are required on modifiable risk factors in contemporary cohorts *(124)* in view of the global changes in risk factors, such as greater longevity and an increased prevalence of vascular risk factors (diabetes, hypertension, obesity) in some LMIC *(122)*. Participants from some birth cohort studies, such as the British 1946 cohort *(128)*, have now reached old age and would be highly relevant for modelling life course exposure to risk and late-life outcomes.

Risk scores

Several risk scores have been developed, some of which have been validated and used in tools for widespread screening *(129)*. For accurate prediction of the risk of dementia, risk scores include both modifiable and non-modifiable risk factors, such as age and sex. No risk scores have been developed specifically for LMIC, and only a few tools developed in HIC have been found to be suitable for use in LMIC *(118)*.

Interactive effects

There is little evidence on the potentially interactive effects of modifiable risk factors, which has implications for the optimal design of multidomain interventions, their cost–effectiveness and the identification of best buys.

Whole-population approaches to dementia risk reduction

More evidence is necessary for the implementation of whole-population approaches, which require commitment from diverse stakeholders, including government, industry and workplaces. These include investment in green spaces and built infrastructure to promote physical activity, policies to promote access to healthy diets and decrease the salt content in food, age-friendly environments, internet access in rural areas to improve social cohesion and integration and policies for decreasing air pollution *(17, 118)*.

Outcome measures

Few intervention studies on dementia risk reduction have included incident dementia as the outcome *(107)* or classified the incidence of dementia *(124)*. Dementia risk scores may be useful surrogate outcomes in prevention trials, but evidence for their validity is currently limited.

Implementation

There has been little research on implementation strategies, particularly in LMIC, and on the effectiveness of individual behaviour change outside the controlled environment of a clinical trial (118). Promising interventions must be appropriately tailored for diverse contexts before their effectiveness can be assessed and their scalability and sustainability adequately accounted for to maximize benefits.

8.3 Strategic goals, actions and milestones

STRATEGIC GOAL 13

Methodologies and approaches for risk reduction research

Improve and generate standardized methodology for research on risk reduction, reach consensus on outcome measures, improve the diversity of samples, and promote collaboration and consumer participation.

Actions:

- **Develop a framework for global harmonization of data.** Develop international guidelines to harmonize standards and best practice, building on projects such as World-Wide FINGERS *(121)*. International consensus should be reached on measures of risk factors and outcomes, increasing synergy with preventive measures for other NCDs and with appropriate diversity and representation.
- **Adopt a life course perspective, including early life experience.** Start new birth cohorts and maintain existing ones (and/or extend their outcome measures to include cognitive and neuroimaging variables) to obtain prospective lifelong epidemiological data. Individuals who develop dementia during follow-up periods should remain in cohorts and not be excluded. Consider age and cumulation of exposure to risk factors in retrospective cohorts.
- **Develop methods to assess interventions at various levels.** Support the development of methods to evaluate and generate high-quality data on large-scale, multi-domain interventions with individual, whole-population and a combination of both approaches to risk reduction.
- **Increase diversity and representativeness.** As risk factors can vary among population groups, prioritize diversity and representativeness (especially with respect to LMIC, culturally and linguistically diverse subpopulations, Indigenous peoples and other marginalized communities). Funders should require applicants to address this aspect by designing research in collaboration with diverse stakeholders.
- **Include incident dementia and cognition as outcome measures.** Ensure that population-level and policy research on other diseases include cognition and dementia incidence (including disease subtypes) as outcome measures. Treatment trials for NCDs that are risk factors for dementia (including diabetes mellitus, hypertension, coronary artery disease, stroke) must include cognitive assessment and/or neuroimaging in order to explore the role of treatment on cognitive outcomes.
- **Facilitate data collection in many fields (e.g., health, education, environment).** Promote capacity-building in data science and "big data" to ensure optimal, ethical use of large datasets from various sectors (e.g., national, administrative and online data, medical records) and linkage to observational and interventional datasets. Projects such as the Methods for longitudinal studies in dementia *(130)*, the DEMON Network *(131)*, the Social Health and Reserve in the Dementia Patient Journey project *(132)* and the iMAP cohort study *(133)* for the built environment should be expanded. Data-sharing and harmonization are also applicable to strategic goals 14 and 15.

