World Health Organization

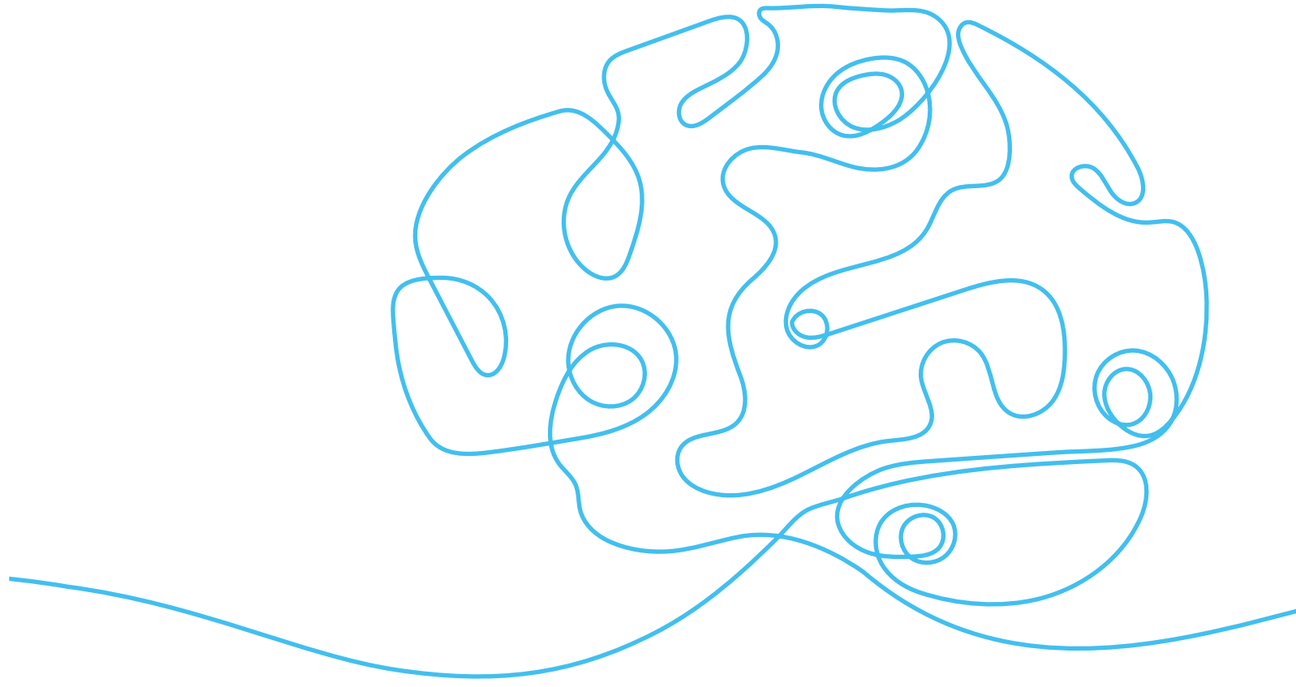
Optimizing brain health across the life course:

WHO position paper

World Health Organization

Optimizing brain health across the life course:

WHO position paper



Optimizing brain health across the life course: WHO position paper

ISBN 978-92-4-005456-1 (electronic version)
ISBN 978-92-4-005457-8 (print version)

© World Health Organization 2022

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (http://www.wipo.int/amc/en/mediation/rules/).

Suggested citation. Optimizing brain health across the life course: WHO position paper. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo/.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see https://www.who.int/copyright.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Photos credits: Cover photo © Unsplash/Gita Krishnamurti. Page vi photo © Unsplash/Sebastián León Prado. Page ix photo © Unsplash/Alvaro Reyes. Page xi photo © Unsplash/Lawrence Crayton. Page 3 photo © Unsplash/ Dario Valenzuela; Page 5 photo © Unsplash/Annie Spratt. Page 7 photo © Unsplash/Vince Fleming. Page 11 photo © Unsplash/Heri Mulyana. Page 17 photo © Unsplash/Tim Mossholder. Page 23 photo © Unsplash/Jakayla Toney. Page 27 photo © Unsplash/Raychan. Page 29 photo © Unsplash/Jaddy Liu. Page 37 photo © Unsplash/Chander R. Page 43 photo © Unsplash/Stéphane Hermellin. Page 53 photo © Unsplash/ Thiago Cerqueira. Page 57 photo © Unsplash/Andrea Ricketts. Page 59 photo © Unsplash/Rajat Sarki. Page 61 photo © Unsplash/Vladimir Soares. Page 63 photo © Unsplash/Nathan Anderson. Page 70 photo © Unsplash/Annie Spratt. Page 70 photo © Unsplash/Mohit Tomar. Page 75 photo © Unsplash/Mohit Tomar. Page 79 photo © Unsplash/Robin Noguier. Page 105 photo © Unsplash/M.T ElGassier.

Layout by Café.art.br

Contents

Foreword v
Acknowledgements vi
Abbreviations vii
Executive summary ix

1. Introduction 1
1.1 Why is brain health important? 2
1.2 Intergovernmental response to date 8
1.3 About this position paper 10
1.4 Methodology of this position paper 12

2. A framework for brain health optimization 15
2.1 What is brain health? 17
2.2 What is brain health optimization? 20

3. Determinants of brain health 27
3.1 Physical health 20
3.2 Healthy environments 37
3.3 Safety and security 40
3.4 Learning and social connection 42
3.5 Access to quality services 44

4. Impacts of brain health optimizationon health and other outcomes 51
4.1 Impact on health and well-being 52
4.2 The social and economic impact of brain health optimization 55

5. Future directions for brain health policy, research and data 59

5.1 Intersectoral actions for optimizing brain health across the life course 61

5.2 Driving brain health research 71

5.3 Operationalizing and measuring brain health 74

References 78

Annexes 88

Annex 1. Resolutions and global commitments relevant to brain health 88

Annex 2. Different definitions of brain health and relevant initiatives aimed at promoting brain health 91

Annex 3. WHO technical tools, norms and standards to address brain health determinants and optimize brain health for all 99

Foreword

The brain is by far the most complex organ of the human body, allowing us to sense, feel, think, move and interact with the world around us. The brain also helps regulate and influence many of our body's core functions including those of the cardiovascular, respiratory, endocrine and immune systems. A multitude of factors can affect our brain health from as early as pre-conception. These factors can pose great threats to the brain, leading to immense missed developmental potential, global disease burden and disability. Yet, these factors also represent great opportunities for action. Optimizing brain health across the life course means addressing five major groups of determinants, namely: physical health; healthy environments; safety and security; life-long learning and social connection; as well as access to quality services.

Advances in neuroscience and neuroimaging – in combination with other disciplines such as artificial intelligence, machine learning and data science – are drivers of research into the human brain, lifting multisectoral discourse and discovery to entirely new levels. This is a cause for great excitement and optimism.

However, if the factors that have a dire impact on brain health are left unaddressed, we shall fail both to promote everyone's full potential and to reduce the burden of neurological conditions, thereby impeding not only health but also social and economic development globally. We will achieve bold global commitments – such as the United Nations Sustainable Development Goals, WHO's Triple Billion targets and the recently-adopted Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031 – only if we work together to address brain health at all societal levels and across all sectors of society.

With this WHO position paper I am pleased to present a conceptual framework for optimizing brain health across the life course that will help us to raise awareness of the pressing need to establish brain health as a global priority. As such, this position paper represents an important tool for supporting the implementation of the new intersectoral global action plan. Let's not forget, optimizing brain health across the life course will improve health outcomes and well-being for all people in all corners of the world.

Dr REN Minghui
Assistant Director General
Universal Health Coverage/Communicable and Noncommunicable Diseases

Acknowledgements

This position paper was developed by the Brain Health Unit of the World Health Organization (WHO), under the overall supervision and guidance of Tarun Dua and Dévora Kestel.

The paper was written by Kavitha Kolappa and Katrin Seeher of the WHO Brain Health Unit, with substantial inputs from the following WHO Brain Health Unit colleagues (in alphabetical order): Elaine Brohan; Rodrigo Cataldi; Vanessa Cavallera; Jorge Castro; Neerja Chowdhary; Batool Fatima; Stéfanie Fréel; Laura Garcia Diaz; Gergana Manolova; Nicoline Schiess; Chiara Servili; and Jessica Spagnolo.

The following experts and people with lived experience provided valuable technical inputs and/or reviewed the draft position paper: Ignacio Amorín (Ministry of Health, Uruguay); Charles Alessi (Healthcare Information and Management Systems Society, United Kingdom of Great Britain and Northern Ireland); Silja Nicoline Angellsen (Norwegian Directorate of Health, Norway); Kaarin Anstey (University of New South Wales, Australia); Claudio Bassetti (University Hospital of Bern, Switzerland); Coriene Catsman-Berrevoets (Erasmus MC Rotterdam, Netherlands); William Carroll (World Federation of Neurology, Australia); Augustina Charway-Felli (37 Military Hospital, Ghana); Christopher Chen Li-Hsian (National University of Singapore, Singapore); Walter Dawson (Oregon Science and Health University, United States of America (USA)); Kirsty Donald (University of Cape Town, South Africa); Lorraine M. Duffy (Independent Consultant, Ireland); Isabel Elicer (Hospital Dr. Sótero del Río, Chile); Alan Evans (McGill University, Canada); Harris Eyre (Organisation for Economic Co-operation and Development, France); Lucila Falcone (Parkinson Argentina, Argentina); Valery Feigin (Auckland University of Technology, New Zealand); Gregory Fricchione (McCance Center for Brain Health, USA); David García Azorín (Hospital Clínico Universitario de Valladolid, Spain); David Good (Pennsylvania State University, USA); Riadh Gouider (Razi Hospital La Monouba, Tunisia); Phillippe Grandjean (University of Southern Denmark, Denmark); Wolfgang Grisold (World Federation of Neurology, Austria); Alla Guekht (Russian National Research Medical University, Russian Federation); Vladimir Hachinski (Western University, Canada); Tadeusz Hawrot (European Federation of Neurological Associations, Belgium); Volker Hömberg (World Federation for Neurorehabilitation, United Kingdom); William Hynes (Organisation for Economic Co-operation and Development, France); Vijeth Iyengar (Centres for Disease Control and Prevention, Healthy Brains Initiative, USA); Hanan Khalil (Jordan University of Science and Technology, Jordan); Mika Kivimäki (University of Helsinki, Finland and University College of London, United Kingdom); Miia Kivipelto (Karolinska Institute, Sweden); Ambar Kulshreshtha (Emory University, USA); Phil Landrigan (Boston College, USA); Brian Lawlor (Global Brain Health Institute, Ireland); Matilde Leonardi (Fondazione IRCCS Istituto Neurologico C. Besta-Milan, Italy); Iracema Leroi (Global Brain Health Institute, Ireland); Sarah Lenz Lock (American Association of Retired Persons, USA); Shen-Yang Lim (University of Malaya, Malaysia); Henk Lindeman (Instituut voor toegepaste Neurowetenschappen, Netherlands); Kate Loveys (University of Auckland, New Zealand); Jim Mann (Global Dementia Observatory Knowledge Exchange (GDO KE) Platform Focus Group Member, Canada); Soania Mathur (Unshakeable MD, Canada); Chandrashekhar Meshram (Brain and Mind Institute, India); Helen Medsger (Dementia Community Research Advisory Panel Member, Global Brain Health Institute, USA); Bo Norrving (Lund University, Sweden); Adesola Ogunniyi (University College Hospital, Ibadan, Nigeria); Njideka Okubadejo (University of Lagos, Nigeria); Mayowa Owolabi (University of Ibadan, Nigeria); Damien Peelo (Dementia Community – Research Advisory Panel (DC-RAP) member, Ireland); Gustavo Petroni (Centro de Informatica e Investigacion Clinica, Hospital de Emergencias, Argentina); Sebastian Porta (Parkinson Argentina, Argentina); Phurpa (Khesar Gyalpo University of Medical Sciences of Bhutan, Royal Government of Bhutan); Kameshwar Prasad (All India Institute of Medical Sciences, India); Andrea Sofía Prato Chichiraldi (Escleriosis Multiple del Uruguay, Uruguay); Salvador Ramirez Gallegos (Independent consultant, Mexico); Thomas Rannstad Hauge (Norwegian Directorate of Health, Norway); Patricia Ripoll (Patient advocate, MamaTieneMigraña.com, Spain); Helen Rochford-Brennan (GDO KE Platform Focus Group Member, Ireland); Jonathan Rosand (McCance Center for Brain Health, USA); Séverine Sabia (Université de Paris, France); Shekhar Saxena (Harvard University, USA); Deanna Saylor (Johns Hopkins University, USA); Annemarie Schumacher Dimech (Women's Brain Project, Switzerland); Osheik Seidi (University of Khartoum, Sudan); Jack Shonkoff (Harvard University, USA); Raliza Stoyanova (Healthy Brains Global Initiative, United Kingdom); Pawel Sweiboda (Human Brain Project and EBRAINS, Belgium); Tashi Tenzin (Khesar Gyalpo University of Medical Sciences of Bhutan, Royal Government of Bhutan); Veronique Theberge (Weird Wonderful Brain, New Zealand); Chahnez Triki (Hedi Chaker Hospital, Tunisia); Maya Uccheddu (A.I.M. Associazione Italiana Miastenia, Italy); Pedro Valdes-Sosa (C-Neuro, Cuba); Lucia Wang (Parkinson Argentina, Argentina); Claire Wright (Meningitis Research Foundation, United Kingdom).

Valuable technical inputs were received from the following WHO colleagues at headquarters and in regional offices: Onyema Ajuebor (Policy and Standards); Florence Baingana (Regional Office for Africa); Valentina Baltag (Adolescent Health); Anshu Banerjee (Maternal, Newborn, Child and Adolescent Health and Ageing); Prebo Barango (WHO Regional Office for Africa); Julia Berenson (Health Equity); Richard Brown (Chemical Safety and Health); Marie-Noël Bruné Drisse (Chemical Safety and Health); Matteo Cesari (Ageing and Health); Alarcos Cieza (Sensory Functions, Disability and Rehabilitation); Bernadette Daelmans (Newborn Health); Chencho Dorji (Regional Office for South-East Asia); Michelle Funk (Policy, Law and Human Rights); Brandon Gray (Mental Health); Dzmitry Krupchanka (Alcohol, Drugs and Addictive Behaviours); Ledia Lazeri (Regional Office for Europe); Jason Maurer (Regional Office for Europe); Christopher Mikton (Healthy Ageing); Asiya Odugleh-Kolev (Quality of Care); Alana Officer (Demographic Change and Healthy Ageing); Renato Oliveria Souza (Regional Office for the Americas); Mark van Ommeren (Mental Health); Leslie Jayne Onyon (Chemical Safety and Health); Vladimir Poznyak (Alcohol, Drugs and Addictive Behaviours); Marie-pierre Preziosi (Immunization, Vaccines and Biologicals, Agenda Policy and Strategy); Cassie Redlich (Regional Office for Europe); Dag Rekve (Alcohol, Drugs and Addictive Behaviours); Khalid Saeed (Regional Office for the Eastern Mediterranean); Yuka Sumi (Ageing and Health); Nuhamin Tekle Gebre (Clinical Services and Systems L); Ana Maria Tijerino Inestroza (Regional Office for Europe); Martin Vandendyck (Regional Office for the Western Pacific); Cherian Varghese (Noncommunicable diseases); Marco Vitoria (Global HIV, Hepatitis and STIs); and Juana Willumsen (More Physical Activity).

Special thanks to the following persons who provided their testimonies and perspectives on the importance of brain health: Carola Deurwaarder (Netherlands); Kaie Klaassen (Netherlands); Henk Lindeman (Netherlands); Jim Mann (Canada); Soania Mathur (Canada), Anja Minheere (Netherlands), Salvador Ramírez (Mexico); and Veronique Theberge (New Zealand).

Financial support for this publication was provided by the Ministry of Foreign Affairs of the Government of Iceland.

Abbreviations

ACEs	Adverse childhood experiences
BDNF	Brain-derived neurotrophic factor
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
CST	Caregiver skills training
CT	Computed tomography
DALYs	Disability-adjusted life years
DNA	Deoxyribonucleic acid
GSED	Global Scale for Early Development
HAT	Helping adolescents thrive
HPA axis	Hypothalamic–pituitary–adrenal axis
ICF	International Classification of Functioning, Disability and Health
IHME	Institute for Health Metrics and Evaluation
MRI	Magnetic resonance imaging
NCDs	Noncommunicable diseases
NCF	Nurturing Care Framework
OECD	Organisation for Economic Co-operation and Development
PHC	Primary health care
RNA	Ribonucleic acid
SDGs	Sustainable development goals
TBI	Traumatic brain injury
TCE	Trichloroethylene
UHC	Universal health coverage
UN	United Nations
UN CRPD	United Nations Convention on the Rights of Persons with Disabilities
UNICEF	United Nations Children's Fund
USA	United States of America
WHO	World Health Organization

Executive summary

> Lack of brain health is often invisible; make it visible! Brain health affects us all. Not only the person with a brain condition but also their family, friends, colleagues, etc.”

Anja Minheere, Netherlands

Introduction

Brain health is an evolving concept that is attracting increasing attention not only from the health sector but also from wider society, stimulating rich debate – and for good reasons. The brain and central nervous system (CNS) are widely recognized as the command centre of the human body, controlling both conscious and unconscious body functions and thereby influencing every aspect of life. If our brains are challenged by disease or other factors, this poses significant risks not only to the individual's overall health and well-being but also global development and productivity. Optimizing brain health, on the other hand, can lead to a wide array of benefits for the individual and society.

One way to stress the importance of optimizing brain health is to quantify the impacts of missed developmental potential in children which lead to cycles of poverty and health inequities. For example, in 2017, 43% of children under the age of 5 years in low- and middle-income countries (nearly 250 million children) were at risk of not reaching their developmental potential due to extreme poverty and stunting. The costs of inaction are high, with the financial losses alone for this missed developmental potential projected to be around 26% lower annual earnings in adulthood. Moreover, too few countries globally have family-friendly policy protections in place with the aim of safeguarding child brain development, such as programmes to offer tuition-free pre-primary school education, legislation to support breastfeeding, or paid maternity and paternity leave. Additionally, growing hazards from environmental pollutants imperil brain health globally. For example, WHO estimates that 99% of all people worldwide breathe polluted air in their ambient environment, which poses grave threats to brain development in early life and brain health across the life course. Other compelling arguments for optimizing brain health throughout our lives are the morbidity and mortality caused by neurological disorders worldwide. Neurological disorders led by stroke, migraines, dementia and meningitis are currently the number one cause of disability globally. In addition, neurological disorders are the second leading cause of death, responsible for 9 million deaths per year. Global trends over the past three decades – largely driven by worldwide demographic changes and population ageing – suggest that these numbers will only increase. Nearly one in three people globally will develop a neurological disorder at some point in their lifetime, which means that virtually all readers of this paper will be touched by neurological disorders, either directly or indirectly. Further, the financial costs of neurological disorders are enormous, with common neurological disorders accounting for US$789 billion in the United States of America alone.

Unfortunately, global action on brain health is grossly insufficient. Despite growing threats to brain health, there is limited policy response to address brain health comprehensively and there are inadequate services to promote and optimize brain health for people with lived experience. Regardless of the huge global burden, access to services and support are both inadequate and unevenly distributed across country income brackets and between urban and rural areas within countries. Numerous barriers to accessing timely and responsive services for neurological disorders exist globally, including the limited number of health workers with neurology-specific training in lower-resource settings. For example, there is a 70-fold difference in the availability of neurologically-trained workforce between high-income countries and low-income countries. Additional barriers to accessing services include limited social and financial protections for people with neurological disorders, lack of access to medicines and diagnostics, as well as stigma and discrimination.

The World Health Organization (WHO) worked with a group of international experts, including people with lived experience of neurological disorders, to develop a position paper on optimizing brain health across the life course through an iterative process of desk reviews, consultations and peer review. The position paper provides a conceptual framework of brain health and brain health optimization **(see Box 1)**.

The paper outlines the determinants of brain health, describes the impact that optimizing brain health would have for the individual as well as for society, and offers practical policy solutions and future directions for the field.

A framework for brain health optimization

Numerous concepts and definitions of brain health exist and have gained traction in various settings in recent years. Many definitions of brain health focus on older life, with implications for specific neurological conditions (e.g. dementia or stroke), while others focus mainly on one domain of brain functioning (e.g. cognition), which also holds implications for specific neurological conditions (e.g. dementia). Some definitions of brain health span multiple domains of brain functioning, developmental phases across the life course, and disorder categories (including mental health, neurological, substance use and pain conditions).

Box 1.

What is brain health and what does optimizing brain health mean?

Brain health can be defined as the state of brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders.

Continuous interactions between different determinants and a person's individual context lead to lifelong adaptation of brain structure and functioning.

Optimizing brain health improves mental and physical health and also creates positive social and economic impacts, all of which contribute to greater well-being and help advance society.

The brain's ability to grow and build strong neuronal connections, as well as adapt, repair and/or compensate over time in ways that allow us to sense, feel, think, move and interact in the world around us is key to brain health. Additionally, the brain directs many of our body's core involuntary functions (e.g. breathing and heart rate, endocrine and immune functions).

It is important that brain health extends beyond conceptions of disease (or the absence thereof) and focuses on brain structure and brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains. Brain health exists on a continuum that can be considered to range from well-being to disorders and disability across each of the aforementioned domains. There are many disorders affecting the CNS including cerebrovascular diseases such as stroke; epilepsy; headache disorders such as migraine; neurodegenerative disorders such as dementia and Parkinson disease; neurodevelopmental disorders such as autism spectrum disorder; neuroinfections such as meningitis, HIV, neurocysticercosis, or cerebral malaria; neuroimmunological disorders such as multiple sclerosis; tumours of the brain; and traumatic injuries.

Importantly, while many brain health definitions include mental health conditions, WHO considers mental and brain health as two separate but closely-related concepts. In fact, brain health is a crucial determinant of mental health across the life course.

Addressing brain health determinants

Many factors are known to have an impact on brain health at different stages of life (e.g. perinatal, infancy, early childhood, adolescence, adulthood and older age). Stages of brain development are characterized by neuroplasticity, pruning and senescence – i.e. rapid growth of neuronal connections in utero and in early childhood, directed shedding of neuronal connections in later childhood and adolescence, and neuronal loss in adulthood. While these stages were traditionally conceptualized as consecutive and non-overlapping, we now know that this is not the case. We can improve our brain health throughout our lifetimes by minimizing risk factors, as well as by enhancing protective factors that promote neuroplasticity, or the brain's ability to grow, create new connections and recover or compensate for injuries.

Of note, no single factor is solely deterministic for a person's brain health outcomes. Broadly speaking, however, brain health can be optimized through actions across the following clusters: physical health, healthy environments, safety and security, learning and social connection, and access to quality services. Brain health determinants are often interlinked and can be affected by various types of adversities. Importantly, structural inequities associated with racism, ethnic and religious discrimination, or other systematic causes of oppression and marginalization constitute important macro-level sources of adversity.

Brain health determinants

Physical health

A person's physical health and their health behaviours can impact their brain health in innumerable ways across their life course. This is because there are multi-directional interactions between the brain and the body. Important aspects of physical health that influence the brain include: maternal health and the intrauterine environment; genetic and epigenetic factors; nutrition; infections; noncommunicable diseases and sensory impairments; health behaviours (including good-quality sleep, physical activity and substance use); and traumatic injuries.

Healthy environments

Healthy environments can also have a profound impact on brain health, especially during developmentally sensitive stages such as early childhood, adolescence and older age. There has been increasing information in recent years on environmental factors that affect brain health, including pollutants found in air, water and food. Neurotoxic chemicals include heavy metals and inorganic compounds, pesticides, organic solvents and other organic compounds. In addition, natural disasters (e.g. volcanic eruptions), man-made disasters (e.g. nuclear explosions or chemical spills), climate change contributing to ambient air pollution and increased risk of wildfires threaten the brain health of individuals and society as a whole.

Safety and security

Physical safety and financial security can also impact brain health over the life course in multiple ways. Physical safety is the absence of actual physical harm (including abuse, maltreatment and neglect) and the threat of physical harm; it requires stable and safe housing, and safety within the home and broader community. Financial security is not merely the absence of poverty, but also the absence of strain or stress due to financial concerns; it means that one can reasonably afford the necessities of life – including food, housing, health care, education and transport. Both physical safety and financial security can have impacts on individuals and their families, as well as the communities in which people live.

Learning and social connection

Access to opportunities for learning and social connection are important determinants for brain health across the life course and overlap in multiple ways. Learning in early life, for instance, is closely connected with responsive and nurturing caregiving. Similarly, formal learning relies on schools and other educational institutions, while cognitive stimulation in adulthood is often linked to employment and social networks within communities. Additionally, interventions aimed at optimizing brain health – especially in early life – may involve support for both learning and social connection.

Access to quality services

Managing many risk factors of brain health will require access to quality health and social services. Despite best efforts to minimize risk factors, many people still develop conditions that affect the CNS at some point in their lifetime. Therefore, access to quality services represents an important determinant of brain health and, similarly, strengthening health and social care systems so that they provide equitable access to diagnosis, treatment, care and rehabilitation, as and when needed, is crucial for optimizing brain health for all.

Impacts of optimizing brain health

Optimizing brain health improves mental and physical health and also creates positive social and economic impacts, all of which contribute to greater well-being and help advance society, irrespective of the presence or absence of disorders.

First, addressing the determinants of brain health through promotion and prevention can reduce the incidence of disorders that affect the CNS. Additionally, because optimizing brain health improves brain structure and functioning across all domains (cognitive, sensory, social-emotional, behavioural and motor), it can also lead to lower rates of mental health conditions and substance use. Importantly, measures taken to address determinants of brain health not only reduce the incidence of neurological, mental health and substance use conditions, but can also improve the quality of life for people living with these conditions. Optimizing brain health can additionally have impacts on physical health as the brain plays a role in regulating cardiovascular, endocrinological and immunological health. For example, the brain controls many autonomic processes including our heart rate, breathing rate and blood pressure. Importantly, the brain is also a crucial mediator of the impacts of social adversity on several health outcomes across the life course.

Optimizing brain health not only reduces health-care costs by virtue of improving overall health and reducing the incidence of many chronic health conditions – neurological, mental, substance use and physical – but additionally leads to multiple social and economic benefits across the life course, which are perhaps understood best in early life. For example, investment in early child development for children who are at risk can bring about great gains across the life course, including improving school retention and graduation rates, reducing teenage pregnancy, reducing incarceration rates and increasing employment and wealth. All of these outcomes contribute to greater well-being for the individual and society at large and thereby increase human potential globally. This sentiment is reflected in the emergence of terms inspired by the fields of economics or ecology – such as “brain capital”, “healthy brain years” or “cognitive footprint”. This terminology recognizes the immense impact of brain functioning on societies and at the same time attempts to quantify potential losses to society if we fail to preserve brain health.

Future directions for optimizing brain health

Global momentum is building to address brain health comprehensively. In 2022, the World Health Assembly adopted the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031*. The action plan envisages “a world in which brain health is valued, promoted and protected across the life course; neurological disorders are prevented, diagnosed and treated, and premature mortality and morbidity are avoided; and people affected by neurological disorders and their carers attain the highest possible level of health, with equal rights, opportunities, respect and autonomy.” All policy and programmatic actions to optimize brain health and implement the new action plan will require multi-stakeholder collaboration. They must be integrated across all sectors of society: health and social care; education; legislature and governance; finance and economy; employment; infrastructure, urban planning and housing; and ecology, nature and climate.

