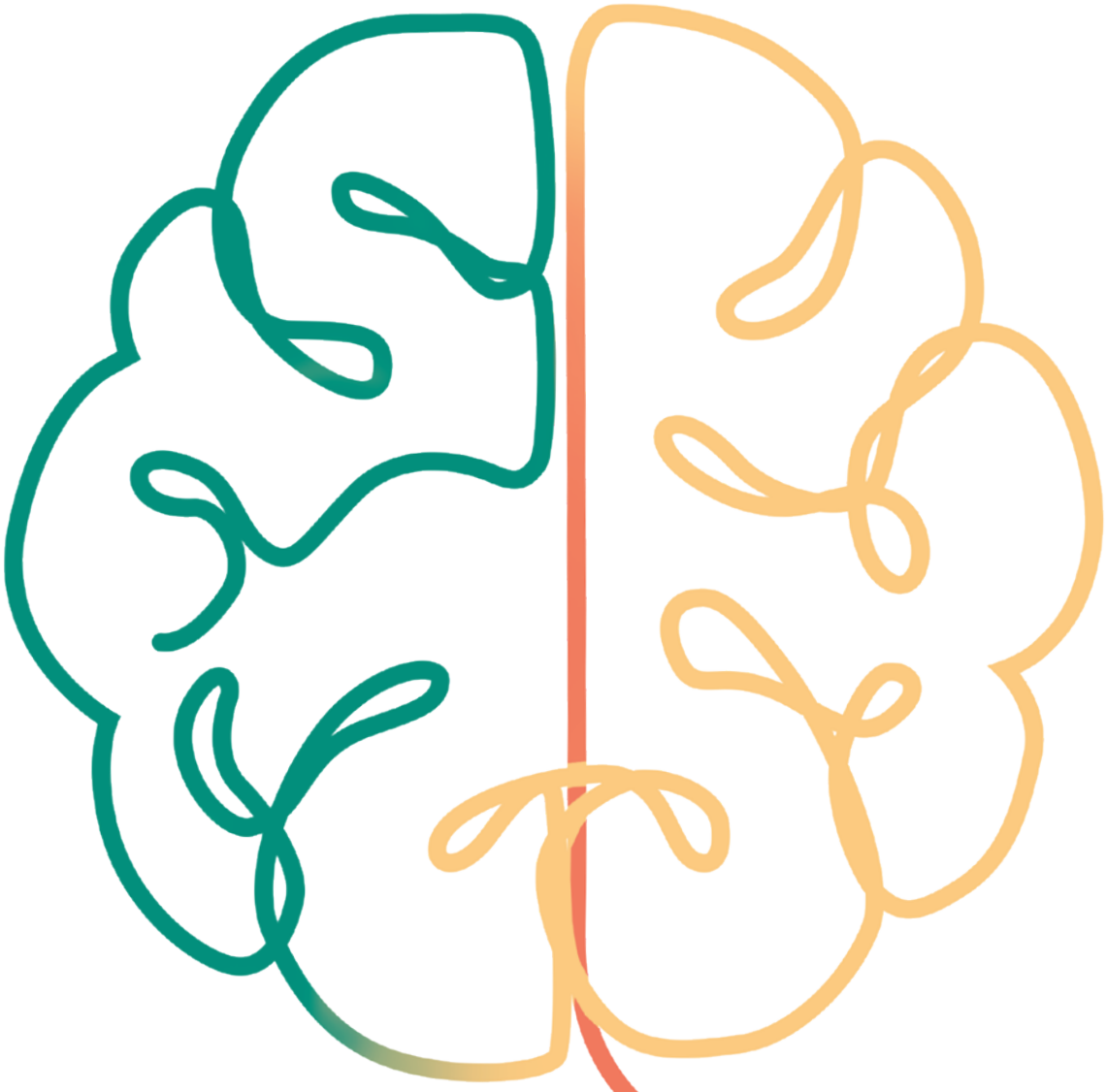
RISK REDUCTION OF COGNITIVE DECLINE AND DEMENTIA

WHO GUIDELINES



World Health Organization

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Risk reduction of cognitive decline and dementia: WHO guidelines

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FOREWORD

Dementia is a rapidly growing public health problem affecting around 50 million people around the world. There are nearly 10 million new cases every year and this figure is set to triple by 2050. Dementia is a major cause of disability and dependency among older people and can devastate the lives of affected individuals, their carers and families. Additionally, the disease inflicts a heavy economic burden on societies as a whole, with the costs of caring for people with dementia estimated to rise to US$ 2 trillion annually by 2030.

While there is no curative treatment for dementia, the proactive management of modifiable risk factors can delay or slow onset or progression of the disease. In May 2017, the Seventieth World Health Assembly endorsed a *Global Action Plan on the Public Health Response to Dementia 2017–2025,* urging Member States to develop, as soon as feasible, ambitious national responses to address this challenge. Dementia risk reduction is one of the seven action areas in the global action plan.

These new WHO guidelines provide the knowledge base for health care providers, governments, policy-makers and other stakeholders to reduce the risks of cognitive decline and dementia through a public health approach. As many of the risk factors for dementia are shared with those of non-communicable diseases, the key recommendations can be effectively integrated into programmes for tobacco cessation, cardiovascular disease risk reduction and nutrition.

I urge all stakeholders to make the best use of these recommendations to improve the lives of people with dementia, their carers and their families.

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ACKNOWLEDGEMENTS

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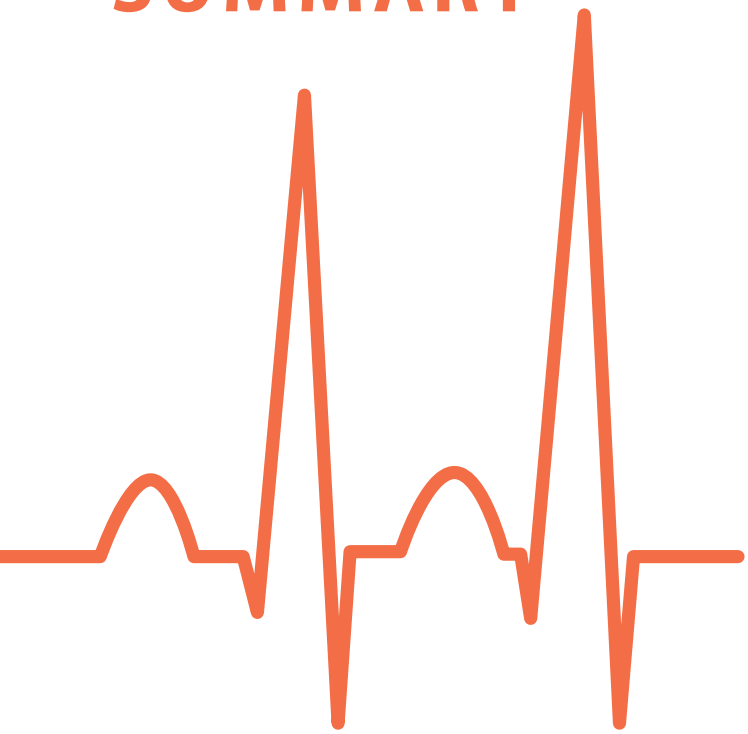
ACRONYMS

ACE	angiotensin converting enzyme
AD	Alzheimer disease
ADAS-cog	Alzheimer Disease Assessment Scale-Cog
ADL	activities of daily living
AHRQ	Agency for Healthcare Research and Quality (United States of America)
ARB	angiotensin receptor blocker
BMI	body mass index
CCB	calcium channel blocker
CI	confidence interval
CVRF	cardiovascular risk factors
CVD	cardiovascular disease
DALYs	disability-adjusted life years
DASH	dietary approaches to stop hypertension
DoI	declaration of interest
EMBASE	Excerpta Medica dataBASE
ERG	external review group
GDG	guideline development group (WHO)
GDP	gross domestic product
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
IADL	instrumental activities of daily living
ICOPE	Integrated Care for Older People (WHO)
LMIC	low- and middle-income countries
MCI	mild cognitive impairment
MDRS	Mattis Dementia Rating Scale
MeSH	Medical Subject Headings
mhGAP	Mental Health Gap Action Programme (WHO)
MMSE	Mini Mental State Examination
NCDs	noncommunicable diseases
NIA	National Institute on Aging (United States of America)
NICE	National Institute of Health and Care Excellence (United Kingdom)
OR	odds ratio

PEN	Package of Essential Noncommunicable Disease Interventions (WHO)
PICO	population, intervention, comparison, outcome
PUFA	polyunsaturated fatty acids
RCT	randomized controlled trial
RR	relative risk
SMD	standardized mean difference

EXECUTIVE SUMMARY



INTRODUCTION

Dementia is a rapidly growing global public health problem. Worldwide, around 50 million people have dementia, with approximately 60% living in low- and middle-income countries (LMIC). Every year, there are nearly 10 million new cases. The total number of people with dementia is projected to reach 82 million in 2030 and 152 million in 2050. Dementia leads to increased costs for governments, communities, families and individuals, and to loss in productivity for economies. In 2015, the total global societal cost of dementia was estimated to be US$ 818 billion, equivalent to 1.1% of global gross domestic product (GDP).

Crucially, while age is the strongest known risk factor for cognitive decline, dementia is not a natural or inevitable consequence of ageing. Several recent studies have shown a relationship between the development of cognitive impairment and dementia with lifestyle-related risk factors, such as physical inactivity, tobacco use, unhealthy diets and harmful use of alcohol. Certain medical conditions are associated with an increased risk of developing dementia, including hypertension, diabetes, hypercholesterolemia, obesity and depression. Other potentially modifiable risk factors include social isolation and cognitive inactivity. The existence of potentially modifiable risk factors means that prevention of dementia is possible through a public health approach, including the implementation of key interventions that delay or slow cognitive decline or dementia.

In May 2017, the Seventieth World Health Assembly endorsed the *Global action plan on the public health response to dementia 2017–2025* (WHO, 2017a). The action plan includes seven strategic action areas and

dementia risk reduction is one of them. The action plan calls upon the WHO Secretariat to strengthen, share and disseminate an evidence base to support policy interventions for reducing potentially modifiable risk factors for dementia. This involves providing a database of available evidence on the prevalence of those risk factors and the impact of reducing them; and supporting the formulation and implementation of evidence-based, multisectoral interventions for reducing the risk of dementia.

The risk reduction guidelines for cognitive decline and dementia are aligned with WHO's mandate to provide evidence-based guidance for a public health response to dementia.

GUIDELINE DEVELOPMENT METHODS

The process of development of these guidelines followed the *WHO handbook for guideline development* and involved:

1. recruitment of the guideline development group (GDG);
2. declaration of interest by GDG members and peer reviewers;
3. scoping review to formulate questions and select outcomes;
4. identification, appraisal and synthesis of available evidence;
5. formulation of recommendations with inputs from a wide range of stakeholders; and
6. preparation of documents and plans for dissemination.

The GDG, an international group of experts, provided input into the scope of the guidelines and assisted the steering group in developing the key questions. A total of 12 PICO (population, intervention, comparison and outcome) questions were developed.

To address the PICO questions, a series of searches for systematic reviews was conducted and Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profiles prepared. During a meeting at WHO headquarters in Geneva, 2–3 July 2018, the GDG discussed the evidence, sought clarifications and interpreted the findings in order to develop recommendations. The GDG considered the balance of benefit and harm of each intervention; values and preferences; costs and resource use; and other relevant practical issues for providers in LMIC.

When making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweigh any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. **Strong recommendations** imply that most individuals would want the intervention and should receive it, while **conditional recommendations** imply that different choices may be appropriate for individual patients and they may require assistance at arriving at management decisions. The GDG members reached a unanimous agreement on all the recommendations and ratings.

SUMMARY OF RECOMMENDATIONS

Physical activity interventions	**Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline.** *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***strong***
	Physical activity may be recommended to adults with mild cognitive impairment to reduce the risk of cognitive decline. *Quality of evidence:* ***low*** *Strength of the recommendation:* ***conditional***
Tobacco cessation interventions	**Interventions for tobacco cessation should be offered to adults who use tobacco since they may reduce the risk of cognitive decline and dementia in addition to other health benefits.** *Quality of evidence:* ***low*** *Strength of the recommendation:* ***strong***
Nutritional interventions	**The Mediterranean-like diet may be recommended to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***conditional***
	A healthy, balanced diet should be recommended to all adults based on WHO recommendations on healthy diet. *Quality of evidence:* ***low to high (for different dietary components)*** *Strength of the recommendation:* ***conditional***
	Vitamins B and E, polyunsaturated fatty acids and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***moderate*** *Strength of the recommendation:* ***strong***
Interventions for alcohol use disorders	**Interventions aimed at reducing or ceasing hazardous and harmful drinking should be offered to adults with normal cognition and mild cognitive impairment to reduce the risk of cognitive decline and/or dementia in addition to other health benefits.** *Quality of evidence:* ***moderate (for observational evidence)*** *Strength of the recommendation:* ***conditional***
Cognitive interventions	**Cognitive training may be offered to older adults with normal cognition and with mild cognitive impairment to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***very low to low*** *Strength of the recommendation:* ***conditional***
Social activity	**There is insufficient evidence for social activity and reduction of risk of cognitive decline/dementia.**
	Social participation and social support are strongly connected to good health and well-being throughout life and social inclusion should be supported over the life-course.

Weight management	**Interventions for mid-life overweight and/or obesity may be offered to reduce the risk of cognitive decline and/or dementia.** *Quality of evidence:* ***low to moderate*** *Strength of the recommendation:* ***conditional***
Management of hypertension	**Management of hypertension should be offered to adults with hypertension according to existing WHO guidelines.** *Quality of evidence:* ***low to high (for different interventions)*** *Strength of the recommendation:* ***strong***
	Management of hypertension may be offered to adults with hypertension to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***very low (in relation to dementia outcomes)*** *Strength of the recommendation:* ***conditional***
Management of diabetes mellitus	**The management of diabetes in the form of medications and/or lifestyle interventions should be offered to adults with diabetes according to existing WHO guidelines.** *Quality of evidence:* ***very low to moderate (for different interventions)*** *Strength of the recommendation:* ***strong***
	The management of diabetes may be offered to adults with diabetes to reduce the risk of cognitive decline and/or dementia. *Quality of evidence:* ***very low*** *Strength of the recommendation:* ***conditional***
Management of dyslipidaemia	**Management of dyslipidaemia at mid-life may be offered to reduce the risk of cognitive decline and dementia.** *Quality of evidence:* ***low*** *Strength of the recommendation:* ***conditional***
Management of depression	**There is currently insufficient evidence to recommend the use of antidepressant medicines for reducing the risk of cognitive decline and/or dementia.**
	The management of depression in the form of antidepressants and/or psychological interventions should be provided to adults with depression according to existing WHO mhGAP guidelines.
Management of hearing loss	**There is insufficient evidence to recommend use of hearing aids to reduce the risk of cognitive decline and/or dementia.**
	Screening followed by provision of hearing aids should be offered to older people for timely identification and management of hearing loss as recommended in the WHO ICOPE guidelines.

1

INTRODUCTION

1.1
BACKGROUND AND RATIONALE FOR THESE GUIDELINES

Dementia, a group of disorders characterized by a decline from a previously attained cognitive level that affects activities of daily living (ADL) and social functioning, poses one of the greatest global challenges for health and social care in the 21st century.

In 2015, dementia affected 50 million people worldwide (or roughly 5% of the world's elderly population, i.e. those above the age of 60 years). The number of people with dementia is expected to increase to 82 million in 2030 and 152 million by 2050 with the estimated proportion of the population aged 60 and over with dementia at a given time between 5 to 8%[1] because dementia rises exponentially during old age and the world's population is ageing. These projections assume constant age- and sex-specific prevalence of dementia over time, and, accordingly, the steepest rises are expected especially in low- and middle-income countries (LMIC), where the demographic changes will be more marked.

Dementia is a major cause of disability and dependency among older people worldwide, and it has a significant impact not only on individuals but also on carers, families, communities and societies. Dementia accounts for 11.9% of the years lived with disability due to a noncommunicable disease (NCD) worldwide. Dementia leads to increased costs for governments, communities, families and individuals, and to loss in productivity for economies. The annual global cost of dementia is estimated to be US$ 818 billion (OECD, 2015; WHO, 2017b). Nearly 85% of costs are related to family and social, rather than medical, care (GBD 2015 Neurological Disorders Collaborator Group, 2017). Most health systems are ill-equipped and under-resourced to respond to the current needs associated with dementia. Thus, societal ageing and the associated increases in dementia prevalence will likely have major health-service implications for the care of people with dementia and support for affected families.