Milestone 13.1: By 2027, to have reached international consensus on outcome measures for studies of risk factors and prevention that are flexible enough to include new risk factors and methodological advances in the measurement of risk factors.

Milestone 13.2: By 2027, to have a framework for harmonization of data on risk reduction.

STRATEGIC GOAL 14

Understanding risk factors

Develop a better understanding of the risk factors for dementia, including the diverse health, social and environmental determinants of brain health, resilience and promotion mechanisms, as well as differences between and within countries.

Actions:

- **Dementia risk factors within the context of brain health promotion.** Foster research on the effects of wider brain health determinants across the life course on dementia risk at individual and population level *(17)*.
  - Promote research to improve the quality of evidence and investigate physical health determinants of dementia and brain health more broadly, including maternal health, genetic and epigenetic factors, nutrition, infections, comorbidity with other NCDs and sensory impairment, traumatic brain injuries and health behaviours.
  - Examine the extent to which the level of education influences the rate of dementia. Investigate whether protective factors reduce the incidence of dementia by improving cognitive reserve (e.g., social interaction, multilingualism, complexity of occupation, physical activity and other indicators of a healthy lifestyle).
  - Promote research to better understand the impact of air pollution and climate change, health emergencies such as the COVID-19 pandemic and exposure to chemicals (e.g., heavy metals and pesticides) on the brain and dementia risk.
- **Interactive risk factors.** Given the multifactorial etiology of dementia and the interactive effects of modifiable and non-modifiable risk factors on dementia risk, use multidomain approaches to study reduction of dementia risk.
- **Inequality and cultural differences.** Investigate how social, financial and health inequalities and various cultural aspects impact the determinants listed above. Conduct longitudinal studies to better understand the impact of structural, economic and social inequalities on the risk of developing dementia and how interventions aiming to mitigate these inequalities can be designed, implemented at scale, and yield positive outcomes.
- **Risk scores.** Develop scores for modifiable and non-modifiable risk factors that can be used in various resource environments and regions and that take into account the entire life course.

Milestone 14.1: By 2027, to have initiated comprehensive analytical epidemiological studies in diverse ethnic, regional and geographical settings to address current inequity in data availability and to understand changes in the prevalence and incidence of risk factors.

Milestone 14.2: By 2027, to have established and validated risk scores for identification of individuals who are likely to develop dementia.

STRATEGIC GOAL 15

Risk reduction interventions

Generate robust evidence of the efficacy, cost-effectiveness and return on investment of interventions to reduce the risk of dementia across the life course and in different settings. This should include promotion of healthy behaviours and non-pharmacological interventions for both individual behaviour change and societal approaches, grounded in better awareness and understanding of dementia by the general population, to promote informed, extensive adherence to risk reduction programmes.

Actions:

- **Evidence of interventions.** In line with the 2019 WHO Guidelines on reducing the risk of cognitive decline and dementia *(107)*, the following actions should be taken according to the strength of current evidence:
  - **High-quality evidence.** For these interventions (e.g., for management of hypertension), conduct and evaluate the outcomes of large individual and population-based interventions, including post-implementation surveillance and policy analysis; and study approaches to improve the scalability and generate evidence on return of investment.
  - **Moderate-quality evidence.** For these interventions (e.g., for physical activity), conduct large randomized controlled trials of single or multiple domains, and use evidence for policy making and implementation at population level.
  - **Low-quality evidence.** For these interventions (e.g., for cognitive interventions), perform large-scale clinical trials with appropriate representation of minority populations and standardized methods to develop strategies for improving the robustness and reliability of data.
  - **Insufficient evidence.** For these interventions (e.g., for management of depression), facilitate the conduct of high-quality clinical trials on safety and efficacy and on implementation strategies to reduce the risk of cognitive decline and/or dementia.

- **Population approaches.** Derive robust, representative data on the effectiveness of population or policy interventions, such as taxation of alcohol, tobacco and sugar, prevention of head injuries and reducing air pollution and the use of pesticides. The scale and intensity of these interventions must be proportionate and tailored to the degree of disadvantage in an entire community and in subpopulations of that community *(118)*.

- **WHO risk reduction guidelines.** Update the WHO Guidelines on risk reduction of cognitive decline and dementia with the new evidence generated.