Brain health is a rapidly expanding field, hugely benefitting from advances in neuroscience and research. While much is known about the determinants of brain health, there is much left to be discovered about new and emerging determinants (e.g. environmental exposures, use of new technologies), novel treatment options, and the impacts of brain health interventions. There is an ongoing need to generate evidence in basic and clinical research, implementation science, and epidemiological and health economics research.

In addition, as of 2022, no simple, direct or global measure of brain health across the life course exists. Due to the multi-dimensionality of the concept, capturing the full spectrum of brain health across all domains of brain functioning and taking into account the wide range of brain health determinants is challenging. Yet, operationalizing brain health and developing validated metrics and tools for measuring brain health will be vital for closing knowledge gaps and understanding the impacts of interventions as well as the returns on investment for brain health.

Conclusion

Optimizing brain health for all is paramount to ensuring human health and well-being globally. It is central to achieving global commitments such as the new *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031*, WHO’s Triple Billion targets, the United Nations Sustainable Development Goals and the 2021 Geneva Charter for Well-being. Efforts to optimize brain health require multi-stakeholder collaboration and must be integrated across all sectors of society. In return, robust investments in actions that optimize brain health across the life course promise to improve multiple health outcomes and lift development and well-being globally. Multisectoral engagement and collaboration are urgently needed in order to move the brain health agenda forward for all people.

> When I attend meetings I make sure to start well rested. So, my clients and colleagues mostly see the 'old me'. But if a meeting runs over or is too busy, my energy level drops to zero and my overstimulation starts to show. Inside my brain works the same but way slower and I just can't get the words out of my mouth. So, nowadays we all joke: “Because Carola is attending, we all have to work more effectively and on time.” It feels good to laugh about it. And it really helps me to still do the work I love.”
>
> **Carola Deurwaarder, Netherlands**

1. Introduction

> Neurological illnesses are pervasive, affecting those afflicted not only physically but often mentally, emotionally and socially. You must be an active participant in optimizing your brain health. Self-care which includes exercise, nutrition, sleep and stress reduction are all beneficial.”

Soania Mathur, Canada

1.1 Why is brain health important?

Brain health is not only a crucial outcome in and of itself, but also an important mediator for other health and societal outcomes

Brain health is an evolving concept that has emerged in the academic literature in recent decades and has become increasingly popular within science, research, journalism and the general public, stimulating rich debate – and for good reasons. The brain and CNS are widely recognized as the command centre of the human body, controlling both conscious and unconscious body functions and thereby influencing every aspect of life. If our brains are challenged by disease or other factors, this poses significant risks not only to the individual's overall health and well-being but also to global development and productivity.

In other words, brain health is not only a crucial outcome in and of itself, but also an important mediator for other health and societal outcomes. Promoting brain development and protecting brain health across the life course present important opportunities for cross-sectoral action and intervention to benefit individuals and societies. This is reflected in the emergence of terms inspired by the fields of economics or ecology – such as "brain capital",[1] "healthy brain years"[2] or "cognitive footprint"[3] *(1—4)*. This terminology recognizes the immense impact of brain functioning on societies and at the same time attempts to quantify potential losses to society if we fail to preserve brain health.

The immense potential for action, paired with advances in neuroscience and neuroimaging – as well as the emergence of, and collaboration with, nonmedical disciplines such as artificial intelligence, machine learning and data science – continue to drive research into the human brain and spark multisectoral discourse. With this position paper, WHO provides a conceptual framework for optimizing brain health across the life course and makes the case for establishing brain health as a global policy priority.

1. "Brain capital" refers to the "knowledge, creative skills and optimal brain health that people accumulate throughout their lives, enabling them to realize their potential as productive members of society" *(1—3)*

2. "Healthy brain years", in reference to healthy life expectancy, is a concept that WHO is presently working on with partners to quantify the burden associated with brain diseases, for example, to estimate years at birth that a person can expect to live with optimal brain functioning.

3. "A cognitive footprint, as with a carbon footprint, can be either negative (impair cognition) or positive (enhance cognition). It could be used to assess and model potential cognitive effects of medical and public health interventions through to social and wider public policies" *(4)*.

One way to stress the importance of optimizing brain health is to quantify the impacts of missed developmental potential in children which lead to cycles of poverty and health inequities *(5)*. The long-term consequences of missed developmental potential not only have an impact on children and their families, but also on the communities they live in. For example, in 2017 43% of children under the age of five in low- and middle-income countries (nearly 250 million children) were at risk of not reaching their developmental potential due to extreme poverty and stunting *(6)*. The costs of inaction are high: the financial losses alone for these children as a result of missed developmental potential are projected to be around 26% lower annual earnings in adulthood *(7)*. Moreover, too few countries have family-friendly policy protections in place to safeguard child brain development – such as programmes that offer tuition-free pre-primary school education, legislation that supports breastfeeding, or paid maternity and paternity leave *(8)*. In addition, growing hazards from environmental pollutants imperil brain health globally. WHO estimates that 99% of all people worldwide breathe polluted air in their ambient environment, posing grave threats to brain development in early life and brain health across the life course *(9)*.

43%

of children under the age of five in low- and middle-income countries were at risk of not reaching their developmental potential due to extreme poverty and stunting

One in three people globally will develop a neurological disorder at some point in their lifetime

Other compelling arguments for optimizing brain health throughout our lives are demographic change, worldwide population ageing and the associated increase in age-related disorders affecting the brain. For instance, neurological disorders are the leading global cause of disability-adjusted life years (DALYs) and the second leading cause of death (16.5% of all deaths globally), responsible for 9 million deaths in 2016 *(10)*, with nearly 8 million of these deaths caused by stroke and dementia (see Figure 1). Global trends over the past three decades propelled by demographic changes and population ageing suggest that these numbers will continue to increase. Almost one in three people globally will develop a neurological disorder at some point in their lifetime *(11)* – which means that virtually all readers of this paper will be touched by neurological disorders, either directly or indirectly. Further, the financial costs of neurological disorders are enormous, with common neurological disorders incurring US$ 789 billion in the United States of America (USA) alone *(12)*.

Unfortunately, global action on brain health is grossly insufficient. Irrespective of the growing threats to brain health, there is limited policy response to address brain health comprehensively and there are inadequate services to promote and optimize brain health for people with lived experience. Despite the huge global burden, access to services and supports are both inadequate and unevenly distributed across country income brackets and between urban and rural areas within countries. Numerous barriers to accessing timely and responsive services exist globally – including limited health workers with neurology-specific training in lower-resource settings, limited social and financial protections for people with lived experience, and a lack of access to medicines and diagnostics, as well as the continued presence of stigma and discrimination *(13)*. **Figure 1** summarizes key facts and figures on the global brain health-related burden, the inequitable access to relevant services worldwide and inadequate policy responses globally.

Figure 1.

Key facts and figures on the global need for action on brain health

Worldwide, only 15 countries

report having three essential, family-friendly national policies that provide caregivers with resources and time needed for their child's development *(8)*.

1

2 years
of tuition-free pre-primary school education.

2

6 months
of paid breast-feeding breaks.

3

6 months
of paid maternity leave and one month of paid paternity leave.

85 million children
under the age of 5 globally were not protected by any of these essential policies *(8)*.

Nearly 250 million children
in low- and middle-income countries risk not reaching their developmental potential due to extreme poverty and stunting *(6)*.

Missed developmental potential
due to poverty and stunting is projected to cause 26% lower annual earnings in adulthood *(7)*.

Growing environmental threats to brain health[1]

- Air pollution
- Heavy metals
- Certain pesticides
- Industrial solvents
- Other toxic chemicals

Over 200 chemicals
are known to be neurotoxic.

Over 200 million
people are exposed to arsenic in their ground water.

99% of the world
breathes polluted air *(9)*.

Global burden associated with brain health

Neurological disorders
are the #1 cause of DALYs, with the biggest contributors being stroke, migraine, dementia, meningitis and epilepsy *(10)*.

Neurological disorders are **the second leading cause of death** *(10)*.

Over 70% of people with neurological disorders reside in low- and middle-income countries

Yet, access to services is grossly insufficient.[2]

Only 1 in 10
people living with dementia in low-income countries receive a diagnosis.

Only 1 in 4
people with epilepsy receive treatment.

Only 1 low-income country
had warfarin available for stroke prevention compared with 73% of high-income countries.

Stroke units
are operational in >90% of high-income countries, compared with only 18% of low- and middle-income countries.

Distribution of neurological workforce
is grossly uneven. There is 7.1 neurological workforce/100K population in high-income countries vs 0.1/100K in low-income countries.

1. See Section 3.2 of this position paper for more details

2. For further information see: Synergies in addressing the burden of epilepsy and other neurological disorders. Consolidated report by the Director-General (A73/5). Item 11.6. Geneva: World Health Organization; 2020. (https://cdn.who.int/media/docs/default-source/mental-health/a73-5-en.pdf?sfvrsn=4f601918_2, accessed 16 July 2022).

1.2 Intergovernmental response to date

In recent years, neurology and brain health more broadly have slowly gained attention in both domestic and international policy agendas. Most notably, in May 2022, the World Health Assembly adopted the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* *(14)*. The Intersectoral global action plan envisages "a world in which: brain health is valued, promoted and protected across the life course; neurological disorders are prevented, diagnosed and treated, and premature mortality and morbidity are avoided; and people affected by neurological disorders and their carers attain the highest possible level of health, with equal rights, opportunities, respect and autonomy". In service of this vision, the strategic objectives of the Intersectoral global action plan cover essential components of brain health optimization, namely: 1) promotion of brain health; 2) prevention of neurological disorders; and 3) effective, timely and responsive services for people with neurological disorders. The Intersectoral global action plan proposes actions for countries, the WHO secretariat and civil society partners to take in optimizing brain health, alongside global targets. For more details on the Intersectoral global action plan, **see Figure 2**.

Figure 2.

Overview of the Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031

The goal of the action plan is

to reduce the stigma, impact and burden of neurological disorders – including associated mortality, morbidity and disability – and to improve the quality of life of people with neurological disorders, their carers and families.

The strategic objectives of the action plan include the following:

1. raise the prioritization and strengthen governance;
2. provide effective, timely and responsive diagnosis, treatment and care;
3. implement strategies for promotion and prevention;
4. foster research and innovation and strengthen information systems; and
5. strengthen the public health approach to epilepsy.

The action plan relies on the following guiding principles:

- people-centred primary health care (PHC) and universal health coverage (UHC);
- an integrated approach to care across the life course;
- evidence-informed policy and practice;
- intersectoral action;
- empowerment and involvement of persons with neurological disorders and their carers; and
- gender, equity and human rights.

Optimizing brain health is closely linked to advancing other high-level, intergovernmental commitments

Optimizing brain health is closely linked to advancing other high-level, intergovernmental commitments such as the 2030 Agenda for Sustainable Development *(15)*, the United Nations Decade of Healthy Ageing 2021–2030 *(16)*, the Geneva Charter for Well-being *(17)* and WHO's Triple billion targets *(18)*.[4] Relevant international multilateral commitments – covering a wide spectrum of health conditions, disciplines and sectors in support of a global brain health agenda – are summarized in **Annex 1** and demonstrate how intertwined and crucial brain health is for advancing global policy agendas.

1.3 About this position paper

This position paper, which is a technical complement to the Intersectoral global action plan, is intended as a tool for facilitating dialogue, galvanizing action and mobilizing resources for brain health globally. Accordingly, the objectives of this position paper are:

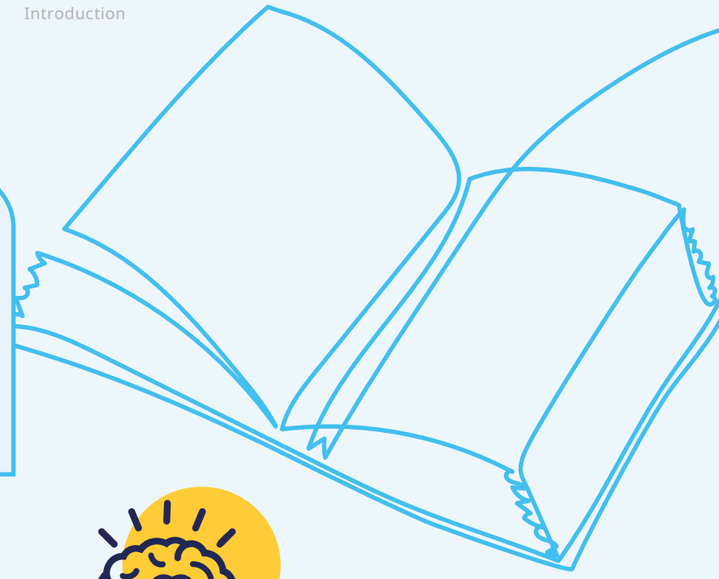
- to conceptualize brain health and present a framework for brain health optimization;
- to present an overview of the determinants of brain health and how to address them; and
- to demonstrate the relevance of optimizing brain health within the broader context of public health and society and to offer practical policy solutions and future directions for the field.

The primary target audience for this paper includes policy-makers, health officials and programme managers. The paper may also be helpful for clinicians, researchers, and organizations involved in brain health or public health, as well as persons with lived experience and their families.

4. WHO's Triple billion targets envision 1 billion more people enjoying better health and well-being, 1 billion more people benefitting from universal health coverage, and 1 billion more people better protected from health emergencies. The promotion of brain health is an essential aspect of being able to enjoy better health and well-being, while increasing access to universal health coverage is needed to enhance prevention of neurological disorders and ensure effective and timely services for people with those disorders. Finally, it is crucial to protect brain health and development during humanitarian crises and health emergencies.

Chapter 1

summarizes the global context of brain health and describes recent intergovernmental progress in addressing brain health.



Chapter 2

presents a conceptualization of brain health and the framework for brain health optimization.

Chapter 4

discusses the outcomes of brain health optimization for health, well-being and society.

Chapter 3

provides a broad overview of the determinants of brain health and how to address these determinants, namely: physical health, healthy environments, safety and security, learning and social connection, and access to quality services.

Chapter 5

discusses future directions for optimizing brain health, including examples of policy actions across sectors, driving brain health research by generating and synthesizing evidence, and developing metrics to operationalize and measure brain health in order to move the brain health agenda forward.

1.4 Methodology of this position paper

This position paper was developed through an iterative process of desk reviews, drafting and consultations with a wide range of technical experts and people with lived experience. The position paper is envisioned as a technical complement to the Intersectoral global action plan and was developed concurrently with the action plan.

In 2021, WHO published a discussion paper *(19)* and subsequently a first draft of the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* *(20)* for public, web-based consultations. Comments were received during both consultations from WHO Member States, United Nations agencies, civil society organizations, academics, researchers and people with lived experience, as well as carers and families. Comments received during the public consultations not only informed the revision of the Intersectoral global action plan, but also the drafting of this position paper.

In addition, WHO conducted a scoping exercise of different brain health definitions and related initiatives aimed at optimizing brain health using sources of academic and grey literature, as well as other relevant WHO definitions such as those for mental health *(21)*, early child development *(22)* and intrinsic capacity *(23)*. **Annex 2** includes a list of brain health definitions and related initiatives that were identified in this scoping exercise.

Of particular relevance are two recently conducted systematic literature reviews and concept analyses *(24, 25)* that identified existing definitions and attributes of brain health, including the antecedents of brain health (e.g. determinants) and the consequences of brain health (e.g. outcomes and impact).

WHO shared the results of this scoping exercise in virtual consultations and meetings in October and November 2021 with a wide range of technical experts in brain health, early childhood development, brain–body medicine, environmental health and people with lived experience. In total, over 100 people from close to 40 countries from all WHO regions participated in the virtual consultations.

As a result of these consultations, the definition of brain health and the framework for brain health optimization were refined on an iterative basis. Feedback received during the consultations was incorporated into the draft of this position paper, which was then circulated for peer review by expert reviewers during March and April 2022.

The evidence presented in this position paper is largely based on the findings from systematic reviews and large cohort studies. However, as this is a rapidly expanding field, original, high-quality peer-reviewed articles have also been included where relevant.

2. A framework for brain health optimization

> Brain health allows health workers and society as a whole to consider concepts such as educational status, financial situation or social security as fundamental components of neurodevelopment and the general well-being of individuals."

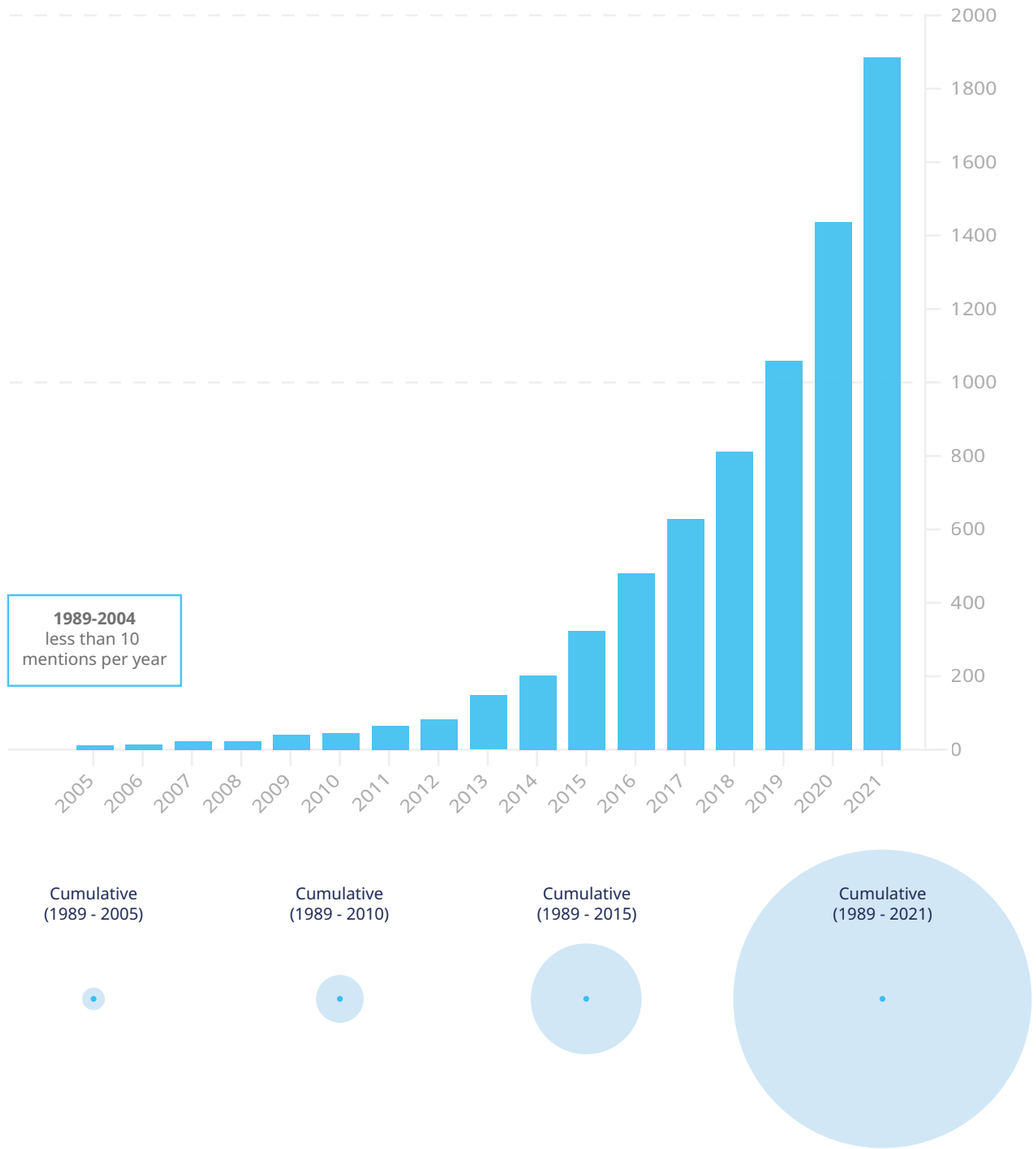
Salvador Ramirez, Mexico

The term "brain health" first appeared in the academic literature in 1989 *(25)*, preceding the designation of "The Decade of the Brain" from 1990 to 1999 in the USA *(26)*. Brain health became exponentially popular in the literature some 10 years ago **(see Figure 3)**, with different definitions emerging over time. **Annex 2** summarizes different definitions and related initiatives that have been identified by the scoping review for this position paper.

Figure 3.

Number of studies referencing "brain health" each year

To estimate the number of studies that have been published related to brain health a search in PubMed was conducted using the search term "brain health". The number of studies published per year was extracted and the cumulative number of studies is presented in the figure from 1989 to 31 December 2021.



Many definitions of brain health to date have focused on older life, with implications for specific neurological conditions (e.g. dementia or stroke), while others concentrated mainly on one domain of brain functioning (e.g. cognitive function) which also has implications for specific neurological conditions. Some definitions have spanned multiple domains of brain functioning, developmental phases across the life course or wider disorder categories (including mental health, substance use and pain conditions) – which would be more in line with WHO's overall definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" *(27)*. Similarly, going beyond conceptions of disease and instead focusing on abilities and well-being is consonant with the *International Classification of Functioning, Disability and Health* (ICF)[5] – a multi-purpose framework for describing and organizing information on functioning and disability *(28)* – and also WHO's definitions of mental health *(21)*[6] and intrinsic capacity *(23)*.[7]

2.1 What is brain health?

Brain health is the state of brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains, allowing persons to realize their full potential over the life course **(see Box 2).** Brain health is expressed in the brain's ability to grow and build strong neuronal connections, as well as to adapt, repair and/or compensate over time in ways that allow us to sense, think, feel, move and interact in the world around us. Additionally, the brain directs and affects many of our body's core involuntary functions, including cardiorespiratory, endocrine and immunological functions.

Box 2.

What is brain health?

- Brain health is the state of brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders.
- Continuous interactions between different determinants and a person's individual context lead to lifelong adaptation of brain structure and functioning.
- Optimizing brain health improves mental and physical health and also creates positive social and economic impacts, all of which contribute to greater well-being and help advance society.

5. The ICF views disability and functioning as outcomes of interactions between health conditions (diseases, disorders and injuries) and contextual factors, including external environmental factors and personal factors.

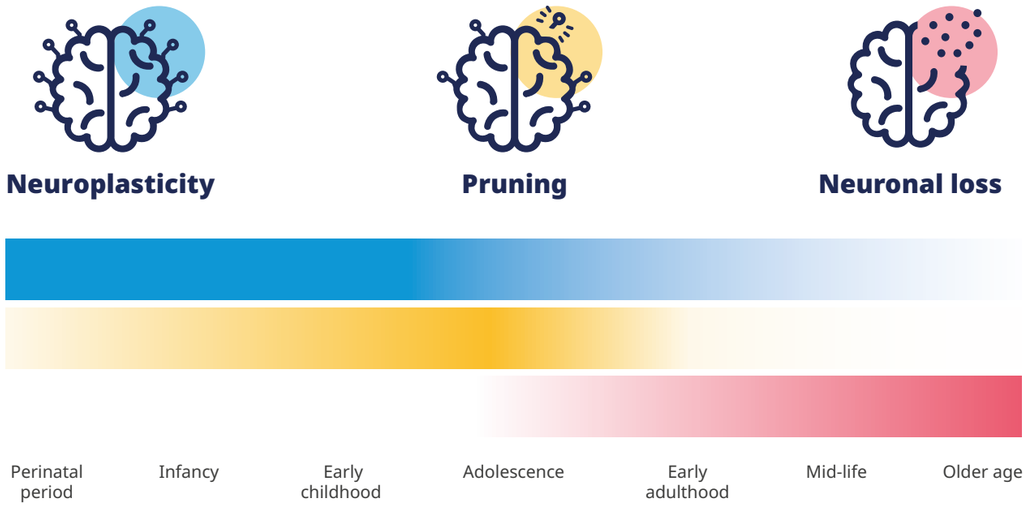
6. WHO defines mental health as a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community.

7. WHO defines intrinsic capacity as the composite of all the physical and mental capacities of an individual. These interact with the environment (i.e. all the factors in the extrinsic world that form the context of an individual's life) to determine a person's functional ability.

Our brains develop rapidly in early life and continue to adapt over our lifetimes as a result of complex, ongoing interactions between our genetics, environment and circumstances, as well as the interactions between the brain and the rest of the body, leading to continuous adaptations of brain structure and functioning. The different stages of brain development across the life course – such as neuroplasticity, pruning and senescence that are characteristic of the lifelong adaptations of the brain as we age – are depicted in **Figure 4**. These stages are primarily characterized by rapid growth of neuronal connections in utero and in early childhood (neuroplasticity), directed shedding of neuronal connections in later childhood and adolescence (pruning), and neuronal loss in adulthood (senescence) *(29)*. While these stages were traditionally conceptualized as consecutive and non-overlapping, we now know that even the ageing brain can continue to change and adapt. In fact, brain health can be improved across the life course by minimizing risk factors, as well as by enhancing protective factors that promote neuroplasticity – i.e. the brain's ability to grow, build new connections and recover or compensate for injuries.

Figure 4.

Stages of brain development across the life course



Extending the definition of brain health beyond conceptions of disease (or the absence thereof) by focusing instead on brain structure and cognitive, sensory, social-emotional, behavioural and motor functioning, means understanding brain health on a lifelong continuum. This brain health continuum ranges from well-being to disorders and disability for each of the aforementioned domains of functioning. Disorders that have an impact on the brain can emerge throughout the life course and are characterized by disruptions in usual brain growth, damage to brain structure and/or impaired brain functioning *(30)*.

Generally, neurology as a discipline includes disorders that can have an impact on the brain or spinal cord (i.e. CNS), the peripheral nervous system, neuromuscular junction and muscles. This position paper, however, mainly covers disorders affecting the CNS **(see Figure 5)**. While some of these conditions are rare, they are nevertheless responsible for high morbidity and mortality *(14)*. WHO is currently collaborating with the Institute for Health Metrics and Evaluation (IHME) and the Global Burden of Disease Study collaborators to quantify the brain burden associated with these conditions.

Importantly, while some brain health definitions include mental health conditions, WHO considers mental health and brain health as two separate but closely related concepts. In fact, brain health is a crucial determinant of mental health across the life course **(see Box 3)**.

Figure 5.

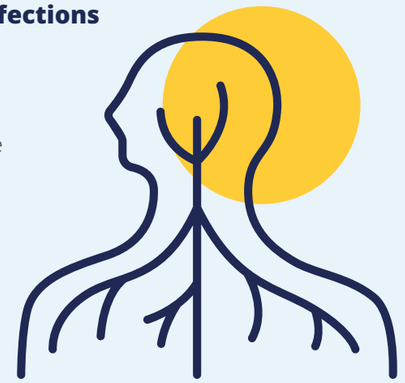
Disorders affecting the CNS

Common neurological conditions
- Dementia
- Epilepsy
- Headaches disorders
- Motor neuron disease
- Multiple sclerosis
- Parkinson disease
- Stroke

Injuries
- Spinal cord injury
- Traumatic brain injury

Tumours
- Tumours of the nervous system

Neurological complications associated with infections
- Cysticercosis
- COVID-19
- Encephalitis
- Guillain-Barré syndrome
- HIV
- Malaria
- Meningitis
- Rabies
- Syphilis
- Tetanus
- Zika virus



Neurodevelopmental disorders
- Attention-deficit/hyperactivity disorder
- Autism spectrum disorders
- Cerebral palsy
- Fetal alcohol syndrome
- Idiopathic developmental intellectual disability

Congenital conditions
- Congenital birth defects
- Down syndrome
- Neural tube defects
- Other genetic defects

Box 3.