There are many different causes and types of dementia. Primary dementias include: dementia due to Alzheimer disease (AD), vascular dementia, dementia with Lewy bodies and frontotemporal dementia (in which the decline in cognitive abilities itself is mostly due to an underlying neurodegenera-tive process and not directly caused by other etiologies). Alzheimer disease is the most common, followed by vascular dementia and dementia with Lewy bodies. Mixed dementia with features of more than one type is also common, especially in older adults, while frontotemporal dementia is a less common form but relatively more frequent before old age.

Secondary dementias are those caused by, or closely related to, some other recognizable disease, such as HIV, head injury, multiple sclerosis, thyroid disorders or vitamin B12 deficiency. In these secondary dementias, cognitive impairment is typically accompanied by symptoms and signs in other organ systems and the treatment focuses on management of the underlying disease.

For the scope of these guidelines we refer to primary dementias. Though early treatment of some diseases may have the potential to prevent the onset of secondary dementias, we are not including these

[1] WHO & King's College London (2017). Global prevalence of dementia – updated figures 2017. Available at: https://www.who.int/news-room/fact-sheets/detail/dementia

secondary dementias in the scope of these guidelines since there are prevention or appropriate management and treatment strategies for most of these specific diseases and conditions, which effectively reduce dementia-related signs and symptoms. However, late-onset dementia is a heterogeneous and multifactorial condition and some factors (i.e. head trauma, B12 deficiency earlier in life) may also contribute to the development of dementia later in life (not only secondary dementia).

RISK FACTORS FOR DEMENTIA

Non-modifiable risk factors for dementia include gene polymorphisms, age, gender, race/ethnicity and family history. Crucially, while age is the strongest known risk factor for cognitive decline, dementia is not a natural or inevitable consequence of ageing. During the last two decades, several studies have shown a relationship between the development of cognitive impairment and dementia with educational attainment, and lifestyle-related risk factors, such as physical inactivity, tobacco use, unhealthy diets and harmful use of alcohol. Further, certain medical conditions are associated with an increased risk of developing dementia, including hypertension, diabetes, hypercholesterolemia, obesity and depression. Other potentially modifiable risk factors may include social isolation and cognitive inactivity. The risk factors included in the scope of these guidelines were chosen based on recent systematic reviews and guidelines, i.e. National Institute of Health and Care Excellence (United Kingdom) (NICE, 2015); the United States of America Agency for Healthcare Research and Quality (AHRQ) systematic review (Kane et al., 2017); the World Alzheimer report 2014 (Prince, et al., 2014) and the report by the Lancet Commission on Dementia Prevention, Intervention, and Care (Livingston et al., 2017). The current focus on modifiable risk factors is justified by their potential to be targeted for prevention of dementia, and/or the delay of the progression of cognitive decline.

NEED FOR THESE GUIDELINES

The existence of potentially modifiable risk factors means that prevention of dementia is possible through a public health approach, including the implementation of key interventions that delay or slow cognitive decline or dementia.

In May 2017, the Seventieth World Health Assembly endorsed the *Global action plan on the public health response to dementia 2017–2025* (WHO, 2017a). The vision of the action plan is a world in which dementia is prevented and people with dementia and their carers live well and receive the care and support they need to fulfil their potential with dignity, respect, autonomy and equality. The goal of the action plan is to improve the lives of people with dementia, their carers and families, while decreasing the impact of dementia on them as well as on communities and countries. The action plan includes seven strategic action areas, and dementia risk reduction is one of them. The action plan calls upon the WHO Secretariat to strengthen, share and disseminate an evidence base to support policy interventions for reducing potentially modifiable risk factors for dementia. This involves providing a database of available evidence on the prevalence of those risk factors and the impact of reducing them; and supporting the formulation and implementation of evidence-based, multi-sectoral interventions for reducing the risk of dementia. These current guidelines represent the first steps to support countries as they develop approaches to delay or prevent the onset of dementia.

The risk reduction guidelines for cognitive decline and dementia are aligned with WHO's mandate to provide evidence-based guidance for a public health response to dementia. By supporting health and social care professionals, particularly by improving their capacity to provide evidence-based, multisectoral, gender and culturally appropriate interventions to the general population, including modifiable dementia risk factors that are shared with other NCDs, the risk of developing dementia can be potentially reduced, or its progression delayed. Thus, the guidelines align with WHO's work in the area of prevention and management of NCDs, which aims to support countries to reduce the incidence, morbidity and mortality of NCDs. WHO has collaborated with a range of stakeholders, including international and national public health agencies working in the area of prevention of NCDs and dementia.

The guidelines are in close conceptual and strategic synergy with other WHO action plans and strategies, i.e. the *Comprehensive mental health action plan 2013–2020,*[2] *the Global action plan for the prevention and control of noncommunicable diseases 2013–2020,*[3] the *Global strategy and action plan on ageing and health 2016–2020,*[4] the *Global strategy to reduce harmful use of alcohol*[5] and the *Global strategy on diet, physical activity and health*.[6] Furthermore, this work is aligned with the WHO move towards making health services more people-centred. Finally, the work will contribute to the attainment of Sustainable Development Goal 3, target 3.8, i.e. achieve universal health coverage, including financial risk protection, access to quality essential healthcare services and access to safe, effective, quality and affordable essential medicines and vaccines for all (UN, 2019).

[2] Available at http://www.who.int/mental_health/action_plan_2013/en/
[3] Available at http://www.who.int/nmh/publications/ncd-action-plan/en/
[4] Available at http://who.int/ageing/global-strategy/en/
[5] Available at http://www.who.int/substance_abuse/activities/gsrhua/en/
[6] Available at http://www.who.int/dietphysicalactivity/Indicators%20English.pdf

1.2 RELATED WHO GUIDELINES AND TOOLS

Several existing WHO guidelines and tools designed for the general population are relevant for addressing health conditions that may increase the risk of cognitive decline or dementia in individuals with normal cognition or mild cognitive impairment (MCI). The following WHO guidelines and tools were consulted when developing the current guidelines:

- mhGAP Intervention guide – Version 2.0 for mental, neurological and substance use disorders in non-specialized health settings. Geneva: WHO, 2016. *http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/*

- Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings. Geneva: WHO, 2012. *http://apps.who.int/iris/bitstream/10665/76173/1/9789241548397_eng.pdf*

- Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Geneva: WHO, 2010. *http://www.who.int/cardiovascular_diseases/publications/pen2010/en/*

- Global recommendations on physical activity for health. Geneva: WHO, 2010. *http://www.who.int/dietphysicalactivity/publications/9789241599979/en/*

- Integrated care for older people (ICOPE): Recommendations on interventions to improve physical and mental capacities of older people at community level. Geneva: WHO, 2016.

- HEARTS Technical package for cardiovascular disease management in primary health care: evidence-based treatment protocols. *http://www.who.int/cardiovascular_diseases/hearts/en/*

- Global age-friendly cities: a guide. Geneva: WHO, 2007. *http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf*

- Recommendations on healthy diet. Geneva: WHO, 2019. *http://www.who.int/en/news-room/fact-sheets/detail/healthy-diet*

- Strengthening health systems for treating tobacco dependence in primary care. Geneva: WHO, 2013. *http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/*

- Framework on integrated people-centred health services. Geneva: WHO, 2016. *http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_39-en.pdf?ua=1*

These existing WHO guidelines and tools address some of the interventions that are included in the scope of the current guidelines, but they do not include cognitive decline or dementia as outcomes. Where the current guidelines overlap with the other guidelines, e.g. ICOPE guidelines, which provide recommendations on cognitive interventions in people with MCI, we have referred to these existing recommendations, rather than developing new ones. The current guidelines, therefore, complement, but do not duplicate, existing work.

1.3
TARGET AUDIENCE

The guidelines are primarily targeted at health care providers working at a first or second level facility or at district level, including basic outpatient and inpatient services. The health care providers could be doctors, nurses or other cadres of health workers. Quality improvement teams at all levels of the system will benefit from the work.

In addition, the guidelines and their derivative products have implications for policy-makers, health care planners and programme managers at national and international level, as well as the general population.

1.4
GOALS AND OBJECTIVES

- To provide evidence-based recommendations on lifestyle behaviours and interventions to delay or prevent cognitive decline and dementia in the general population.

- To provide evidence-based recommendations on management of specific physical and mental health conditions to delay or prevent cognitive decline and dementia.

These guidelines provide up-to-date WHO evidence-based recommendations to facilitate implementing the *Global action plan on the public health response to dementia 2017–2025*, the *Comprehensive mental health action plan 2013–2020* and *WHO's Mental Health Gap Action Programme (mhGAP)*,[7] the *Global action plan for the prevention and control of noncommunicable diseases 2013–2020*,[8] the *Global strategy and action plan on ageing and health 2016–2020*,[9] the *Global strategy to reduce harmful use of alcohol*,[10] and the *Global strategy on diet, physical activity and health*.[11]

1.5 GUIDING PRINCIPLES

The following principles have informed the development of these guidelines and should guide their implementation:

- The guidelines should expedite the achievement of the goals outlined in the *Global action plan on the public health response to dementia 2017–2025*, as well as target 3.4 of the Sustainable Development Goals, which focuses on reducing the premature mortality from NCDs and the promotion of mental health and well-being (UN, 2019).
- The process of developing these guidelines, and their subsequent implementation, should concretely foster the right to equal levels of health for people at risk of cognitive decline and dementia and promote their active involvement.
- The recommendations should be implemented with accompanying efforts to safeguard the human rights of persons living with cognitive decline and dementia, including reduction of stigma and discrimination, reducing barriers to seek health and social care services, and ensuring informed decision-making in treatment choices.

Implementation of the recommendations should be tailored to the local context, including the availability of financial and human resources. However, the inequities addressed in these guidelines are common across all countries, and should be made a priority in health services.

[7] Available at http://www.who.int/mental_health/action_plan_2013/en/
[8] Available at http://www.who.int/nmh/publications/ncd-action-plan/en/
[9] Available at http://who.int/ageing/global-strategy/en/
[10] Available at http://www.who.int/substance_abuse/activities/gsrhua/en/
[11] Available at http://www.who.int/dietphysicalactivity/Indicators%20English.pdf

2

GUIDELINE DEVELOPMENT PROCESS

The process of developing these guidelines followed the *WHO Handbook for guideline development* (2nd edition, *http://apps.who.int/medicinedocs/en/m/abstract/Js22083en/).*

It consisted of the following steps.

2.1 GUIDELINE DEVELOPMENT GROUP

A WHO guideline steering group, led by the Department of Mental Health and Substance Abuse, was established with representatives from WHO regional offices and relevant WHO departments and programmes. The guideline steering group provided overall support to the guideline development process. Two additional groups were established: a guideline development group (GDG) and an external review group (ERG). The GDG included a panel of academicians and clinicians with multidisciplinary expertise on the conditions covered by the guidelines. Consideration was given to geographic diversity and gender balance (see Annex 1).

As a respected researcher in the field, the Chairperson was selected for their extensive experience of guideline development methodology, and their participation in other guideline development groups. Each potential GDG member was asked to complete the WHO declaration of interest (DoI) form. These were reviewed by the steering group.

2.2 DECLARATIONS OF INTEREST BY THE GDG MEMBERS AND EXTERNAL REVIEWERS

All GDG members, peer reviewers and systematic review team members were requested to complete the DoI prior to the evidence review process for guideline development. Invitations to participate in the GDG meeting were sent only after the DoI had been reviewed and approved. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs, as well as additional information (internet and bibliographic database search), and evaluated if there were any conflicts of interest and if so, whether these required a management plan. The group composition was finalized after this process.

The names and brief biographies of the members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member were presented and GDG members, as well as external partners, were asked to update their DoI with relevant changes by notifying the WHO Secretariat.

Declarations of interest were reassessed for potential conflict before the face-to-face meeting in Geneva. None of the members had major conflicts of interest. All decisions were documented (see Annex 2).

2.3 COLLABORATION WITH EXTERNAL PARTNERS

The Center for Alzheimer Research at the Karolinska Institutet, Stockholm, Sweden, and the School of Psychology at the University of New South Wales and Neuroscience Research, Australia, supported the development of the guidelines by conducting the evidence review and synthesis.

2.4 IDENTIFYING, APPRAISING AND SYNTHESIZING AVAILABLE EVIDENCE

The procedure of the scoping review to identify the draft population, intervention, comparison, outcome (PICO) questions consisted of the identification of potentially modifiable risk factors and interventions for cognitive decline or dementia. These interventions are summarized in existing WHO guidelines listed earlier, such as the *Prevention and control of noncommunicable diseases; Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings;* and *Integrated care for older people (ICOPE) guidelines*. These guidelines, however, do not include cognitive decline or dementia as outcomes.

Among recent summary reports, the Lancet Commission on Dementia Prevention, Intervention, and Care report summarizes the emerging knowledge on dementia risk factors and interventions (Livingston et al., 2017). The risk factors and interventions reported in this set of systematic reviews included education, exercise, maintaining social engagement, reducing smoking, and management of hearing loss, depression, hypertension, diabetes and obesity. Another systematic review requested and supported by the National Institute on Aging (NIA) at the National Institutes of Health, United States of America, also identified risk factors and evidence for interventions, specifically cognitive training, blood pressure management and exercise (Kane et al., 2017). The interventions reported in these reviews have formed the basis of the interventions included in the PICO questions.

The population in these guidelines considered adults with normal cognition as well as those with MCI. We use the term MCI to refer to a disorder characterized by impairment of memory, learning difficulties and reduced ability to concentrate on a task for more than brief periods, beyond what is expected in normal ageing. There is often a marked feeling of mental fatigue when mental tasks are attempted, and new learning is found to be subjectively difficult even when objectively successful. None of these symptoms is so severe that a diagnosis of dementia can be made. Individuals diagnosed with MCI, however, are at greater risk of developing dementia; the inclusion of adults with MCI in these guidelines will enable the use of interventions to slow the progression of cognitive decline, i.e. the transition from MCI to dementia itself.

The scope of these guidelines is prevention/risk reduction of cognitive decline or dementia (main outcomes of interest). Cognitive decline is defined as a noticeable and measurable loss or abnormality in attention functions, memory functions or higher level cognitive functions (including attention, language and reasoning). Dementia is a syndrome that includes cognitive decline and other symptoms and can be diagnosed based on ICD-10 criteria. It involves a decline in memory with impairment of at least one other cognitive function, such as skilled movements (limb apraxia), language (aphasia) or executive function (e.g. planning, attention and abstract reasoning). This decline should represent a change from previous behaviour, and impair social and/or occupational functioning. As stated in the background section, when we use the word dementia in this document, we are referring to the primary or neurodegenerative dementias.

The GDG provided input into the scope of the guidelines and assisted the steering group in developing the key questions. Twelve PICO-structured questions were developed (Annex 3).

Outcomes were rated by GDG members according to their importance, as "critical", "important" or "unimportant". Those outcomes rated as critical and important were selected for inclusion into the PICO. Regular communication and discussions with the GDG were held by email and teleconferences, respectively.

The systematic review team developed protocols to review the evidence that existed for the interventions to reduce the risk of cognitive decline and/or dementia (as outlined in the PICO questions) for adults with normal cognition or MCI (Annex 4). Existing relevant systematic reviews were identified for each of the PICO questions. The steering group assessed the quality of existing reviews using the assessment of multiple systematic reviews (AMSTAR) checklist. Systematic reviews found to be of high quality were also assessed for timeliness to ensure that the most current evidence was used.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Guyatt et al., 2011), as well as the *WHO Handbook for guideline development*, were used to develop the evidence profiles. The quality assessment of the evidence was performed according to GRADE considering study design – randomized controlled trials (RCT) or observational studies, risk of bias, inconsistency, indirectness, imprecision and risk of reporting bias. Evidence was characterized as either high, moderate, low or very low.

2.5
DECISION-MAKING DURING THE GDG MEETING

The GDG met at the WHO headquarters in Geneva, 2–3 July 2018. The evidence review was sent out in advance and it was summarized in a presentation during the meeting. The GDG members discussed the evidence, clarified points and interpreted the findings in order to develop recommendations based on the draft prepared by the WHO Secretariat. The GDG considered the relevance of the recommendations for adults with normal cognition or MCI based on the GRADE Evidence-to-Decision (EtD) framework (Alonso-Coello et al., 2016), considering the balance of benefit and harm of each intervention; values and preferences of the individuals involved; costs and resource use; acceptability of the intervention to health care providers in LMIC; feasibility of implementation; and impact on equity and human rights. No surveys or formal cost-effectiveness studies to determine resource constraints were conducted but discussions of these domains were informed by the combined expertise and experience of the GDG members. Equity and human rights were considered by specifically searching databases that include studies from LMIC, examining data for disaggregation for specific subgroups. Potential differential effects of the interventions on different subgroups of people related to economic status, employment or occupation, education, place of residence, gender or ethnicity were considered by the GDG.