- **Interventions at various levels.** Initiate studies to understand the efficacy of both individual and population-level interventions for risk reduction, and investigate potential synergistic effects.

- **Interventions across the life course.** Initiate ambitious, large-scale, long-term studies starting early in life, or extend existing studies to investigate incident dementia or cognition as outcomes; also, validate other measures as surrogate or proxy end-points for diverse populations. The risk scores described in strategic goal 14 are promising surrogate end-points, but their validity should be established across the life course and in different national and sub-national contexts *(134)*.

- **Novel technologies.** In the context of both single and multi-domain interventions to enhance cognition and brain health, assess the efficacy of and adherence to new technologies and e-health solutions to scale up and broaden the reach of risk reduction interventions, including in LMIC and under-resourced subpopulations in HIC. The extent to which these solutions are effective in isolation or require additional face-to-face support should also be considered.

Milestone 15.1: By 2027, to have extended the breadth and geographical representativeness of studies of individual- and population-level approaches to dementia risk reduction, including not only individual behaviour changes but also the efficacy of policy interventions.

Milestone 15.2: By 2030, to have established evidence of efficient interventions on health, environmental and social determinants that reduce the risk for dementia throughout the life course.

9. Conclusion

The blueprint for dementia research is WHO's first initiative of this kind in the context of non-infectious diseases. It acknowledges that significant scientific advances have been made in the last decades towards a better understanding of dementia and its underlying diseases. Yet, collectively, we are far behind finding a cure for dementia by 2025, a goal set during the 2013 G8 dementia summit, or achieving the global targets outlined in the global action plan on the public health response to dementia 2017—2025. Addressing this challenge requires the global prioritisation of dementia, and this blueprint will support coordinating efforts among stakeholders, closing research gaps, fast-tracking research development and innovation, as well as ensuring the successful implementation of research outcomes.

WHO's blueprint for dementia research summarizes the current state of dementia research across six broad research themes, identifies existing research gaps, and outlines 15 strategic goals with actions and timebound milestones to address these gaps. For example, the blueprint reiterates our still limited understanding of the underlying diseases causing dementia and the dire need for disease-modifying therapies, better diagnostic tools, and care strategies. The blueprint also emphasizes the urgency to strengthen evidence on risk factors and effective risk reduction interventions, as well as to develop better methodologies to track epidemiological trends, identify cost-effective interventions, and measure the economic impact associated with dementia.

To accelerate global research efforts related to dementia and to create an enabling research environment, the blueprint identifies eight cross-cutting drivers of research. For instance, an essential driver of research is the empowerment and engagement of people with lived experience in all aspects of research including, but certainly not limited to, training and capacity building of researchers; their engagement in research will increase the impact of scientific discoveries and ensure that research meets the needs of people most affected by dementia. Other drivers essential to the advancement of dementia research include diversity and equity; funding; access to science, data and materials; capacity building for research; technology; knowledge translation; and regulatory environments. To bring about impactful scientific advances for dementia, it is imperative to implement and monitor these drivers so that they become the norm rather than rare examples of good practice.

As the global research community and political decision-makers learn from the COVID-19 pandemic response, stakeholders at all levels — including people with lived experience, researchers, funders, and policy makers — must collaborate and set out comprehensive strategies for the adequate and timely response to dementia. As such, WHO encourages national and international research agencies, together with other funding bodies, to use this blueprint to inform upcoming funding streams and operationalize the outlined drivers of research. Civil society can ensure that advocacy efforts are likewise aligned, supporting the drive for a more equitable, efficient, and collaborative research landscape. Finally, researchers can support the achievement of milestones and strategic goals of this blueprint by addressing the research gaps identified.

The implementation, impact, and achievement of the milestones detailed in this blueprint will be measured using existing WHO frameworks and resources, such as the Global Dementia Observatory, WHO Global Health Observatory, WHO Global Observatory on Health Research and Development, WHO's Health Equity Monitor. In addition, WHO's monitoring mechanisms for the blueprint are aligned with the *Global action plan on the public health response to dementia 2017–2025*, the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031*, as well as with SDGs targets and other World Health Assembly mandates. Other existing monitoring platforms and information gathered from academic literature and reports will also be included. In addition, to support monitoring efforts, regular technical meetings and seminars will be held with relevant stakeholders, which will inform on the scientific progress.