WHO definition of mental health and its relationship with brain health

WHO defines mental health as a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community. Mental health is more than the absence of mental health conditions or disabilities; it is fundamental to our collective and individual ability as humans to think, emote, interact with each other, earn a living and enjoy life *(21)*.

Brain health is an important determinant of mental health across the life course. Many of the risk and protective factors that impact mental health (e.g. social adversities, air pollution, physical activity) are likely mediated through changes in brain structure and/or function *(31—34)*.

See Section 4.1 for more information.

2.2 What is brain health optimization?

Optimizing brain health is paramount to ensuring that individuals can achieve their full potential

Optimizing brain health is paramount to ensuring that individuals can achieve their full potential for both health and well-being. Optimizing brain health preserves and improves brain structure and function, reduces the risk of developing CNS disorders, and promotes overall health. As noted, brain health is the result of complex, continuous interactions between a person's genetics, environment and circumstances. Multiple interconnected determinants can affect brain functioning and structure from pre-conception through to the end of life. These determinants influence the way our brains develop, adapt and respond to stress and adversity, to different degrees across stages of our neurodevelopment **(see Figure 4)**. It is essential to address these determinants in order to minimize risk factors and enhance protective factors and thereby optimize brain health to the extent possible.

Figure 6

Framework for brain health optimization

Optimizing brain health improves mental and physical health and also creates positive and economic impacts, all of which contribute to greater well-being and help advance society.

Addressing brain health determinants

at individual and societal level

Healthy environments

Physical health

Safety & security

Access to quality services

Learning & social connection

Optimized brain structure and function

across the life course

Enhanced well-being

Brain health is the state of brain functioning across cognitive, sensory, social-emotional, behavioural and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders.

Continuous interactions between different determinants and a person's individual context lead to lifelong adaptation of brain structure and functioning.

Improved health

Social & economic benefits

Efforts to optimize brain health should be made for everyone, respecting the principles of inclusion and empowerment

The proposed framework for brain health optimization **(Figure 6)** describes five overarching, interconnected categories of brain health determinants that affect a person's brain function and structure **(detailed in Chapter 3)**. By addressing these determinants for all people, we not only optimize brain health across the life course but also improve mental and physical health as well as create positive social and economic impacts **(detailed in Chapter 4)**, all of which contribute to greater well-being and help advance society, irrespective of the presence or absence of disorders.

Efforts to optimize brain health should be made for everyone, respecting the principles of inclusion and empowerment. Importantly, individuals' needs may vary at different points in their lives depending on their personal and medical circumstances and the social and cultural contexts in which they live. Brain health can be affected by various types of adversity, and brain health determinants are often interlinked. Structural inequities associated with systemic causes of discrimination, oppression and marginalization (e.g. on the basis of race, ethnicity, gender, age) constitute important macro-level sources of adversity *(35)*. It is essential to address adversities to promote health equity, which is achieved when everyone can attain their full potential for health and well-being *(36)*. Additionally, efforts to optimize brain health should combat stigma, prejudice and discrimination specifically faced by people with lived experience and their carers.

Lastly, strategies to optimize brain health require multisectoral and interdisciplinary collaboration that involve all sectors of human society with integrated, person-centred approaches focused on promotion, prevention, timely diagnosis, treatment and care, as well as the active engagement of persons with lived experience. The rationale for integrating brain health across sectors, as well as recommendations for policy actions and future steps, are discussed in **Chapter 5**.

3. Determinants of brain health

“After my diagnosis, I realized the need to keep my brain healthy and active. I started exercising; paid more attention to my diet and stopped my very stressful activities as owner of a film production company. All this I should have done way before, because prevention is the key. In 2019, I had a deep brain stimulation system implanted. This helps a lot. The underlying disease still progresses but the symptoms like tremors and shaking are pretty much under control.”

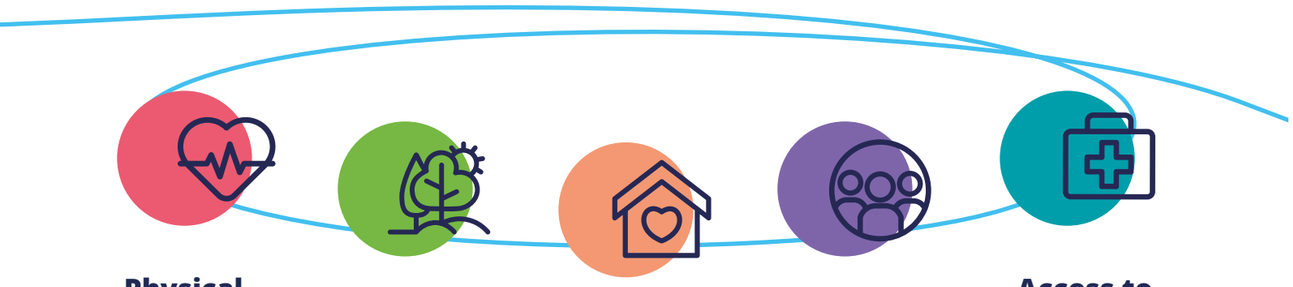
Kaie Klaassen, Netherlands

Addressing brain health determinants is a crucial element of brain health optimization

Addressing brain health determinants is a crucial element of brain health optimization for everyone, including people with lived experience. This chapter gives an overview of the determinants of brain health, which can be clustered into five categories, namely: physical health, healthy environments, safety and security, learning and social connection, and access to quality services **(Figure 7)**. Many determinants can act at both the individual or societal levels, and it is important to note that no single factor is solely deterministic of a person's brain health outcomes. The brain is an ever-changing system with its structure and functioning reflecting complex interactions between a person's genetics, environment and circumstances.

Figure 7.

Determinants of brain health across the life course



Physical health

Maternal health, intrauterine environment

Genetic and epigenetic factors

Nutrition

Infections

NCDs

Health behaviours

Traumatic injuries

Healthy environments

Safe use of chemicals

Protection from radiation

Healthy and safe workplaces and agricultural practices

Air and water quality

Stable climate

Access to preserved nature and health-supportive built environments

Safety & security

Physical safety

Financial security

Humanitarian crises and emergencies

Learning & social connection

Education

Lifelong learning

Nurturing care

Social connection/ social isolation

Social networks

Access to quality services

Integrated care at all health/social care levels

Skilled workforce and Interdisciplinary teams

Access to essential medicines, diagnostics and health products

Carer support

A child's brain creates over 1 million new neuronal connections each second in the first few years of life

Since many determinants have an impact on the brain to different degrees across various life stages (e.g. perinatal, infancy, early childhood, adolescence, adulthood and older age), a life-course approach is needed to understand the determinants of brain health. WHO and its partners have previously developed frameworks, guidelines and other technical documents detailing the determinants of brain development in early childhood and adolescence, as well as the brain health of older adults *(37—39)*.

Early childhood

represents a time of highest plasticity and thus extraordinary potential for intervention. It is estimated that a child's brain creates over 1 million new neuronal connections each second in the first few years of life *(40)*. Nurturing care[8] positively influences structural brain development in early life and allows children to thrive and reach their potential, while disruptions to or the absence of nurturing care can lead to changes in brain development that have long-term negative impacts *(37)*. Many of the components of nurturing care continue to affect on brain health as a child becomes an adolescent and grows into adulthood.

Adolescence

is additionally a time of great potential. The process of pruning means that the brain undergoes dramatic changes with active remodelling of neuronal circuits that were established early in life. In fact, during adolescence processes leading to increasingly efficient functioning within and across brain networks peak in the context of increased autonomy and independence *(41)*. In other words, the second decade of life represents an important opportunity to respond to a person's circumstances, especially in relation to cognitive and social-emotional functioning as well as habits and health behaviours. Multiple family, cultural, societal, economic and environmental factors can influence adolescent development – including school connectedness, social and gender norms and community cohesion among other factors *(38)*.

Adulthood and older age

present additional opportunities for intervention as the brain continues to adapt in response to our circumstances. Numerous determinants are known to have impacts on brain health in mid-life and later life, including: physical activity, diet, tobacco and alcohol use, cognitive activity and metabolic factors (including weight, blood pressure, cholesterol and insulin sensitivity) *(39)*. Determinants of healthy ageing that are also relevant to brain health include levels of education, healthy lifestyles, social connection and enabling environments *(42)*.

8. The components of nurturing care are: 1) good health, 2) adequate nutrition, 3) safety and security, 4) responsive caregiving and 5) opportunities for early learning.

3.1 Physical health

There are multi-directional interactions between the brain and the body. A person's physical health can influence their brain health in many ways across the life course. Important aspects of physical health that influence brain health include:

- maternal health and the intrauterine environment
- genetic and epigenetic factors
- nutrition
- infections
- noncommunicable diseases (NCDs)
- sensory impairments
- health behaviours
- traumatic injuries.

Maternal health and the intrauterine environment

Many factors influence maternal health and the uterine environment which in turn have an impact on the baby's brain development. These factors include the mother's nutritional status, stress, physical or mental health conditions, congenital infections, toxic exposures during pregnancy (including from the environment such as air pollution and pesticides or from substance use), and access to prenatal care and safe labour and delivery *(43)*.

Maternal malnutrition (including undernutrition and overnutrition) has been shown to affect brain development *(44)*. In particular, deficiencies of specific nutrients during pregnancy can have serious impacts; for instance, maternal folate deficiency can cause congenital neural tube defects and maternal iron deficiency can impact neurodevelopmental outcomes and may also potentially increase the risk of schizophrenia *(45—47)*. In addition, certain physical health conditions such as maternal diabetes can affect a baby's neurodevelopment, especially if left untreated *(43, 48)*. Likewise, mental health conditions in pregnant women can also affect neurodevelopmental outcomes; for instance, maternal depression has been linked to intrauterine growth restriction, preterm birth, low birthweight, stunting and an increased risk of developmental impairment *(22)*. In addition, several congenital infections can harm brain development in utero – such as rubella virus, cytomegalovirus, herpes simplex virus, Zika virus, syphilis, malaria and toxoplasmosis *(49, 50)*. Additionally, exposure to severe stressors in pregnancy (faced by either parent) can have an impact on child development, and this may be mediated by increased inflammation and epigenetic changes *(51)*.

Exposure to air pollution, pesticides, heavy metals and other toxic chemicals during pregnancy can also affect brain development **(see Section 3.2)** *(52—54)*. Maternal substance use – including tobacco, alcohol or drug use – can also affect a baby's brain in utero through direct toxic effects on neuronal development and additionally in infancy by affecting mother–infant interactions *(55)*.

Finally, access to perinatal care for mother and child, including safe labour and delivery, are crucial for ensuring that mothers receive all necessary health and social services during pregnancy and birth so that they and their child can be as healthy as possible *(56, 57)*.

Genetic and epigenetic factors

Many genetic factors have been found to be related to brain structure and to have impacts on the domains of brain functioning. As an example, polymorphisms, or variations, of genes relating to brain-derived neurotrophic factor (BDNF) – a factor that is needed for neuronal growth and neuroplasticity – has been found to be linked to differences in cognition (specifically related to memory and executive function) *(58)*. Genetic factors are also implicated in several neurodevelopmental disorders such as Down syndrome, Fragile X syndrome, Rett syndrome, Prader Willi syndrome, amongst others *(59)*. On the other hand, for many neurodevelopmental and neurological disorders, while genetic links have been identified, the disorders are likely caused by interactions between certain genetic profiles and the person's environment leading to epigenetic changes, i.e. changes in gene expression. Examples include autism spectrum disorders, Alzheimer disease and other dementias, Parkinson disease, and certain forms of epilepsy *(60—63)*.

Nutrition

Adequate nutrition (and the absence of undernutrition or overnutrition) is vital for brain health. As discussed earlier, adequate nutrition during pregnancy is crucial for healthy brain development in utero. Breastfeeding is also an important factor for brain development because of its exclusive benefits not only for nutrition but also for immune protection and mother-infant bonding *(37)*.

Nutrition remains an important determinant of brain health across the life course, with nutritional deficiencies, especially in later life, being linked with the onset of cognitive decline and dementia. On the other hand, healthy, balanced diets and healthy weight management for adults are known to reduce these risks *(39)*.

Several congenital infections can harm brain development in utero – such as rubella virus, cytomegalovirus, herpes simplex virus, Zika virus,syphilis, malaria and toxoplasmosis

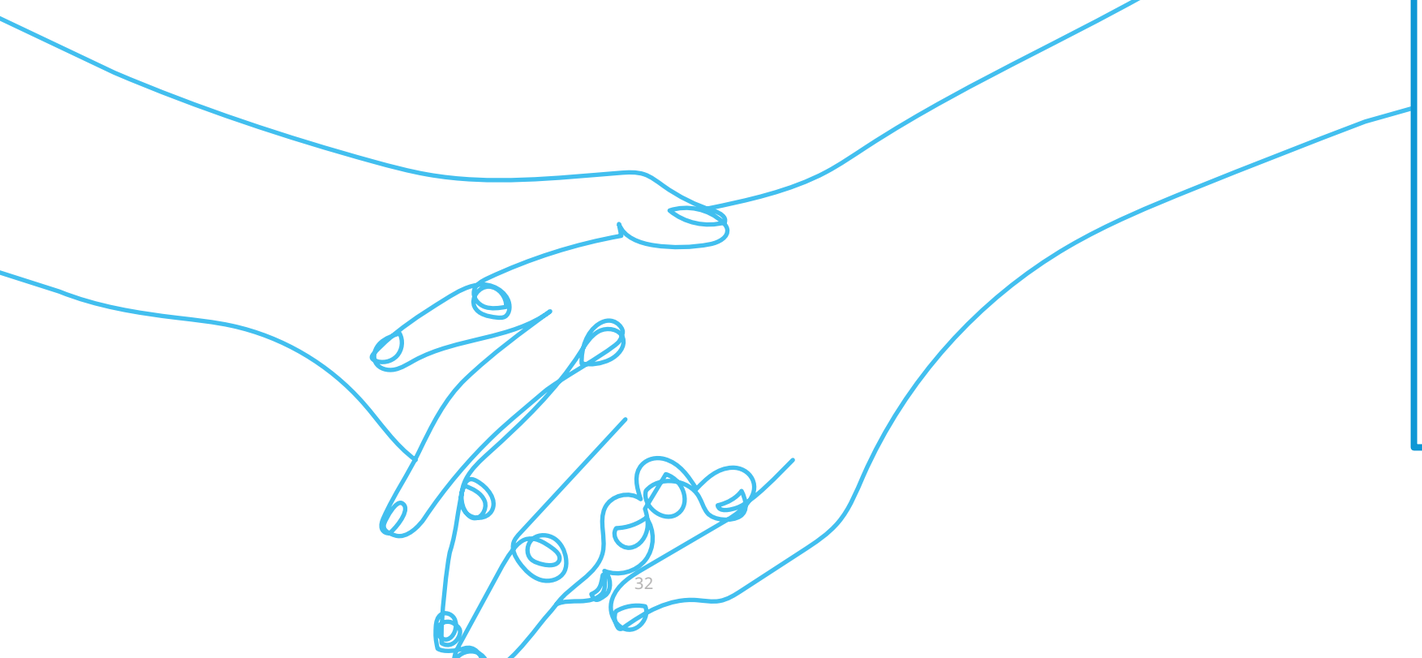
Infections

Numerous infections can harm the brain directly by attacking the nervous system, while others may cause neurological sequelae from secondary inflammatory processes. Infections causing meningitis and encephalitis (of viral, bacterial or fungal origin) contribute significantly to the global burden of neurological disease. Other infections that can have a direct impact on the brain include enterovirus, HIV, neurocysticercosis, malaria, polio, syphilis, rabies, toxoplasmosis and Zika virus. These infections can also cause sequalae such as neurodevelopmental disorders in children, vision and hearing loss, epilepsy, and cognitive or motor impairment and may necessitate specialized follow-up care, including rehabilitation.

Some infectious diseases do not attack the nervous system directly but may nevertheless affect brain health through other mechanisms, including systemic inflammation triggering neuroinflammation (such as seasonal influenza, HIV, malaria and COVID-19 *(64, 65)*. Similarly, a history of a wide range of infectious diseases requiring hospitalization has been linked to increased incidence of dementia, irrespective of whether the infection primarily affected the CNS or not *(66)*. However, many infections can be prevented through infectious disease control strategies – including robust and routine immunization (in childhood and adulthood), vector control and access to sexual and reproductive health services.

Additionally, global pandemics can affect brain health in many ways, either directly or indirectly. For instance, the Zika virus epidemics in 2016 were linked with multiple neurological manifestations – including Guillain-Barré syndrome, neuropathy and myelitis. Zika infection during pregnancy in particular was found to cause microcephaly and other congenital malformations in infants *(67)*. The COVID-19 pandemic has also had multiple impacts on brain health, including direct impacts by the SARS-CoV-2 virus on the nervous system as well as indirect impacts on the determinants of brain health. Further information is contained in WHO's Scientific brief on neurology and COVID-19 *(68)* and **Box 4**.

Global pandemics can affect brain health in many ways, either directly or indirectly



Box 4.

COVID-19 and brain health

The COVID-19 pandemic continues to have far-reaching impacts on brain health, both directly by the SARS-CoV-2 virus and indirectly through the multitude of stressors brought on by the pandemic.

First, SARS-CoV-2 has been associated with over two dozen neurological symptoms and over 10 neurological diagnoses during the acute phase of illness, including headaches, changes in smell and taste, muscle aches, fatigue, delirium (or confusion), strokes and seizures. A meta-analytic review of data from over 145 000 COVID-19 cases found that one in every 50 patients were diagnosed with stroke and, in patients over the age of 60 years, the presence of any neurological manifestation was associated with a mortality rate nearly twice as high *(69)*.

Second, post-COVID-19 condition is increasingly associated with neurological sequelae, including fatigue, headaches, sleep disturbances and cognitive dysfunction *(70)*. These reports are reflected in WHO's definition of post-COVID-19 condition, which indicates common symptoms such as fatigue and cognitive dysfunction among others *(71)*.

Moreover, COVID-19 has disproportionately affected people with pre-existing neurological disorders. Chronic neurological disorders have been associated with increased mortality in hospitalized COVID-19 patients. Additionally, people with neurological disorders have also experienced disruptions to essential services and routine neurological care *(72, 73)*. WHO's first pulse survey on the continuity of essential health services during the COVID-19 pandemic, released in August 2020, revealed that 48% of 105 countries surveyed reported at least partial disruptions in all services for NCDs and mental health *(74)*. WHO's second and third rounds of the global pulse survey on the continuity of essential health services during the COVID-19 pandemic found that disruptions to essential mental, neurological and substance use services persist: at the end of 2021, at least one third of countries were still reporting disruptions to services for mental health, neurological and substance use disorders *(75, 76)*.

Furthermore, the pandemic incurred myriad social consequences that included widening disparities and adversities, increased social isolation and loneliness, as well as limited opportunities for play/leisure activity, physical activity and intellectual stimulation – all of which are known to affect brain health across the life course **(see Figure 7)** *(77)*. Early data regarding development in infancy have been concerning; for instance, one cohort study of children born during the pandemic found that these children had lower neurodevelopmental scores at 6 months of age than children who were born before the pandemic *(78)*. Additionally, a 2020 survey of participants from 101 countries found that 21% of respondents experienced severe loneliness during the pandemic and around 20% were socially isolated *(79)*.

Cardiovascular disease, respiratory disease, diabetes and associated risk factors are harmful to brain health

Noncommunicable diseases (NCDs)

such as cardiovascular disease, respiratory disease, diabetes and associated risk factors are harmful to brain health. High blood pressure, obesity and diabetes in particular are well-known risk factors for both stroke and dementia. Together, these risk factors are thought to be responsible for 4% of the dementia prevalence globally *(80)*.

Importantly, early prevention to reduce the risk of chronic health conditions is crucial; a recent large cohort study showed that multi-morbidity (i.e. having two or more chronic conditions) in mid-life leads to well over twice the risk of developing dementia *(81)*. In relation to stroke, high blood pressure is linked to over 60% of the DALYs due to stroke globally, while high body mass index (indicative of overweight and obesity) is linked to over 20% and high fasting sugar (indicative of insulin resistance) is linked to over 10% *(82)*.

Sensory impairments

are increasingly recognized as a risk factor for brain health – especially later in life. For instance, hearing loss is responsible for 8% of the dementia prevalence globally; importantly, the use of hearing aids may be able to obviate this risk *(80)*. Recent studies suggest that vision impairment may also confer risk for cognitive decline in older adults *(83, 84)*.

Health behaviours

including the quantity and quality of sleep, physical activity and substance use can also have impacts on brain development and brain health. Good-quality sleep (and a sufficient quantity of it) is essential for healthy child development *(85)*. The quantity of sleep also has a profound impact on brain health in older age; for instance, sleeping six hours or less nightly in the 6th and 7th decades of life confers a 30% higher risk of dementia *(86)*. Abnormal sleep durations (short or long) have also been linked with an increased risk of stroke *(87)*. The impact of sleep disturbance on the brain may be at least partially explained by increased inflammation because sleep disturbance is linked to increased C-reactive protein and interleukin-6, both of which are indicative of inflammation in the body *(88)*.

Adequate physical activity is also essential for childhood development and can have impacts on cognitive function and educational attainment *(89)*. Similarly, physical activity is known to affect brain health across the life course, with physical inactivity being responsible for nearly 8% of DALYs due to stroke globally *(82)* as well as 2% of global dementia prevalence *(80)*. Increased physical activity, on the other hand, has been shown to have neuroprotective and neuroplastic benefits for the brain later in life. Physical activity is thought to enhance neuroplasticity in

multiple ways, including by increasing levels of BDNF and other neurotrophic factors and buffering inflammation in the body *(90)*. A recent systematic review found that physical activity in older adults was linked to preserved structure in the brain's frontal and temporal areas, including prefrontal cortex and hippocampal grey matter volume, which are important for emotional processing and memory *(91)*. Similarly, physical activity can also improve brain health in the context of neurological disorders such as Alzheimer disease, Parkinson disease, Huntington disease and multiple sclerosis or during post-stroke rehabilitation *(92, 93)*.

Smoking is associated with an increased risk of multiple CNS disorders, including stroke, dementia and multiple sclerosis. For instance, smoking is responsible for nearly 21% of the DALYs due to stroke globally, while second-hand smoke exposure is responsible for over 2% *(82)*.

Physical activity can also improve brain health in the context of neurological disorders

Alcohol can have a direct impact on brain health (via cortical atrophy and cerebellar degeneration), as well as an indirect impact through complications from nutritional deficiencies (such as Wernicke's encephalopathy and Korsakoff syndrome or pellagra), impact on cardiovascular and other systems or complicated withdrawal (seizures, delirium tremens, injuries). Harmful use of alcohol confers an increased risk for dementia with a gradient, when higher alcohol use is associated with increased risk of dementia. It has also been shown that alcohol use with loss of consciousness irrespective of the overall alcohol consumption is associated with an increased risk of dementia *(80, 94, 95)* . The harmful use of alcohol is attributable to about 3 million deaths annually and is a causal factor in more than 200 disease and injury conditions, thus affecting a person's overall health and physical safety (**see Section 3.3** on additional links with physical safety, violence, and road traffic accidents).

Traumatic brain injuries (TBIs) have been linked to longer-term processes that are harmful to the brain

Traumatic injuries can be harmful to the CNS in multiple ways depending on their severity and frequency across the life course. Apart from the direct and immediate structural harm that they can cause to the nervous system, traumatic brain injuries (TBIs) have been linked to longer-term processes that are harmful to the brain. For example, severe TBIs have been associated with hyper-phosphorylated tau pathology within the brain, a process which has been implicated in neurodegenerative disorders *(96)*. TBIs, even those that are mild, have been associated with neurological disorders such as epilepsy and stroke *(97, 98)*. Further, TBIs are also thought to be responsible for 3% of the dementia prevalence globally *(80)*; while the risk is higher for severe TBIs or repeated TBIs, mild TBIs still confer increased risk *(99)*. Several societal and individual factors – such as community violence, domestic and intimate partner violence, contact sports without adequate head protection, road traffic accidents, war, conflict and other humanitarian emergencies – can increase the risk of damage to the brain and other parts of the CNS **(see Section 3.3)**.

3.2 Healthy environments

Healthy environments (such as clean air and water, access to green spaces, safe use of chemicals, protection from radiation, and stable climate) can have a profound impact on brain health across the life course, especially during developmentally sensitive stages such as early childhood, adolescence and older age. There has been increasing information in recent years on environmental factors that affect brain health, including pollutants found in air, water and food. This section addresses the brain health impacts of heavy metals, pesticides, industrial solvents, air pollution and natural and man-made disasters.

Currently 214 chemicals are recognized as neurotoxic to the human brain, while over 1000 are recognized as neurotoxic to animals. The number of chemicals recognized as neurotoxic to humans has risen in recent years as research in this field expands *(100)*. Categories of neurotoxic chemicals include heavy metals and inorganic compounds, pesticides, organic solvents and other organic compounds. Within these categories, 12 industrial chemicals are currently known to be neurotoxic for developing brains *(100)*.

214

chemicals are recognized as neurotoxic to the human brain

Heavy metals

Heavy metal exposure in childhood can have lifelong consequences, but heavy metals can also be toxic to adults who may be exposed to them in occupational or household contexts *(101)*. Lead and methylmercury specifically pose serious threats to developing brains in utero, throughout infancy and during early childhood and are associated with the onset of neurodevelopmental disorders *(102—104)*. It is estimated that lead and methylmercury exposure are responsible for over 24 million lost IQ points in children under the age of 5 years in the USA alone *(100)*. Importantly, preventive measures can reduce many sources of lead and mercury, such as banning lead from fuel and household paint and reducing the use of mercury in thermometers, restorative dentistry and consumer products.

Arsenic exposure, which is also linked to neurodevelopmental and other neurological disorders, is a global problem; according to recent estimates, arsenic contamination in groundwater exists in close to 108 countries, putting 230 million people at risk *(100, 105)*.

Pesticides and industrial solvents

Pesticides, including commonly used organophosphates, are recognized as harmful for brain health. Pre-natal exposure to organophosphates (such as chlorpyrifos) are known to have an impact on neurodevelopment and are associated with cognitive, behavioural and motor difficulties in children *(106)*. Exposure to organophosphates is estimated to be responsible for close to 17 million lost IQ points in children under the age of 5 years in the USA *(100)*. Low levels of organophosphate exposure in adulthood, which is a risk in many occupations such as farming and pest control, are also linked to changes in cognitive function *(107)*. Additionally, pesticides that are widely used including paraquat and chlorpyrifos are associated with an increased risk of Parkinson disease *(101)*.

Commonly used industrial solvents can also have neurotoxic effects. For example, trichloroethylene (TCE) which is used as a refrigerant, degreasing solvent and cleaning agent is known to have harmful impacts on neurodevelopment and also changes in cognition, vision, psychomotor and other nervous system functions *(108)*. TCE is also linked with an increased risk of Parkinson disease *(101)*.

Air pollution

is increasingly being recognized as a major global threat to brain health. WHO estimates that 99% of all people worldwide breathe polluted air in their ambient environment which threatens brain development and health across the life course *(9)*.