Taking into account these considerations, when making a strong recommendation, the GDG was confident that the desirable effects of the intervention outweigh any undesirable effects. When the GDG was uncertain about the balance between the desirable and undesirable effects, the GDG issued a conditional recommendation. Strong recommendations imply that most individuals would want the intervention and should receive it, while conditional recommendations imply that different choices may be appropriate for individual patients and they may require assistance at arriving at management decisions. In some instances, even when the quality of evidence was low or very low, it was agreed that if the recommendation would be of general benefit, and this was seen to outweigh the harms, it may still be rated as strong. In the event of a disagreement, the Chair and the Methodologist would ascertain whether the dispute was related to the interpretation of the data or to the way that the recommendation was formulated. If a consensus agreement was not reached, the GDG members agreed to a majority vote of 70%, to determine a decision. WHO staff members present at the meeting, as well as other external technical experts involved in the collection and review of the evidence, were excluded from voting. The GDG members reached a consensus agreement on all recommendations and ratings and voting was not needed.

2.6
DOCUMENT PREPARATION AND PEER REVIEW

The draft guideline and evidence profiles prepared by WHO staff and the GDG were circulated to the ERG and the steering group. The role of the ERG was to identify any errors or missing data and to comment on clarity, setting-specific issues and implications for implementation rather than changing the recommendations. All inputs and remarks were discussed and agreed with the GDG by email.

3

EVIDENCE AND RECOMMENDATIONS

This section provides an overview of each PICO question described under the following headings: background; recommendations and additional considerations; supporting evidence for the recommendations and the rationale for the recommendations based on the evidence synthesized as well as criteria listed in the EtD tables. Complete evidence profiles for each PICO question including the GRADE tables and the EtD tables are included in the Web Annex.

3.1
PHYSICAL ACTIVITY INTERVENTIONS

For adults with normal cognition or MCI, are physical activity interventions more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults (age above 18 years) with normal cognition or MCI

Intervention:
Physical activity interventions (aerobic, resistance training or multicomponent physical activity)

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

A physically active lifestyle is linked to brain health. In large observational studies with follow-up periods extending decades, physically active people seem less likely to develop cognitive decline, all-cause dementia, vascular dementia and Alzheimer disease when compared with inactive people (Gallaway et al., 2017; Hamer & Chida, 2009; Sofi et al., 2011; Stephen et al., 2017). Especially, the highest levels of physical exercise seem to be most protective (Hamer & Chida, 2009; Sofi et al., 2011). Physical activity seems to have beneficial effects on brain structures, which may underlie this association (Rovio et al., 2010).

Other potential mechanisms underlying the association are most likely indirect, such as the positive effects of physical exercise on other modifiable cardiovascular risk factors (CVRFs), including hypertension, insulin resistance and high cholesterol levels as well as other biological mechanisms, including but not limited to enhancing the immune system function, anti-inflammatory properties, and increasing neurotrophic factors. Physical activity interventions are described in WHO's *Global recommendations on physical activity for health* (2010).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

Physical activity should be recommended to adults with normal cognition to reduce the risk of cognitive decline.

Quality of evidence: moderate
Strength of the recommendation: strong

RECOMMENDATION 2:

Physical activity may be recommended to adults with MCI to reduce the risk of cognitive decline.

Quality of evidence: low
Strength of the recommendation: conditional

WHO's Global recommendations on physical activity for health (2010)

(http://www.who.int/dietphysicalactivity/publications/9789241599979/en/)

Below is an extract from these recommendations for adults 65 years and above:

For adults 65 years and above, physical activity includes recreational or leisure-time physical activity, transportation (e.g. walking or cycling), occupational (if the person is still engaged in work), household chores, play, games, sports or planned exercise, in the context of daily, family, and community activities. In order to improve cardiorespiratory and muscular fitness, bone and functional health, and reduce the risk of NCDs, depression and cognitive decline, the following are recommended:

1. Adults aged 65 years and above should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week, or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity.

2. Aerobic activity should be performed in bouts of at least 10 minutes' duration.

3. For additional health benefits, adults aged 65 years and above should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.

4. Adults of this age group with poor mobility should perform physical activity to enhance balance and prevent falls on 3 or more days per week.

5. Muscle-strengthening activities should be done involving major muscle groups, on 2 or more days per week.

6. When adults of this age group cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow.

Overall, across all the age groups, the benefits of implementing the above recommendations, and of being physically active, outweigh the harms. At the recommended level of 150 minutes per week of moderate-intensity activity, musculoskeletal injury rates appear to be uncommon. In a population-based approach, in order to decrease the risks of musculoskeletal injuries, it would be appropriate to encourage a moderate start with gradual progress to higher levels of physical activity.

Additional considerations include:

- Physical activity is easily available for everybody and has a large range of beneficial effects.
- Aerobic activity plays a key role in the beneficial effect of physical activity.

SUPPORTING EVIDENCE AND RATIONALE

For physical activity interventions (e.g. aerobic, resistance training or multicomponent physical activity) compared with usual care or no intervention, four systematic reviews were identified for six different physical activity interventions (Barha et al., 2017; Barreto et al., 2017; Northey et al., 2018; Song et al., 2018). These were:

1. Aerobic exercise intervention versus usual care or no intervention in adults with normal cognition.
2. Training exercise intervention versus usual care or no intervention in adults with normal cognition.
3. Multimodal exercise intervention versus usual care or no intervention in adults with normal cognition.
4. Aerobic exercise intervention versus usual care or no intervention in adults with MCI.
5. Training exercise intervention versus usual care or no intervention in adults with MCI.
6. Multimodal exercise intervention versus usual care or no intervention in adults with MCI.

For cognitive outcomes in healthy adults, there is moderate quality evidence which indicates that physical activity interventions have a positive effect on cognition. There is low to moderate quality evidence that suggests that physical activity does not affect risk of MCI and dementia. For cognitive outcomes in adults with MCI, there is low quality evidence that indicates that physical activity interventions have a positive effect on cognition. However, these benefits are not consistent across all cognitive domains.

The evidence shows that the effect size is larger for aerobic training versus resistance training and there is stronger evidence for adults with normal cognition (especially aerobic training) than in adults with MCI.

The GDG concluded that the desirable effects of physical activity outweighed the undesirable effects. Overall, low to moderate quality evidence has shown that physical activity has a small but beneficial effect on cognition. Even in MCI populations, low quality evidence suggests cognitive benefits of physical exercise. The effect of these interventions seems to be mostly due to aerobic exercise. Based on the quality of evidence, a strong recommendation was made for healthy adults and a conditional one for adults with MCI.

3.2
TOBACCO CESSATION INTERVENTIONS

For adults with normal cognition or MCI who use tobacco, are interventions for tobacco cessation more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI who use tobacco

Intervention:
Interventions for tobacco cessation (behavioural interventions and pharmacological interventions including nicotine replacement therapy, bupropion, varenicline)

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Tobacco dependence is the leading cause of preventable death globally, causing an estimated 5 million deaths per year (WHO, 2011) and worldwide medical costs ranging in billions of US dollars (Lightwood et al., 2000). Tobacco is the major risk factor for a number of conditions, including many types of cancers, cardiovascular diseases (CVDs) and risk factors, and respiratory disorders (US Department of Health Human Services, 2004), and tobacco cessation has been demonstrated to significantly reduce these health risks (Pirie et al., 2013). Tobacco cessation has also been associated with reduced depression, anxiety and stress, and improved mood and quality of life compared with continuing to smoke (Taylor et al., 2014).

Tobacco dependence is also associated with other disorders and age-related conditions, such as frailty and work ability in older people (Amorim et al., 2014; Kojima et al., 2015), as well as dementia and cognitive decline (Durazzo et al., 2014).

Interventions to treat tobacco dependence can be very diverse, based on either or both behavioural/psychological strategies and various pharmacological treatments. Non-pharmacological interventions can have mixed results (Niaura, 2008). Counselling is the most frequently used approach, but others have also been explored, such as mindfulness-based approaches, cognitive behavioural therapy, behavioural activation therapy, motivational interviewing, contingency management, and exposure and/or aversion to smoking. Among the pharmacological therapies for tobacco cessation, nicotine replacement therapy, bupropion and varenicline are the most common, but low overall treatment efficacy and adverse effects are key limitations (Gómez-Coronado et al., 2018). Combinations of non-pharmacological and pharmacological approaches seem to be the most effective in supporting tobacco cessation (Gómez-Coronado et al., 2018).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION:

Interventions for tobacco cessation should be offered to adults who use tobacco since they may reduce the risk of cognitive decline and dementia in addition to other health benefits.

Quality of evidence: low
Strength of recommendation: strong

Additional considerations include:

- In keeping with interventions described in the WHO training package for tobacco dependence, people who make use of tobacco should be advised to quit and the appropriate programmes aimed at preventing tobacco use uptake, promoting tobacco cessation, as well as diagnosing and treating tobacco dependence, should be established *(http://www.who.int/tobacco/publications/building_capacity/training_package/treatingtobaccodependence/en/)*. The interventions include behavioural interventions, as well as pharmacological ones (i.e. nicotine replacement therapy, bupropion, varenicline).

- Individual level interventions should be provided in the context of population level tobacco cessation programmes.

SUPPORTING EVIDENCE AND RATIONALE

No systematic reviews comparing tobacco cessation interventions with no intervention were identified.

A large body of observational evidence is available on tobacco smoking as a risk factor for cognitive impairment and dementia. These studies show an association between tobacco smoking (including in mid-life) and dementia, or cognitive decline, in later life (Beydoun et al., 2014; Di Marco et al., 2014; Lafortune et al., 2016; North et al., 2015; Xu et al., 2015; Zhong et al., 2015). Only limited adverse events have been reported and only for pharmacological interventions (Motooka et al., 2018). Therefore, any type of intervention aimed at tobacco cessation is likely to be more beneficial than detrimental.

The GDG made a strong recommendation although evidence from experimental intervention trials is not available, since tobacco use has substantial established harm and the epidemiological/observational evidence on tobacco use and increased risk of dementia fulfils most of the Bradford-Hill's criteria for causation (Lafortune et al., 2016). The evidence is strong, the population attributable risk is high, reproducible in different settings and with different study designs, specific, and indicates a dose-response effect. In addition, criteria such as temporality (mid-life smoking is correlated to a higher risk of late life dementia) (Lafortune et al., 2016), coherence (experimental laboratory results are in keeping with the observational evidence) (Durazzo et al., 2014) and mechanistic evidence suggest that smoking causes brain damage, underpinning subsequent cognitive decline.

3.3
NUTRITIONAL INTERVENTIONS

3.3a

For adults with normal cognition or MCI, are nutritional interventions including dietary supplements more effective than usual care or no intervention in reducing the risk/progression of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI

Intervention:
Dietary supplements (e.g. B vitamins, antioxidants, omega-3 and ginkgo)

Comparison:
Care as usual/placebo or one treatment versus another

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

3.3b

For adults with normal cognition or MCI, are nutritional interventions such as healthy dietary patterns (e.g. the Mediterranean diet) more effective than usual care or no intervention in reducing the risk/progression of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI

Intervention:
Healthy dietary pattern (e.g. the Mediterranean diet)

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

A healthy diet throughout the life course plays a crucial role in optimal development, and in maintaining health and preventing NCDs. Previous dietary intervention studies have shown that dietary changes are involved in prevention of many conditions that increase the risk of dementia, such as diabetes (Diabetes Prevention Program Research Group, 2002; Tuomilehto et al., 2001) and CVD (Rees et al., 2013). Mechanistic and animal models have

suggested a variety of pathways that link dietary factors to neuropathological changes in the development of dementia (Swaminathan & Jicha, 2014). Therefore, dietary factors may be involved in the development of dementia, both directly and through their role on other risk factors, and a healthy diet may have a great preventive potential for cognitive impairment.

The Mediterranean diet is the most extensively studied dietary approach, in general as well as in relation to cognitive function. Several systematic reviews of observational studies have concluded that high adherence to the Mediterranean diet is associated with decreased risk of MCI and AD, but modest adherence is not (Singh et al., 2014; Wu & Sun, 2017). Moreover, among participants with normal cognition, higher adherence is associated with better episodic memory and global cognition (Loughrey et al., 2017). Other promising dietary approaches associated with better cognitive function include: dietary approaches to stop hypertension (DASH) (Berendsen et al., 2017; Morris et al., 2015a; 2015b; Wengreen et al., 2013); and the brain health-specific Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet.

Concerning individual foods and nutrients, consumption of fruit and vegetables (Jiang et al., 2017; Wu et al., 2017) and fish (Bakre et al., 2018; Zhang et al., 2016) are most consistently associated with decreased risk of dementia. Higher fish consumption has been linked to lower memory decline among healthy participants in many studies (Samieri et al., 2018), as well as intake of polyunsaturated fatty acids (PUFA) (fish-derived) (Zhang et al., 2016). Other foods and nutrients that have been associated with reduced risk of dementia or cognitive impairment are nuts, olive oil and coffee (Solfrizzi et al., 2017). Evidence has also been reported concerning folate, vitamin E, carotenes, vitamin C and vitamin D (Balion et al., 2012; Dangour et al., 2010; Rafnsson et al., 2013; Travica et al., 2017), but findings are inconsistent.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

The Mediterranean-like diet may be recommended to adults with normal cognition and MCI to reduce the risk of cognitive decline and/or dementia.

Quality of evidence: moderate
Strength of the recommendation: conditional

RECOMMENDATION 2:

Healthy, balanced diet should be recommended to all adults based on WHO recommendations on healthy diet.

Quality of evidence: low to high (for different dietary components)
Strength of the recommendation: strong

RECOMMENDATION 3:

Vitamins B and E, PUFA and multi-complex supplementation should not be recommended to reduce the risk of cognitive decline and/or dementia.

Quality of evidence: moderate
Strength of the recommendation: strong

WHO recommendations on a healthy diet

(http://www.who.int/en/news-room/fact-sheets/detail/healthy-diet)

For adults, the WHO guidelines recommend the following.

A healthy diet contains:

- Fruits, vegetables, legumes (e.g. lentils, beans), nuts and whole grains (e.g. unprocessed maize, millet, oats, wheat, brown rice).
- At least 400 g (five portions) of fruits and vegetables a day. Potatoes, sweet potatoes, cassava and other starchy roots are not classified as fruits or vegetables.
- Less than 10% of total energy intake from free sugars which is equivalent to 50 g (or around 12 level teaspoons) for a person of healthy body weight consuming approximately 2000 calories per day, but ideally less than 5% of total energy intake for additional health benefits. Most free sugars are added to foods or drinks by the manufacturer, cook or consumer, and can also be found in sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates.
- Less than 30% of total energy intake from fats. Unsaturated fats (found in fish, avocado, nuts, sunflower, canola and olive oils) are preferable to saturated fats (found in fatty meat, butter, palm and coconut oil, cream, cheese, ghee and lard) and trans-fats of all kinds, including both industrially produced trans-fats (found in processed food, fast food, snack food, fried food, frozen pizza, pies, cookies, biscuits, wafers, margarines and spreads) and ruminant trans-fats (found in meat and dairy foods from ruminant animals, such as cows, sheep, goats, camels and others). It is suggested to reduce the intake of saturated fats to less than 10% of total energy intake and trans-fats to less than 1% of total energy intake. In particular, industrially produced trans-fats are not part of a healthy diet and should be avoided.
- Less than 5 g of salt (equivalent to approximately 1 teaspoon) per day and use iodized salt.

Additional considerations include:

- The evidence and recommendations provided assume that the nutritional status and potential micronutrients deficiencies in both mid-life and old age have been assessed and treated.
- A balanced and varied diet represents a natural source of polyphenols and protein.
- The recommendation about vitamins B and E, PUFA and multi-complex supplementation applies to people without nutrient deficiency.

SUPPORTING EVIDENCE AND RATIONALE

Observational studies have consistently reported that a healthy diet is associated with better cognitive performance (Berendsen et al., 2017; Frith et al., 2018; Loughrey et al., 2017; Morris et al., 2015; Wengreen et al., 2013), but the evidence from clinical trials is more inconsistent (D'Cunha et al., 2018; Fitzpatrick-Lewis et al., 2015a; 2015b; Forbes et al., 2015; Radd-Vagenas et al., 2018; Solfrizzi et al., 2018). It is important to acknowledge that interventions with dietary modifications that improve several aspects of dietary intake at once are more likely to promote better cognition compared with supplementation with only some nutrients. Dietary factors may have synergistic effects that are only evident in combinations of foods (Jacobs Jr et al., 2009).