WHO will work with all stakeholders across relevant sectors to ensure that the actions outlined in the blueprint are implemented, milestones are achieved, and strategic goals are realised, with the ultimate goal of improving the quality of life of and supports offered to people living with dementia, their carers and families.

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Annex
Summary of research themes, strategic goals and milestones

Research theme	Strategic goals	Milestones
 **Dementia epidemiology and economics**	**Strategic goal 1:** Ensure availability of high-quality epidemiological data from widely representative geographical, ethnic and socioeconomic groups with appropriate disaggregation by gender and sex, age, disease severity and subtypes and relevant measures of inequity.	**Milestone 1.1:** By 2027, to have international benchmarks for epidemiological studies and use of open-access, inter-operable, international platforms to archive and share epidemiological data from regions around the world. **Milestone 1.2:** By 2030, to have a comprehensive dataset from high-quality epidemiological studies that include geographical, ethnic and regional populations for whom there are currently insufficient data to fill major gaps in international data. **Milestone 1.3:** By 2030, to have ensured that countries have high-quality dementia registries to monitor dementia and the quality of its assessment and care.
	Strategic goal 2: Establish better understanding of the economic impact of dementia on society, and generate robust evidence on the cost–effectiveness of risk reduction, treatment and care.	**Milestone 2.1:** By 2027, to have established a database on burden of disease and cost estimates for dementia from different geographical, ethnic and regional groupings around the world. **Milestone 2.2:** By 2030, to have generated robust evidence on the cost–effectiveness of treatment and care interventions and strategies to reduce the risk of dementia to support establishment of public health interventions throughout the life course.
 **Dementia disease mechanisms and models**	**Strategic goal 3:** Increase understanding of the origins and mechanisms of the diseases that cause dementia through a life course approach.	**Milestone 3.1:** By 2027, to have developed an international collaborative network for sharing basic scientific data and techniques, technical innovations and materials that includes both HIC and LMIC, academia, government and industry. **Milestone 3.2:** By 2027, to have established new life course cohorts to investigate the development and progression of various diseases causing dementia. **Milestone 3.3:** By 2030, to increase understanding of the cellular and molecular mechanisms (e.g., protein aggregation, inflammation, lysosomal dysfunction, oxidative stress) of the different diseases causing dementia and the relevance of determinants and pathways throughout the life course.
	Strategic Goal 4: Develop models of the diseases that cause dementia that reflect their complex mechanisms and downstream molecular events.	**Milestone 4.1:** By 2030, to have improved ex-vivo and animal models that represent molecular disease characteristics and phenotypes, and are ecologically valid for dementia in humans and underlying diseases.

Annex: Summary of research themes, strategic goals and milestones continued

Research theme	Strategic goals	Milestones
 **Diagnosis of dementia**	**Strategic goal 5:** Develop highly sensitive, specific diagnostic for neurodegenerative disease that are cost-effective and can distinguish the underlying diseases that cause dementia.	**Milestone 5.1:** By 2027, to have developed an affordable test for diagnosis of AD that is acceptable worldwide. **Milestone 5.2:** By 2030, to have developed affordable tests for diagnosis of non-AD dementias such as dementia with Lewy bodies, frontotemporal dementia and neurogenerative diseases associated with TDP-43.
	Strategic goal 6: Develop or improve clinical assessments of cognition and function that are applicable to diverse settings and cover the entire disease spectrum.	**Milestone 6.1:** By 2027, to have developed and incorporated into existing digital platforms curated clinical assessment tools for dementia diagnosis that are open access, used in primary care, culturally fair and readily adaptable to different contexts.
	Strategic goal 7: Improve understanding and diagnosis of prodromal stages of diseases causing dementia and of the clinical, legislative and economic implications of such diagnosis.	**Milestone 7.1:** By 2030, to have developed diagnostic benchmarks for diseases causing dementia at the prodromal stages (such as mild cognitive decline and subjective cognitive decline) that are applicable in diverse settings and are identified by accessible markers.
 **Drug development and clinical trials for dementia**	**Strategic goal 8:** Develop novel molecules, repurpose drugs currently in use or newly developed and investigate next-generation biotherapeutics for effective treatment of dementia.	**Milestone 8.1:** By 2027, to have established therapeutics development networks and national research databases for dementia treatment, with support from governments, academia, industry and philanthropic organizations, and to have integrated national databases into international platforms. **Milestone 8.2:** By 2027, to have ensured that new trials on treatment of diseases such as diabetes mellitus, hypertension, stroke and coronary artery disease include cognitive assessment as a secondary outcome and make the data available to researchers for analysis and consideration for repurposing of therapies. **Milestone 8.3:** By 2030, to have developed disease-modifying therapy for AD that is safe and affordable and has a clear clinical benefit.
	Strategic goal 9: Facilitate the translation of preclinical findings into human trials in all phases up to approval and introduction of treatments, hallmarks of the trials being efficiency, consistency and equity.	**Milestone 9.1:** By 2027, to have developed standardized expert guidance on the design of clinical trials for drug development. **Milestone 9.2:** By 2027, to have developed capacity in countries to conduct clinical intervention trials for dementia, especially in LMIC, including basic infrastructure and workforce and ensuring appropriate involvement and recruitment of people living with dementia.
	Strategic goal 10: Develop legislative frameworks and appropriate regulatory environments in countries for the execution of trials, approval of drugs and devices, cost–benefit analyses and post-marketing surveillance.	**Milestone 10.1:** By 2027, countries to have strengthened their national ethical and regulatory frameworks for the conduct of trials, approval of drugs and devices, their cost–benefit analysis and post-marketing surveillance, that are internationally harmonized.