99%

of all people worldwide breathe polluted air in their ambient environment which threatens brain health across the life course

Air pollution is harmful for developing brains. Exposure to air pollution during pregnancy and early childhood has been associated with neurodevelopmental delays; emerging studies also raise concern for potential links between air pollution and autism spectrum and attention deficit hyperactivity disorders *(109—112)*. In 2019, air pollution exposure was thought to be responsible for a loss of at least 1.96 billion performance IQ points in children in Africa alone *(113)*. Recent cohort studies utilizing neuroimaging help to elucidate the impacts of air pollution on the developing brain, linking exposure to air pollution in pregnancy and childhood to a smaller hippocampus (which is important for emotional functioning, learning and memory) and a larger amygdala (fear centre) by pre-adolescence *(114)*. Similarly, the exposure to traffic-related air pollution by 1 year of age has been linked to reduced volume of brain grey matter and cortical thickness by early adolescence, which has implications for cognitive functions such as attention *(115)*.

In addition, air pollution is linked to the development of neurological disorders in adulthood, including stroke, dementia and Parkinson disease *(101)*. For instance, 30% of the global stroke burden is attributable to ambient or household air pollution *(116)*. Additionally, exposure to fine particulate matter or PM 2.5, nitrogen dioxide, nitrous oxides and carbon monoxide is associated with the development of dementia *(117)*. Interestingly, improving ambient air quality may improve brain health outcomes by slowing the rate of cognitive decline, as suggested by recent analyses of a longitudinal cohort study across 48 states in the USA *(118)*.

Multiple mechanisms have been proposed for how air pollution may affect the human brain, including direct neurotoxicity, neuroinflammation, oxidative stress, impaired energy metabolism and injury to brain vessels *(119, 120)*. These mechanisms can lead to changes in brain architecture during developmentally sensitive periods and brain functioning across the life course.

Natural disasters

such as volcanic eruptions can also have direct impacts on the brain health of whole populations by releasing toxic chemicals and gases, and polluting the air people breathe downwind from the volcano *(121)*. Volcanic eruptions can also lead to mass displacement and housing and financial insecurity, all of which can have an impact on brain health. **Man-made disasters** such as nuclear explosions and chemical spills have also been linked to neurological syndromes as a direct consequence of either radiation or heavy metal exposures *(122, 123)*. Additionally, climate change is contributing to ambient air pollution as well as increasing the risk and severity of wildfires. Wildfires can harm brain health directly by releasing fine particulate matter and can also lead to indirect impacts through separation from or loss of loved ones, mass displacement and financial strain *(124)*.

3.3 Safety and security

Physical safety and financial security can have impacts on brain health over the life course. Physical safety is the absence of actual physical harm (including abuse, maltreatment and neglect) and the threat of physical harm; it requires stable and safe housing, and safety within the home and within the broader community. Financial security is not merely the absence of poverty but also the absence of strain or stress due to financial concerns; it means that one can reasonably afford the necessities of life, including food, housing, health care, education and transport. Both physical safety and financial security can have impacts on individuals, their families and the communities in which they live. This section addresses aspects of physical safety and financial security that affect brain health, as well as exposure to humanitarian crises which can be major safety and security risks.

Physical safety

In addition to the impact of traumatic brain injuries on the individual **(as discussed in Section 3.1)**, exposure to violence within the home and community can have indirect impacts on brain health. **Section 3.4** explains in more detail how adverse childhood experiences including physical abuse can impact brain development. Recent neuroimaging studies also suggest that exposure to violence within the neighbourhood has an impact on developing brains and has been associated with lower hippocampus volume in adolescents and altered hippocampus functioning in children and adolescents *(125, 126)*. The hippocampus is a part of the brain within the limbic system, which is important for emotional functioning, learning and memory.

Financial security

As with physical safety, emerging evidence suggests that financial security at both the individual and community levels can have impacts on brain health. For instance, lower income and financial strain have both been associated with an increased risk of developing dementia in older adults *(127)*.

Recent studies have shown that living in neighborhoods at greater socioeconomic disadvantage may be linked with decreased brain volume in both children and adults, as well as with lower neurocognitive performance in children *(128, 129)*. Neighbourhood disadvantage during childhood has also been associated with decreases in the growth of myelin (brain white matter) during adolescence and young adulthood *(130)*. Similarly, neighbourhood disadvantage may also confer increased risk of dementia *(131)*.

Importantly, the impacts of both neighbourhood disadvantage and exposure to violence in early life can be mitigated by positive family functioning and parenting *(132)*. Interventions in early life can bring great gains for brain health across the life course, which will be discussed further in **Section 4.2**.

Humanitarian crises and emergencies

These pose numerous threats to brain health for individuals and communities. It is important to protect the brain development of children and the brain health of all people affected during epidemics, natural or man-made disasters, conflicts and other emergencies. There are many impacts to anticipate and consider at the onset of humanitarian crises and emergencies. The origin and duration of a humanitarian crisis or emergency will influence the depth and breadth of the impact it has on the brain health of individuals and communities. (For more information on the Zika epidemics and COVID-19 pandemic, **see Section 3.1**. For more information on volcanic eruptions, climate change and wildfires, **see Section 3.2**).

All humanitarian crises and emergencies can cause new social adversities and psychosocial stressors, or heighten existing ones, for large parts of the community. During periods of crises the most vulnerable populations – who already face one or more social adversities – may be subject to further adversities and be distanced from sources of financial, legal and social support and protection. Chronic stress due to socioeconomic adversity can lead to disruptions in brain-directed stress physiology and a multitude of inflammatory conditions which, for example, have been hypothesized to worsen COVID-19 outcomes in vulnerable populations – including racial and ethnic minorities *(133)*.

Wars and other conflicts can cause separation from (or loss of) loved ones as well as mass displacement, financial insecurity, traumatic injuries, and disruption or impairment of health and social systems. Special considerations should be made for people living with neurological disorders who may be affected by disruptions in routine services after mass displacement *(134)*.

3.4 Learning and social connection

Lifelong learning, including access to education, and social interactions are important determinants for brain health across the life course. They overlap in multiple ways. For instance, learning in early life is closely connected with responsive and nurturing caregiving – i.e. the social interactions that a child has with his or her primary caregiver. Formal learning relies on schools and other educational institutions, while cognitive stimulation in adulthood is often linked to employment and social networks within communities, all of which also represent important sources of interaction with peers and other human beings and provide social support and social connection. Consequently, interventions aimed at optimizing brain health – especially in early life – often involve support for both learning and social interactions.

Support for lifelong learning

Opportunities for early cognitive, social and emotional learning are crucial for brain development in infancy and early childhood. Such opportunities may include loving and supportive interactions with caregivers that stimulate the growing mind through talking, singing, playing and reading *(8)*. In addition to early learning from caregivers, access to formal education in childhood and adolescence is associated with better brain health outcomes. Higher rates of educational attainment are associated with better cognitive function later in life, which may be due to the impact of education on cognitive reserve *(80)*. Although opportunities for cognitive stimulation may have the greatest impact on brain architecture in early life (from early childhood through adolescence), studies show that lifelong learning and cognitive stimulation in adulthood and later life – including speaking another language, reading, playing music, and intellectual engagement – also confer benefits for brain health *(80)*. Employment can also be an important source of cognitive stimulation in adults. A recent multicohort study utilizing data from five countries showed that people with cognitively stimulating jobs had a lower risk of developing dementia than persons with non-stimulating jobs. In the same study, people with higher cognitive stimulation in their jobs had lower levels of certain proteins that are known to impair the creation of neuronal axons and synapses; this may provide some insight into how cognitive stimulation may be protective against dementia in later life *(135)*.

Higher rates of educational attainment are associated with better cognitive function later in life

Social connection

In early childhood, the responsiveness of a caregiver influences the structural development of a child's brain and stimulates the creation of neuronal connections in the brain. All children face stress and many may face serious adversities in their life, but the way in which these stressors affect them vary greatly according to the kind of support they receive from caregivers. Adverse childhood experiences (ACEs) may include the following: maltreatment (physical abuse, sexual abuse, neglect); parental maladjustment (parental mental health conditions, substance use, parental criminal behavior, family violence); interpersonal loss (parental divorce, parental death, other parental loss); and other childhood adversities (physical illness, family economic adversities).[9]

Loving and responsive interactions between a child and his or her caregiver are referred to as "serve and return" interactions and have a positive impact on the structural development of a child's brain *(136)*. Caregivers can serve as important buffers to ensure that the stresses faced by children remain tolerable *(137)*. Importantly, the absence of a supportive and responsive caregiver in the setting of prolonged exposure to one or more adversities leads to "toxic stress." *(138)*. Toxic stress can cause changes in the development of brain architecture, including areas of the brain that are responsible for modulating our body's responses to stress (overactivation of the amygdala, hypothalamus and pituitary and weaking of the prefrontal cortex and anterior cingulate), with lifelong implications for a person's vulnerability for stress-related mental and physical health conditions *(139—142)*. In recent years, studies have provided insights into the intergenerational impact of ACEs, with lower brain volumes and changes in neural connectivity involving the amygdala (fear centre) seen in infants of mothers who experienced maltreatment or emotional neglect from their own caregivers *(143, 144)*.

Importantly, the quality of attachments and social connection a person has throughout their life affects their brain health. During adolescence and adulthood, the quality of attachments, social connection and social support continue to have impacts on brain health. Greater numbers of social connections as an adult are associated with larger volumes of multiple brain structures in the cerebral cortex, and the quality of social connections are additionally linked with areas of the brain associated with memory *(145, 146)*. The availability of social support in older adults has been linked to networks that involve areas of the brain that are responsible for executive functioning, emotional regulation and memory *(147)*. Additionally, social support in the form of supportive listening correlates with higher cognitive resilience in older adults *(148)*. On the other hand, social isolation and loneliness in older adulthood are associated with a higher risk of developing cognitive impairment and dementia *(80, 149)*.

Toxic stress can cause changes in the development of brain architecture, including areas of the brain that are responsible for modulating our body's responses to stress

9. For more information on, and full definition of, ACEs see the WHO/World Mental Health Survey Initiative at https://www.hcp.med.harvard.edu/wmh/ (accessed 6 July 2022).

3.5 Access to quality services

Strengthening health and social care systems so that they provide equitable access to diagnosis, treatment, care and rehabilitation as and when needed is crucial for optimizing brain health for all

Managing the many risk factors of brain health will require access to quality health and social services. Despite best efforts to minimize risk factors, many people still develop conditions that affect their CNS at some point in their lifetime, and this is likely to continue in the future. Consequently, access to quality services is an important determinant of brain health. Similarly, strengthening health and social care systems so that they provide equitable access to diagnosis, treatment, care and rehabilitation as and when needed is crucial for optimizing brain health for all.

Access to effective, timely and responsive services is essential – particularly for people with CNS disorders so that they can fulfill their developmental potential, exercise their functional abilities and improve their quality of life. To achieve this, services need to be available within the community and grounded in evidence-based policies and practices that cover the full spectrum of care, namely diagnosis, treatment, rehabilitation, palliative and social care. Within the context of UHC, it is crucial to have affordable and equitable access to these services at the primary-care level without discrimination or risk of financial hardship. Likewise, continuity of these services should be ensured during humanitarian crises and emergencies.

Furthermore, services need to be people-centred and responsive to a person's unique needs. Services should be tailored to different stages of life and should ensure continuity of care across providers and sectors – particularly for children and adolescents with neurodevelopmental and/or neurological disorders as they transition into adulthood. Services should be culturally sensitive, gender appropriate and accessible to vulnerable groups such as: racial and ethnic minorities and indigenous people; refugees, internally displaced people and migrants; and people facing socioeconomic disadvantage, domestic and gender-based violence, or incarceration, among others.

Services should also take a human rights-based approach, consistent with the United Nations Convention on the Rights of Persons with Disabilities (CRPD) *(150)*. Providing people with lived experience and their carers with evidence-based and accessible information relevant to their care can empower them to make informed choices about their care. A rights-based approach also addresses the fact that many people with CNS disorders and their

carers encounter major barriers to accessing care because of stigma, prejudice and discrimination both in the health-care system and in their communities *(101, 151—153)*. Importantly, people with lived experience and their carers should never be blamed for their circumstances or health conditions. **Box 5** presents ways to address stigma and discrimination.

In line with the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031 (14)*, the following sections of the position paper summarize specific aspects of effective and responsive services that are required to optimize brain health across the life course for everyone.

Box 5.

Addressing stigma faced by people with CNS disorders and their carers

Stigma, prejudice and discrimination remain pervasive challenges faced by people living with CNS disorders, their carers and families. These negative attitudes contribute to multiple forms of social exclusion.

Stigma against CNS disorders is widespread in all sectors of society *(154—156)*. People living with these conditions often face discriminatory actions, violations of their rights and social exclusion by members of the public – and at times even by health-care providers. As a result, people with CNS disorders may find themselves excluded from education, employment or housing and may have difficulty in accessing health care.

Stigma usually results from a lack of understanding and information or from misinformation. Stigma can be combatted by correcting myths and misconceptions and replacing them with correct information to improve public understanding. It is very important to involve people with CNS disorders in the planning and implementation of these interventions in order to empower them to make their own decisions. In fact, interventions grounded in interpersonal contact are shown to be the most effective means to combat stigma and discrimination *(29)*.

Examples of actions to combat stigma include the following *(152)*:

- treat people with lived experience positively and with respect;
- avoid stigmatizing language and encourage others to do the same;
- use people-centred language such as a "person with a specific disorder/condition" or "person with lived experience"; and
- work with people with lived experience, their carers and families to organize programmes to raise awareness and dispel myths about neurological disorders, the nervous system and the brain.

Integrated, interdisciplinary care at all levels of the health and social care system

Conditions affecting the brain – especially neurodevelopmental and many neurological disorders such as dementia, Parkinson disease or multiple sclerosis – can have an impact on a person's cognitive, sensory, social-emotional, behavioural and motor functioning. As such, these disorders affect activities of daily living, mobility and self-care, creating very complex care needs. In addition, many conditions affecting the brain are chronic and/or progressive. Consequently, people living with these conditions may require long-term care. As a result, services for optimizing brain health need to provide a wide range of coordinated, integrated health and social care, guided by evidence and delivered by a competent and motivated interdisciplinary workforce at primary, secondary and tertiary levels.

Besides neurology, neurosurgery, general medicine and nursing, the disciplines required for optimizing brain health include radiology, (neuro)psychology, neurorehabilitation, occupational therapy, physical therapy, speech-language pathology, palliative care, mental health and psychosocial support, as well as spiritual care, social work and welfare (e.g. for advice on advance care planning and disability supports).

The complex service needs are largely unmet globally and need to be strengthened, particularly at the primary care and community levels

These complex service needs are largely unmet globally *(13)* and need to be strengthened, particularly at the primary care and community levels. In addition, pre-service and ongoing training, continuing medical education, and adequate supervision and support are needed for both specialists and non-specialists. However, training, supervision and support are not consistently available for health and social care workers in all areas *(151, 157)*. Where needed, options should exist to invest in health workers with fewer years of training and to provide services limited to their scope. The promotion of self-care (according to established guidelines) can also go a long way to reducing the burden of care at secondary and tertiary levels, especially in settings where highly skilled workers are not readily available *(157)*.

Lastly, specialized facilities are sometimes used to treat certain conditions affecting the CNS – such as stroke units, spinal injury units, neurorehabilitation centres and neurosurgical facilities for surgical procedures relating to epilepsy, tumors and ischaemic strokes or intracranial bleeds. Such specialized care units may improve mortality and morbidity for some conditions, such as stroke *(158)* or spinal cord injuries *(159)*, but their accessibility is uneven across countries and income settings *(13, 160)* and evidence is scarce for other conditions such as dementia. This situation requires further evaluation at national and international levels.

Access to essential medicines, diagnostics and other health products

Medicines and diagnostics – as well as other health products such as assistive technology, biological products and cell and gene therapy – are essential for optimizing brain health as they can reduce mortality and morbidity and improve the quality of life.

Certain neurological disorders – such as epilepsy, stroke, treatable neurometabolic diseases or multiple sclerosis – require treatment with medicines for many years and sometimes for a lifetime. The abrupt withdrawal of certain medications, such as antiseizure medicines, may be life-threatening. Consequently, it is essential to ensure that access to high-quality, safe and affordable neurological medicines is sustained over time. Policies should be in place to monitor supply chains and stock-outs in health facilities and to address possible disruptions, particularly in health emergencies and humanitarian crises. Medications for neurological disorders should be used appropriately in order to avoid unnecessary polypharmacy and increased risks of adverse effects, including physiological dependency and addiction to controlled substances.

Similarly, appropriate use of diagnostics such as laboratory tests, neuroimaging or electroencephalography are essential tools for optimizing brain health as they allow for early and rapid detection of pathologies, disorders and risk factors. Diagnostics also support disease monitoring and can inform the utilization of targeted, effective interventions which may slow disease progression and reduce complications.

The abrupt withdrawal of certain medications, such as antiseizure medicines, may be life-threatening

Assistive technologies that compensate for functional impairments and losses enable people to live healthy, productive, independent and dignified lives within their communities and reduce the need for formal health and support services. Examples of assistive technologies include hand rails, wheelchairs, walkers, motorized mobility detectors, fall detectors, hearing aids, braille displays and writing equipment, spectacles, simplified mobile telephones, time management products and pill organizers *(161)*.

Unfortunately, there is limited access to essential medicines for neurological disorders within primary care settings. The availability of imaging modalities including computed tomography (CT), magnetic resonance imaging (MRI) and access to assistive technologies also remain inequitable globally *(13, 162—164)*.

Carer support

Because many neurodevelopmental and neurological disorders are chronic and/or have long-lasting impacts, people living with such conditions may need substantial ongoing care. In many parts of the world, this care is provided informally by unpaid carers, mostly female family members or close friends, making them an invaluable cornerstone of service provision. It is estimated that more than half of the global care costs associated with dementia are attributable to informal care, with family members of people with dementia globally providing approximately 90 billion hours of informal care (excluding supervision time) in 2019 (about 5 hours per day per person with dementia) *(151)*. Further, approximately 70% of informal dementia care globally is provided by women *(151)*, highlighting a tremendous gender imbalance. Carers face numerous financial, social and psychological stressors (e.g. role strain; financial losses due to reduced, or lack of, income; social isolation; and bereavement in the event of loss).

Carers' roles and the challenges they face may vary depending on the condition, whether they are caring for children, adolescents or adults, and the carer's age, health status and abilities. Caregiving responsibilities often widen gender gaps and often have a negative impact on the carer's own physical and mental health, which in turn can lead to the breakdown of informal home-based care arrangements and costly institutional long-term care.

Consequently, support to carers is an essential element of optimizing brain health *(14, 101, 151)*. This entails building capacity in the health and social care workforce to identify and manage carer stress effectively as well as to provide access to information, training and services for carers. Effective training programmes and support represent important elements in building carers' capacity not only to protect their own well-being but also to help address a variety of care needs, including neurorehabilitation, and to provide overall better care in the long term *(151)*. **Box 6** gives two examples of carer support resources developed by WHO.

Carer support schemes – such as social, tax and disability benefits – can lessen the social and financial strain that carers may otherwise feel. The schemes represent powerful policy mechanisms that not only support carers and affected families but also strengthen the national health and social care system by enabling family carers to care for longer.

Importantly, the stigma, prejudice and discrimination that many informal carers face, like people with neurological disorders themselves, represent significant barriers for carers seeking help and support. Due attention should therefore be given to addressing stigma and any form of discrimination through awareness-raising and through supportive policies and legislation that promote full inclusion and empowerment of people with lived experience and their carers.

Carers face numerous financial, social and psychological stressors

Box 6.

Examples of carer support resources developed by WHO

Support for caregivers of children with developmental disabilities or delays

In April 2022, WHO launched a caregiver skills training (CST) programme for caregivers of children with developmental delays or disabilities, including autism *(165—169)*. The goal of the CST is to teach parents and other caregivers day-to-day skills that help boost the well-being and development of their children. The programme was designed to be implemented by non-specialist providers and has been piloted in a face-to-face format in 30 countries.

An online version of this training programme is also available. The online training includes prerecorded information sessions on topics such as using everyday routines as opportunities for children to learn and engaging with children through play and problem-solving. The training also includes sessions to help caregivers improve their own well-being. There are additionally quick-tip videos, quizzes and reminders to support sustained learning.

For more information see: https://www.who.int/teams/mental-health-and-substance-use/treatment-care/who-caregivers-skills-training-for-families-of-children-with-developmental-delays-and-disorders.

Support for carers of people with dementia

To support people living with dementia and their carers, WHO developed iSupport, a knowledge and skills training programme *(170)*. iSupport is a self-help tool which aims to prevent and/or decrease mental and physical health problems associated with caregiving, and to improve the quality of life of carers.

iSupport consists of five modules with accompanying exercises, namely: 1) introduction to dementia; 2) being a carer; 3) caring for me; 4) providing everyday care; and 5) dealing with behaviour changes. iSupport can be used as an online programme and can also be printed as a manual and used offline. iSupport is currently being adapted in 36 countries and 31 languages.

iSupport Lite was released in 2020 in order to support carers of people living with dementia, especially during the early phases of the COVID-19 pandemic when usual community-based supports were unavailable in many places. iSupport Lite includes a set of short, practical support messages for carers. iSupport Lite offers tips for carers in video, poster and question and answer formats.

For more information on iSupport, see: http://www.isupportfordementia.org

4. Impacts of brain health optimization on health and other outcomes

A stroke 30 years ago forced me to cut down work to three days a week. Fortunately, I received a benefit in the Netherlands that compensated for the lost income. Having to rest every day, while others can just carry on living, has been depressing for me. But this way I can still contribute a little to society. I was very lucky because the company that I worked for had the flexibility to accommodate my needs. If that was not possible I would have become unemployed."

Henk Lindeman, Netherlands

Optimizing brain health leads to a wide range of health-related and societal benefits

Optimizing brain health leads to a wide range of health-related and societal benefits. First, optimizing brain health leads to reduced neurological disorders and fewer mental health and substance use conditions. It also improves the quality of life for people with these conditions. Optimizing brain health also affects physical health more broadly, as the brain controls many of the body's important physiological processes. Moreover, optimizing brain health across the life course can have a multitude of social and economic impacts, including: lower health-care costs, lower rates of disability, increased school retention and lower rates of dropouts, lower rates of crime and incarceration, higher productivity and greater wealth. All these outcomes contribute to greater well-being for the individual and for society at large and are discussed in this chapter.

4.1 Impact on health and well-being

Impacts on neurological disorders, mental health and substance use conditions

As noted in **Chapter 3**, addressing brain health determinants can, through promotion and prevention, reduce the incidence of CNS disorders. Additionally, because the optimization of brain health improves brain structure and functioning across all domains (cognitive, sensory, social-emotional, behavioural, motor), it can lead to lower rates of mental health conditions and substance use. Social adversities for example are associated with mental health conditions, and this is thought to be at least partially mediated by changes to brain structure and function, especially in early life *(31, 34, 171, 172)*. As discussed earlier, interventions that address brain health determinants can have positive impacts on brain structure and function, and in doing so, can also have benefits for mental health. For example, positive family functioning and parenting have been found to lessen the impacts of neighbourhood disadvantage on brain development in adolescence, which may be protective for mental health *(132)*. In addition, a recent systematic review identified mother–child and peer relationships as targets for interventions to prevent substance use in young people exposed to adversity *(173)*.

For some of the determinants discussed in this paper (or interventions to address them), there are clear associations with mental health. Separately, there are emerging studies showing the impacts of these determinants and interventions on brain structure and function, though how exactly these impacts contribute to mental health benefits or harm are not yet completely understood.

For example, a recent overview of Cochrane reviews shows that physical activity is linked to multiple health benefits including mental health *(32)*. As discussed in **Section 3.1**, physical activity is thought to improve the brain's neuroplasticity in multiple ways including by increasing levels of BDNF and other neurotrophic factors and buffering inflammation in the body *(90)*. Some of these mechanisms may also be beneficial for mental health *(32, 174)*. As another example, a recent meta-analytic review found that air pollution exposure is associated with the risk of depression, anxiety and suicide risk *(33)*. As discussed in **Section 3.2**, air pollution is thought to impact the brain via multiple mechanisms including direct neurotoxicity, neuroinflammation, oxidative stress, impaired energy metabolism and injury to brain vessels *(119, 120)*. Such mechanisms may also be partially responsible for the observed associations between air pollution and mental health conditions *(33)*.

Importantly, measures taken to address determinants of brain health may not only reduce the incidence of neurological, mental health and substance use conditions, but can also improve the quality of life for people living with these conditions. For instance, a recent meta-analysis found that physical exercise as an intervention improved quality of life for people with Alzheimer disease, Parkinson disease, Huntington disease, multiple sclerosis, depression and schizophrenia *(92)*. As another example, mind–body therapies aimed at stress reduction can improve quality of life for people with dementia *(175)* and Parkinson disease *(176)*. **See Box 7** for more information on mind–body therapies.

Box 7.

Mind–body interventions for stress reduction

Growing evidence demonstrates the benefits of a variety of mind–body interventions for brain health – and for overall health – in the face of chronic stress or adversity. Mindfulness meditation for example has been used for decades for stress reduction and has been shown to enhance neuroplasticity in multiple brain regions including the anterior cingulate, insula, temporo-parietal junction, and fronto-limbic and default mode networks *(177)*; these areas of the brain play important roles in attention, emotional regulation and awareness of the body. Some studies additionally suggest that meditation practices may help preserve brain structure, protect against cognitive decline as we get older and potentially improve some aspects of cognitive function such as executive function and attention *(178)*. Additionally, the practice of yoga is now thought to help regulate the hypothalamic–pituitary–adrenal (HPA) axis (as demonstrated by lower cortisol peaks throughout the day) with subsequent downstream impacts including lower blood pressure, resting heart rate and other metabolic markers such as fasting glucose and cholesterol *(179)*.

Moreover, a recent systematic review of clinical and nonclinical studies found that multiple mind–body interventions (including mindfulness and other meditation techniques, relaxation response, breath regulation, stress management and resilience training programmes, yoga, Tai Chi and Qigog) are associated overall with gene expression changes that lead to downregulation of inflammatory processes that are upregulated in response to chronic stress *(180)*. Mind–body interventions may therefore mitigate the impacts of adversity on the brain-directed stress response.

Impacts on physical health

As **Chapter 3** shows, there are multi-directional relationships between the brain and physical health. Many aspects of physical health (including maternal health, genetics, nutrition, infections, NCDs and sensory impairments, sleep, physical activity, substance use, and traumatic injuries) can influence brain health across the life course. At the same time, the brain can actually have an impact on physical health because the brain plays a role in regulating cardiovascular, endocrinological and immunological health. The brain also mediates our responses to stress and adversities which can have impacts on our physical health (**see Section 3.4** for impacts of toxic stress on brain development). In this way, the brain has an important role in maintaining allostasis, or the stability of our body's physiological and metabolic systems in the face of environmental change *(141, 142)*. Over time, excessive activation of our stress response leads to allostatic overload with metabolic wear and tear and inflammatory dysregulation, lowering the threshold for the development of stress-related health conditions *(181, 182)*.

Chronic stress in adulthood can also cause changes in the brain, most notably overactivation of the amygdala and HPA axis, with weakening of mitigating cortical structures and subsequent impacts on the body's response to repeated stressors and inflammation *(183)*. As just one example, individual studies have linked socioeconomic adversity in adulthood to cardiovascular events such as heart attacks, mediated by a brain-directed stress cascade beginning with increased amygdalar activation leading to downstream bone marrow changes and cardiovascular arterial inflammation *(184, 185)*. Similarly, recent studies showed that increased amygdalar activity due to psychosocial stress in adulthood is associated with higher adiposity (a risk factor for overweight and obesity) and incident diabetes *(186, 187)*. Lower amygdalar activity has actually been associated with a lower risk of cardiovascular events in the face of chronic stress, which means that reducing amygdalar activity has the potential to improve neurobiological resilience to stress *(188)*.