Regarding nutritional interventions, such as dietary supplements or healthy dietary patterns (e.g. the Mediterranean diet) compared with usual care or no intervention, six systematic reviews were identified for nine different nutritional interventions. These interventions were:

1. Multi-supplement complexes versus placebo in adults with normal cognition (D'Cunha et al., 2018).
2. Multi-supplement complexes versus placebo in adults with MCI (Fitzpatrick-Lewis et al., 2015).
3. PUFA versus placebo (Forbes et al., 2015).
4. Vitamin B versus placebo (Forbes et al., 2015).
5. Vitamin E versus placebo (Forbes et al., 2015).
6. Polyphenols versus placebo (Solfrizzi et al., 2018).
7. Protein supplementation versus placebo (Solfrizzi et al., 2018).
8. Chicken essence versus placebo (Teoh et al., 2016).
9. Mediterranean diet versus alternate or usual diet (Radd-Vagenas et al., 2018).

The outcomes of incident MCI and dementia were only reported for interventions involving multi-supplement complexes in adults with normal cognition and the Mediterranean diet (D'Cunha et al., 2018; Radd-Vagenas et al., 2018). However, neither of these interventions showed a direct effect in reducing the incidence of dementia and/or MCI.

All of the interventions/comparisons reported cognitive outcomes. There was moderate quality evidence that the Mediterranean diet can improve verbal and visual memory (Radd-Vagenas et al., 2018). A meta-analysis showed results that approached significance for global cognition and consistently positive, but non-significant, results were reported for all other cognitive outcomes (attention, working memory, processing speed, language and executive function) (Radd-Vagenas et al., 2018). A consistent positive effect of polyphenols on cognitive performance was also found, however, the quality of the evidence was low (Solfrizzi et al., 2018). Similarly, protein supplementations were found to have a beneficial effect on cognition in older adults, but the results were inconsistent and the quality of the evidence was low (Solfrizzi et al., 2018).

Overall, no effects were found for multi-complex (D'Cunha et al., 2018; Fitzpatrick-Lewis et al., 2015), vitamins B and E (Forbes et al., 2015), and PUFA supplementation (Forbes et al., 2015). Low-quality evidence was reported for protein and polyphenols supplementation (Solfrizzi et al., 2018), and moderate evidence of a beneficial effect of the Mediterranean diet was found (Radd-Vagenas et al., 2018).

Three multi-supplement complex interventions: docosahexaenoic acid (DHA) + eicosapentaenoic acid (EPA) + vitamin E + soy phospholipids + tryptophan + melatonin; vitamin E + multivitamin; lyophilized royal jelly + gingko biloba + Panax ginseng; were examined and none showed an increased risk of any serious adverse event during the follow-up period (moderate quality evidence, Fitzpatrick-Lewis et al., 2015).

The GDG concluded that the benefits of a Mediterranean diet and a balanced diet outweighed the harms and provided conditional and strong recommendations respectively. The GDG noted that vitamin E and protein supplementation at high doses have been associated with undesirable non-anticipated effects that outweigh the benefits and recommended against their use.

3.4
INTERVENTIONS FOR ALCOHOL USE DISORDERS

For adults with normal cognition or MCI and alcohol use disorders, are behavioural and psychological interventions to treat alcohol use disorders more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI and excessive use of alcohol

Intervention:
- Behavioural and psychological interventions to treat alcohol use disorders (e.g. motivational interviewing)
- Pharmacological interventions to treat alcohol use disorders

Comparison:
Care as usual or no intervention

Outcomes:
- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Excessive alcohol consumption is common in many countries (Gell et al., 2015). In 2012, 5.9% of all deaths worldwide (about 3.3 million) were directly attributable to harmful use of alcohol (WHO, 2014). Furthermore, excessive consumption of alcohol is one of the leading causes of general disability globally (WHO, 2014), being a direct cause in more than 200 diseases including risk factors for dementia and injury conditions (WHO, 1992; WHO 2019a).

There is extensive evidence on excessive alcohol as a risk factor for dementia and cognitive decline (Langballe et al., 2015; Sachdeva et al., 2016; Zhou et al., 2014).

Several approaches have been applied in interventions aimed at hazardous and harmful use of alcohol. Pharmacological therapies with different types of drugs (e.g. opioid antagonists, ALDH2 inhibitors) have shown various degrees of efficacy for adults with alcohol use disorders, although none of them showed to be superior in comparison trials. Behaviour and psychological interventions have shown to be effective in alcohol use disorders, and especially among those with hazardous and harmful drinking. Screening and brief intervention in primary care is one of the most cost-effective means of reducing alcohol-attributable morbidity and deaths (Kaner, 2018). Interventions for alcohol use disorders have been described in the *mhGAP Intervention guide - Version 2.0 for mental, neurological and substance use disorders in non-specialized health settings (http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/).*

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION

Interventions aimed at reducing or ceasing hazardous and harmful drinking should be offered to adults with normal cognition and MCI to reduce the risk of cognitive decline and/or dementia in addition to other health benefits.

Quality of evidence: moderate (for observational evidence)
Strength of the recommendation: conditional

WHO mhGAP Intervention guide - Version 2 for mental, neurological and substance use disorders in non-specialized health settings

(http://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/)

The WHO mhGAP Intervention guide recommends the following:

Harmful use of alcohol

- Provide psychoeducation and emphasize that the level/pattern of alcohol use is causing harm to health.
- Explore the person's motivations for alcohol use. Conduct motivational interviewing.
- Advise stopping alcohol completely or consuming at a non-harmful level (if a non-harmful level exists) and indicate your intention in supporting the person in doing so. Ask the person if they are ready to try to make this change.
- Explore strategies for reducing or stopping use and strategies for reducing harm.
- Address food, housing and employment needs.
- Offer regular follow-up.

Alcohol dependence

- Thiamine during alcohol use.
- Diazepam during alcohol detoxification to treat withdrawal symptoms.
- Naltrexone, acamprosate or disulfiram to prevent relapse after detoxification.
- Psychosocial interventions if available, e.g. cognitive behaviour therapy, motivational enhancement therapy, contingency management therapy, family counselling or therapy, problem-solving counselling or therapy; self-help groups.

Additional considerations include:

- Interventions can be based on lifestyle/ behavioural changes or pharmacological treatments in accordance with the WHO mhGAP guidelines. Lifestyle behavioural interventions are likely to be more acceptable and have fewer adverse events.

- A U-shaped relationship between alcohol consumption and cognitive function has been reported. However, due to methodological limitations in most studies that describe this effect, it is not possible to assume that a light to moderate consumption of alcohol is, in fact, protective toward dementia and/or cognitive decline. This, in addition to other health risks and the social and economic burden associated with alcohol, do not favour a general recommendation of its use.

- Individual level interventions should be provided in the context of WHO Global strategy to reduce harmful use of alcohol (WHO 2010) and population level interventions, through strengthening restrictions on alcohol availability, enforcing drink driving countermeasures, facilitating access to screening, brief interventions, and treatment, enforcing bans or comprehensive restrictions on alcohol advertising, sponsorship, and promotion, raising prices on alcohol through excise taxes and pricing policies.

SUPPORTING EVIDENCE AND RATIONALE

No systematic reviews were identified for interventions for hazardous and harmful alcohol consumption (behavioural, psychological and pharmacological interventions) and reduced the risk of cognitive decline and/or dementia.

However, a large body of observational evidence is available on alcohol as a risk factor for cognitive decline and dementia (Beydoun et al., 2014; Hersi et al., 2017; Ilomaki et al., 2015; Lafortune et al., 2016; Piazza-Gardner et al., 2013; Xu et al., 2017). Generally, single studies did not always show similar results (mostly due to differences in study design) but the most consistent pattern is that of a U-shaped relationship between alcohol consumption and dementia and/or cognitive impairment, which clearly links excessive alcohol consumption to a significantly increased risk (Xu et al., 2017).

A range of adverse events has also been reported for pharmacological interventions aimed at reducing excessive alcohol consumption while lifestyle interventions are mostly based on behavioural interventions and no evidence of adverse events (apart from those related to withdrawal syndrome) have been identified (NICE, 2011).

Overall, the GDG concluded that the benefits outweighed the harms and, based on the strong observational evidence, made a conditional recommendation for interventions to reduce or cease hazardous and harmful alcohol use.

3.5
COGNITIVE INTERVENTIONS

For adults with normal cognition or MCI is cognitive stimulation or cognitive training more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI

Intervention:

- Cognitive stimulation
- Cognitive training

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Dementia is preceded by cognitive decline. However, not everyone who is exposed to dementia risk factors will go on to develop cognitive impairment. The concept of cognitive reserve has been proposed as a protective factor that may reduce the risk of clinical onset of dementia and cognitive decline (Stern, 2012). Cognitive reserve refers to the brain's ability to cope with or compensate for neuropathology or damage (Stern, 2012). Studies have shown that increased cognitive activity may stimulate (or increase) cognitive reserve and have a buffering effect against rapid cognitive decline (Stern & Munn, 2010) as well as a significant reduction in the risk of MCI or AD diagnosis in those who reported high compared with low levels of cognitive activities (combined OR = 0.38, 95% CI: 0.15–0.99) (Sattler, 2012).

Increased cognitive activity can be achieved through cognitive stimulation therapy and/or cognitive training. Cognitive stimulation therapy refers to "participation in a range of activities aimed at improving cognitive and social functioning" (Clare & Woods, 2004), while cognitive training refers to "guided practice of specific standardized tasks designed to enhance particular cognitive functions" (Clare & Woods, 2004). The NIA (United States of America) identified cognitive training as an intervention aimed at preventing or delaying the onset of age-related cognitive decline, MCI, or clinical Alzheimer's-type dementia (Kane et al., 2017). Additionally, the *WHO ICOPE guidelines* (http://www.who.int/ageing/publications/guidelines-icope/en/) recommend cognitive stimulation for older adults with cognitive impairment.

These interventions were assessed against outcomes that were judged as critical and important for this population.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION:

Cognitive training may be offered to older adults with normal cognition and with MCI to reduce the risk of cognitive decline and/or dementia.

Quality of evidence: very low to low
Strength of the recommendation: conditional

SUPPORTING EVIDENCE AND RATIONALE

For cognitive stimulation versus usual care or no intervention in healthy older adults, evidence was extracted from one systematic review (Strout et al., 2016). No evidence for adults with MCI was available. The review reported that half of the interventions evaluated proved to be effective in improving cognitive outcomes in at least one cognitive domain – executive function, attention, memory, language and/or processing speed (Strout et al., 2016). The quality of the evidence was low. The results were reported in narrative form and no meta-analysis was conducted. No evidence for incident MCI or dementia was available.

For cognitive training versus usual care or no intervention in healthy older adults, evidence was extracted from one systematic review (Chiu et al., 2017). The review conducted a meta-analysis which showed that cognitive training in healthy older adults has a moderate positive effect on overall cognitive functioning. The quality of evidence was low. No evidence for incident MCI or dementia was available.

For cognitive training versus usual care or no intervention in adults with MCI, evidence was extracted from two systematic reviews (Chandler et al., 2016; Sherman et al., 2017). With regards to cognitive function outcome, the quality of evidence is low showing that cognitive training in adults with MCI has a small positive effect on cognition. With regards to incident dementia outcome, the quality of evidence is very low as the results were narratively reported. It was reported that one study found that half of the control group, but none of the intervention group, developed dementia at the 8-month follow-up, while another found that more of the intervention group reported incident dementia at the 2-year follow-up (Chandler et al., 2016). With regards to quality of life and functional level, the quality of evidence is low showing that cognitive training in adults with MCI has a small positive effect on ADL but not quality of life.

The evidence for cognitive interventions is mainly in studies with older adults. The GDG concluded that in this population the desirable effects of the intervention outweighed the undesirable effects and provided a conditional recommendation for cognitive training. The evidence for cognitive stimulation in reducing the risk of dementia was insufficient and no recommendation was made by the GDG.

3.6
SOCIAL ACTIVITY

For adults with normal cognition or MCI is preserving and promoting a high level of social activity more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI

Intervention:

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Social engagement is an important predictor of well-being throughout life (Cherry et al., 2011). Social disengagement conversely, has been shown to place older individuals at increased risk of cognitive impairment and dementia (Fratiglioni et al., 2004). A systematic review and meta-analysis of longitudinal cohort studies showed that lower social participation, less frequent social contact and loneliness were associated with higher rates of incident dementia (Kuiper et al., 2015).

The Lancet Commission on Dementia Prevention, Intervention, and Care identified social engagement as an intervention that could be used to prevent dementia (Livingston et al., 2017).

RECOMMENDATIONS AND CONSIDERATIONS

There is insufficient evidence for social activity and reduction of risk of cognitive decline/dementia.

Social participation and social support are strongly connected to good health and well-being throughout life and social inclusion should be supported over the life-course.
(Global age-friendly cities: a guide, http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf)

SUPPORTING EVIDENCE AND RATIONALE

For preservation and promotion of social activity including community and family engagement versus care as usual or no intervention, evidence was extracted from one systematic review examining adults with normal cognition (Kelly et al., 2017). No evidence for adults with MCI was available. For cognitive function outcomes, the quality of the evidence is very low. Three RCTs, which assessed the association between cognitive function and social activity, were deemed eligible. The review findings were reported narratively (Kelly et al., 2017). Overall cognition was measured by varied composite measures of global cognition, including the ADAS-cog, MMSE and MDRS. One of the three RCTs found social activity intervention to be significantly associated with improvements in cognitive function (Pitkala et al., 2011). No data were available for incident MCI or dementia, quality of life, functional level (ADL, IADL), adverse events or drop-outs.

The GDG concluded that the evidence is limited and inconclusive, so no recommendation was made for social activity and risk of cognitive decline/dementia. Furthermore, there is a risk of bias arising from reverse causality whereby low social engagement prior to diagnosis of cognitive decline or dementia may be at least in part due to the disease process. The GDG did not make a recommendation against social activity as they concluded that social activity has a wide range of other benefits to health and well-being.

3.7
WEIGHT MANAGEMENT

For adults with normal cognition or MCI who are overweight or obese, are interventions for weight reduction (or control of obesity) more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI who are overweight or obese

Intervention: Weight management

- Non-pharmacological interventions, e.g. cognitive behavioural intervention strategies, lifestyle interventions
- Pharmacological interventions, e.g. weight loss medication (e.g. orlistat)

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Overweight and obesity are some of the best characterized and established risks for a variety of NCDs, responsible for at least 2.8 million deaths each year worldwide, and of an estimated 35.8 million (2.3%) of global disability-adjusted life years (DALYs) (WHO, 2019b). In 2008, 35% of adults aged 20+ were overweight (BMI ≥ 25 kg/m^2) (34% men and 35% of women), with significantly variable prevalence among world areas, with the United States of America, Europe and the Eastern Mediterranean regions with the highest concentration of people with overweight/obesity (WHO, 2019b). Overweight and obesity, in particular, have been linked to a number of medical complications such as Type 2 diabetes (Chan et al., 1994), cancer (Renehan et al., 2015), premature mortality (Fontana & Hu, 2014), and CVD (Eckel, 1997), both as direct risk factors as well as risks for other cardiovascular risk factors, such as high cholesterol and hypertension.

Obesity has been steadily rising, particularly among older adults in the last few decades (Nguyen & El-Serag, 2010) and although an increasing body of evidence suggests that overweight (25 < BMI < 30) in older adults could be more protective than normal weight in terms of overall mortality (Flicker et al., 2010), a link has also been established between excess of fat body mass and cognitive impairment (Xu et al., 2011). A recent systematic review and meta-analysis of observational studies conducted on a total of about 600 000 individuals showed that obesity (but not overweight) at mid-life increases the risk of dementia (RR = 1.33; 95% CI: 1.08–1.63) (Albanese et al., 2017).

It has been suggested that weight loss could indirectly reduce the risk of dementia by improving a variety of metabolic factors linked with the pathogenesis of cognitive impairment and dementia (i.e. glucose

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION:

Interventions for mid-life overweight and/or obesity may be offered to reduce the risk of cognitive decline and/or dementia.

Quality of evidence: low to moderate
Strength of the recommendation: conditional

WHO guidance on overweight and obesity outlined in *Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings* (2012) *(http://www.who.int/nmh/publications/phc2012/en/)*

WHO guidance on overweight and obesity should be followed.

- Advise overweight patients to reduce weight by following a balanced diet.
- Advise patients to give preference to low glycaemic-index foods (beans, lentils, oats and unsweetened fruit) as the source of carbohydrates in their diet.
- Advise patients to reduce sedentary behaviour and practise regular daily physical activity appropriate for their physical capabilities (e.g. walking).

tolerance, insulin sensitivity, blood pressure, oxidative stress, and inflammation) (Bennett et al., 2009). However, a direct beneficial effect of weight reduction intervention is also plausible. Although, so far, evidence of potential cognitive benefits of weight loss seem to be strongly associated with increased physical activity (Colcombe et al., 2006; Erickson et al., 2010), in 2011 a systematic review concluded that intentional weight loss can improve performance in some cognitive domains, at least in people with obesity (Siervo et al., 2011).