Annex: Summary of research themes, strategic goals and milestones continued

Research theme	Strategic goals	Milestones
 **Dementia care and support**	**Strategic goal 11:** Have high-quality tools and methodologies for the design, adaptation and evaluation of dementia care interventions that are applicable internationally and can be adapted locally.	**Milestone 11.1:** By 2027, to have created a toolkit for implementation of care interventions that can be tailored to various areas of care provision and easily adapted in different resource settings. **Milestone 11.2:** By 2027, to have developed internationally applicable guidance on the ethics, practicality, capture, storage and use of health administrative data on dementia.
	Strategic goal 12: Develop affordable and cost-effective care models across the continuum of care from diagnosis to the end of life for primary care/community, long-term care, rehabilitation, hospital and specialist settings that are appropriate for ethnic, regional, economic and cultural contexts.	**Milestone 12.1:** By 2030, to have evidence-based, effective, sustainable models of community and institutional long-term care and rehabilitation programmes that are tailored to populations, culturally appropriate, financially viable, account for diversity in the population and prioritize the needs of people with dementia and their carers.
 **Dementia risk reduction**	**Strategic goal 13:** Improve and generate standardized methodology for population-based research on risk reduction, reach consensus on outcome measures, improve the diversity of samples, and promote collaboration and consumer participation.	**Milestone 13.1:** By 2027, to have reached international consensus on outcome measures for studies of risk factors and prevention that are flexible enough to include new risk factors and methodological advances in the measurement of risk factors. **Milestone 13.2:** By 2027, to have a framework for harmonization of data on risk reduction.
	Strategic goal 14: Develop a better understanding of the risk factors for dementia, including the diverse health, social and environmental determinants of brain health, resilience and promotion mechanisms, as well as differences between and within countries.	**Milestone 14.1:** By 2027, to have initiated comprehensive analytical epidemiological studies in diverse ethnic, regional and geographical settings to address current inequity in data availability and to understand changes in the prevalence and incidence of risk factors. **Milestone 14.2:** By 2027, to have established and validated risk scores for identification of individuals who are likely to develop dementia.
	Strategic goal 15: Generate robust evidence of the efficacy, cost-effectiveness and return on investment of interventions to reduce the risk of dementia across the life course and in different settings. This should include promotion of healthy behaviours and non-pharmacological interventions for both individual behaviour change and societal approaches, grounded in better awareness and understanding of dementia by the general population, to promote informed, extensive adherence to risk reduction programmes.	**Milestone 15.1:** By 2027, to have extended the breadth and geographical representativeness of studies of individual- and population-level approaches to dementia risk reduction, including not only individual behaviour changes but also the efficacy of policy interventions. **Milestone 15.2:** By 2030, to have established evidence of efficient interventions on health, environmental and social determinants that reduce the risk for dementia throughout the life course.

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