Brain-directed stress responses can influence health trajectories across the life course

In other words, brain-directed stress responses can influence health trajectories across the life course, in addition to a multitude of other important factors such as lifestyle, behavioural risk factors and access to health care *(189)*. Actions aimed at optimizing brain health by reducing stress and buffering the HPA axis can also improve health outcomes. Such interventions may include social connection and support *(190, 191)*, physical exercise, healthy diets, good-quality sleep and mind–body interventions, all of which have been shown to protect brain integrity and function, with the potential to buffer stress axes and reduce excessive inflammation, leading to benefits for both mental and physical health.

4.2 The social and economic impact of brain health optimization

Optimizing brain health additionally leads to multiple social and economic benefits across the life course, though these are best understood in early life. For instance, **Chapter 3** noted the impact of toxic stress on the developing brain. The costs of inaction in early life for children at risk are high, with toxic stress linked to school attrition, incarceration and lower economic productivity *(171, 192)*. On the other hand, investment in early childhood development can bring about great gains across the life course by mitigating or counteracting at least some of these negative impacts *(193)*.

Early interventions to foster and promote childhood development have been proven to be cost-effective

Early interventions to foster and promote childhood development have been proven to be cost-effective. In fact, the highest returns on investment for social interventions are in early life, given how rapidly a child's brain responds to their environment. The Heckman equation for the economic impact of investment in education yields a steep parabolic curve, with the highest returns on investment for the early childhood and pre-school period. While intervening early is critical and the most cost-effective, continued support through childhood and adolescence still offers substantial gains from the Kindergarten through 12th grade period and more modest gains in post-school age job training *(194)*.

Box 8 provides more information on the importance of early interventions for improving child development.

Box 8.

The importance of intervening early for child development

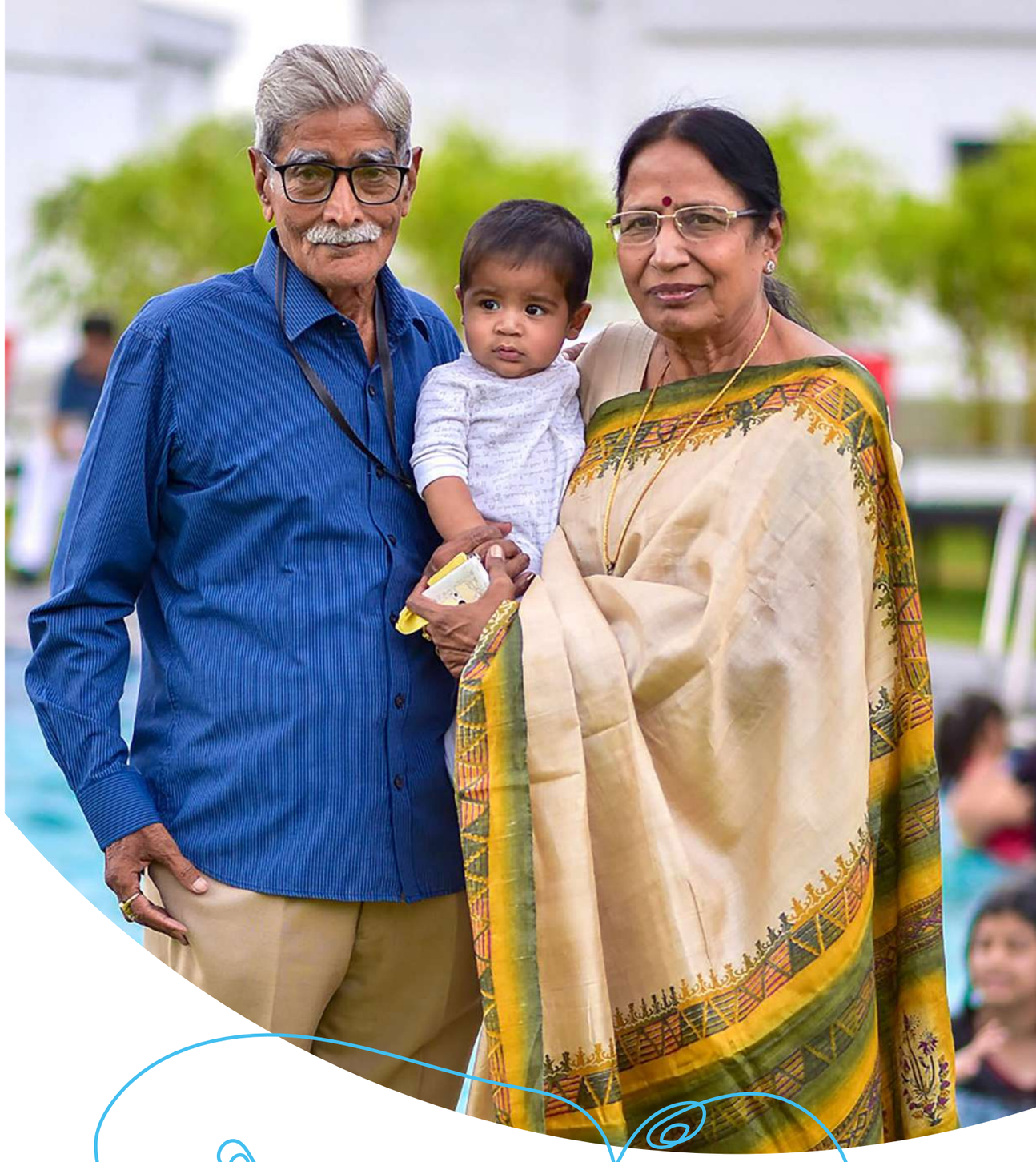
Nurturing care and interventions to promote early childhood development yield lifelong benefits. They are designed to protect against, or compensate for, adversities that are known to affect healthy brain development in children *(193)*. Biological and psychosocial evidence supports the notion of intervening as early as possible to protect and promote child development *(193, 195)*.

For instance, interventions such as the High Scope Perry Preschool study, which offered pre-school and parental support through home visits for at-risk children *(196)*, have demonstrated incredibly positive long-term results including higher educational performance and future earnings, lower rates of teenage pregnancy, as well as fewer crime, arrests and prison time in adulthood *(193)*.

Although the cost-benefit ratios between different studies cannot be compared due to different estimation methods, robust evidence overall suggests a positive return to society with early interventions *(197)*. The High Scope Perry Preschool study for instance reported a return on investment over the course of 40 years reaching close to US$ 13 for every dollar invested *(196)*.

Though the case for investment is strongest for early childhood interventions, supporting programmes that intervene beyond the age of three also translate into positive return and are crucial to ensuring continuity of these efforts made in early life, and for promoting positive development throughout childhood and adolescence.

Moreover, as noted in **Section 4.1** efforts to optimize brain health have the potential to improve overall health and reduce the incidence of many chronic health conditions. This would in turn be expected to reduce health and social care costs. Further investigations are warranted in order to fully understand the returns on investment for actions aimed at addressing brain health determinants **(see Sections 5.2 and 5.3)**.



5. Future directions for brain health policy, research and data

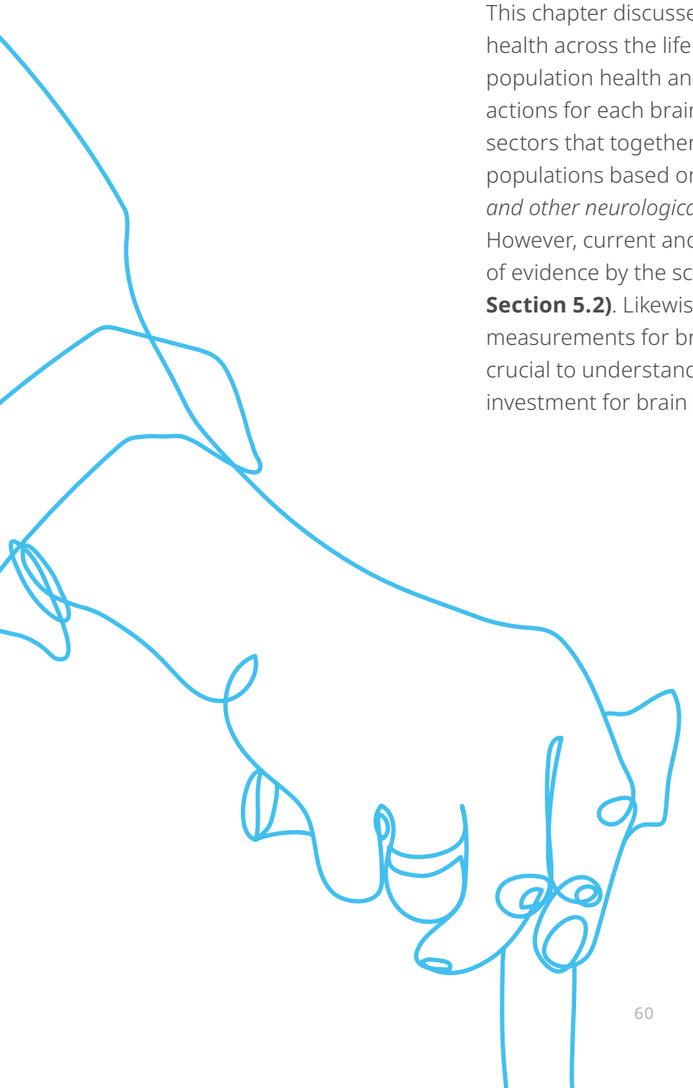
> The brain is a complex organ and although medicine has made leaps and bounds since the 90s, when it comes to understanding the brain, there is lots more to be discovered to fully grasp all its intricacies.”
>
> **Veronique Theberge, New Zealand**

Investing in building cognitive and brain capital is fundamental to meet modern societal challenges and to drive innovation

In a post-industrial era, the demand on societies for a highly skilled and knowledgeable workforce is rapidly increasing *(198)*. Optimizing brain health and investing in building cognitive and brain capital (e.g. by addressing brain health determinants including education, health care and healthy environments) is fundamental to meet these modern societal challenges and to drive innovation *(4)*. This necessitates integrated action across all sectors of society in order to address adequately all the brain health determinants across the life course.

As brain health is a rapidly evolving field, there is an ongoing need to develop evidence-based guidance in the areas of promotion, prevention, diagnosis, treatment, care and rehabilitation of CNS disorders. WHO has generated – and will continue to generate – norms and standards for addressing the determinants of brain health and optimizing brain health for all (**see Annex 3**), with the goal that these norms and standards will be translated into policy and programmatic recommendations with practical relevance.

This chapter discusses future directions for optimizing brain health across the life course, with the goal of improving overall population health and well-being. The chapter outlines exemplar actions for each brain health determinant across a wide range of sectors that together help optimize brain health for individuals and populations based on the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* **(see Section 5.1)**. However, current and future actions rely on the robust generation of evidence by the science, research and technology sector **(see Section 5.2)**. Likewise, arriving at commonly accepted and validated measurements for brain health across the life course will be crucial to understand the impacts of interventions and returns on investment for brain health **(see Section 5.3)**.



5.1 Intersectoral actions for optimizing brain health across the life course

The *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031* provides a comprehensive roadmap for actions for countries, international partners and intergovernmental agencies to optimize brain health in line with this position paper. The action plan includes related voluntary global targets and indicators to monitor progress in service of the goals and objectives of the action plan *(14)*.

Meeting these global targets and implementing key actions listed in the action plan will necessitate intersectoral collaboration. As this position paper outlines, brain health determinants span multiple sectors of society and addressing them requires a coordinated whole-of-society approach – including, for example, health and social care, education, legal, finance, employment, infrastructure/urban planning and environmental sectors. **Table 1** provides a wide range of examples for intersectoral action. The list is not exhaustive but rather an attempt to demonstrate how different sectors can play important roles in optimizing brain health for all across the life course.

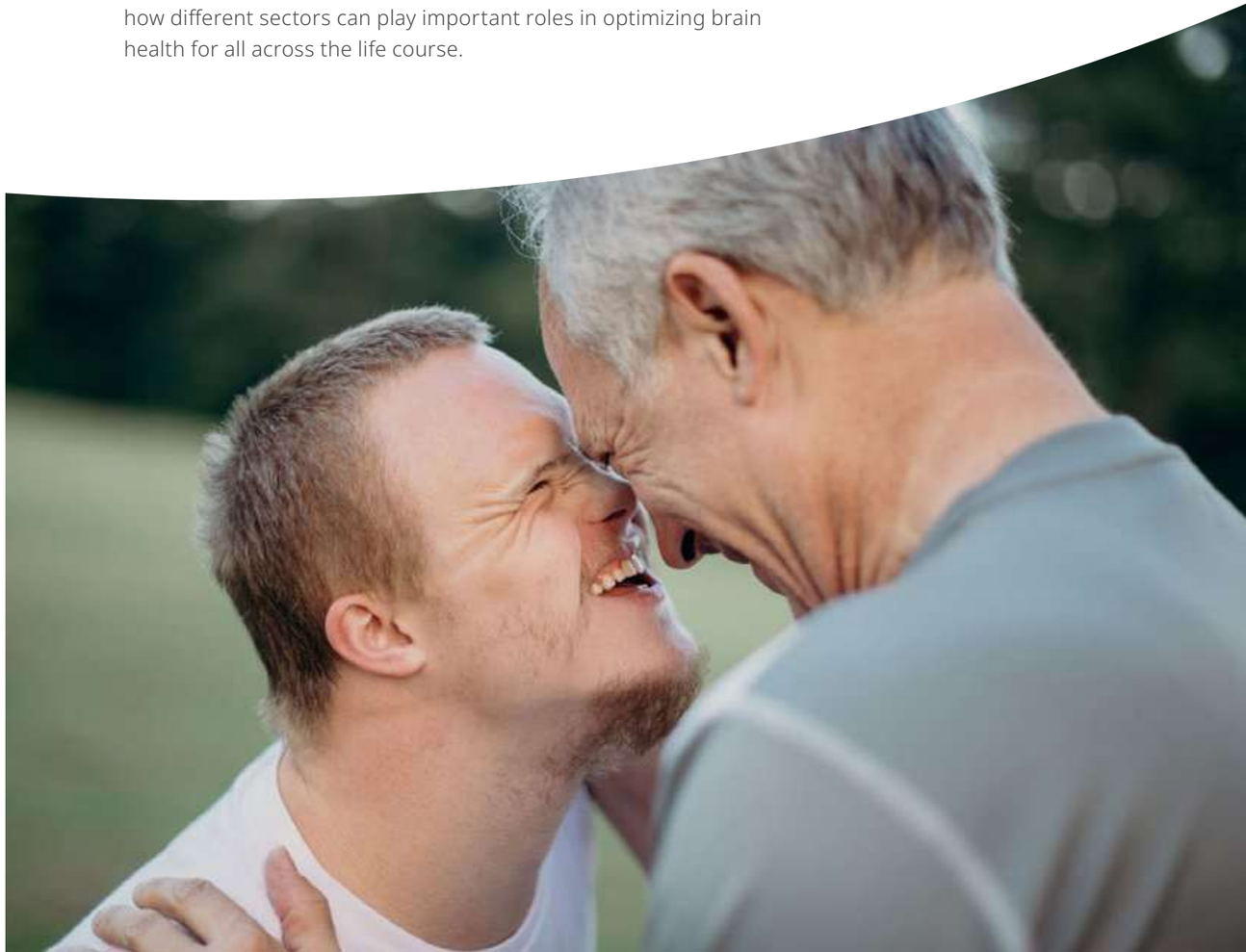


Table 1

Exemplar intersectoral actions to address brain health determinants

Physical health

Health and social care sector

- Increase access to perinatal, child and adolescent health care, including neurodevelopmental assessments.
- Improve access and appropriate use of essential medicines and diagnostics.
- Implement infectious disease management, eradication/control and immunization programmes.
- Run targeted prevention efforts to address obesity, hypertension, high cholesterol and diabetes.
- Improve post-accident emergency care and long-term rehabilitation.
- Promote tobacco cessation and reduction of harmful alcohol use, as well as physical activity and healthy diets.

Education

- Include growth monitoring and neurodevelopmental assessments in school health programmes.
- Design school curricula to teach children and adolescents about brain health promotion in an age-appropriate way.
- Implement healthy food programmes in schools.
- Include quality physical activity programmes in schools.
- Require helmet use for contact sports within schools to reduce the incidence of head injuries.

Legislature and governance

- Strengthen social and financial protection schemes under UHC, such as general health insurance for primary care.
- Strengthen breastfeeding and national food and nutrition policies and action plans.
- Implement WHO's Framework Convention on Tobacco Control.
- Implement and strengthen legislation pertaining to helmet and seatbelt use as well as drink–driving.

Finance and economy

- Dedicate a portion of the health budget to promoting brain health.
- Dedicate funding for school food and physical activity programmes.
- Introduce tobacco, alcohol and sugar taxation schemes.

Employment

- Promote physical activity and other healthy behaviours in the workplace, such as smoke-free workplaces.

Infrastructure, urban planning and housing

- Implement safety measures for roads and vehicles.
- Improve safety of home and community environments to reduce the risk of falls and traumatic brain injury, especially for older adults.
- Design cities to promote access to outdoor spaces for safe physical activity.
- Encourage urban planning and infrastructure development that improve access to outdoor spaces for safe physical activity and alternatives to a sedentary lifestyle.

Ecology, nature and climate

- Strengthen vector control for infectious diseases (e.g. Zika virus, malaria, taenia solium).
- Coordinate closely for the implementation of water, sanitation and hygiene actions to increase access to safe/clean drinking-water.

Table 1 (continued)

Healthy environments

Health and social care sector

- Train health workers to recognize risks to brain health, signs and management of environmental toxicants.
- Implement testing of lead poisoning for infants and children.
- In partnership with humanitarian actors, strengthen emergency preparedness plans for natural and man-made disasters to ensure access to services for people with pre-existing or emergency-induced CNS disorders such as traumatic injuries.

Education

- Design school curricula to teach children and adolescents in an age-appropriate way about environmental impacts on brain health.

Legislature and governance

- Strengthen regulatory and legal measures to accelerate the global phase-out of lead paint.
- Strengthen legislation prohibiting pesticides and other chemicals known to be harmful to human health and development.
- Strengthen legislation to reduce the use of fossil fuels, provide incentives for the use of cleaner energy alternatives and cleaner cooking stoves.
- Enact environmental protection laws to ensure clean air (ambient and household) and water.

Finance and economy

- Dedicate a portion of the health budget to identifying and managing environmental risks to health.
- Dedicate funding for monitoring of environmental health-related legislation.

Employment

- Invest in civil engineers, scientists, educational and health workers.
- Protect workers against/limit exposure to pesticides, heavy metals such as mercury, industrial solvents and other high-priority chemicals known to be neurotoxic.

Infrastructure, urban planning and housing

- Design new buildings to promote cleaner household and indoor air.
- Design cities to improve walkability and use of public transport versus personal vehicles.

Ecology, nature and climate

- Protect the population against/limit exposure to pesticides, heavy metals such as mercury, industrial solvents and other high-priority chemicals known to be neurotoxic.
- Monitor air and water quality with routine testing, make results publicly available and implement measures to improve air and water quality.
- Strengthen national capacity to prepare for, respond to, and recover after natural disasters, chemical spills and radiological and nuclear emergencies.

Safety and security

Health and social care sector

- Train health and social care workers to recognize signs of violence, abuse, maltreatment and neglect (especially of children, adolescents and older adults) and establish appropriate protective mechanisms.
- Streamline protection of brain health and neurological care within response plans for humanitarian crises.

Education

- Train education workers to identify cases of abuse, maltreatment and neglect in children and adolescents.

Legislature and governance

- Implement policies and programmes to:
  - prevent abuse/maltreatment/neglect of children, adolescents and older adults;
  - protect survivors of violence, including domestic/intimate partner violence; and
  - reduce violence at community level.
- Introduce social and financial protection schemes to increase financial security, prevent catastrophic health spending and prevent poverty.

Finance and economy

- Dedicate funding for housing protection programmes, as well as social and financial protection schemes.

Employment

- Abide by fair labour and minimum wages Acts and legislation.

Infrastructure, urban planning and housing

- Design communities and neighbourhoods to enhance physical safety (e.g. adequate lighting, frequent transportation stops).

Ecology, nature and climate

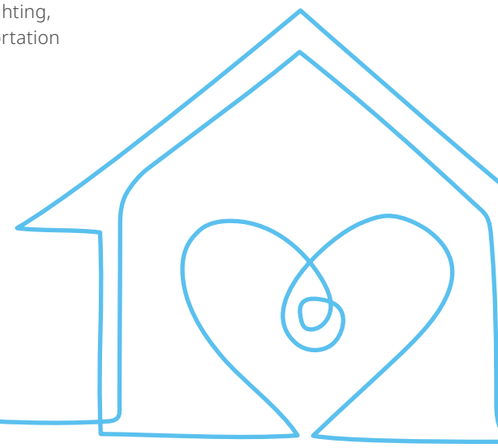


Table 1 (continued)

Learning and social connection

Health and social care sector

- Implement interventions for responsive caregiving and early learning.
- Train health and social care workers to identify loneliness and social isolation across the life course.

Education

- Increase access to early childhood learning programmes.
- Increase access to formal education and inclusive education.
- Implement interventions to promote adolescent brain health and development.
- Design school curricula to teach children and adolescents how to combat stigma, prejudice and discrimination in an age-appropriate way.

Legislature and governance

- Implement laws and legislation that:
  - mandate school attendance for primary and secondary school-age children;
  - prohibit child labour; and
  - aim to protect the rights of, and reduce stigma, prejudice and discrimination against, vulnerable populations, people with CNS conditions and their carers.

Finance and economy

- Eliminate school fees.
- Introduce payment schemes for childcare and early childhood education programmes.

Employment

- Strengthen adequate monitoring to ensure that children are not used for labour.
- Promote lifelong learning in the workplace.

Infrastructure, urban planning and housing

- Design cities, towns and communities to ensure easy access to school for children and adolescents, as well as access to workplaces, social and leisure activities for adults.

Ecology, nature and climate

Access to quality services

Health and social care sector

- Develop evidence-based coordinated health and social care services and integrate CNS disorders into existing relevant health services (at all three levels), ensuring continuity of care across levels and disciplines.
- Establish, strengthen and train skilled interdisciplinary health and social care teams to diagnose, treat and manage CNS disorders and identify/treat carer stress.
- Expand the role of specialists to train and supervise generalists.
- Improve availability and appropriate use of essential medicines and diagnostics for CNS disorders, including workforce training on their use.
- Provide accessible and evidence-based information on available resources for carers in the community.
- Develop mechanisms to involve people with neurological disorders and their carers in care planning.

Education

- Include growth monitoring and neurodevelopmental assessments in school health programmes for early diagnosis and intervention.
- Provide robust primary, secondary and university-level education for the future health and social care workforce, including continuing education.

Legislature and governance

- Implement social and financial protection schemes for people with CNS disorders and their carers (e.g. general health insurance, disability pension, tax benefits, or flexible working hours).
- Establish transparent regulatory frameworks for health products and diagnostics.
- Develop mechanisms to involve people with CNS disorders and their carers in policy-making and legal review.

Finance and economy

- Dedicate a portion of the health budget to the management and prevention of CNS disorders, including access to essential medicines.
- Implement social and financial benefits/financial protection for carers.

Employment

- Address projected health workforce needs in the future.
- Establish compensation and incentives for workforce trained in CNS disorders to work in underserved areas.
- Implement employment protection schemes for carers (e.g. leave or flexible working hours).

Infrastructure, urban planning and housing

- Ensure availability of public transportation to access health facilities within the community.

Ecology, nature and climate

Civil society can play a fundamental role in driving popular discourse about brain health, raising population awareness, and reducing stigma

In addition, civil society can play a fundamental role in driving popular discourse about brain health, raising population awareness, and reducing stigma, prejudice and discrimination to ensure that everyone's brain health is valued, promoted and protected across the life course. The media and communication sector can additionally support these efforts by amplifying public health messages.

Growing numbers of countries are establishing policies, strategies or programmes specific to brain health in order to address the need for multisectoral action. **Boxes 9 and 10** highlight the approaches taken by Norway and Uruguay. These national responses allow for raising the profile of brain health within a country, prompting cross-sectoral collaboration, and encouraging efficient use of resources and planning.

Box 9.

Country spotlight: Norway's brain health strategy

Norway's Ministry of Health and Care Services created the *National brain health strategy (2018–2024)* with the aim of improving brain health through improved health and care services for patients and users. The Norwegian brain health strategy primarily concerns the responsibility of the health and care services in municipalities and in the specialist health service. The strategy also emphasizes a person's ability to promote their own brain health and/or to master life with impaired function due to a brain disease.

To support the development of the Norwegian brain health strategy, a brain team was established within the Norwegian Directorate of Health in order to make the concept of brain health known, to achieve broad support on the *National brain health strategy (2018-2024)* and to identify synergies between ongoing assignments, initiatives and activities within the directorate. The Directorate of Health has many assignments, measures and activities that concern brain health. Because of the wide range of issues that relate to brain health, it has been necessary to establish an overview of initiatives and activities that can contribute, either directly or indirectly, to achieving goals for the different areas of the strategy.

Additionally, a partnership was established to bring together academic communities and organizations for patients and consumers around a common understanding of and approach to brain health. Establishing this partnership was necessary as many organizations are involved in brain health in Norway although many are not coordinated.

The mandate of the partnership is to serve as an arena for dialogue and cooperation, to contribute to coordinated implementation of goals and initiatives, to discuss challenges and solutions for the strategy and to contribute to implementing agreed measures.

The National brain health strategy has four main objectives.

1. Good brain health all of your life – prevention and quality of life.
2. More patient-oriented health and care services and better care of next of kin.
3. Good course – from symptom to diagnosis, treatment, habilitation and rehabilitation.
4. Good knowledge and quality through research and innovation.

The Norwegian government believes that every country that invests in brain health should ensure there is cooperation between the authorities, professional communities and consumer organizations. It is necessary to spend time gaining a common understanding of what brain health is and what the needs are. Together, efforts must be made to create common goals and measures. There is no doubt that this work must have a long-term perspective, and brain health is an area that must have continuous attention and be integrated into a holistic perspective of human health.

Source: Norwegian Directorate of Health.

Box 10.

Country spotlight: Uruguayan Brain Health Programme

The Brain Health Programme of the Ministry of Public Health of Uruguay was created in March 2020. It fulfills an advisory role in health policies in the area of neurology. The programme aims to improve the prevention and treatment of neurological disorders and rehabilitation of patients through the coordination of efforts between different providers, academia and civil society organizations. Uruguay's Brain Health Programme considers that improved brain health leads to improved health of the body because of the brain's salutogenic potential, and that brain health contributes to better quality of life and healthy ageing. Brain health requires specific care that is tailored according to each stage of life and the social and cultural context. Optimizing brain health means making the relevant tools for each life stage universally available to the population.