Additional considerations include:

- Lifestyle interventions that included both diet and physical activity components seemed to show the best results.

- In addition to interventions at individual level, lifestyle interventions at the population level, such as activity parks, green spaces and infrastructure to support active commuting, need to be considered.

- Being underweight in both late-mid-life and old age might be associated with a higher risk of dementia. However, it is likely that this association is explained, at least in part, by reverse causality, whereby brain pathology may cause weight loss before the clinical onset of dementia.

- Unintentional weight loss and malnutrition are associated with poor health outcomes and should be investigated and treated at all ages. However, it is unlikely that interventions that favour weight gain in people who are underweight in either mid- or late life can reduce the risk of dementia or cognitive impairment.

SUPPORTING EVIDENCE AND RATIONALE

For weight reduction with behavioural and/or lifestyle interventions (or control of obesity) compared with usual care or no intervention, evidence was extracted from one systematic review examining adults with normal cognition who are overweight or obese (Veronese et al., 2017). No evidence for adults with MCI was available. There was low to moderate evidence that lifestyle interventions aimed at weight reduction could improve cognitive function in the attention, memory and language domains. Interventions were very short (ranging from 8 to 48 weeks). No data were found in relation to incident MCI and dementia outcomes. No evidence of adverse events was identified.

For pharmacological interventions for weight reduction (or control of obesity) compared with usual care or no intervention, no systematic reviews were found.

The GDG concluded that the benefits of the interventions outweighed the harms and provided a conditional recommendation. Since the observational evidence of a correlation between overweight/obesity and increased risk of dementia is stronger and more consistent in mid-life than in late life (Hersi et al., 2017; Lafortune et al., 2016; Pedditzi et al., 2016; Prickett et al., 2015; Xu et al., 2015), the GDG made a conditional recommendation for this population.

3.8
MANAGEMENT OF HYPERTENSION

For adults with normal cognition or MCI and hypertension, is treatment of hypertension more effective than placebo/no intervention in reducing the risk of cognitive decline/dementia?

Population:
Adults with normal cognition or MCI with hypertension

Intervention:
Antihypertensive medication, lifestyle interventions

Comparison:
Placebo/no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Hypertension in mid-life has been associated with an increased risk of late life dementia (Kivipelto et al., 2001). In particular, a pattern of increased blood pressure during mid-life followed by a rapid decrease in blood pressure later in life has been found in individuals who go on to develop dementia (Kivipelto et al., 2001; Launer et al., 2000; Stewart et al., 2009).

There is mixed evidence relating to the reduction of blood pressure in late mid- or late life and subsequent cognitive decline or dementia, however, there is evidence to show that the reduction of hypertension can have substantial benefits in reducing cardiovascular morbidity and mortality and thus improving overall health of the ageing population (Musini et al., 2009).

Hypertension can be prevented through a range of lifestyle factors, including eating a healthy diet, maintaining a healthy weight and participating in an adequate amount of physical activity. It can also be controlled through antihypertensive medication. However, the evidence for the effectiveness of blood pressure lowering treatments in reducing the risk of cognitive decline and dementia risk is mixed.

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

Management of hypertension should be offered to adults with hypertension according to existing WHO guidelines.

Quality of evidence: low to high (for different interventions)
Strength of the recommendation: strong

RECOMMENDATION 2:

Management of hypertension may be offered to adults with hypertension to reduce the risk of cognitive decline and/or dementia.

Quality of evidence: very low (in relation to dementia outcomes)
Strength of the recommendation: conditional

HEARTS Technical package for cardiovascular disease management in primary health care: evidence-based treatment protocols

(http://apps.who.int/iris/bitstream/handle/10665/260421/WHO-NMH-NVI-18.2-eng.pdf?sequence=1)

Medications used to treat hypertension

- There are four main classes of antihypertensive medications: angiotensin converting enzyme (ACE) inhibitors; angiotensin receptor blockers (ARB); calcium channel blockers (CCB); and thiazide and thiazide-like diuretics. Any of these four classes of antihypertensive medication may be used unless there are specific contraindications. Proper treatment of hypertension usually requires a combination of hypertension medications.

Notes on specific hypertension medications

- Pregnant women and women of childbearing age not on effective contraception should not be given ACE inhibitors, ARBs or thiazide/thiazide-like diuretics; CCBs should be used. If not controlled with intensification dose of medication, refer to specialist.
- Beta blockers are not recommended as first-line therapy. If a heart attack has been diagnosed within the previous three years, or there is atrial fibrillation or heart failure, then a beta blocker should be added to the starting dose of antihypertensive medication. Patients with angina may also benefit from treatment with a beta blocker.

Other treatment considerations

- If there is a prior heart attack or stroke, or the person is otherwise at high risk of CVD, start a statin at the same time as starting antihypertensive medication. (Statins should not be used in women who are or who may become pregnant.)
- If there is a prior heart attack or ischemic stroke, start low-dose aspirin.
- The hypertension protocols included in this module serve well for initiation and maintenance of successful treatment. If there are serious adverse events, lack of control of blood pressure, or if a major medical event intervenes, then referral to a specialist will be needed.
- If the patient is already on another medication regimen, blood pressure is controlled to the target level, and the medications the patient is taking are accessible and affordable, there is no reason to change the regimen.
- If the patient feels faint on standing, check blood pressure while standing. If the systolic blood pressure is consistently less than 110 mm Hg in a patient on medical treatment, consider reducing the dosage or number of medications used.

SUPPORTING EVIDENCE AND RATIONALE

For treatment of hypertension in the form of antihypertensive medication versus placebo or no intervention, evidence was extracted from two systematic reviews examining adults with normal cognition and hypertension (Parsons et al., 2016; Weiss et al., 2016). No evidence for adults with MCI was available. With regard to cognitive function and incident dementia outcomes, the quality of the evidence was low, which showed that antihypertensive therapy has no effect on cognitive decline or incidence of dementia. With regard to quality of life and functional level outcomes, the quality of evidence is very low, showing that antihypertensive therapy does not decrease quality of life or functional level. With regard to adverse events, the quality of evidence was very low, showing mixed findings with regard to antihypertensive use. There were no data on incident MCI and overall drop-out rates. Initial results from the SPRINT-MIND trial, a substudy of the Systolic Blood Pressure Intervention Trial (SPRINT) that aims to evaluate the effect of intensive blood pressure control on risk of dementia, support the possibility of a dose-response relationship between blood pressure and risk of cognitive decline or dementia (SPRINT-MIND 2019). Observational evidence suggests a strong association between hypertension and incident cognitive decline/dementia.

For treatment of hypertension in the form of lifestyle interventions versus placebo or no intervention, no systematic reviews were found.

The GDG made a strong recommendation for management of hypertension for its established health benefits and a conditional recommendation for hypertension management for reducing the risk of cognitive decline/dementia. The GDG concluded that though there is limited clinical trial evidence that treatment of hypertension reduces the risk of cognitive decline or dementia, the benefits outweighed the harms since the evidence suggests that intervention does not lower quality of life or functional level and there are mixed results regarding adverse effects which may depend on the drug used. Additionally, robust evidence for a causal relationship is available.

3.9
MANAGEMENT OF DIABETES

For adults with normal cognition or MCI and diabetes mellitus, is treatment of diabetes more effective than placebo/no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI with diabetes mellitus

Intervention:

- Medications for glycaemic control
- Diet and lifestyle interventions

Comparison:
Placebo/no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

The presence of late life diabetes has been linked to an increased risk of dementia (Luchsinger, 2010; Prince et al., 2014; Profenno et al., 2010). However, the mechanism by which this occurs is unclear. Poor glucose control has been associated with lower cognitive functioning and greater cognitive decline (Yaffe et al., 2012). In addition, the complications associated with diabetes, such as nephropathy (kidney damage), retinopathy (eye damage), hearing impairment and CVD, have all been found to increase the risk of dementia (Bruce et al., 2014; Exalto et al., 2013).

The literature examining interventions that aim to improve glycaemic control shows mixed findings with regard to cognitive outcomes (Launer et al., 2011; Luchsinger et al., 2011). In addition, the evidence on the effectiveness of medication for diabetes in reducing dementia risk is inconsistent (Cheng et al., 2014; Moore et al., 2013; Parikh et al., 2011). There is some evidence to suggest that treating the cardiovascular comorbidities associated with diabetes, such as high cholesterol and hypertension, may mediate the risk for dementia (Johnson et al., 2012; Parikh et al., 2011).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION 1:

Management of diabetes in the form of medications and/or lifestyle interventions should be offered to adults with diabetes according to existing WHO guidelines.

Quality of evidence: very low to moderate (for different interventions)
Strength of the recommendation: strong

RECOMMENDATION 2:

Management of diabetes may be offered to adults with diabetes to reduce the risk of cognitive decline and/or dementia.

Quality of evidence: very low
Strength of the recommendation: conditional

Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings *(https://www.who.int/cardiovascular_diseases/publications/pen2010/en/).*

For individuals with diabetes, the WHO guidelines recommend the following treatments:

Type 1 diabetes

- Daily insulin injections (Level 1).

Type 2 diabetes

- Oral hypoglycaemic agents for Type 2 diabetes, if glycaemic targets are not achieved with modification of diet, maintenance of a healthy body weight and regular physical activity (Level 1).
- Metformin as initial drug in overweight patients (Level 1) and non-overweight (Level 4).
- Other classes of antihyperglycaemic agents, added to metformin if glycaemic targets are not met (Level 3).
- Reduction of cardiovascular risk for those with diabetes and 10-year cardiovascular risk > 20% with aspirin, angiotensin converting enzyme inhibitor and statins (Level 1).

SUPPORTING EVIDENCE AND RATIONALE

For treatment of diabetes in the form of medications for glycaemic control versus placebo or no intervention, evidence was extracted from one systematic review examining adults with normal cognition and Type 2 diabetes (Areosa Sastre et al., 2017). No evidence for adults with MCI was available. The quality of the evidence was moderate for cognitive function outcomes and very low for incident dementia outcomes, which showed intensive as opposed to standard glycaemic control has an unclear effect on cognitive function and no effect on incident dementia. The evidence reviewed included data from a large study set across 215 collaborating centres in 20 countries in Asia, Australasia, Europe and North America. The quality of evidence for adverse events was very low, showing intensive glycaemic control increases the risk of hypoglycaemic events. No data on incident MCI, quality of life, functional outcomes or drop-out rates were available. Overall, in adults with normal cognition, the evidence may favour standard glycaemic control because intense glycaemic control has no effect on cognitive function but may result in increased episodes of hypoglycaemia.

For treatment of diabetes in the form of diet and life-style interventions versus placebo or no intervention, evidence was extracted from one systematic review examining adults with normal cognition and Type 2 diabetes (Podolski et al., 2017). No evidence for adults with MCI was available. The quality of evidence was very low and the findings were mixed. No meta-analysis was conducted and there were no robust data on clinical significance.

The GDG made a strong recommendation for management of diabetes for its established health benefits and a conditional recommendation for diabetes management for reducing the risk of cognitive decline/dementia. The GDG concluded that though there is limited clinical trial evidence on the management of diabetes to reduce the risk of cognitive decline or dementia, the benefits outweighed the harms and there is robust observational evidence to suggest diabetes increases the risk of cognitive decline and dementia.

3.10
MANAGEMENT OF DYSLIPIDAEMIA

For adults with normal cognition or mild cognitive impairment and dyslipidaemia, is treatment of dyslipidaemia more effective than placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI with dyslipidaemia

Intervention:

- Statins (e.g. simvastatin and pravastatin)
- Lifestyle interventions

Comparison:
Placebo or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Elevated serum cholesterol is one of the key modifiable cardiovascular risk factors. A third of ischaemic heart disease worldwide is attributable to dyslipidaemia and it is estimated to be the cause of 2.6 million deaths (4.5% of total) per year, as well as a considerable proportion of disability (WHO, 2019b). The prevalence of raised total cholesterol among countries seems to correlate with wealth: in high-income countries, more than 50% of adults have elevated total cholesterol level, more than double the rate in low-income countries (WHO, 2019c).

The idea that raised level of blood cholesterol could be related to an increased risk of dementia was already introduced in the mid-1970s (Richardson et al., 2000). Since then, a number of epidemiological studies have demonstrated a close relationship between high serum cholesterol levels and the onset of AD/dementia (Kivipelto et al., 2002; Solomon et al., 2007; Whitmer et al., 2005), but results have been inconsistent, with other studies showing no or negative correlation (Mainous et al., 2005; Mielke et al., 2005).

Based on the severity of the dyslipidaemia and CVD overall risk, lifestyle or pharmacological approaches can be undertaken to reduce blood cholesterol. Weight reduction and decreasing saturated fats in the diet (decreasing the consumption of food of animal origin) are the most common and effective lifestyle recommendations (Perk et al., 2012). However, dyslipidaemia is often controlled and managed pharmacologically, with statins being the drugs of first choice. Several observational studies have investigated the possible beneficial effect of statins therapy in preventing dementia, but bias and heterogeneity hampered the overall quality of the evidence (Song et al., 2013; Swiger et al., 2013; Wong et al., 2013). Recently, a re-analysis of statin use in AD patients from failed clinical trials suggested that the use of simvastatin may slow the progression of cognitive decline in some people (Geifman et al., 2017).

RECOMMENDATIONS AND CONSIDERATIONS

RECOMMENDATION:

Management of dyslipidaemia at mid-life may be offered to reduce the risk of cognitive decline and dementia.

Quality of evidence: low
Strength of the recommendation: conditional

Additional considerations include:

- Statin treatment in older adults should not be specifically initiated for preventing cognitive decline and/or dementia but may be used for other health benefits according to WHO's *Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings* (http://www.who.int/nmh/publications/phc2012/en/).

SUPPORTING EVIDENCE AND RATIONALE

For control of dyslipidaemia through treatment with statins compared with placebo, evidence was extracted from one systematic review examining adults with normal cognition and dyslipidaemia (McGuinness et al., 2016). No evidence for adults with MCI was available. The quality of the evidence was moderate for cognitive function outcomes and low for incident dementia outcomes, showing that treatment with statins has no effect on either incident dementia and/or cognitive decline. There is moderate quality evidence that the treatment with statins does not increase the incidence of serious adverse events.

A large body of observational evidence has linked dyslipidaemia to an increased risk of dementia and/or cognitive decline and found an association between control of dyslipidaemia and reduction of dementia and/or cognitive decline risk (Geifman et al., 2017; Hersi et al., 2017; Reitz, 2013; Song et al., 2013). Overall, indirect evidence suggests that managing dyslipidaemia in mid-life can help reduce the risk of cognitive decline and/or dementia.

No studies were identified that specifically aimed at controlling dyslipidaemia through lifestyle interventions and included outcomes related to dementia and/or cognitive impairment.

The GDG concluded that the desirable effects of dyslipidaemia treatment outweigh the undesirable effects and made a conditional recommendation.

The observational evidence reported a stronger correlation between high cholesterol and dementia in mid-life rather than late life (Hersi et al., 2017; Reitz, 2013). The systematic review evidence that focused on clinical trials in older adults (65+) showed that statin treatment has no effect on cognition or dementia outcomes (McGuinness et al., 2016). Therefore, the GDG concluded that there were no grounds to recommend the use of statin and the control of cholesterol in late life but only in mid-life.

3.11
MANAGEMENT OF DEPRESSION

For adults with normal cognition or mild cognitive impairment and depressive disorder, is treatment of depression more effective than usual care, placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI with moderate to severe depressive disorder

Intervention:

- Pharmacological interventions to treat depression (antidepressant medication)
- Psychological interventions to treat depression (e.g. cognitive behavioural therapy, problem-solving therapy, interpersonal therapy, behavioural activation)

Comparison:
Care as usual or placebo or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

There is a substantial body of evidence linking depression to cognitive decline and dementia. A review carried out as part of the World Alzheimer Report in 2014 combined 32 studies into a meta-analysis which looked at the effect of depression on the risk of incident dementia. This involved 62,568 participants with a median follow-up of 5 years (range 2 to 17). The review reported that the presence of depression nearly doubled the risk of dementia (pooled effect size = 1.97, 95% CI: 1.67–2.32) (Prince et al., 2014).

The authors also carried out a meta-regression looking at follow-up time. They reported a trend toward smaller effect sizes in studies with longer follow-up suggesting that depression may have a prodromal role in dementia. It is noteworthy to mention that cognitive impairment may be the main symptom of depression in the elderly; a phenomenon that used to be called pseudodementia.

There are several potential explanations for the link between depression and cognitive impairment or dementia. Some of these include associations between depression, noradrenergic changes and white matter lesions, depression which stems from insight into impairment at early stages of decline, depression highlighting underlying deficits, i.e. by reducing motivation and bringing its own cognitive deficits (Camus et al., 2004; Jorm, 2001; Kales et al., 2005; Schweitzer et al., 2002).