The Brain Health Programme has been involved in a number of initiatives since its inception, namely:

- promoting and disseminating campaigns for the prevention of neurological disorders among the general public;
- including the "pillars of brain health" in school curricula (including the Mediterranean diet, physical activity, quality of sleep, avoiding toxins and controlling vascular risk factors);
- improving the perception of the risk of alcohol and cannabis use in adolescents and young people;
- planning vaccinations for neuroinfections;
- establishing updated guidelines for specific approaches to different neurological conditions, including therapies with proven cost-effective benefits;
- improving neurological care services at the public and private levels;
- ongoing training of health professionals linked to the area of neurology, and improving the knowledge of neurological disorders among family doctors and general practitioners;
- developing scientific research relating to neurology; and
- improving services for neurological rehabilitation through tele-rehabilitation, with special emphasis on inclusion, in coordination with the System of Care and the Ministry of Social Development.

Connections have been established with international public health organizations and neurological research reference centres abroad for the purpose of fulfilling these objectives. Specific action plans have been developed and in the case of stroke, the action plan has been recognized as innovative and equitable by the World Stroke Organization and other bodies.

Source: Uruguay Ministry of Public Health

5.2 Driving brain health research

Substantial progress has been made in improving our understanding of the human brain and its fundamental role in regulating conscious and unconscious body functions. We also have a fuller understanding of the impact of different determinants on brain health, the pathophysiological mechanisms of certain brain diseases, and novel treatment options. Nevertheless, much remains to be discovered. As mentioned in **Section 4.1**, for some brain health determinants, epidemiological associations have been made in relation to other health outcomes and basic science and clinical studies have shown impacts of these determinants on the brain, but there are yet to be large-scale studies or meta-analyses proving exactly how brain changes due to specific determinants lead to a specific health outcomes.

Ongoing brain health research initiatives should cover the essential components of brain health optimization in ways that harmonize investigative approaches across disciplines, facilitate knowledge exchange internationally, reduce redundancies and increase equity and inclusion. Because our knowledge regarding brain health determinants, many CNS disorders and the impacts of therapeutics and other interventions is incomplete, more research is needed at all levels of science. This also requires the systematic synthesis and review of existing evidence to inform the development of new norms and standards. Areas of essential brain health and neuroscience research include the following:

Basic research

- Improve understanding of neurophysiology related to brain development and brain health including understanding brain structure, function and disease development.
- Develop tools and assessments to evaluate, quantify and monitor brain health parameters in regards to domains of functioning and disease development.
- Understand the influence and interplay of the multitude of determinants in brain health.
- Understand causes and mechanisms of brain injury, repair and compensation.

Intervention research

- Investigate novel strategies to promote brain health and enhance mechanisms for brain resilience.
- Support the design of prevention strategies and identification of risk factors across the life course.
- Develop efficient and cost-effective pharmacological and non-pharmacological treatments for neurological disorders.

Implementation research, including health systems evaluation

- Improve the monitoring of interventions, the systematic uptake of research findings and the application of evidence-based strategies in practice.
- Design strategies for implementation that take equity and diversity measures into account.

Epidemiological and cost of disease research

- Acquire representative data on brain development, developmental disabilities and neurological disorders.
- Understand the impact on health systems and the economic cost of neurological disorders.
- Monitor emerging threats to brain health.

Dedicated research funding for brain health must be a priority

The complexity surrounding brain and neuroscience research requires coordination and close collaboration between all stakeholders as well as strong partnerships between the public and private sectors. Dedicated research funding for brain health must be a priority at intergovernmental, national and regional levels and should be both driven and supported by governments. Funding could be supplied by ministries of health and finance, national research councils and funding bodies, intergovernmental agencies, national medical associations or relevant allied health associations, and private/industry donors as well as philanthropic institutions interested in brain health. Research efforts must be rooted in equity, diversity and inclusiveness, thus necessitating greater research capacity across regions and differing income settings. This will require multi-stakeholder engagement and collaboration for consensus-building and priority-setting, a process in which the involvement of people with lived experience of neurological conditions will be critical.

Importantly, financing streams for brain health research should be sustainable in order to support the kinds of longitudinal cohort studies that are needed to understand the lifelong determinants of brain health and the impacts of interventions and treatments. The road from evidence generation to guidelines and policy change can be long. For instance, early cohort studies looking at physical activity were initiated in the 1960s, and nearly 50 years later both meta-analyses of longitudinal studies and randomized controlled trials were published, leading to guidelines highlighting the importance of physical activity for brain health *(199)*, including the *WHO guidelines on Risk reduction of cognitive decline and dementia*.

Priority-setting is crucial in order to identify existing knowledge gaps and to plan harmonized approaches to close them. Priority-setting exercises may also involve technical experts (i.e. with clinical, academic, research and policy backgrounds spanning the fields of medicine, child development, social determinants of health, and environmental health and climate change), representatives from the private sector, civil society representatives from nongovernmental organizations, and groups representing persons with lived experience. To facilitate global priority-setting, WHO is currently developing the Dementia research blueprint which is the result of global collaboration **(see Box 11)**.

Box 11.

WHO's Dementia research blueprint

The development of WHO's Dementia research blueprint builds on the prior success of previous WHO research and development prioritization exercises for infectious diseases *(200, 201)*. As the first such blueprint for NCDs, the Dementia research blueprint aims to accelerate global dementia research and innovation and make the research more productive and efficient. It will also promote research capacity-building in low-resource settings and ensure inclusiveness at all stages from generation to implementation.

More specifically, the Dementia blueprint will support the identification of gaps and the definition of actions and milestones to achieve strategic research goals. It will also foster the establishment of collaboration and data-sharing initiatives, promotion of the availability of open access data, equitable access to research funding, and the institution of co-research environments. Finally, the blueprint will also promote the involvement of people with lived experience of dementia and their carers throughout all stages of research, from conceptualization to implementation. It is hoped that the blueprint will catalyze processes for increased investment in dementia research and innovation, provide direction for harmonized dementia research and innovation, and ultimately raise the profile of and facilitate policy-making in the area of dementia.

5.3 Operationalizing and measuring brain health

As of now, no simple, direct or global measure of brain health exists

Closely related to brain health research and innovation is the issue of operationalizing and measuring brain health. As of now, no simple, direct or global measure of brain health exists *(4)*. Due to the multi-dimensionality of the concept, capturing the full spectrum of brain health across all domains of brain functioning while taking into account the wide range of brain health determinants is a challenging task. While several clinical or neuroimaging measures have been proposed to quantify brain health (most typically cognitive function) these are not yet able to capture the full complexity of the human brain, nor do they yield a single reliable metric that can be used across ages as a proxy for brain health at individual and population levels *(4, 25)*.

In recent years, the fields of neuroscience, neurology and radiology have made inroads into understanding the impacts of various determinants and interventions on brain health in terms of what we can see on brain imaging (structurally or functionally), as well as on aspects of clinical functioning. The recently published brain charts for the human lifespan *(202)* represent one such achievement, offering for the first-time reference charts for the human brain across the life course, including previously undocumented neurodevelopmental milestones. This work demonstrates the importance of international collaboration, data sharing and data harmonization and represents an essential step towards quantifying brain health using neuroimaging.

However, clinical tools used across studies to measure cognitive or other brain functions vary and have in most cases not been validated across geography, cultures, ethnicities and variations between formal versus informal education. Greater funding is required to support efforts to address barriers to the development of brain health metrics and tools that are widely validated across varied settings. The development of accepted and validated metrics and tools will be critical to understanding the impacts of determinants, interventions and returns on investment for brain health. Such tools would have great clinical and public health relevance *(30)*.

The development of brain health risk and resiliency scales may translate our collective understanding of the science of brain health promotion into clinical tools for use in understanding an individual's risk for health outcomes on the basis of their

current health status and exposure to risk and protective factors. These tools may be useful for monitoring and gauging responses to treatment in people who have neurological disorders, and may also be useful for an individual's health and social care plan. Various brain health scales have already been developed – such as the Brain Health Self-Efficacy Scale in China and the Resilience Index and Cognitive Clock in the USA – although these scales have yet to be validated across cultures *(203—205)*. WHO is currently leading efforts to develop internationally validated scales to measure early child development **(see Box 12)**.

Brain health risk and resilience scores may be developed for cities and societies in the interest of public health. Metrics for instance may include measures for air pollution, water quality, levels of violent crime/homicide, access to early childhood education programmes, and access to safe spaces for physical activity – all of which are important markers of well-being in societies *(80, 206, 207)*. Ideally, such metrics would be used to inform advocacy efforts in order to support intersectoral collaboration to promote the brain health of whole societies and monitor progress over time.

The development of widely validated brain health metrics will also allow for identifying effective interventions to improve brain health and, ultimately, to translate implementation science on the scale-up of priority interventions into the formulation of investment "best-buys" for brain health. Tracking the impacts of interventions aimed at optimizing brain health and the returns on these investments will additionally allow for a more robust understanding of the relationships between brain health and outcomes within neurology, other areas of health and society at large. Similarly, tracking returns on investments and developing "best-buys" will inform policy development and resource rationalization.

Box 12.

The Global Scale for Early Development

The Global Scale for Early Development (GSED) package is created by a WHO-led international team to measure child development in children from birth to 3 years of age at the population level globally. The GSED has two measures: a caregiver short form (SF) that can be administered through surveys to generate population-level estimates of child development, and a complementary long form (LF) that includes direct assessment of children and is intended for programme evaluations. As an additional measure, the psychosocial form (PF) was created to index non-normative developmental patterns that provide a window into early manifestations of children's mental health challenges. The GSED has been developed through a global consortium of scientists, and it is currently in the process of being validated in seven countries.

For more information, see: https://www.who.int/teams/mental-health-and-substance-use/data-research/global-scale-for-early-development (accessed 6 June 2022).

Optimizing brain health for all is paramount to ensuring human health and well-being globally

In conclusion, optimizing brain health for all is paramount to ensuring human health and well-being globally. It is central to achieving global commitments outlined in the *Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031*, WHO's Triple Billion targets, the United Nations Sustainable Development Goals, and the 2021 Geneva Charter for Well-being. Efforts to optimize brain health require multi-stakeholder collaboration and must be integrated across all sectors of society in order to address the determinants of brain health, namely physical health, healthy environments, safety and security, learning and social connection, and access to quality services. In return, robust investments in actions that optimize brain health across the life course promise to improve multiple health outcomes and lift development and well-being globally. Multisectoral engagement and collaboration are urgently needed in order to move the brain health agenda forward for all people.

> The importance of brain health cannot be overstated. When you think about it, activities to promote brain health benefit your entire body. They can lead to socializing with others and encourage a person to consider making positive life changes. It sounds and is easy; with multiple long-term benefits."
>
> **Jim Mann, Canada**

References

1. Eyre HA, Ayadi R, Ellsworth W, Aragam G, Smith E, Dawson WD et al. Building brain capital. Neuron. 2021;109:1430—2. doi:10.1016/j.neuron.2021.04.007.
2. Smith E, Ali D, Wilkerson B, Dawson WD, Sobowale K, Reynolds C et al. A Brain Capital Grand Strategy: toward economic reimagination. Mol Psychiatry. 2021;26:3–22. doi:10.1038/s41380-020-00918-w.
3. Neuroscience-inspired policy Initiative. Paris: Organisation for Economic Co-operation and Development; (https://www.oecd.org/naec/brain-capital/, accessed 23 May 2022).
4. Rossor M, Knapp M. Can we model a cognitive footprint of interventions and policies to help to meet the global challenge of dementia? Lancet. 2015;386:1008–10. doi:10.1016/S0140-6736(15)60248-3.
5. Schiariti V, Simeonsson RJ, Hall K. Promoting developmental potential in early childhood: a global framework for health and education. Int J Environ Res Public Health. 2021;18:2007. doi:10.3390/ijerph18042007.
6. Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C et al. Early childhood development coming of age: science through the life course. Lancet. 2017;389:77–90. doi:10.1016/S0140-6736(16)31389-7.
7. Richter LM, Daelmans B, Lombardi J, Heymann J, Boo FL, Behrman JR et al. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. Lancet. 2017;389:103–18. doi:10.1016/S0140-6736(16)31698-1.
8. Early moments matter for every child. New York (NY): United Nations Children's Fund; 2017.
9. WHO air quality database 2022. Geneva: World Health Organization; 2022 (https://www.who.int/publications/m/item/who-air-quality-database-2022, accessed 22 May 2022).
10. Feigin VL, Nichols E, Alam T, Bannick MS, Beghi E, Blake N et al. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurology. 2019;18:459–80. doi: https://doi.org/10.1016/S1474-4422(18)30499-X.
11. Feigin VL, Vos T, Nichols E, Owolabi MO, Carroll WM, Dichgans M et al. The global burden of neurological disorders: translating evidence into policy. Lancet Neurology. 2020;19:255–65. doi:10.1016/S1474-4422(19)30411-9.
12. Gooch CL, Pracht E, Borenstein AR. The burden of neurological disease in the United States: A summary report and call to action. Ann Neurol. 2017;81:479–84. doi:https://doi.org/10.1002/ana.24897.
13. Atlas: country resources for neurological disorders, second edition. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/258947, accessed 23 May 2022).
14. Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. Geneva: World Health Organization; 2022 (https://apps.who.int/gb/ebwha/pdf_files/WHA75/A75_10Add4-en.pdf, accessed 6 June 2022).
15. Sustainable development goals. New York (NY): United Nations; 2015 (https://sdgs.un.org/goals, accessed 23 May 2022).
16. The United Nations Decade of Healthy Ageing. Geneva: United Nations; 2020 (https://www.decadeofhealthyageing.org/, accessed 7 June 2022).
17. The Geneva Charter for Well-being. Geneva: World Health Organization; 2021 (https://www.who.int/publications/m/item/the-geneva-charter-for-well-being, accessed 23 May 2022).
18. Thirteenth General Programme of Work, 2019–2023. Geneva: World Health Organization; 2018 (https://www.who.int/about/what-we-do/thirteenth-general-programme-of-work-2019---2023, accessed 25 June 2022).
19. Discussion paper - Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. Geneva: World Health Organization; 2021 (https://www.who.int/publications/m/item/intersectoral-global-action-plan-on-eepilepsy-and-other-neurological-disorders-2022-2031, accessed 23 May 2022).
20. First draft - Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. Geneva: World Health Organization; 2021 (https://www.who.int/publications/m/item/intersectoral-global-action-plan-on-epilepsy-andother-neurological-disorders2022-2031, accessed 23 May 2022).
21. World Mental Health Report. Geneva: World Health Organization; 2022 (https://www.who.int/publications/i/item/9789240049338, accessed 24 June 2022).
22. Improving early childhood development: WHO guideline. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/331306, accessed 22 May 2022).

23. Cesari M, Araujo de Carvalho I, Amuthavalli Thiyagarajan J, Cooper C, Martin FC, Reginster JY et al. Evidence for the domains supporting the construct of intrinsic capacity. J Gerontol A Biol Sci Med Sci. 2018;73:1653–60. doi:10.1093/gerona/gly011.
24. Harerimana B, Forchuk C, Walsh J, Fogarty J, Borrie M. Brain health: a concept analysis. Issues Ment Health Nurs. 2021;42:145–52. doi:10.1080/01612840.2020.1789781.
25. Chen Y, Demnitz N, Yamamoto S, Yaffe K, Lawlor B, Leroi I. Defining brain health: a concept analysis. Int J Geriatr Psychiatry. 2021;37. doi:https://doi.org/10.1002/gps.5564.
26. Project on the decade on the brain. Washington (DC): United States Library of Congress; 1990 (https://www.loc.gov/loc/brain/, accessed 23 May 2022).
27. International Health Conference. Constitution of the World Health Organization 1946. Bull World Health Organ. 2002;80:983–4. (https://apps.who.int/iris/handle/10665/268688, accessed 23 May 2022).
28. International classification of functioning, disability and health: ICF. Geneva: World Health Organization; 2001 (https://apps.who.int/iris/handle/10665/42407, accessed 23 May 2022).
29. Patel V, Saxena S, Lund C, Thornicroft G, Baingana F, Bolton P et al. The Lancet Commission on global mental health and sustainable development. Lancet. 2018;392:1553–98. doi:10.1016/S0140-6736(18)31612-X.
30. Wang Y, Pan Y, Li H. What is brain health and why is it important? BMJ. 2020;371:m3683. doi:10.1136/bmj.m3683.
31. Cay M, Gonzalez-Heydrich J, Teicher MH, van der Heijden H, Ongur D, Shinn AK et al. Childhood maltreatment and its role in the development of pain and psychopathology. Lancet Child Adolesc Health. 2022;6:195–206. doi:10.1016/S2352-4642(21)00339-4.
32. Posadzki P, Pieper D, Bajpai R, Makaruk H, Könsgen N, Neuhaus AL et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. BMC Public Health. 2020;20:1724. doi:10.1186/s12889-020-09855-3.
33. Braithwaite I, Zhang S, Kirkbride JB, Osborn DPJ, Hayes JF. Air pollution (particulate matter) exposure and associations with depression, anxiety, bipolar, psychosis and suicide risk: a systematic review and meta-analysis. Environ Health Perspect. 2019;127:126002-. doi:10.1289/EHP4595.
34. Hakamata Y, Suzuki Y, Kobashikawa H, Hori H. Neurobiology of early life adversity: a systematic review of meta-analyses towards an integrative account of its neurobiological trajectories to mental disorders. Front Neuroendocrinol. 2022;65:100994. doi:10.1016/j.yfrne.2022.100994.
35. Shonkoff JP, Slopen N, Williams DR. Early childhood adversity, toxic stress, and the impacts of racism on the foundations of health. Annu Rev Public Health. 2021;42:115–34. doi:10.1146/annurev-publhealth-090419-101940.
36. Health equity. Geneva: World Health Organization; (https://www.who.int/health-topics/health-equity#tab=tab_1, accessed 23 May 2022).
37. Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/272603, accessed 22 May 2022).
38. Guidelines on mental health promotive and preventive interventions for adolescents: helping adolescents thrive. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336864, accessed 22 May 2022).
39. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/312180, accessed 22 May 2022).
40. Brain architecture. Cambridge (MA): Harvard University Center on the Developing Child; 2022 (https://developingchild.harvard.edu/science/key-concepts/brain-architecture, accessed 22 May 2022).
41. Grigorenko EL. Brain development: the effect of interventions on children and adolescents. In: Disease control priorities, Volume 8, Child and adolescent health and development. Washington (DC): The World Bank; 2017:13.
42. Decade of healthy ageing: baseline report. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/338677, accessed 22 May 2022).
43. Pulli EP, Kumpulainen V, Kasurinen JH, Korja R, Merisaari H, Karlsson L et al. Prenatal exposures and infant brain: review of magnetic resonance imaging studies and a population description analysis. Hum Brain Mapp. 2019;40:1987–2000. doi:10.1002/hbm.24480.
44. Vohr BR, Poggi Davis E, Wanke CA, Krebs NF. Neurodevelopment: the impact of nutrition and inflammation during preconception and pregnancy in low-resource settings. Pediatrics. 2017;139:S38–49. doi:10.1542/peds.2016-2828F.
45. Georgieff MK. Iron deficiency in pregnancy. Am J Obstet Gynecol. 2020;223:516—24. doi:10.1016/j.ajog.2020.03.006.

46. Insel BJ, Schaefer CA, McKeague IW, Susser ES, Brown AS. Maternal iron deficiency and the risk of schizophrenia in offspring. Arch Gen Psychiatry. 2008;65:1136–44. doi:10.1001/archpsyc.65.10.1136.

47. Sørensen HJ, Nielsen PR, Pedersen CB, Mortensen PB. Association between prepartum maternal iron deficiency and offspring risk of schizophrenia: population-based cohort study with linkage of Danish national registers. Schizophrenia bulletin. 2011;37:982—7. doi:10.1093/schbul/sbp167.

48. Carpita B, Muti D, Dell'Osso L. Oxidative stress, maternal diabetes, and autism spectrum disorders. Oxid Med Cell Longev. 2018;2018:3717215. doi:10.1155/2018/3717215.

49. Megli CJ, Coyne CB. Infections at the maternal-fetal interface: an overview of pathogenesis and defence. Nature reviews Microbiology. 2022;20:67—82. doi:10.1038/s41579-021-00610-y.

50. WHO toolkit for the care and support of people affected by complications associated with Zika virus. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255718, accessed 15 June 2022).

51. Chan JC, Nugent BM, Bale TL. Parental advisory: maternal and paternal stress can impact offspring neurodevelopment. Biological psychiatry. 2018;83:886—94. doi:10.1016/j.biopsych.2017.10.005.

52. Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect. 2011;119:1189—95. doi:10.1289/ehp.1003185.

53. Addissie YA, Kruszka P, Troia A, Wong ZC, Everson JL, Kozel BA et al. Prenatal exposure to pesticides and risk for holoprosencephaly: a case-control study. Environmental Health. 2020;19:65. doi:10.1186/s12940-020-00611-z.

54. Ambient air pollution: training for health care providers. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/331797, accessed 24 June 2022).

55. Punamäki RL, Flykt M, Belt R, Lindblom J. Maternal substance use disorder predicting children's emotion regulation in middle childhood: the role of early mother—infant interaction. Heliyon. 2021;7:e06728-e. doi:10.1016/j.heliyon.2021.e06728.

56. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250796, accessed 22 May 2022).

57. WHO recommendations: intrapartum care for a positive childbirth experience. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/260178, accessed 22 May 2022).

58. Toh YL, Ng T, Tan M, Tan A, Chan A. Impact of brain-derived neurotrophic factor genetic polymorphism on cognition: a systematic review. Brain Behav. 2018;8:e01009. doi: https://doi.org/10.1002/brb3.1009.

59. Huang Y, Yu S, Wu Z, Tang B. Genetics of hereditary neurological disorders in children. Transl Pediatr. 2014;3:108—19. doi:10.3978/j.issn.2224-4336.2014.03.04.

60. Stefanski A, Calle-López Y, Leu C, Pérez-Palma E, Pestana-Knight E, Lal D. Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: a systematic review and meta-analysis. Epilepsia. 2021;62:143—51. doi:10.1111/epi.16755.

61. Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Mol Autism. 2017;8:13. doi:10.1186/s13229-017-0121-4.

62. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: a systematic review of the evidence. Neurotoxicology. 2017;61:143—87. doi:10.1016/j.neuro.2017.03.006.

63. Gwinn-Hardy K. Genetics of parkinsonism. Mov Disord. 2002;17:645—56. doi:10.1002/mds.10173.

64. Fernando SD, Rodrigo C, Rajapakse S. The 'hidden' burden of malaria: cognitive impairment following infection. Malar J. 2010;9:366. doi:10.1186/1475-2875-9-366.

65. Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza-like illness as a trigger for ischemic stroke. Ann Clin Transl Neurol. 2018;5:456—63. doi:10.1002/acn3.545.

66. Sipilä PN, Heikkilä N, Lindbohm JV, Hakulinen C, Vahtera J, Elovainio M et al. Hospital-treated infectious diseases and the risk of dementia: a large, multicohort, observational study with a replication cohort. Lancet Infect Dis. 2021;21:1557—67. doi:10.1016/S1473-3099(21)00144-4.

67. Zika strategic response plan, revised for July 2016 - December 2017. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246091, accessed 22 May 2022).

68. Neurology and COVID-19: scientific brief, 29 September 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345574, accessed 22 May 2022).

69. Misra S, Kolappa K, Prasad M, Radhakrishnan D, Thakur KT, Solomon T et al. Frequency of neurologic manifestations in COVID-19. A systematic review and meta-analysis. 2021;97:e2269—81. doi:10.1212/wnl.0000000000012930.

70. Crivelli L, Palmer K, Calandri I, Guekht A, Beghi E, Carroll W et al. Changes in cognitive functioning after COVID-19: a systematic review and meta-analysis. Alzheimers Dement. 2022;18:1047—66. doi:10.1002/alz.12644.

71. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345824, accessed 22 May 2022).

72. Triki CC, Leonardi M, Mallouli SZ, Cacciatore M, Karlshoej KC, Magnani FG et al. Global survey on disruption and mitigation of neurological services during COVID-19: the perspective of global international neurological patients and scientific associations. J Neurol. 2022;269:26—38. doi:10.1007/s00415-021-10641-3.

73. García-Azorín D, Seeher KM, Newton CR, Okubadejo NU, Pilotto A, Saylor D et al. Disruptions of neurological services, its causes and mitigation strategies during COVID-19: a global review. Journal of Neurology. 2021;268:3947—60. doi:10.1007/s00415-021-10588-5.

74. Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report, 27 August 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/334048, accessed 22 May 2022).

75. Second round of the national pulse survey on continuity of essential health services during the COVID-19 pandemic: Januaryr–March 2021: interim report, 22 April 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/340937, accessed 22 May 2022).

76. Third round of the global pulse survey on continuity of essential health services during the COVID-19 pandemic: November–December 2021: interim report, 7 February 2022. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/351527, accessed 22 May 2022).

77. United Nations Policy Brief: COVID-19 and the need for action on mental health. Geneva: United Nations; 2020 (https://unsdg.un.org/sites/default/files/2020-05/UN-Policy-Brief-COVID-19-and-mental-health.pdf, accessed 22 May 2022).

78. Shuffrey LC, Firestein MR, Kyle MH, Fields A, Alcántara C, Amso D et al. Association of birth during the COVID-19 pandemic with neurodevelopmental status at 6 months in infants with and without in utero exposure to maternal SARS-CoV-2 infection. JAMA Pediatrics. 2022:e215563-e. doi:10.1001/jamapediatrics.2021.5563.

79. O'Sullivan R, Burns A, Leavey G, Leroi I, Burholt V, Lubben J et al. Impact of the COVID-19 pandemic on loneliness and social isolation: a multi-country study. Int J Environ Res Public Health. 2021;18. doi:10.3390/ijerph18199982.

80. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396:413—46. doi:10.1016/S0140-6736(20)30367-6.

81. Ben Hassen C, Fayosse A, Landré B, Raggi M, Bloomberg M, Sabia S et al. Association between age at onset of multimorbidity and incidence of dementia: 30 year follow-up in Whitehall II prospective cohort study. BMJ. 2022;376:e068005. doi:10.1136/bmj-2021-068005.

82. Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S et al. Global burden of stroke and risk factors in 188 countries, during 1990—2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet Neurology. 2016;15:913—24. doi:10.1016/S1474-4422(16)30073-4.

83. Varadaraj V, Munoz B, Deal JA, An Y, Albert MS, Resnick SM et al. Association of vision impairment with cognitive decline across multiple domains in older adults. JAMA Network Open. 2021;4:e2117416-e. doi: 10.1001/jamanetworkopen.2021.17416.

84. Shang X, Zhu Z, Huang Y, Zhang X, Wang W, Shi D et al. Associations of ophthalmic and systemic conditions with incident dementia in the UK Biobank. Br J Ophthalmol. 2021. doi:10.1136/bjophthalmol-2021-319508.

85. Standards for healthy eating, physical activity, sedentary behaviour and sleep in early childhood education and care settings: a toolkit. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345926, accessed 22 May 2022).

86. Sabia S, Fayosse A, Dumurgier J, van Hees VT, Paquet C, Sommerlad A et al. Association of sleep duration in middle and old age with incidence of dementia. Nat Commun. 2021;12:2289. doi:10.1038/s41467-021-22354-2.

87. Li W, Wang D, Cao S, Yin X, Gong Y, Gan Y et al. Sleep duration and risk of stroke events and stroke mortality: a systematic review and meta-analysis of prospective cohort studies. Int J Cardiol. 2016;223:870—6. doi:10.1016/j.ijcard.2016.08.302.

88. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biol Psychiatry. 2016;80:40—52. doi:10.1016/j.biopsych.2015.05.014.

89. Bidzan-Bluma I, Lipowska M. Physical activity and cognitive functioning of children: a systematic review. Int J Environ Res Public Health. 2018;15. doi:10.3390/ijerph15040800.

90. de Sousa Fernandes MS, Ordônio TF, Santos GCJ, Santos LER, Calazans CT, Gomes DA et al. Effects of physical exercise on neuroplasticity and brain function: a systematic review in human and animal Studies. Neural Plast. 2020;2020:8856621. doi:10.1155/2020/8856621.

91. Domingos C, Pêgo JM, Santos NC. Effects of physical activity on brain function and structure in older adults: a systematic review. Behav Brain Res. 2021;402:113061. doi:10.1016/j.bbr.2020.113061.

92. Dauwan M, Begemann MJH, Slot MIE, Lee EHM, Scheltens P, Sommer IEC. Physical exercise improves quality of life, depressive symptoms, and cognition across chronic brain disorders: a transdiagnostic systematic review and meta-analysis of randomized controlled trials. J Neurol. 2021;268:1222—46. doi:10.1007/s00415-019-09493-9.

93. Mang CS, Campbell KL, Ross CJ, Boyd LA. Promoting neuroplasticity for motor rehabilitation after stroke: considering the effects of aerobic exercise and genetic variation on brain-derived neurotrophic factor. Phys Ther. 2013;93:1707—16. doi:10.2522/ptj.20130053.

94. Sabia S, Fayosse A, Dumurgier J, Dugravot A, Akbaraly T, Britton A et al. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. BMJ. 2018;362:k2927. doi:10.1136/bmj.k2927.

95. Kivimäki M, Singh-Manoux A, Batty GD, Sabia S, Sommerlad A, Floud S et al. Association of alcohol-induced loss of consciousness and overall alcohol consumption with risk for dementia. JAMA Network Open. 2020;3:e2016084-e. doi:10.1001/jamanetworkopen.2020.16084.

96. Zanier ER, Bertani I, Sammali E, Pischiutta F, Chiaravalloti MA, Vegliante G et al. Induction of a transmissible tau pathology by traumatic brain injury. Brain. 2018;141:2685—99. doi:10.1093/brain/awy193.

97. Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. Lancet. 2009;373:1105—10. doi:10.1016/s0140-6736(09)60214-2.

98. Turner GM, McMullan C, Aiyegbusi OL, Bem D, Marshall T, Calvert M et al. Stroke risk following traumatic brain injury: systematic review and meta-analysis. Int J Stroke. 2021;16:370—84. doi:10.1177/17474930211004277.

99. Graham A, Livingston G, Purnell L, Huntley J. Mild traumatic brain injuries and future risk of developing Alzheimer's disease: systematic review and meta-analysis. J Alzheimers Dis. 2022. doi:10.3233/jad-220069.

100. Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurology. 2014;13:330—8. doi:10.1016/S1474-4422(13)70278-3.

101. Parkinson disease: a public health approach: technical brief. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/355973, accessed 15 June 2022).

102. Childhood lead poisoning. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/136571, accessed 22 May 2022).

103. Children's exposure to mercury compounds. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/44445, accessed 22 May 2022).

104. WHO-UNICEF Global report on children and young people developmental disabilities. Geneva: World Health Organization; (in press).

105. Shaji E, Santosh M, Sarath KV, Prakash P, Deepchand V, Divya BV. Arsenic contamination of groundwater: a global synopsis with focus on the Indian Peninsula. Geoscience Frontiers. 2021;12:101079. doi:https://doi.org/10.1016/j.gsf.2020.08.015.

106. Muñoz-Quezada MT, Lucero BA, Barr DB, Steenland K, Levy K, Ryan PB et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: a systematic review. Neurotoxicology. 2013;39:158—68. doi:10.1016/j.neuro.2013.09.003.

107. Ross SM, McManus IC, Harrison V, Mason O. Neurobehavioral problems following low-level exposure to organophosphate pesticides: a systematic and meta-analytic review. Crit Rev Toxicol. 2013;43:21—44. doi:10.3109/10408444.2012.738645.

108. Risk Evaluation for Trichloroethylene. Washington (DC): United States Environmental Protection Agency; (https://www.epa.gov/sites/default/files/2020-11/documents/1._risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf, accessed 24 June 2022).

109. Costa LG, Cole TB, Dao K, Chang Y-C, Garrick JM. Developmental impact of air pollution on brain function. Neurochem Int. 2019;131:104580. doi:https://doi.org/10.1016/j.neuint.2019.104580.

110. Guxens M, Garcia-Esteban R, Giorgis-Allemand L, Forns J, Badaloni C, Ballester F et al. Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts. Epidemiology. 2014;25. (https://journals.lww.com/epidem/Fulltext/2014/09000/Air_Pollution_During_Pregnancy_and_Childhood.4.aspx , accessed 25 June 2022).

111. Costa LG, Chang Y-C, Cole TB. Developmental neurotoxicity of traffic-related air pollution: focus on autism. Curr Environ Health Rep. 2017;4:156—65. doi:10.1007/s40572-017-0135-2.

112. Saez M, Barceló MA, Farrerons M, López-Casasnovas G. The association between exposure to environmental factors and the occurrence of attention-deficit/hyperactivity disorder (ADHD). A population-based retrospective cohort study. Environ Res. 2018;166:205—14. doi:https://doi.org/10.1016/j.envres.2018.05.009.

113. Fisher S, Bellinger DC, Cropper ML, Kumar P, Binagwaho A, Koudenoukpo JB et al. Air pollution and development in Africa: impacts on health, the economy, and human capital. Lancet Planet Health. 2021;5:e681—8. doi:https://doi.org/10.1016/S2542-5196(21)00201-1.

114. Lubczyńska MJ, Muetzel RL, El Marroun H, Hoek G, Kooter IM, Thomson EM et al. Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. Environ Res. 2021;198:110446. doi:10.1016/j.envres.2020.110446.

115. Beckwith T, Cecil K, Altaye M, Severs R, Wolfe C, Percy Z et al. Reduced gray matter volume and cortical thickness associated with traffic-related air pollution in a longitudinally studied pediatric cohort. PLoS One. 2020;15:e0228092.

116. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990—2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2021;20:795—820. doi:10.1016/s1474-4422(21)00252-0.

117. Peters R, Ee N, Peters J, Booth A, Mudway I, Anstey KJ. Air pollution and dementia: a systematic review. J Alzheimers Dis. 2019;70:S145—63. doi:10.3233/jad-180631.

118. Younan D, Wang X, Millstein J, Petkus AJ, Beavers DP, Espeland MA et al. Air quality improvement and cognitive decline in community-dwelling older women in the United States: a longitudinal cohort study. PLoS Med. 2022;19:e1003893. doi:10.1371/journal.pmed.1003893.

119. White A, Kanninen K, Malm T, Schins R. Editorial: Air pollution and brain health. Neurochem Int. 2020;141:104900. doi: 10.1016/j.neuint.2020.104900.

120. Lee KK, Miller MR, Shah ASV. Air pollution and stroke. Journal of Stroke. 2018;20:2—11. doi:10.5853/jos.2017.02894.

121. Volcanoes. Washington (DC): United States Environmental Protection Agency (https://www.epa.gov/natural-disasters/volcanoes#:~:text=Volcanic%20gases%20that%20pose%20the,a%20volcano%20that%20erupts%20violently, accessed 22 May 2022).

122. Yamazaki JN, Schull WJ. Perinatal loss and neurological abnormalities among children of the atomic bomb. Nagasaki and Hiroshima revisited, 1949 to 1989. JAMA. 1990;264:605—9.

123. Eto K. Minamata disease. Neuropathology. 2000;20 Suppl:S14-9. doi:10.1046/j.1440-1789.2000.00295.x.

124. Yu P, Xu R, Abramson MJ, Li S, Guo Y. Bushfires in Australia: a serious health emergency under climate change. Lancet Planet Health. 2020;4:e7—8. doi:10.1016/S2542-5196(19)30267-0.

125. Saxbe D, Khoddam H, Piero LD, Stoycos SA, Gimbel SI, Margolin G et al. Community violence exposure in early adolescence: longitudinal associations with hippocampal and amygdala volume and resting state connectivity. Dev Sci. 2018;21:e12686. doi:https://doi.org/10.1111/desc.12686.

126. Reda MH, Marusak HA, Ely TD, van Rooij SJH, Stenson AF, Stevens JS et al. Community violence exposure is associated with hippocampus-insula resting state functional connectivity in urban youth. Neuroscience. 2021;468:149—57. doi:10.1016/j.neuroscience.2021.06.010.

127. Samuel LJ, Szanton SL, Wolff JL, Ornstein KA, Parker LJ, Gitlin LN. Socioeconomic disparities in six-year incident dementia in a nationally representative cohort of U.S. older adults: an examination of financial resources. BMC Geriatrics. 2020;20:156. doi:10.1186/s12877-020-01553-4.

128. Hackman DA, Cserbik D, Chen JC, Berhane K, Minaravesh B, McConnell R et al. Association of local variation in neighborhood disadvantage in metropolitan areas with youth neurocognition and brain structure. JAMA Pediatr. 2021;175:e210426. doi:10.1001/jamapediatrics.2021.0426.

129. Hunt JFV, Buckingham W, Kim AJ, Oh J, Vogt NM, Jonaitis EM et al. Association of neighborhood-level disadvantage with cerebral and hippocampal volume. JAMA Neurol. 2020;77:451—60. doi:10.1001/jamaneurol.2019.4501.

130. Ziegler G, Moutoussis M, Hauser TU, Fearon P, Bullmore ET, Goodyer IM et al. Childhood socio-economic disadvantage predicts reduced myelin growth across adolescence and young adulthood. Hum Brain Mapp. 2020;41:3392—402. doi:https://doi.org/10.1002/hbm.25024.

131. Powell WR, Buckingham WR, Larson JL, Vilen L, Yu M, Salamat MS et al. Association of neighborhood-level disadvantage with Alzheimer disease neuropathology. JAMA Network Open. 2020;3:e207559-e. doi:10.1001/jamanetworkopen.2020.7559.

132. Whittle S, Vijayakumar N, Simmons JG, Dennison M, Schwartz O, Pantelis C et al. Role of positive parenting in the association between neighborhood social disadvantage and brain development across adolescence. JAMA Psychiatry. 2017;74:824—32. doi:10.1001/jamapsychiatry.2017.1558.

133. Gelaye B, Foster S, Bhasin M, Tawakol A, Fricchione G. SARS-CoV-2 morbidity and mortality in racial/ethnic minority populations: a window into the stress related inflammatory basis of health disparities? Brain Behav Immun Health. 2020;9:100158. doi:10.1016/j.bbih.2020.100158.

134. Rezaei S, Sakadi F, Hiew F-L, Rodriguez-Leyva I, Kruja J, Wasay M et al. Practical needs and considerations for refugees and other forcibly displaced persons with neurological disorders: recommendations using a modified Delphi approach. 2021; 5: 178 (http://europepmc.org/abstract/MED/35299829, accessed 25 June 2022).

135. Kivimäki M, Walker KA, Pentti J, Nyberg ST, Mars N, Vahtera J et al. Cognitive stimulation in the workplace, plasma proteins, and risk of dementia: three analyses of population cohort studies. BMJ. 2021;374:n1804. doi:10.1136/bmj.n1804.

136. Serve and Return. Cambridge (MA): Harvard University Center on the Developing Child; 2022 (https://developingchild.harvard.edu/science/key-concepts/serve-and-return/, accessed 23 May 2022).

137. Toxic stress. Cambridge (MA): Harvard University Center on the Developing Child; 2022 (https://developingchild.harvard.edu/science/key-concepts/toxic-stress/, accessed 23 May 2022).

138. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA. 2009;301:2252—9. doi:10.1001/jama.2009.754.

139. Boyce WT, Levitt P, Martinez FD, McEwen BS, Shonkoff JP. Genes, environments, and time: the biology of adversity and resilience. Pediatrics. 2021;147. doi:10.1542/peds.2020-1651.

140. Godoy LC, Frankfurter C, Cooper M, Lay C, Maunder R, Farkouh ME. Association of adverse childhood experiences with cardiovascular disease later in life: a review. JAMA Cardiol. 2021;6:228-35. doi:10.1001/jamacardio.2020.6050.

141. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev. 2007;87:873—904. doi:10.1152/physrev.00041.2006.

142. Fricchione GL. Evolving a new neuropsychiatry. Dialogues Clin Neurosci. 2018;20:141—5. doi: 10.31887/DCNS.2018.20.2/gfricchione.

143. Moog NK, Entringer S, Rasmussen JM, Styner M, Gilmore JH, Kathmann N et al. Intergenerational effect of maternal exposure to childhood maltreatment on newborn brain anatomy. Biol Psychiatry. 2018;83:120—7. doi:10.1016/j.biopsych.2017.07.009.

144. Hendrix CL, Dilks DD, McKenna BG, Dunlop AL, Corwin EJ, Brennan PA. Maternal childhood adversity associates with frontoamygdala connectivity in neonates. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;6:470—8. doi:10.1016/j.bpsc.2020.11.003.

145. Kwak S, Joo WT, Youm Y, Chey J. Social brain volume is associated with in-degree social network size among older adults. Proc Biol Sci. 2018;285. doi:10.1098/rspb.2017.2708.

146. Blumen HM, Verghese J. Gray matter volume covariance networks associated with social networks in older adults. Social neuroscience. 2019;14:559—70. doi:10.1080/17470919.2018.1535999.

147. Cotton K, Verghese J, Blumen HM. Gray matter volume covariance networks, social support, and cognition in older adults. J Gerontol B Psychol Sci Soc Sci. 2020;75:1219—29. doi:10.1093/geronb/gbz023.

148. Salinas J, O'Donnell A, Kojis DJ, Pase MP, DeCarli C, Rentz DM et al. Association of social support with brain volume and cognition. JAMA Network Open. 2021;4:e2121122. doi:10.1001/jamanetworkopen.2021.21122.

149. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Loneliness and risk of dementia. J Gerontol B. 2018;75:1414—22. doi:10.1093/geronb/gby112.

150. Convention on the Rights of Persons with Disabilities. New York (NY): United Nations; 2006 (https://www.un.org/disabilities/documents/convention/convoptprot-e.pdf, accessed 23 May 2022).

151. Global status report on the public health response to dementia. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/344701, accessed 23 May 2022).

152. Field test version: mhGAP community toolkit: Mental Health Gap Action Programme (mhGAP). Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/328742, accessed 23 May 2022).

153. Towards a dementia-inclusive society: WHO toolkit for dementia-friendly initiatives (DFIs). Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/343780, accessed 21 June 2022).

154. Young WB, Park JE, Tian IX, Kempner J. The stigma of migraine. PLoS One. 2013;8:e54074. doi:10.1371/journal.pone.0054074.

155. Shi Y, Liu S, Wang J, Li C, Zhang J. Stigma experienced by patients with epilepsy: a systematic review and meta-synthesis of qualitative studies. Epilepsy Behav. 2021;118:107926. doi:10.1016/j.yebeh.2021.107926.

156. Herrmann LK, Welter E, Leverenz J, Lerner AJ, Udelson N, Kanetsky C et al. A systematic review of dementia-related stigma research: can we move the stigma dial? Am J Geriatr Psychiatry. 2018;26:316—31. doi:10.1016/j.jagp.2017.09.006.

157. Global competency and outcomes framework for universal health coverage. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352711, accessed 23 May 2022).

158. Langhorne P, Ramachandra S. Organised inpatient (stroke unit) care for stroke: network meta-analysis. Cochrane Database Syst Rev. 2020;4:Cd000197. doi:10.1002/14651858.CD000197.pub4.

159. Maharaj MM, Hogan JA, Phan K, Mobbs RJ. The role of specialist units to provide focused care and complication avoidance following traumatic spinal cord injury: a systematic review. Eur Spine J. 2016;25:1813—20. doi:10.1007/s00586-016-4545-x.

160. Owolabi MO, Thrift AG, Martins S, Johnson W, Pandian J, Abd-Allah F et al. The state of stroke services across the globe: report of World Stroke Organization—World Health Organization surveys. Int J Stroke. 2021;16:889-901. doi:10.1177/17474930211019568.

161. Rapid assistive technology assessment tool (rATA). Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/341939, accessed 23 May 2022).

162. Hricak H, Abdel-Wahab M, Atun R, Lette MM, Paez D, Brink JA et al. Medical imaging and nuclear medicine: a Lancet Oncology Commission. Lancet Oncology. 2021;22:e136—72. doi:10.1016/S1470-2045(20)30751-8.

163. IMAGINE—IAEA Medical Imaging and Nuclear Medicine Global Resources Database. Vienna: International Atomic Energy Agency; 2019 (https://humanhealth.iaea.org/HHW/DBStatistics/IMAGINE.html, accessed 22 May 2022).

164. Fact sheet: Assistive technology. Geneva: World Health Organization; 2018 (https://www.who.int/news-room/fact-sheets/detail/assistive-technology, accessed 23 May 2022).

165. Caregiver skills training for families of children with developmental delays or disabilities: introduction. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353579, accessed 23 May 2022).

166. Caregiver skills training for families of children with developmental delays or disabilities: adaptation and implementation guide. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353581, accessed 23 May 2022).

167. Caregiver skills training for families of children with developmental delays or disabilities: home visit guide for facilitators. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353583, accessed 23 May 2022).

168. Caregiver skills training for families of children with developmental delays or disabilities: participants' guide, group sessions 1–9. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353582, accessed 23 May 2022).

169. Caregiver skills training for families of children with developmental delays or disabilities: facilitators' guide, group sessions 1–9. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353580, accessed 23 May 2022).

170. iSupport for dementia: training and support manual for carers of people with dementia. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/324794, accessed 23 May 2022).

171. Shonkoff JP, Garner AS. The lifelong effects of early childhood adversity and toxic stress. Pediatrics. 2012;129:e232—46. doi:10.1542/peds.2011-2663.

172. Kessler RC, McLaughlin KA, Green JG, Gruber MJ, Sampson NA, Zaslavsky AM et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. Br J Psychiatry. 2010;197:378—85. doi:10.1192/bjp.bp.110.080499.

173. Grummitt L, Kelly E, Barrett E, Keyes K, Newton N. Targets for intervention to prevent substance use in young people exposed to childhood adversity: a systematic review. PLoS One. 2021;16:e0252815. doi:10.1371/journal.pone.0252815.

174. Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, Leclair E et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans — possible implications for reward and depression. Psychoneuroendocrinology. 2012;37:844—51. doi:10.1016/j.psyneuen.2011.09.017.

175. Wang Y, Tang C, Fan X, Shirai K, Dong JY. Mind—body therapies for older adults with dementia: a systematic review and meta-analysis. Eur Geriatr Med. 2022. doi:10.1007/s41999-022-00639-z.

176. Song R, Grabowska W, Park M, Osypiuk K, Vergara-Diaz GP, Bonato P et al. The impact of Tai Chi and Qigong mind—body exercises on motor and non-motor function and quality of life in Parkinson's disease: A systematic review and meta-analysis. Parkinsonism Relat Disord. 2017;41:3-13. doi:10.1016/j.parkreldis.2017.05.019.

177. Hölzel BK, Lazar SW, Gard T, Schuman-Olivier Z, Vago DR, Ott U. How does mindfulness meditation work? Proposing mechanisms of action from a conceptual and neural perspective. Perspect Psychol Sci. 2011;6:537—59. doi:10.1177/1745691611419671.

178. Gard T, Hölzel BK, Lazar SW. The potential effects of meditation on age-related cognitive decline: a systematic review. Ann N Y Acad Sci. 2014;1307:89—103. doi:https://doi.org/10.1111/nyas.12348.

179. Pascoe MC, Thompson DR, Ski CF. Yoga, mindfulness-based stress reduction and stress-related physiological measures: A meta-analysis. Psychoneuroendocrinology. 2017;86:152-68. doi:https://doi.org/10.1016/j.psyneuen.2017.08.008.

180. Buric I, Farias M, Jong J, Mee C, Brazil IA. What is the molecular signature of mind-body interventions? A systematic review of gene expression changes induced by meditation and related practices. Front Immunol. 2017;8:670. doi:10.3389/fimmu.2017.00670.

181. McEwen BS, Akil H. Revisiting the stress concept: implications for affective disorders. J Neurosci. 2020;40:12—21. doi:10.1523/jneurosci.0733-19.2019.

182. Fricchione GL. The science of mind body medicine and the public health challenges of today. S Afri J Psychol. 2014;44:404—15. doi:10.1177/0081246314541025.

183. McEwen BS. The brain on stress: toward an integrative approach to brain, body, and behavior. Perspect Psychol Sci. 2013;8:673—5. doi:10.1177/1745691613506907.

184. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y et al. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet. 2017;389:834—45. doi: 10.1016/s0140-6736(16)31714-7.

185. Tawakol A, Osborne MT, Wang Y, Hammed B, Tung B, Patrich T et al. Stress-associated neurobiological pathway linking socioeconomic disparities to cardiovascular disease. J Am Coll Cardiol. 2019;73:3243—55. doi: 10.1016/j.jacc.2019.04.042.

186. Ishai A, Osborne MT, Tung B, Wang Y, Hammad B, Patrich T et al. Amygdalar metabolic activity independently associates with progression of visceral adiposity. J Clin Endocrinol Metab. 2019;104:1029—38. doi:10.1210/jc.2018-01456.

187. Osborne MT, Ishai A, Hammad B, Tung B, Wang Y, Baruch A et al. Amygdalar activity predicts future incident diabetes independently of adiposity. Psychoneuroendocrinology. 2019;100:32—40. doi:10.1016/j.psyneuen.2018.09.024.

188. Dar T, Osborne MT, Abohashem S, Abbasi T, Choi KW, Ghoneem A et al. Greater neurobiological resilience to chronic socioeconomic or environmental stressors associates with lower risk for cardiovascular disease events. Circ Cardiovasc Imaging. 2020;13:e010337. doi:10.1161/circimaging.119.010337.

189. Integrating social determinants of health into health workforce education and training. Geneva: World Health Organization; (in press).

190. Yang YC, Schorpp K, Harris KM. Social support, social strain and inflammation: evidence from a national longitudinal study of U.S. adults. Soc Sci Med. 2014;107:124—35. doi:10.1016/j.socscimed.2014.02.013.

191. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci. 2015;10:227—37. doi:10.1177/1745691614568352.

192. Heckman JJ. The case for investing in disadvantaged young children. In: Big ideas for children: investing in our nation's future: Washington (DC): First Focus; 2008: (https://heckmanequation.org/www/assets/2017/01/Heckman20Investing20in20Young20Children.pdf, accessed 1 June 2022).

193. Karoly LA, Kilburn MR, Cannon JS. Early childhood interventions: proven results, future promise. Santa Monica (CA): Rand Corporation; 2006. (https://www.rand.org/pubs/monographs/MG341.html, accessed 25 June 2022).

194. Heckman JJ. The Heckman Curve. Chicago (IL): The Heckman Equation Project; 2022 (https://heckmanequation.org/resource/the-heckman-curve/, accessed 23 May 2022).

195. Britto PR, Lye SJ, Proulx K, Yousafzai AK, Matthews SG, Vaivada T et al. Nurturing care: promoting early childhood development. Lancet. 2017;389:91—102. doi:10.1016/S0140-6736(16)31390-3.

196. Heckman JJ, Moon SH, Pinto R, Savelyev PA, Yavitz A. The rate of return to the HighScope Perry Preschool Program. J Public Econ. 2010;94:114—28. doi:https://doi.org/10.1016/j.jpubeco.2009.11.001.

197. Karoly LA. Toward standardization of benefit-cost analyses of early childhood interventions. Santa Monica (CA): RAND Corporation; 2011 (https://www.rand.org/pubs/working_papers/WR823.html, accessed 25 June 2022).

198. Prioritizing health: a prescription for prosperity. McKinsey Global Institute. 2020 (https://www.mckinsey.com/industries/healthcare-systems-and-services/our-insights/prioritizing-health-a-prescription-for-prosperity, accessed 24 May 2022).

199. Anstey KJ. Global guidelines for dementia risk reduction. Video presentation. VJDementia: 24 July 2020 (https://vjdementia.com/video/supbvzgwgwy-global-guidelines-for-dementia-risk-reduction/, accessed 25 June 2022).

200. R&D blueprint. Geneva: World Health Organization; 2016 (https://www.who.int/teams/blueprint, accessed 22 May 2022).

201. An R&D blueprint for action to prevent epidemics. Geneva: World Health Organization; 2016 (https://www.who.int/publications/m/item/an-r-d-blueprint-for-action-to-prevent-epidemics, accessed 22 May 2022).

202. Bethlehem RAI, Seidlitz J, White SR, Vogel JW, Anderson KM, Adamson C et al. Brain charts for the human lifespan. Nature. 2022;604:525—33. doi:10.1038/s41586-022-04554-y.

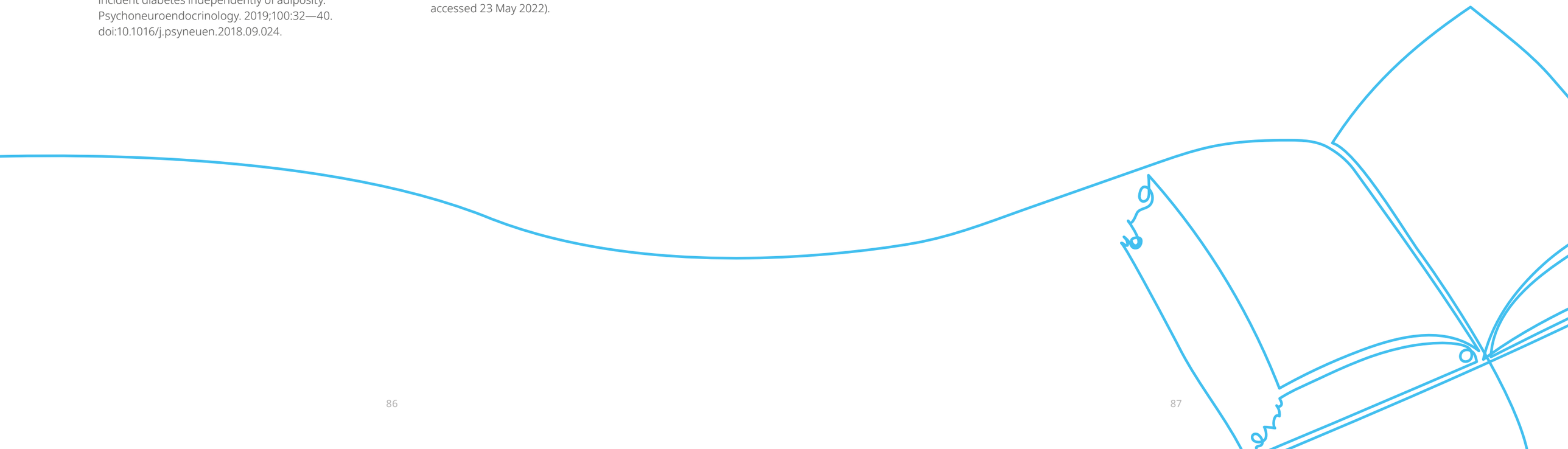
203. Gao Y, Cui M, Yang C, Wu Y, Long Y, Chen Y et al. Validity and reliability of the Brain Health Self-Efficacy Scale for the elderly. Gen Psychiatr. 2020;33(5):100208. doi:10.1136/gpsych-2020-100208.

204. Galvin JE, Kleiman MJ, Chrisphonte S, Cohen I, Disla S, Galvin CB et al. The Resilience Index: a quantifiable measure of brain health and risk of cognitive impairment and dementia. J Alzheimers Dis. 2021;84:1729—46. doi:10.3233/jad-215077.