RECOMMENDATIONS AND CONSIDERATIONS

There is currently insufficient evidence to recommend the use of antidepressant medicines for reducing the risk of cognitive decline and/or dementia.

The management of depression, in the form of antidepressants and/or psychological interventions, should be provided to adults with depression according to existing WHO mhGAP guidelines.

WHO mhGAP Intervention guide - Version 2 for mental, neurological and substance use disorders in non-specialized health settings

(https://www.who.int/mental_health/mhgap/mhGAP_intervention_guide_02/en/)

For adults with moderate to severe depressive disorder, the WHO guidelines recommend the following treatments:

Psychosocial/non-pharmacological treatment and advice

- Psychoeducation (for the person and his or her family, as appropriate).
- Addressing current psychosocial stressors.
- Reactivate social networks.
- Brief psychological treatments, if available.
- Offer regular follow-up.

Antidepressant medication

- Select an antidepressant from the National or WHO Formulary. Selective serotonin reuptake inhibitors (fluoxetine) and tricyclic antidepressants (amitriptyline) are antidepressants mentioned in the WHO Formulary and are on the *WHO model list of essential medicines*.
- In selecting an antidepressant, consider the symptom pattern of the person, the side-effect profile of the medication, and the efficacy of previous antidepressant treatments, if any.
- For co-morbid medical conditions, before prescribing antidepressants, consider potential for drug-disease or drug-drug interaction. Consult the National or the WHO Formulary.
- Combining antidepressants with other psychotropic medication requires supervision by, or consultation with a specialist.

SUPPORTING EVIDENCE AND RATIONALE

For pharmacological interventions to treat depression (antidepressant medication) compared with usual care or placebo, evidence was extracted from one systematic review examining adults with normal cognition and major depressive disorder (Baune et al., 2018). No evidence for adults with MCI was available. The review conducted a network meta-analysis and reported standardized mean differences in the Digit Symbol Substitution Test as a measure of cognition function. The review reported that vortioxetine (versus placebo) improved cognitive functioning while duloxetine, sertraline, citalopram, escitalopram, phenelzine and nortriptyline showed no effect (Baune et al., 2018). The quality of the evidence was very low and no data were reported for incident MCI or dementia outcomes, quality of life, adverse events, functional level or drop-out rates. Overall, the true balance of effects is difficult to ascertain. The evidence favours the use of vortioxetine (but not other pharmacological interventions) to treat depression for reducing the risk of cognitive decline or dementia. However, no data on adverse effects were available, e.g. drug-related side-effects or interactions.

For psychological interventions to treat depression compared with placebo or no intervention, no relevant systematic reviews were found.

The GDG therefore concluded that there was insufficient evidence currently for depression management and reduction of risk of cognitive decline/dementia. They also concluded that the management of depression is important for its other benefits and did not make a negative recommendation against this intervention.

3.12
MANAGEMENT OF HEARING LOSS

For adults with normal cognition or MCI and hearing loss, is treatment of hearing loss more effective than usual care, or no intervention in reducing the risk of cognitive decline and/or dementia?

Population:
Adults with normal cognition or MCI with hearing loss

Intervention:
Interventions to treat hearing loss (e.g. hearing aids)

Comparison:
Care as usual or no intervention

Outcomes:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

BACKGROUND

Hearing loss is a prevalent age-related disorder. As the fourth leading cause of years lived with disability in the global population (WHO, 2012), it is estimated to affect one in three adults aged 65 and older, with this statistic growing annually (Wilson et al., 2017). The implications of hearing loss, however, are often underestimated both at the individual and population level (Blustein et al., 2018).

Hearing impairment has debilitating consequences on functional ability and social and emotional well-being. Deteriorations in hearing impact on individuals' ability to communicate with others, which in turn can result in feelings of frustration, isolation, loneliness (Ciorba et al., 2012). Older adult populations who already experience the isolating effects of age-related factors, such as diminished mobility, driving cessation, death of partners or living alone, are particularly vulnerable to these psychosocial impacts.

Hearing loss is also associated with increased risk of cognitive decline or dementia (Lin et al., 2013). A recent meta-analysis of prospective cohort studies showed that the relative risk of hearing impairment on incident Alzheimer's and MCI was 2.82 (95% CI: 1.47–5.42). (Zheng et al., 2017). Additionally, a meta-analysis published by the Lancet Commission showed that hearing loss can almost double the risk of incident dementia (RR = 1.94, 95% CI: 1.38–2.73) (Livingston et al., 2017). Hearing loss and cognitive impairment or dementia, individually, and in combination, predict functional ability and burden of care. Hearing loss interventions, therefore, have the potential to substantially improve outcomes for older people on multiple domains.

RECOMMENDATIONS AND CONSIDERATIONS

There is insufficient evidence to recommend use of hearing aids to reduce the risk of cognitive decline and/or dementia.

Screening followed by provision of hearing aids should be offered to older people for timely identification and management of hearing loss as recommended in the WHO ICOPE guidelines.

WHO Guidelines on integrated care for older people (ICOPE)

(http://www.who.int/ageing/publications/guidelines-icope/en/)

For older adults, WHO recommends the following:

Screening followed by provision of hearing aids should be offered to older people for timely identification and management of hearing loss.

Considerations for recommendation:

- Community awareness about hearing loss and the positive benefits of audiological rehabilitation in older people, through community case finding and outreach activities, should be promoted.
- Health care professionals should be encouraged to screen older adults for hearing loss by periodically questioning them about their hearing. Audiological examination, otoscopic examination and the whispered voice test are also recommended.
- Hearing aids are the treatment of choice for older people with hearing loss, because they minimize reduction in hearing and improve daily functioning.
- Medications should be reviewed for potential ototoxicity.
- People with chronic otitis media or sudden hearing loss, or who fail any screening tests, should be referred to an otolaryngologist.

SUPPORTING EVIDENCE AND RATIONALE

For interventions to treat hearing loss (e.g. hearing aids) versus care as usual or no intervention, evidence was extracted from one systematic review examining adults with normal cognition and hearing loss (Cherko et al., 2016). No evidence for adults with MCI was available. For cognitive function and quality of life, the quality of evidence is very low. No meta-analyses were performed and results were reported narratively with no numerical data to support conclusions (Cherko et al., 2016). Based on two studies including measures of cognitive function, the review concluded that while hearing aids use was found to be associated with improvements in cognitive function, these benefits may be limited in that cognitive improvements have been shown to revert to baseline at 1 year follow-up. They also concluded that use of hearing aids in older people was associated with improvements in quality of life outcomes based on two studies. Overall, the evidence does not favour either the intervention or the comparison. Hearing aids may improve quality of life but the amount of evidence available is limited. No data are available for incident MCI or dementia, functional level (ADL, IADL), adverse events or drop-outs.

The GDG concluded that there is currently insufficient evidence to recommend the use of hearing aids to reduce the risk of cognitive decline/dementia. The GDG also concluded that the use of hearing aids is important to correct hearing loss in older adults for their other benefits and recommend following the ICOPE guidelines in this regard.

4

IMPLEMENTATION CONSIDERATIONS

Countries will be supported to implement the guidelines through training of health care personnel and using centres of excellence on improved quality of care. The implementation will also be supported locally through the adoption of the *Global action plan on the public health response to dementia 2017–2025*; the *Comprehensive mental health action plan 2013–2020*; and the *Global action plan for the prevention and control of noncommunicable diseases 2013–2020* at country level. The national capacity building process will also be supported through WHO collaboration with international organizations and associations.

Given that many of the interventions included in these guidelines are strongly related to the management of risk factors for CVD and diabetes, the implementation of these recommendations should be combined, whenever possible and in the relevant target population, with the ongoing prevention programmes to reduce the risk of these conditions. The optimal preventive effect may be obtained by addressing several risk factors at the same time. Collaboration among different stakeholders and multidisciplinary approaches will also be needed.

The recommendations contained in these guidelines should be adapted into a locally appropriate document that can meet the needs of each country and its health services. WHO headquarters will work closely with the regional and country offices, as well as implementing partners and public health agencies at the national level, to ensure communication and country-specific adaptations of the guidelines, through regional and national meetings.

As countries consider how to implement these guidelines, the budgetary and human resource requirements, and other health systems implications should be analysed to identify which inputs and systems are currently available, and which areas require additional investment. These may include training of health workers, supply of medicines and adaptations of health information systems to collect data on service utilization.

To support country implementation, WHO will produce a series of subsidiary tools that will address clinical and service delivery aspects of the implementation of the recommendations included in these guidelines.

5

PUBLICATION, DISSEMINATION AND EVALUATION

5.1
PUBLICATION AND DISSEMINATION

The guidelines will be disseminated as a print publication and electronically on a dedicated internet space on the WHO website.

The guidelines will be disseminated through both the mental health and NCD dissemination activities of the *Global action plan on the public health response to dementia 2017–2025* (such as the Global Dementia Observatory knowledge exchange platform), the *Comprehensive mental health action plan 2013–2020* and the *Global action plan for the prevention and control of noncommunicable diseases 2013–2020*. These guidelines will be appended to the mhGAP guidelines and disseminated through the mhGAP evidence resource centre and other mhGAP derivative products, including the mhGAP Intervention guide. Since these guidelines are linked to other WHO guidelines such as NCD and ICOPE guidelines and other resources on ageing, dissemination will occur along with these guidelines.

The guidelines and products are developed in English, and will be translated into other WHO official languages for wider dissemination and in collaboration with WHO regional offices. Local adaptation is necessary to ensure that the guidelines are appropriate for the local conditions that affect the care of people with cognitive decline and dementia in health facilities and the community. Adaptation will include language translation and ensuring that the interventions are acceptable in the specific socio-cultural context and suitable for the local health system. The ADAPTE manual for guideline adaptation outlines the approach to be used.[12] The acceptability and applicability of the recommendations will be examined in the specific cultural context, including the availability of health services, expertise and resources, and the organization of health services, as well as population characteristics, cultural beliefs and value judgments.

Relevant departments in ministries of health will be notified of the guidelines through WHO regional and country offices. A briefing package will be prepared for technical officers outside of WHO headquarters that will include an executive summary and Q&A related to policy and programme implications.

Dissemination will also be encouraged through WHO collaboration with international organizations and associations. In coordination with WHO Communications, the media will be notified of the new guidelines.

Countries will be supported to implement the guidelines through the training of health care personnel on improved quality of care and using centres of excellence. Capacity-building activities will be undertaken through web-based platforms and regional workshops.

Dissemination will be supported by the publication of selected systematic reviews and evidence in peer review journals, and presentations and workshops at key conferences and events.

[12] http://www.g-i-n.net/document-store/working-groups-documents/adaptation/adapte-resource-toolkit-guideline-adaptation-2-0.pdf

5.2 MONITORING AND EVALUATION

Following publication of these guidelines, WHO will continue to collect regular feedback from implementation activities in order to evaluate their usefulness and impact. Information will be used to evaluate the quality of the guidelines and to identify areas where improvement is required. WHO's Global Dementia Observatory, an online data and knowledge exchange platform for dementia, provides the framework for monitoring implementation of these guidelines[13].

5.3 IMPLICATIONS FOR FURTHER RESEARCH

The majority of the recommendations align with current guidelines for the treatment of pre-existing health conditions and dependencies. However, more evidence is needed to determine what the impact of these interventions are on the outcomes of incident MCI or dementia.

No recommendations could be made for social activity and hearing loss due to insufficient evidence. Some trials are currently being conducted for hearing loss interventions. These guidelines may need to be updated once these results are released. However, currently there is little research being conducted that examines the impact of social activity on cognitive decline and dementia. Part of the difficulty in conducting this type of research is that social activity is difficult to define and quantify, and it is also difficult to differentiate it from the physical or mental activities which are often a component of this type of intervention. The development of standardized protocols for social activity interventions may therefore need to precede the running of clinical trials.

Some of the evidence presented here is based on RCTs with relatively short follow-up periods (e.g. interventions for cognitive training, depression, social activity). This limits our ability to judge the potential impact of the interventions on the development of cognitive decline and dementia as they have long prodromal periods. More evidence needs to be gathered with longer term follow-up periods in order to more accurately estimate the impact of these interventions in reducing the risk of cognitive decline/dementia in the long run. In addition, more research needs to be conducted to understand how timing affects the impact of these interventions on cognitive decline and dementia (e.g. mid-life versus late life physical activity).

The prevalence of dementia is increasing in LMIC. However, the majority of clinical trials have been conducted in high-income countries, so there is very little evidence on the effectiveness of these interventions for LMIC. More attention needs to be given to understanding how best to reduce the risk of cognitive decline and dementia in LMIC.

[13] Available at: https://www.who.int/mental_health/neurology/dementia/Global_Observatory/en/

The PICO questions applied to gather evidence for the preparation of these guidelines included interventions on single risk factors. However, given the multifactor etiology of dementia, and the interaction of risk factors across the lifestyle of each individual, multidomain approaches have been increasingly researched and show potential to be more effective than single-factor strategies. Recently, three large multidomain RCTs – the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER); Effect of long-term omega-3 PUFA supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT); and Prevention of dementia by intensive vascular care (preDIVA) – have been completed (Ngandu et al., 2015; Andrieu et al., 2017; Moll von Charante et al., 2016). Although only the multidomain lifestyle intervention tested in FINGER reported significant results in the primary analysis, the overall findings from the three trials suggested that targeting individuals at increased risk could be the most effective strategy. In particular, other interventions showed significant results in participants with an elevated dementia risk score, in MAPT (as in FINGER), and individuals with untreated hypertension at baseline, in preDIVA, respectively.

In the context of multidomain interventions, new technologies and e-health solutions could also provide useful tools for risk reduction, by broadening the reach of such interventions (Barbera et al., 2018).

Given the heterogeneity of risk profiles among older populations, global initiatives, such as the World Wide FINGERS Network (www.wwfingers.com), have been launched recently with the specific purpose of testing similar interventions, which have been adapted in diverse geographical and cultural settings (Kivipelto et al., 2017).

Further research on the efficacy of multidomain interventions that are adjusted to specific geographical and cultural contexts, in populations at increased risk, and by making use of novel e-health tools (if possible) is, therefore, needed.

5.4
FUTURE REVIEW AND UPDATE

It is expected that the guidelines will be reviewed again in five years. New evidence in these areas is regularly monitored by the WHO Secretariat, in consultation with GDG members and technical experts identified for the evidence review process, WHO collaborating centres and academic institutions. With the increasing evidence from multidomain intervention trials expected to be reported in the coming years, the addition of a PICO question addressing such interventions should be considered in future revisions.

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ANNEX 1: GUIDELINE DEVELOPMENT GROUP MEMBERS

	Name	Gender	WHO region	Affiliation	Area of expertise
1.	**Charles Alessi**	M	**European**	Public Health England, United Kingdom	Health reform, preventable dementia
2.	**Kaarin Anstey**	F	**Western Pacific**	University of New South Wales and Neuroscience Research, Australia	Research in dementia epidemiology and risk reduction and cognitive ageing
3.	**Kimberly Ashby-Mitchell**	F	**Americas**	Caribbean Public Health Agency, Trinidad and Tobago	Research on effects of diet and physical activity on cognitive status
4.	**Corrado Barbui**	M	**European**	University of Verona, Italy	Mental health research and training, public health, health systems strengthening
5.	**Adelina Comas-Herrera**	F	**European**	London School of Economics, United Kingdom	Health economist, dementia research
6.	**Amit Dias**	M	**South-East Asia**	Department of Preventive and Social Medicine, Goa Medical College, India	Dementia, public health in LMIC
7.	**Cleusa P Ferri**	F	**Americas**	Federal University of São Paulo, Brazil	Research in dementia and 10/66 group, dementia risk factors in LMIC
8.	**Riadh Gouider**	M	**Eastern**	Alzheimer's Centre, Razi Hospital, Tunis; Tunisian Society of Neurology, Tunisia	Dementia research in areas of epidemiology, neuropsychological assessment and risk factors
9.	**Shinya Ishii**	M	**Western Pacific**	Health and Welfare Bureau for the Elderly; Ministry of Health, Labour and Welfare, Tokyo, Japan	Health policy, neurology of Alzheimer's disease and dementia
10.	**Yves Joanette**	M	**Americas**	Canadian Institutes of Health Research, Government of Canada	Dementia research
11.	**Joseph Kibachio**	M	**African**	Ministry of Health, Nairobi, Kenya	Public health, health policy, NCDs
12.	**Miia Kivipelto**	F	**European**	Karolinska Institutet, Stockholm University, Stockholm, Sweden	Dementia research in the field of early diagnosis and prevention
13.	**Shanthi Mendis**	F	**South-East Asia**	Independent consultant in global health, Sri Lanka	NCDs and cardiology, health policy development, capacity strengthening, implementation research particularly in LMIC

	Name	Gender	WHO region	Affiliation	Area of expertise
14.	**Ayesha Motala**	F	**African**	University of KwaZulu-Natal, South Africa	Epidemiology and genetics of diabetes mellitus
15.	**Ronald Petersen**	M	**Americas**	Mayo Clinic, United States of America	Memory disorders, aging and Alzheimer's disease
16.	**Dorairaj Prabhakaran**	M	**South-East Asia**	Centre for Chronic Conditions and Injuries & Public Health Foundation of India	Cardiovascular disease prevention, epidemiology, developmental origin, and biomarkers of cardiovascular diseases and diabetes
17.	**Martin Prince**	M	**European**	Health Foundation of India	Public health aspects of ageing and chronic disease in LMIC, dementia, guideline development
18.	**Suzana Shahar**	F	**Western Pacific**	Universiti Kebangsaan, Malaysia	Nutrition, micronutrients, dietary interventions
19.	**Ameenah Bibi Mia Sorefan**	F	**African**	Alzheimer's Association of Mauritius; Ministry of Health & Quality of Life, Mauritius	Ageing, dementia and Alzheimer's disease
20.	**Kusumadewi Suharya (Dy)**	F	**Western Pacific**	Alzheimer's Disease International, Indonesia	Dementia and public health
21.	**Huali Wang**	F	**Western Pacific**	Dementia Care & Research Center, Peking University Institute of Mental Health, China	Dementia research and education

ANNEX 2: ASSESSMENT OF CONFLICT OF INTEREST

INDIVIDUALS INVOLVED IN ASSESSMENT OF CONFLICT OF INTEREST:

Tarun Dua, Programme Manager, Department of Mental Health and Substance Abuse, WHO headquarters.

Neerja Chowdhary, Technical Officer, Department of Mental Health and Substance Abuse, WHO headquarters.

To comply with WHO's Conflict of Interest Policy, the Secretariat followed the revised Guidelines for Declaration of Interests (WHO Experts).[14] Declarations of interest (DoI) were requested from: (a) all GDG members; (b) all external partners involved in the evidence review process; (c) all experts invited to review the evidence profiles.

A letter requesting completion of a DoI form and submission of a curriculum vitae as well as was sent to all GDG members, the external review group and external partners. They were asked to agree to the publication of a summary of declarations in the guideline. The GDG members were also required to complete a confidentiality undertaking. Once received, the WHO Secretariat reviewed the DoIs as well as additional information (internet and bibliographic database search) and evaluated if there are any conflicts of interest and if so, whether these require a management plan.

In order to enhance its management of conflicts of interest as well as strengthen public trust and transparency in connection with WHO meetings and activities involving the provision of technical/normative advice, the names and brief biographies members being considered for participation in the GDG were disclosed for public notice and comment prior to the meeting.

At the beginning of the GDG meeting, the DoI of each GDG member were presented and GDG members and external partners were asked to update their DoI with relevant changes by notifying the responsible technical officer.

The follow up and suggested actions agreed upon to manage the conflicts of interest declared are summarized below:

- If members declare interests that are relevant to the meeting, the WHO Secretariat will note any potential conflict of interest and summarize these and then decide whether and to what extent they can participate in the guideline development.

- If the conflict is deemed to be significant, the WHO Secretariat will decide if the conflict necessitates exclusion of that person from participating in the guideline process or if their participation should be limited.

- These decisions are made on a case-by-case basis.

Below is a summary of the Declared conflicts of interest and how these were managed.

A. GDG MEMBERS

GDG Members with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Kaarin J Anstey,** University of New South Wales, Sydney, Australia;
2. **Kimberly Ashby-Mitchell,** Caribbean Public Health Agency, Port of Spain, Trinidad and Tobago;
3. **Corrado Barbui,** University of Verona, Verona, Italy.
4. **Amit Dias,** Department of Preventive and Social Medicine, Goa Medical College Bambolim, Goa, India;
5. **Suharya Dy (Kusumadewi),** Alzheimer's Disease International, Jakarta, Indonesia;
6. **Cleusa P. Ferri,** Federal University of Sao Paulo, Sao Paulo, Brazil.
7. **Riadh Gouider,** Razi Hospital, Faculty of Medicine, Tunis, Tunisia;
8. **Shinya Ishii,** Ministry of Health, Labour and Welfare, Tokyo, Japan;

[14] WHO Office of Compliance, Risk Management and Ethics (CRE) http://intranet.who.int/homes/cre/ethics/doiexperts/

9. **Yves Joanette,** Canadian Institute of Health Research, Government of Canada.
10. **Joseph Kibachio,** Ministry of health, Nairobi, Kenya;
11. **Shanthi Mendis,** Colombo, Sri Lanka;
12. **Dorairaj Prabhakaran,** Public Health Foundation of India, New Delhi, India;
13. **Ameenah Bibi Mia Sorefan,** Ministry of Health and Quality of Life, Quatre-Bornes, Mauritius

GDG members who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Charles Alessi, Public Health England, London, United-Kingdom

Dr Alessi declared that the travel costs for the GDG meeting were covered by his organization.

Action: This interest was deemed insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Alessi's judgement in the development of the present guidelines. He is deemed to be participating in the guideline development process in an individual capacity and not representing any organization. No further action was necessary

Adelina Comas-Herrera, London School of Economics, London, United-Kingdom

Dr Comas-Herrera declared in her DoI from that she had received research support routed via her University on various research projects on dementia in 2015 and 2016. These amounts were used to pay her salary by the University. She also declared receiving a payment of US$1000 in 2017 to advise a pharmaceutical company, Axovant Sciences GmbH. The topic was on the availability of data on dementia costs for a medicine that has since been withdrawn due to lack of effectiveness.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Comas-Herera's judgement in the development of the present guidelines. No further action was necessary.*

Miia Kivipelto, Karolinska Institutet, Stockholm, Sweden

Dr Kivipelto declared in her DoI form that she currently serves on the Advisory Board of a Finnish company that focuses on early diagnosis and e-health solutions for which she received €2500. She is also on the Governance committee of AARP, a non-profit organization for healthy ageing for which she received €800. She also declared that she has received research grants related to risk factors for dementia and is a founding member of World-Wide Fingers, an interdisciplinary network to share experiences, harmonize data and plan joint international initiatives for the risk reduction of cognitive decline and dementia.

Action: *This interest was deemed insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Kivipelto's judgement in the development of the present guidelines. She is deemed to be participating in the guideline development process in an individual capacity and not representing any organization. No further action was necessary*

Ayesha Motala, University of KwaZulu-Natal, Durban, South Africa.

Dr Motala declared that as a public servant working in a government institute, she seeks sponsorships to meetings from various organizations, especially when her scientific abstracts are accepted for presentations. The sponsorships are merely for attending the meetings, with no obligation to the sponsoring companies.

Details of such sponsorship for which she received a total amount of US$26 000:

4–8 December 2017: International Diabetes Federation (IDF) Congress, Abu Dhabi: Sanofi Aventis sponsorship for travel and accommodation;

11–15 September 2017: European Association for the Study of Diabetes (EASD) Congress, Lisbon: Pfizer sponsorship for travel and accommodation;

8–13 June 2018: American Diabetes Association (ADA), San Diego: Boehringer Ingelheim sponsorship for travel and accommodation: a member of her collaborating scientific team presented a paper.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Motala's contribution as an external reviewer for these guidelines. No further action was necessary.*

Ronald C. Petersen, Mayo Clinic, Rochester, USA

Dr Petersen declared that he is a clinical trials consultant for five pharmaceutical companies: from four of these (Roche Inc, Merck Inc, Genetech Inc and GE Healthcare) he receives less than US$ 10 000 and from one (Biogen Inc) he receives less that US$ 15 000 as consultancy fees.

Action: *It was felt that this interest is unlikely to affect, or be reasonably perceived to affect, Dr Petersen's contribution as an external reviewer for these guidelines since these grants are not related to the topic of interest. No further action was necessary.*

Martin Prince, King's College London, London, United Kingdom

Professor Prince declared in his DOI form that he currently receives research support through a grant from the National Institute of Health Research (NIHR, UK) amounting to £7 million over four years. Professor Prince is the PI and 20% of his salary costs are charged to the grant. The work focuses on health systems strengthening in sub Saharan Africa and one theme relates to the topic of these guidelines i.e. integrated primary healthcare for multimorbid conditions.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Professor Prince's judgement in the development of the present guidelines. No further action was necessary*

Suzana Shahar, Universiti Kebangsaan Malaysia, Selangor, Malaysia

Dr Sahar has declared in her DoI form that she has a clinical trial agreement through her University with Biotropics, a company that develops bio-resources into superior natural health product. The research involves evaluating the efficacy of Asian traditional herbs in improving cognition and mood. The funding amount is US$ 100 000 between 2014 and 2018.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Sahar's contribution as an external reviewer for these guidelines. No further action was necessary*

Huali Wang, Dementia Care & Research Center, Peking University Institute of Mental Health, Beijing, China.

Dr Wang declared in her DoI form that prior to 2016, she had worked as a consultant with Neowave Inc. to develop a tablet-based cognitive training program. She also declared that she had received support for travelling to meetings form Eisai China amounting to US$ 7000 prior to 2017. The meeting were all Alzheimer's Disease International (ADI) conferences.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Wang's contribution as an external reviewer for these guidelines. No further action was necessary*

B. EXTERNAL REVIEW GROUP

Members of the external review group with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Abdullah Al Khatami,** Ministry of Health, Saudi Arabia
2. **Alistair Burns,** University of Manchester, UK
3. **Linda Clare,** University of Exeter, UK
4. **Jacqueline Dominguez,** Institute for dementia care Asia, Quezon city, Philippines
5. **Maelënn Guerchet,** The Global Observatory for Ageing and Dementia Care, King's College London, UK
6. **Mariella Guerra,** Institute of Memory, Depression and Related Disorders – IMEDER, Lima, Peru
7. **Luis Miguel F. Gutiérrez Robledo,** Instituto Nacional de Geriatría, Institutos Nacionales de Salud de México, Mexico City, Mexico
8. **Vladimir Hachinski,** University of Western Ontario in London, Ontario, Canada
9. **Qurat ul Ain Khan,** Aga Khan University Hospital, Karachi, Pakistan.
10. **Sebastian Koehler,** Maastricht University, The Netherlands
11. **Jae-hong Lee,** University of Ulsan College of Medicine, Seoul, Korea
12. **Gill Livingstone,** University college London, UK
13. **Jean Claude Mbanya,** Doctoral School of Life Sciences, Health and Environment, University of Yaoundé I, Cameroon.
14. **James McKillop,** Service user group representative, UK
15. **Rajat Ray,** National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India
16. **Helen Rochford Brennan,** European Working Group of people with dementia, Ireland
17. **Kate Swaffer,** Dementia Alliance International, Australia
18. **Weili Xu,** Karolinska Institute, Finland

Members of the external review group who have declared an interest on the DOI form or where a potentially relevant interest has been noted from the CV

Emiliano Albanese, Universita della Svizzera italiana, Switzerland

Dr Albanese declared in his DoI form that he receives research support from the Economic and Research Council UK as part of the STRIDE (Strengthening responses to dementia in developing countries) research consortium which focuses on dementia research in low and middle income countries. The amount of US$ 50 000 is provided to the institution to which he is affiliated.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Albanese's contribution as an external reviewer for these guidelines. No further action was necessary.*

Hillary Doxford, 3 Nations Dementia Working Group, UK

Ms Doxford declared in her DoI form that she has served on a grant review panel assessing and prioritizing grant applications for funding dementia research projects for the National Institute for Health Research, UK. The income she received for this was £450. She is also a voluntary member of the Dementia Programme Board in the UK Department of Health and Social Care as a person with lived experience.

Action: It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Ms Doxford's contribution as an external reviewer for these guidelines. No further action was necessary.

Elaine Rashbrook, Public Health England, UK

Dr Rashbrook declared in her DoI form that she is employed by Public Health England (PHE), a government agency, as Consultant Specialist Life Course since 2015. PHE supports work on dementia risk reduction in line with the government strategy. There is no identified financial value for the work.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Rashbrook's contribution as an external reviewer for these guidelines. She is deemed to be providing her review in an individual capacity and not representing any organization. No further action was necessary.*

Andrew Sommerlad, University College London, UK

Dr Sommerlad declared in his DoI form that he receives research support from the Wellcome Trust in the form of a personal research fellowship to examiner whether social isolation is a risk factor for dementia The amount of funding is £201 311 from 2016 to 2019.

Action: *It was felt that this interest is insignificant or minimal and unlikely to affect, or be reasonably perceived to affect, Dr Sommerlad's contribution as an external reviewer for these guidelines. No further action was necessary*

B. EXTERNAL PARTNERS

External partners with no relevant interests declared on the DOI form and no relevant interests found in the CV

1. **Mariagnese Barbera,** University of Eastern Finland, Kuopio, Finland;
2. **Nicole A. Ee,** University of New South Wales, Sydney, Australia;
3. **Jenni Kumlala,** Karolinska Institutet, Stockholm, Sweden;
4. **Ruth Peters,** University of New South Wales, Sydney, Australia;
5. **Lidan Zheng,** University of New South Wales, Sydney, Australia.

None of the external partners declared relevant interests on the DOI forms nor were relevant interests found in the CV.

ANNEX 3: SCOPING QUESTIONS

INTERVENTIONS ADDRESSING LIFESTYLE AND BEHAVIOUR RISK FACTORS

1. Physical activity interventions

For adults with normal cognition or mild cognitive impairment, are physical activity interventions more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults (age above 18 years) with normal cognition or MCI

I: Physical activity interventions (aerobic, resistance training or multicomponent physical activity)

C: Care as usual or no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

2. Tobacco cessation interventions

For adults with normal cognition or mild cognitive impairment who use tobacco, are interventions for tobacco cessation more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI who use tobacco

I: Interventions for tobacco cessation (behavioural interventions and pharmacological interventions including nicotine replacement therapy, bupropion, varenicline)

C: Care as usual or no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

3. Nutritional interventions

3a. For adults with normal cognition or mild cognitive impairment, are nutritional interventions such as dietary supplements more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI

I: Dietary supplements (e.g. B vitamins, antioxidants, omega-3 and ginkgo);

C: Care as usual or no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

3b. For adults with normal cognition or mild cognitive impairment, are nutritional interventions such as healthy dietary patterns (e.g. Mediterranean diet) more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI

I: Healthy dietary pattern (e.g. Mediterranean diet)

C: Care as usual or no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

4. Interventions for alcohol use disorders

For adults with normal cognition or mild cognitive impairment and alcohol use disorders, are behavioural and psychological interventions to treat alcohol use disorders more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI and excessive use of alcohol

I:

- Behavioural and psychological interventions to treat alcohol use disorders (e.g. motivational interviewing)
- Pharmacological interventions to treat alcohol use disorders

C: Care as usual or no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

SPECIFIC INTERVENTIONS

5. Cognitive interventions

For adults with normal cognition or mild cognitive impairment is cognitive stimulation or cognitive training more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI

I:
- Cognitive stimulation
- Cognitive training

C: Care as usual or no intervention

O:
- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

6. Social activity

For adults with normal cognition or mild cognitive impairment is preserving and promoting a high level of social activity more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI

I: Preservation and promotion of social activity including community and family engagement

C: Care as usual or no intervention

O:
- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

INTERVENTIONS FOR HEALTH CONDITIONS

7. Weight management

For adults with normal cognition or mild cognitive impairment who are overweight or obese, are interventions for weight reduction (or control of obesity) more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI who are overweight or obese

I: Weight management

- Non-pharmacological interventions, e.g. cognitive-behavioural intervention strategies, lifestyle interventions
- Pharmacological interventions, e.g. weight-loss medication (e.g. orlistat)

C: Care as usual or no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

8. Management of hypertension

For adults with normal cognition or mild cognitive impairment and hypertension, is treatment of hypertension more effective than placebo/no intervention in reducing the risk of cognitive decline/dementia?