205. Boyle PA, Wang T, Yu L, Wilson RS, Dawe R, Arfanakis K et al. The "cognitive clock": A novel indicator of brain health. Alzheimers Dement. 2021;17:1923-37. doi:10.1002/alz.12351.

206. Clark H, Coll-Seck AM, Banerjee A, Peterson S, Dalglish SL, Ameratunga S et al. A future for the world's children? A WHO-UNICEF-Lancet Commission. Lancet. 2020;395:605—58. doi:10.1016/S0140-6736(19)32540-1.

207. National Academies of Sciences Engineering Medicine. Brain health across the life span: proceedings of a workshop. Nicholson A, editor. Washington (DC): National Academies Press; 2020 (https://nap.nationalacademies.org/catalog/25703/brain-health-across-the-life-span-proceedings-of-a-workshop, accessed 7 June 2022).



Annexes

Annex 1. Resolutions and global commitments relevant to brain health

Health systems

- United Nations Political declaration of the high-level meeting on universal health coverage (2019) *(1)*
- Declaration of Astana on primary health care (2018) *(2)*
- Resolution on access to essential medicines (WHA67.22) (2014) *(3)*
- Global strategy on human resources for health: Workforce 2030 (2016) *(4)*
- Resolution on improving access to assistive technology (WHA71.8) (2018) *(5)*
- Resolution on health technologies (WHA60.29) (2007) *(6)*

Mental health (including neurological and substance use disorders)

- Comprehensive mental health action plan 2013–2030 *(7)*
- Global action plan on the public health response to dementia 2017–2025 *(8)*
- Global strategy to reduce the harmful use of alcohol (2010) *(9)*
- Action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority *(10)*
- Resolution to address the global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications (WHA68.20) (2015) *(11)*
- Comprehensive and coordinated efforts for the management of autism spectrum disorders (WHA67.8) (2014*) (12)*
- Mental health preparedness for and response to the COVID-19 pandemic (WHA74.14) (2021) *(13)*

Noncommunicable diseases

- Global action plan for the prevention and control of noncommunicable diseases 2013–2030 *(14)*
- Global disability action plan 2014–2021 *(15)*
- Political Declaration of the 3rd high-level meeting of the General Assembly on the prevention and control of non-communicable diseases (2018) *(16)*
- WHO's rehabilitation 2030 initiative *(17)*

Infectious diseases

- Global health sector strategy on HIV 2016–2021: towards ending AIDS *(18)*
- Global technical strategy for malaria 2016–2030 *(19)*
- Global strategy and targets for tuberculosis prevention, care and control after 2015 *(20)*
- Defeating meningitis by 2030: a global roadmap (2020) *(21)*

Neglected tropical diseases

- Decision of the WHO Executive Board on neglected tropical diseases (EB146(9)) (2020) *(22)*
- Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030 (2020) *(23)*

Family and Child Health

- Global strategy for women's, children's and adolescent's health 2016–2030 *(24)*
- Nurturing Care Framework (2018) *(25)*
- Global accelerated action for the health of adolescents (AA-HA!): guidance to support country implementation (2017) *(26)*
- INSPIRE: Seven strategies for ending violence against children (2016) *(27)*

Ageing and Health

- Global strategy and action plan on ageing and health (2016–2020) *(28)*
- The Decade of Healthy Ageing (2021–2030) *(29)*

References Annex 1

1. Political Declaration of the High-Level Plenary Meeting on Universal Health Coverage: resolution. New York (NY): United Nations; 2019 (http://digitallibrary.un.org/record/3833350/files/A_RES_74_2-EN.pdf, accessed 8 June 2022).
2. Declaration of Astana: Global Conference on Primary Health Care: Astana, Kazakhstan, 25 and 26 October 2018. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/328123, accessed 8 June 2022).
3. Sixty-seventh World Health Assembly, 19–24 May 2014: resolutions and decisions: annexes. Geneva: World Health Organization; 2014.
4. Global strategy on human resources for health: workforce 2030. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250368, accessed 13 June 2022).
5. WHA71.8 Improving access to assistive technology. Geneva: World Health Organization; 2018.
6. WHA60.29 Health technologies. Geneva: World Health Organization; 2007.
7. Comprehensive mental health action plan 2013–2030. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345301, accessed 8 June 2022).
8. Global action plan on the public health response to dementia 2017–2025. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259615, accessed 22 May 2022).
9. WHA63.13 Global strategy to reduce the harmful use of alcohol. Geneva: World Health Organization; 2010.
10. Fifth report of Committee A (A75/67): Action plan (2022–2030) to effectively implement the global strategy to reduce the harmful use of alcohol as a public health priority. Geneva: World Health Organization; 2022.
11. Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications. Geneva: World Health Organization; 2015.
12. WHA67.8 Comprehensive and coordinated efforts for the management of autism spectrum disorders. 2014.
13. Seventy-fourth World Health Assembly, 24 May–1 June 2021: resolutions and decisions, annexes. Geneva: World Health Organization; 2021.
14. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/94384, accessed 8 June 2022).
15. WHO global disability action plan 2014–2021: better health for all people with disability. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/199544, accessed 13 June 2022).
16. Political declaration of the 3rd High-Level Meeting of the General Assembly on the Prevention and Control of Non-Communicable Diseases: resolution. New York (NY): United Nations; 2018 (http://digitallibrary.un.org/record/1648984/files/A_RES_73_2-EN.pdf, accessed 13 June 2022).
17. Rehabilitation 2030 Initiative. Geneva: World Health Organization; (https://www.who.int/initiatives/rehabilitation-2030, accessed 13 June 2022).
Global health sector strategy on HIV 2016–2021. Towards ending AIDS. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246178, accessed 8 June 2022).

18. Global technical strategy for malaria 2016–2030. 2021 update ed. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342995, accessed 13 June 2022).

19. WHA67.1 Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014 .

20. Defeating meningitis by 2030: a global road map. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342010, accessed 17 June 2022).

21. Executive Board, 146th session, 3–8 February 2020: resolutions and decisions: annexes. Geneva: World Health Organization; 2020.

22. Ending the neglect to attain the sustainable development goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/338565, accessed 8 June 2022).

23. Global strategy for women's, children's and adolescent's health 2016–2030. Geneva: World Health Organization; 2016 (https://www.everywomaneverychild.org/wp-content/uploads/2017/10/EWEC_GSUpdate_Brochure_EN_2017_web.pdf, accessed 13 June 2022).

24. Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/272603, accessed 22 May 2022).

25. Global accelerated action for the health of adolescents (AA-HA!): guidance to support country implementation: brochure. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255416, accessed 8 June 2022).

26. INSPIRE: seven strategies for ending violence against children. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/207717, accessed 13 June 2022).

27. Global strategy and action plan on ageing and health. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/329960, accessed 8 June 2022).

28. The United Nations Decade of Healthy Ageing. Geneva: United Nations; 2020 (https://www.decadeofhealthyageing.org/, accessed 25 June 2022).

29. Prüss-Üstün A, Wolf J, Corvalán CF, Bos R, Neira MP. Preventing disease through healthy environments: a global assessment of the burden of disease from environmental risks. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/204585, accessed 25 June 2022).

30. Climate change and human health : risks and responses : summary. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/handle/10665/42749, accessed 8 June 2022).

31. Sustainable Development Goals. New York (NY): United Nations; 2015 (https://sdgs.un.org/goals, accessed 23 May 2022).

Annex 2. Different definitions of brain health and relevant initiatives aimed at promoting brain health

Different definitions of brain health (in chronological order by online publication date)

Author(s)
United States of America *(1)*

Year
1990

Other affiliated institutions
United States Library of Congress

Country or countries
United States of America

Definition text (if available)
The Decade of the Brain
"...The need for continued study of the brain is compelling: millions of Americans are affected each year by disorders of the brain ranging from neurogenetic diseases to degenerative disorders such as Alzheimer's, as well as stroke, schizophrenia, autism, and impairments of speech, language, and hearing...."

Comments
"Presidential Proclamation 6158 (17 July 1990) on the Decade of the Brain:
"To enhance public awareness of the benefits to be derived from brain research, the Congress, by House Joint Resolution 174, has designated the decade beginning January 1, 1990, as the "Decade of the Brain"" and has authorized and requested the President to issue a proclamation in observance of this occasion."

Author(s)
Gorelick et al. *(2)*

Year
2017

Other affiliated institutions
American Heart Association and American Stroke Association

Country or countries
United States of America

Definition text (if available)
"Optimal brain health can theoretically be defined as an optimal capacity to function adaptively in the environment. This could be

assessed in terms of competencies across the domains of 'thinking, moving and feeling,' encompassing, for example, the abilities [to] pay attention, perceive and recognize sensory input; to learn and remember; to communicate; to problem solve and make decisions; to have mobility; and to regulate emotional status."

Comments
Brain health on a continuum, broader perspective than absence of disease, life course scope (pregnancy onwards), identifies seven metrics for optimal brain health originating from AHA's Life's Simple 7.

Author(s)
McCance Center for Brain Health *(3)*

Year
2018

Other affiliated institutions
Harvard Medical School,
Massachusetts General Hospital

Country or countries
United States of America

Definition text (if available)
"Brain health is the state that emerges from an interaction between genetic endowment and environmental exposures, bolstering individual resilience to stress in the face of neurodegenerative, vascular and inflammatory risk factors and culminating in the promotion of healthy brain functioning and prevention of brain disease."

Comments
Aims to change the "brain care paradigm" to include promotion from prenatal care onwards. Mission is "to reduce human suffering and maximize human potential through better brain health".

Author(s)
Centers for Disease Control and Prevention (CDC) *(4)*

Year
2020

Other affiliated institutions
Division of Population Health, National Center for Chronic Disease Prevention and Health Promotion

Country or countries
United States of America

Definition text (if available)
"A concept that involves making the most of the brain's capacity and helping to reduce some risks that occur with aging. Brain health refers to the ability to draw on the strengths of the brain to remember, learn play, concentrate and maintain a clear, active mind."

Comments
Mainly focuses on cognitive domain, with strong emphasis on links between the heart and brain. Some determinants discussed include heart health, diet, smoking and physical activity.

Author(s)
Harerimana et al. *(5)*

Year
2020

Other affiliated institutions
Lawson Health Research Institute

Country or countries
Canada

Definition text (if available)
"The brain's ability to optimally adapt to internal and external human conditions through cognitive and emotional responses across one's lifespan, which result in sustainable positive changes in brain structures and functional features."

Comments
Functional brain circuity, neuroplasticity, brain reserve, physical well-being, life-satisfaction.

Author(s)
Wang et al. *(6)*

Year
2020

Other affiliated institutions
Capital Medical University;
China National Clinical Research Center for Neurological Diseases

Country or countries
China

Definition text (if available)
"The preservation of optimal brain integrity and mental and cognitive function at a given age in the absence of overt brain diseases that affect normal brain function."

Comments
Defines brain disorders as those with "overt damage to brain structures", functional brain disorders with "detectable destruction of brain connections or networks", and other brain disorders "without detectable structural or functional impairment". Highlights lack of metrics to assess brain health.

Author(s)

Smith et al. *(7)*

Year
2020

Other affiliated institutions
Stanford University, OECD

Country or countries
Multiple

Definition text (if available)
"...brain health encompasses emotional, behavioural, and cognitive strengths across the life span. Compromised brain health greatly increases the risk of disorders across the life span (e.g. depression, anxiety, substance misuse, dementias and neurocognitive disorders) and hinders the achievement of each individual's full human potential. The concept of Brain Capital encompasses both brain health and brain skills as contributors to this Brain Economy."

Comments
"Brain capital, brain skills, brain economy, human cognitive capital as a dynamic capacity, introduces a Brain Capital Investment Plan. As part of OECD's New Economic Challenges Neuroscience Inspired Policy Institute"

Author(s)

Dawson et al. *(8)*

Year
2020

Other affiliated institutions
Oregon Health and Sciences University, Global Brain Health Institute

Country or countries
Multiple

Definition text (if available)
See comments for details.

Comments
Focuses on determinants of brain health (social and biological) organized by the individual, community and macro levels. Proposes brain health diplomacy model to "transcend disciplinary boundaries and mobilize resources at sufficient scale to improve brain health".

Author(s)

Chen et al. *(9)*

Year
2021

Other affiliated institutions
Trinity College Dublin

Country or countries
Ireland

Definition text (if available)
"a life-long dynamic state of cognitive, emotional and motor domains underpinned by physiological processes. It is multidimensional and can be objectively measured and subjectively experienced. Brain health is influenced by ecobiopsychosocial determinants, resulting in a continuum of quality of life and wellness."

Comments
Continuum across the life course; multidimensionality; along a continuum; not based on the absence of disease; measurable concept.

Author(s)

Hachinski et al. *(10)*

Year
2021

Other affiliated institutions
Western University, London, Ontario

Country or countries
Canada

Definition text (if available)
"Brain health in adults is a state of complete physical, mental, and social wellbeing through the continuous development and exercise of the brain."

Comments
Suggests that "a combined set of neurological, mental health, and wellbeing core elements would begin to unify the three fields and help to understand their interactions." Additionally discusses the need for physical, psychological and socioeconomic measures of brain health.

Author(s)

Bassetti et al *(11)*

Year
2022

Other affiliated institutions
European Academy of Neurology

Country or countries
Multiple

Definition text (if available)
"The EAN Brain Health Strategy: One Brain, One Life, One Approach"

Comments
The EAN Brain Health Strategy includes 5 pillars: 1) to "contribute to a global and international brain health approach"; 2) to support "the implementation of integrated and people-centred campaigns"; 3) to foster research; 4) to promote education; and 5) to raise the awareness of the public about neurological disorders and brain health.

Relevant brain health initiatives (in alphabetical order)

Initiative

European Brain Council *(12)*

Organization/ institution
European Brain Council

Country or countries
Europe

Definition
See comments for details

Comments
"Main mission is to promote brain research with the ultimate goal of improving the lives of the estimated 179 million Europeans living with brain conditions, mental and neurological alike."
Scope of brain disorders includes "developmental, psychiatric, neurodegenerative and pain-related disease".

Initiative

Global Council on Brain Health *(13)*

Organization/ institution
American Association of Retired Persons, Age UK

Country or countries
United States of America and United Kingdom

Definition
Focuses on brain health "relating to people's ability to think and reason as they age, including aspects of memory, perception and judgment".

Comments
Identifies several determinants (or factors) of brain health including physical activity, sleep, nutrition, vascular risk, social engagement, cognitively stimulating activities, among others.

Initiative

Healthy Brains Global Initiative *(14)*

Organization/ institution
Multiple

Country or countries
Multiple

Definition
See comments for details.

Comments
Vision is "a world where no one is limited by neurological or mental health problems and a healthy brain span is equivalent to life span".

Initiative

McKinsey Health Institute Brain Health Programme *(15)*

Organization/ institution
McKinsey Health Institute

Country or countries
Multiple

Definition
"Brain health is a term inclusive of positive mental health and the full range of mental, substance use, and neurological conditions – is a critical determinant of overall health. Regardless of age, income, or geography, brain health materially impacts every person's life.
Brain health is broader than the absence of disease. It includes improving overall cognitive functioning, resilience, and the state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively, and is able contribute to his or her community."

Comments
The McKinsey Health Institute (MHI) addresses brain health challenges globally, such as social norms (including stigma), prevention, early detection, treatment effectiveness, integration of care, and workforce availability – as well as opportunities to further support positive mental health.

Initiative:

Neuroscience-inspired Policy Initiative *(16)*

Organization/ institution
OECD

Country or countries
Multiple

Definition
"The concept of Brain Capital considers brain skills and brain health as an indispensable part of the knowledge economy.
The global economy increasingly places a premium on cerebral, brain-based skills that make us human, such as self-control, emotional intelligence, creativity, compassion, altruism, systems thinking, collective intelligence, and cognitive flexibility."

Comments
OECD's Neuroscience-inspired Policy Initiative examines and drives ideas originating in neuroscience and medicine to economic and social policy, including productivity, gender equality, mental health, education and others.

References Annex 2

1. Project on the Decade on the Brain. Washington (DC): United States Library of Congress; 1990 (https://www.loc.gov/loc/brain/, accessed 23 May 2022).
2. Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM et al. Defining optimal brain health in adults: a Presidential Advisory from the American Heart Association/American Stroke Association. Stroke. 2017;48:e284–303. doi: 10.1161/STR.0000000000000148.
3. McCance Center for Brain Health. Boston: Massachusetts General Hospital; 2018 (https://www.massgeneral.org/neurology/mccance-center/about, accessed 13 June 2022).
4. Healthy Brain Initiative. Atlanta: Centers for Disease Control and Prevention; 2020 (https://www.cdc.gov/aging/healthybrain/index.htm, accessed 13 June 2022).
5. Harerimana B, Forchuk C, Walsh J, Fogarty J, Borrie M. Brain health: a concept analysis. Issues Ment Health Nurs. 2021;42:145–52. doi: 10.1080/01612840.2020.1789781.
6. Wang Y, Pan Y, Li H. What is brain health and why is it important? BMJ. 2020;371:m3683. doi:10.1136/bmj.m3683.
7. Smith E, Ali D, Wilkerson B, Dawson WD, Sobowale K, Reynolds C et al. A Brain Capital Grand Strategy: toward economic reimagination. Mol Psychiatry. 2021;26:3–22. doi: 10.1038/s41380-020-00918-w.
8. Dawson WD, Bobrow K, Ibanez A, Booi L, Pintado-Caipa M, Yamamoto S et al. The necessity of diplomacy in brain health. Lancet Neurol. 2020;19:972–4. doi: 10.1016/S1474-4422(20)30358-6.
9. Chen Y, Demnitz N, Yamamoto S, Yaffe K, Lawlor B, Leroi I. Defining brain health: a concept analysis. Int J Geriatr Psychiatry. 2021;37. doi: https://doi.org/10.1002/gps.5564.
10. Hachinski V, Avan A, Gilliland J, Oveisgharan S. A new definition of brain health. Lancet Neurol. 2021;20:335–6. doi: 10.1016/S1474-4422(21)00102-2.
11. Bassetti CLA, Endres M, Sander A, Crean M, Subramaniam S, Carvalho V et al. The EAN Brain Health Strategy: One Brain, One Life, One Approach. Eur J Neurol. 2022. doi: https://doi.org/10.1111/ene.15391.
12. European Brain Council, Brussels (https://www.braincouncil.eu/about-us/, accessed 13 June 2022).
13. Global Council on Brain Health. American Association of Retired Persons (https://www.aarp.org/health/brain-health/global-council-on-brain-health/, accessed 15 June 2022).
14. Healthy Brains Global Initiative (https://www.hbgi.org/our-vision-and-mission, accessed 15 June 2022).
15. Brain health. McKinsey Global Institute (https://www.mckinsey.com/mhi/focus-areas/brain-health, accessed 13 June 2022).
16. Neuroscience-inspired Policy Initiative. Paris: Organisation for Economic Co-operation and Development; (https://www.oecd.org/naec/brain-capital/, accessed 23 May 2022).

Annex 3. WHO technical tools, norms and standards to address brain health determinants and optimize brain health for all

The list below provides examples of WHO technical tools, norms and standards that address brain health determinants and thus help to optimize brain health for all. The list is organized around the same categories as in Annex 1 and does not claim to be exhaustive.

Mental health (including neurological and substance use disorders)

- Social determinants of mental health (2014) *(1)*
- mhGAP Intervention Guide (mhGAP-IG) for mental, neurological and substance use (2016) *(2)*
- WHO Guidelines on risk reduction of cognitive decline and dementia (2019) *(3)*
- Epilepsy: a public health imperative (2019) *(4)*
- Doing what matters in times of stress: an illustrated guide (2020) *(5)*
- Improving early childhood development: WHO guideline (2020) *(6)*
- Guidelines on mental health promotive and preventive interventions for adolescents: helping adolescents thrive (2020) *(7)*
- WHO Helping adolescents thrive toolkit (2021) *(8)*
- WHO Parkinson disease technical brief (2022) *(9)*
- SAFER: A world free from alcohol related harms (2022) *(10)*
- Integration of mental health and HIV interventions (2022) *(11)*
- Caregiver skills training for families of children with developmental delays or disabilities (2022) *(12–16)*

Noncommunicable diseases

- Life course approach to prevention and control of non-communicable diseases (2019) *(17)*
- WHO guidelines on physical activity and sedentary behavior (2020) *(18)*
- WHO package of essential noncommunicable (PEN) disease interventions for primary health care (2020) *(19)*
- WHO UHC compendium online database *(20)*

Infectious diseases

- Zika strategic response plan (2016) *(21)*
- WHO toolkit for the care and support of people affected by complications associated with Zika virus (2017) *(22)*
- Neurology and COVID-19: scientific brief (2021) *(23)*
- WHO Guidelines for malaria (2022) *(24)*

Neglected tropical diseases

- Helminth control in school-age children: a guide for managers of control programmes (2011) *(25)*
- WHO guidelines on management of Taenia solium neurocysticercosis (2021) *(26)*
- WHO recommendations on antenatal care for a positive pregnancy experience (2016) *(27)*
- WHO recommendations: intrapartum care for a positive childbirth experience (2018) *(28)*
- Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential (2018) *(29)*
- Standards for healthy eating, physical activity, sedentary behaviour and sleep in early childhood education and care settings: a toolkit (2021) *(30)*

Ageing and Health

- Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care (2019) *(31)*
- Integrating health in urban and territorial planning: a sourcebook (2020) *(32)*
- WHO Advocacy brief: Social isolation and loneliness among older people (2021) *(33)*

Environment and climate change

- Childhood lead poisoning (2010) *(34)*
- Children's exposure to mercury compounds (2010) *(35)*
- WHO Guideline for clinical management of exposure to lead (2021) *(36)*
- WHO Global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide (2021) *(37)*
- Mental health and climate change: Policy brief (2022) *(38)*

Health systems

- A conceptual framework for action on the social determinants of health (2010) *(39)*
- WHO Housing and health guidelines (2018) *(40)*
- National workforce capacity to implement the essential public health functions including a focus on emergency preparedness and response (2022) *(41)*
- Tool to assess the impact of human resources for health investments on HIV, TB and malaria services and health outcomes (2022) *(42)*
- Integrating social determinants of health into health workforce education and training (2022) *(43)*

References Annex 3

1. Social determinants of mental health. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/112828, accessed 15 June 2022).
2. mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: mental health Gap Action Programme (mhGAP). version 2.0 ed. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250239, accessed 15 June 2022).
3. Risk reduction of cognitive decline and dementia: WHO guidelines. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/312180, accessed 22 May 2022).
4. Epilepsy: a public health imperative. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/325293, accessed 22 May 2022).
5. Doing what matters in times of stress: an illustrated guide. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/331901, accessed 15 June 2022).
6. Improving early childhood development: WHO guideline. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/331306, accessed 22 May 2022).
7. Guidelines on mental health promotive and preventive interventions for adolescents: helping adolescents thrive. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336864, accessed 22 May 2022).
8. World Health Organization, United Nations Children's Fund. Helping adolescents thrive toolkit: strategies to promote and protect adolescent mental health and reduce self-harm and other risk behaviours. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/341327, accessed 15 June 2022).
9. World Health Organization. Parkinson disease: a public health approach: technical brief. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/355973, accessed 15 June 2022).
10. The SAFER technical package: five areas of intervention at national and subnational levels. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/330053, accessed 15 June 2022).
11. World Health Organization, UNAIDS. Integration of mental health and HIV interventions: key considerations. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353571, accessed 15 June 2022).
12. Caregiver skills training for families of children with developmental delays or disabilities: introduction. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353579, accessed 23 May 2022).
13. Caregiver skills training for families of children with developmental delays or disabilities: adaptation and implementation guide. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353581, accessed 23 May 2022).
14. Caregiver skills training for families of children with developmental delays or disabilities: home visit guide for facilitators. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353583, accessed 23 May 2022).
15. Caregiver skills training for families of children with developmental delays or disabilities: participants' guide, group sessions 1–9. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353582, accessed 23 May 2022).
16. Caregiver skills training for families of children with developmental delays or disabilities: facilitators' guide, group sessions 1–9. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/353580, accessed 23 May 2022).
17. Mikkelsen B, Williams J, Rakovac I, Wickramasinghe K, Hennis A, Shin H-R et al. Life course approach to prevention and control of non-communicable diseases. BMJ. 2019;364:l257. doi: 10.1136/bmj.l257.
18. WHO guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336656, accessed 15 June 2022).
19. WHO package of essential noncommunicable (PEN) disease interventions for primary health care. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/334186, accessed 15 June 2022).
20. WHO UHC compendium online database. Geneva: World Health Organization, (https://www.who.int/universal-health-coverage/compendium/database, accessed 15 June 2022).
21. Zika strategic response plan, revised for July 2016 – December 2017. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246091, accessed 22 May 2022).
22. WHO toolkit for the care and support of people affected by complications associated with Zika virus. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255718, accessed 15 June 2022).

23. Neurology and COVID-19: scientific brief, 29 September 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345574, accessed 22 May 2022).

24. WHO guidelines for malaria, 18 February 2022. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/351995, accessed 15 June 2022).

25. Helminth control in school-age children: a guide for managers of control programmes. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/handle/10665/44671, accessed 15 June 2022).

26. WHO guidelines on management of Taenia solium neurocysticercosis. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/344802, accessed 15 June 2022).

27. WHO recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250796, accessed 22 May 2022).

28. WHO recommendations: intrapartum care for a positive childbirth experience. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/260178, accessed 22 May 2022).

29. Nurturing care for early childhood development: a framework for helping children survive and thrive to transform health and human potential. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/272603, accessed 22 May 2022).

30. Standards for healthy eating, physical activity, sedentary behaviour and sleep in early childhood education and care settings: a toolkit. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345926, accessed 22 May 2022).

31. Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/326843, accessed 15 June 2022).

32. United Nations Human Settlements Programme, World Health Organization. Integrating health in urban and territorial planning: a sourcebook. Geneva: World Health Organization; 2020 (https://unhabitat.org/integrating-health-in-urban-and-territorial-planning-a-sourcebook-for-urban-leaders-health-and, accessed 17 June 2022).

33. Social isolation and loneliness among older people: advocacy brief. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/343206, accessed 15 June 2022).

34. Childhood lead poisoning. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/136571, accessed 22 May 2022).

35. Children's exposure to mercury compounds. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/44445, accessed 22 May 2022).

36. WHO guideline for clinical management of exposure to lead. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/347360, accessed 15 June 2022).

37. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/345329, accessed 15 June 2022).

38. Mental health and climate change: policy brief. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/354104, accessed 15 June 2022).

39. A conceptual framework for action on the social determinants of health. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/44489, accessed 15 June 2022).

40. WHO housing and health guidelines. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/276001, accessed 15 June 2022).

41. National workforce capacity to implement the essential public health functions including a focus on emergency preparedness and response: roadmap for aligning WHO and partner contributions. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/354384, accessed 15 June 2022).

42. Tool to assess the impact of human resources for health investments on HIV, TB and malaria services and health outcomes. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/352552, accessed 15 June 2022).

43. Integrating social determinants of health into health workforce education and training. Geneva: World Health Organization; (in press)

For more information please contact:

Brain Health Unit
Department of Mental Health and Substance Use

World Health Organization
Avenue Appia 20
CH-1211 Geneva 27
Switzerland

Email: brainhealth@who.int
Website: https://www.who.int/health-topics/brain-health

9789240054561