P: Adults with normal cognition or MCI with hypertension

I: Antihypertensive medication, lifestyle interventions

C: Placebo/no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

9. Management of diabetes mellitus

For adults with normal cognition or mild cognitive impairment and diabetes mellitus, is treatment of diabetes more effective than placebo/no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI with diabetes mellitus

I:

- Medications for glycaemic control
- Diet and lifestyle interventions

C: Placebo/no intervention

O:

- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

10. Management of dyslipidaemia

For adults with normal cognition or mild cognitive impairment and dyslipidaemia, is treatment of dyslipidaemia more effective than placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI with dyslipidaemia

I:
- Statins (e.g. simvastatin and pravastatin)
- Lifestyle interventions

C: Placebo or no intervention

O:
- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

11. Management of depression

For adults with normal cognition or mild cognitive impairment and depressive disorder, is treatment of depression more effective than usual care, placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI with moderate to severe depressive disorder

I:
- Pharmacological interventions to treat depression (antidepressant medication)
- Psychological interventions to treat depression (e.g. cognitive behavioural therapy, problem-solving therapy, interpersonal therapy, behavioural activation)

C: Care as usual or placebo or no intervention

O:
- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

12. Management of hearing loss

For adults with normal cognition or mild cognitive impairment and hearing loss, is treatment of hearing loss more effective than usual care, or no intervention in reducing the risk of cognitive decline and/or dementia?

P: Adults with normal cognition or MCI with hearing loss

I: Interventions to treat hearing loss (e.g. hearing aids)

C: Care as usual or no intervention

O:
- Critical
  - Cognitive function
  - Incident MCI
  - Dementia
- Important
  - Quality of life
  - Functional level (ADL, IADL)
  - Adverse events
  - Drop-out rates

ANNEX 4: EVIDENCE REVIEW METHODOLOGY

Comprehensive searches of major bibliographic databases were conducted to identify one systematic review that matched each of the outcomes for each of the PICO questions. The aim was to identify systematic reviews that were timely, of high quality and relevant to each of the PICO questions.

The search strategies differed slightly between the two teams (based in the Karolinska Institutet, Sweden and University of New South Wales, Australia. However, in general, the following process was employed:

1. Search for systematic reviews (including meta-analyses) that were published in the last 2 years for each of the PICO questions. The searches were run from April to June 2018.

2. If no relevant high-quality systematic reviews were identified from the 2 years for any of the PICO questions, the search was expanded to include systematic reviews from the last 5 years for that PICO question. For the relevant PICO questions, the 2016 AHRQ systematic review was also consulted. The aim of the AHRQ review was to examine interventions to prevent cognitive decline and dementia. The review systematically searched records between January 2009 and September 2016.

3. For the hearing loss question, there was very limited evidence available, therefore searches were expanded to include all systematic reviews ever published.

4. Based on the GDG's feedback during the GDG meeting in July 2018, the searches were expanded to further include systematic reviews of observational studies. The searches were re-run July to August 2018.

The following bibliographic databases were searched:

- Bibliographic
- Medline
- Cochrane
- PsycInfo
- Embase
- NICE.

Relevant to LMIC

- Global Index Medicus/Global Health Library
- WHO regional database
- WHOLIS
- Database of impact evaluations
- AJOL
- KoreaMed
- IndMED
- HrCak
- ArabPsycNet
- HERDIN NeON
- EurasiaHealth.

After the searches were run using the search strategies listed below, titles and abstracts of all results were screened in Endnote; subsequently the full texts of those papers were reviewed that could not be excluded based on the title/abstract review.

GRADE EVIDENCE TABLES

For each outcome of each PICO question, one or more systematic reviews were then selected to be used within the GRADE evidence tables. The following criteria were used when selecting which systematic review to use within the GRADE evidence tables:

- Published in the last 5 years, ideally 2 years **(timeliness)**.
- High **quality** (i.e. measured using AMSTAR 2[15] criteria).

[15] Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C et al (2007). Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 7:10.

- Closely **relevant** to the PICO question.
- Comprehensive systematic reviews given preference, where possible.
- Cochrane reviews or other meta-analyses given preference, where possible/appropriate.

The GRADE methodology involves rating the quality of the studies included in the systematic review according to study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias. Together with the effect sizes of studies, an overall "certainty of evidence" is provided of either very low, low, moderate or high.

GRADE evidence tables were completed using the GRADEpro online tool.[16] The same criteria were used as for the *mhGAP Intervention guide* when completing the GRADE evidence tables in terms of the assessment of the quality of studies (for risk of bias, inconsistency, indirectness, imprecision, and publication bias).[17]

SEARCH STRATEGIES

Separate searches were performed for each of the 12 PICO questions. Where PICO questions included both pharmacological and non-pharmacological interventions, searches were run separately for these.

Filters were used in the bibliographic databases where possible to restrict the searches to systematic reviews and meta-analyses, as well as to humans. No further restrictions were employed, for example in terms of language (apart from the publication date, as mentioned above).

The "advanced search" option was selected in bibliographic databases, where possible.

[16] https://gradepro.org/

[17] See http://www.who.int/mental_health/mhgap/evidence/mhgap_guideline_process_2009.pdf

PICO 1

For adults with normal cognition or mild cognitive impairment, are physical activity interventions more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(dementia OR cognit* OR "mild cognitive impairment" OR "Alzheimer disease" OR "dementia vascular" OR "dementia multi-infarct" OR MCI OR "cognitive dysfunction" OR neuropsychologi* OR "Health-Related Quality" Of Life OR "life quality" OR "Activities Daily Living" OR "Chronic Limitation of Activity" OR "Limitation of Activity, Chronic" OR ADL OR "activities of daily living" OR "Drug-Related Side Effects and Adverse Reactions" OR "Adverse Drug Event" OR "Adverse Drug Reaction" OR "Long Term Adverse Effects" OR "Adverse Effects, Long Term Disease-Free Survival" OR "Event-Free Survival" OR "Adverse effects") AND (Exercise OR "exercise therapy" OR "Acute Exercise" OR "Aerobic Exercise" OR "Exercise Training" OR "Exercise, Aerobic" OR "Exercise, Isometric" OR "Exercise, Physical" OR "Isometric Exercise OR Physical Activity" OR "resistance training")

PICO 2

For adults with normal cognition or mild cognitive impairment who use tobacco, are interventions for tobacco cessation more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation

of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Tobacco OR smoking OR Tobacco use cessation OR giving up smoking OR quitting smoking OR stopping smoking OR smoking cessation OR smoking reduction OR tobacco use cessation products OR varenicline OR nicotinic agonists OR Nicotine Inhalant OR Nicotine Lozenge OR Nicotine Lozenges OR Nicotine Nasal Spray OR Nicotine Patch OR Nicotine Polacrilex OR Nicotine Replacement Products OR Nicotine Transdermal Patch OR Smoking Cessation Products) AND (Behavior OR behaviour OR drug therapy OR pharmacologic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment)

PICO 3

3a. For adults with normal cognition or mild cognitive impairment, are nutritional interventions such as dietary supplements more effective than usual care or no intervention in reducing the risk/ progression of cognitive decline and/or dementia?

3b. For adults with normal cognition or mild cognitive impairment, are nutritional interventions such as healthy dietary patterns (e.g. Mediterranean diet) more effective than usual care or no intervention in reducing the risk/progression of cognitive decline and/or dementia?

Search strategy

(dementia OR cognit* OR "mild cognitive impairment" OR "Alzheimer disease" OR Alzheimer* OR "dementia vascular" OR "dementia multi-infarct" OR MCI OR "cognitive dysfunction" OR neuropsychologi* OR "Health-Related Quality Of Life" OR "life quality" OR "quality of life" OR "Activities of Daily Living" OR "Chronic Limitation of Activity" OR "Limitation of Activity, Chronic" OR ADL OR "activities of daily living" OR "Drug-Related Side Effects and Adverse Reactions" OR "Adverse Drug Event" OR "Adverse Drug Reaction" OR "Long Term Adverse Effects" OR "Adverse Effects, Long Term" OR "Disease-Free Survival" OR "Event-Free Survival" OR "Adverse effects") AND ("Dietary supplements" OR "Dietary Supplementations" OR "Food Supplementations" OR "Food Supplements" OR "Herbal Supplements" OR Neutraceuticals OR Nutraceuticals OR Nutriceuticals OR diet or vitamin or food)

PICO 4

For adults with normal cognition or mild cognitive impairment and alcohol use disorders, are behavioural and psychological interventions to treat alcohol use disorders more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Alcohol drinking OR Binge drinking OR Drunkenness OR alcohol intoxication OR alcoholism OR alcohol withdrawal) AND (Add in Behavior OR behaviour OR drug therapy OR pharmacologic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment)

PICO 5

For adults with normal cognition or mild cognitive impairment is cognitive stimulation or cognitive training more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(systemati* or meta analys*) and (dementia or cognit* or MCI or neuropsycholog* or Alzheimer*) and ("Brain training" OR "cognitive training" OR "Brain fitness" OR Games OR "Memory training" OR (Stimulation AND cognit*)

PICO 6

For adults with normal cognition or mild cognitive impairment is preserving and promoting a high level of social activity more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

("social interaction" or "social Networks" or "social processes" or "social behaviour" or "social behavior" or "community networks" or "social media" or family) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheime*) and (systemati* or meta-analys*)

PICO 7

For adults with normal cognition or mild cognitive impairment who are overweight or obese, are interventions for weight reduction (or control of obesity) more effective than usual care or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Overweight OR Body weight or Body mass index OR weight loss OR Body weight changes) AND (Behavior OR behaviour OR drug therapy OR pharmacologic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment OR Appetite depressants)

PICO 8

For adults with normal cognition or mild cognitive impairment and hypertension, is treatment of hypertension more effective than placebo/no intervention in reducing reduce the risk of cognitive decline/dementia?

Search strategy

(systemati* or meta-analys*) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheimer's or Alzheimer) and (behaviour or behavior or "drug therapy" or "pharmacologic therapy" or pharmacotherapy or "cognitive behavioural therapy" or "cognitive behavioral therapy" or "cognitive therapy" or "online therapy" or "anti-hypertensive" or antihypertensive or treatment) and (hypertension or "blood pressure" or systolic or diastolic or prehypertension)

PICO 9

For adults with normal cognition or mild cognitive impairment and diabetes mellitus, is treatment of diabetes more effective than placebo/no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(systemati* or meta-analys*) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheime*) .ab. and diabetes.af. and ("hypoglycemic agents" or treatment or therapy or pharmacotherapy or behaviour or behavior)

PICO 10

For adults with normal cognition or mild cognitive impairment and dyslipidaemia, is treatment of dyslipidaemia more effective than placebo or no intervention in reducing reduce the risk of cognitive decline and/or dementia?

Search strategy

(dementia OR cognit* OR mild cognitive impairment OR Alzheimer disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsychologi* OR Health-Related Quality Of Life OR life quality OR Activities, Daily Living OR Chronic Limitation of Activity OR Limitation of Activity, Chronic OR ADL OR activities of daily living OR Drug-Related Side Effects and Adverse Reactions OR Adverse Drug Event OR Adverse Drug Reaction OR Long Term Adverse Effects OR Adverse Effects, Long Term Disease-Free Survival OR Event-Free Survival OR Adverse effects) AND (Cholesterol OR Hypercholes-terolemia OR lipo-proteins OR HDL cholesterol OR LDL cholesterol OR triglycerides) AND (Behavior OR behaviour OR drug therapy OR pharmalogic therapy OR pharmacotherapy OR Cognitive behavioural therapy OR Cognitive behavioural therapy OR Drug therapy OR cognitive therapy OR online therapy OR treatment OR statins OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Anticholesteremic agents)

PICO 11

For adults with normal cognition or mild cognitive impairment and depressive disorder, is treatment of depression more effective than usual care, placebo or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(depression or depressive) and (systemati* or meta-analys*) and (dementia or cognit* or "mild cognitive impairment" or MCI or "cognitive dysfunction" or neuropsycholog* or Alzheimer's or Alzheimer*) and (treatment or therapy or pharmacotherapy or antidepressan* or antidepressiv*)

PICO 12

For adults with normal cognition or mild cognitive impairment and hearing loss, is treatment of hearing loss more effective than usual care, or no intervention in reducing the risk of cognitive decline and/or dementia?

Search strategy

(hearing aids OR Cochlear implants Or hearing implants) AND (hearing loss OR deafness OR hearing impairment OR hypoacusis OR intervention OR treatment) AND (dementia OR cognit* OR mild cognitive impairment OR Alzheimer's disease OR dementia vascular OR dementia multi-infarct OR MCI OR cognitive dysfunction OR neuropsycholog*)

GLOSSARY

Adverse event
Any untoward medical occurrence in a patient or clinical investigation subject caused by health care management.

Aerobic exercise
A type of physical exercise that requires free oxygen to adequately meet energy demands via the aerobic metabolism. During aerobic exercise, oxygen is used to "burn" fats and glucose in order to produce adenosine triphosphate, the basic energy carrier for all cells. This type of exercise improves physical fitness by promoting the circulation of oxygen through the blood, is associated with an increased rate of breathing, and includes any type of exercise that, when performed at levels of intensity sufficiently supported by the aerobic metabolism, can be performed for extended periods of time.

Behavioural activation
A behavioural treatment for depression in which the person with depression is guided to increase the number of rewarding activities in his or her life.

Body mass index
An objective measurement calculated as body mass (or weight in kg) divided by the square of the body height (in metres), universally expressed in units of kg/m^2. BMI is used as approximate indicator of the amount of tissue mass (muscle, bone, and fat) in an individual. Based on the correlation between BMI and the degree of risk for certain disease, such as diabetes or atherosclerosis, BMI values are categorized as underweight, normal weight, overweight, or obese; obesity can also be subcategorized in moderate severe and morbid.

Cognitive behavioural intervention/therapy
A type of psychological therapy that involves identifying and correcting distorted maladaptive beliefs, while using thought exercises and real experiences to facilitate symptom reduction and improved functioning.

Cognitive decline
The physiological decay of brain functions such as memory, attention or learning ability, for example, which is associated with the normal ageing process. It differs from cognitive impairment in that anyone who ages develops some kind of cognitive decline, although at different degrees. Cognitive impairment, instead, is normally the result of a pathological event: injury, disease, or increased levels of cognitive decline.

Cognitive function
Cerebral activities, i.e. reasoning, memory, attention, and language that lead to the attainment of information and knowledge.

Cognitive stimulation
Participation in a range of activities designed to improve cognitive and social functioning.

Cognitive training
Guided practice of specific standardized tasks designed to enhance particular cognitive functions.

Dementia
Dementia, a group of disorders characterized by a decline from a previously attained cognitive level that affects activities of daily living or social functioning.

Dietary supplements
Dietary supplements include vitamins, minerals, fibre, fatty acids, or amino acids, among other substances. They are either intended to provide nutrients in order to increase their consumption, or to provide non-nutrient chemicals which are claimed to have a biologically beneficial effect.

Health-related quality of life
An individual's or a group's perceived physical and mental health over time. As a multidimensional concept, it includes domains related to physical, mental, emotional and social functioning, and it is a way to assess the impact of health status on quality of life.

Mediterranean diet
A diet which consists of a high intake of cereals, fruits, fish, legumes, and vegetables and low intake of meat and dairy.

Mild cognitive impairment
A disorder characterized by impairment of memory, learning difficulties and reduced ability to concentrate on a task for more than brief periods. There is often a marked feeling of mental fatigue when mental tasks are attempted, and new learning is found to be subjectively difficult even when objectively successful. None of these symptoms are so severe that a diagnosis of either dementia or delirium can be made.

Motivational interviewing
An established evidence-based practice in the treatment of individuals with substance use disorders that focuses on exploring and resolving ambivalence and centres on motivational processes within the individual that facilitate change.

Multidomain intervention
Intervention normally aimed to prevent/address a certain disease or condition by acting simultaneously on a range of risk factors, which may be either correlated or independent from each other.

Nicotine replacement therapy
A type of treatment that makes use of special products which provide small, steady doses of nicotine to help stop cravings and relieve withdrawal symptoms when an individual is trying to stop using tobacco. These products include nicotine gum, nicotine inhaler, nicotine nasal spray, nicotine lozenges, and nicotine patch. They do not contain any of the other chemicals found in tobacco products.

Physical activity
Any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits

Physical exercise: subcategory of physical activity that is planned, structured, repetitive, and aims to improve or maintain one or more components of physical fitness.

Problem-solving therapy
A type of psychological therapy where the patient systematically identifies his or her problems; generates alternative solutions for each problem; selects the best solution; develops and conducts a plan; and evaluates whether this has solved the problem.

Quality of life
An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

Resistance training
A form of physical exercise that, by the moving of the limbs against high loads or fixed resistances, causes skeletal muscles contraction, building their strength, anaerobic endurance, and size. The external resistance can be represented by dumbbells, rubber exercise tubing, the own body weight, bricks, bottles of water, machine specifically designed to this purpose, or any other object that causes the muscles to contract. The forces involved must be such that relatively few repetitions are possible without a substantial rest period. Resistance or strength training is primarily an anaerobic activity, although some proponents have adapted it to provide the benefits of aerobic exercise through circuit training.

Social activity
Social activities are varied and difficult to define, however they may include meeting friends, attending events or functions, volunteering or participating in occupational duties or group recreational activities.

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