Measures of early-life brain health at population level

Report of a technical meeting

Geneva, Switzerland, 2–3 May 2023
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The meeting and this meeting report were prepared under the supervision and guidance of Tarun Dua (Brain Health, WHO) and Devora Kestel (Mental Health and Substance Use, WHO) and coordinated by Katrin Seeher (Brain Health, WHO).

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Abbreviations

D-score  developmental score
ECDI2030  Early Childhood Development Index 2030
EEG  electroencephalogram
GSED  Global Scales for Early Development
MRI  magnetic resonance imaging
Glossary

**Brain health**

WHO defines brain health (1) as:

a 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.

**Conditions that affect brain and nerve functioning**

Conditions that can emerge throughout life, disrupt brain growth, damage brain structure or nerves and impair brain or nerve functioning. They include congenital and neurodevelopmental disorders, cerebrovascular and neurodegenerative diseases, neuroinfections or neuroimmunological disorders, neuromuscular disorders, traumatic injuries and cancers of the nervous system. Their etiology, symptoms and course vary. Some cause lifelong disability, whereas others are associated with high fatality rates; some are treatable or even preventable, while for others there is no cure (2). In line with WHO’s definition of brain health, the presence of any of these conditions does not mean the absence of brain health but may alter brain function in one or more domains.

**Early childhood development**

Children’s cognitive, physical, language, motor, and social and emotional development, between conception and age 8. For the purpose of this report, the main focus is on the period from pregnancy to age 5, as a child’s experiences during the early years provide the foundation for the life course and influence basic learning, school success, social/economic participation and health.
Neurodevelopment  The development of neurological pathways, shaped by biological and environmental factors that influence skills, ability and functioning (e.g. intellectual functioning, reading ability, social skills, memory, attention or focus).

Neurodiversity  The idea that people experience and interact with the world around them in many different ways; there is no one “right” way of thinking, learning or behaving, and differences are not viewed as deficits. Neurodiversity encompasses the view that natural variations of the human brain may manifest as differences in neurological functioning and structure, which contribute to the richness of human society and should therefore be neither pathologized nor normalized.
1. Introduction

Brain health is a rapidly expanding field. In line with the WHO definition of brain health (1) and for the purpose of this report, brain health is understood as an overarching concept that encompasses the life course, from pregnancy to infancy, early childhood, adolescence, adulthood and old age. Brain health includes and extends related concepts, such as neurodevelopment, early childhood development, neurodiversity and neuroplasticity, as brain functioning develops, adapts and fluctuates throughout life in response to internal and external influences and the presence or absence of diseases that affect the brain. Opportunities to promote optimal brain development occur during pregnancy and early childhood, when brain growth is most rapid in terms of both size and complexity (3,4). Thus, ensuring that all children receive time-dependent, nurturing care before the windows of opportunity close is critical for the health and well-being of future generations.

Both adverse and positive experiences during this period shape children’s brain health, educational attainment, psychological well-being and economic capacity, thus, also affecting the well-being of subsequent generations (5–8). Interventions to maximize learning and adaptation in the early years are critical for brain growth and functioning; they are cost-effective, reduce health inequity and lay the foundations for adult health and well-being (3, 5–7, 9–11).

While the concept of brain health extends beyond diseases and disorders of the nervous system, the burden and health loss associated with these conditions still needs to be quantified and characterized. The Global Burden of Disease study led by the Institute for Health Metrics and Evaluation has quantified the global loss of brain health. In 2021, conditions that affect the nervous system were the leading cause of disability-adjusted life years worldwide and the most common cause of mortality (2). While the Global Burden of Disease captures many determinants, health outcomes and risk factors associated with early-life brain health, it does not currently include a comprehensive population metric of brain health in early life. The development of such metric would require better measures of brain health and a framework for integrating such measures throughout life, including relevant determinants and outcomes. This would allow definition of factors that promote or impair early neurodevelopment in order to generate the evidence necessary to prioritize and intervene to optimize brain health.

Many governments and multilateral organizations have begun investing in neurodevelopmental research and programmes for brain health, especially for the promotion of brain development in the early years of life. Current global mandates for early childhood development and brain health include:

- Sustainable Development Goal indicator 4.2.1, the proportion of children aged 24–59 months who are developmentally on track in health, learning and psychosocial well-being, by sex;
- the Nurturing care framework (12), a road map for actions to ensure that children survive and thrive; and
- the Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031 (13), which addresses the challenges and gaps to providing care and services for people living with neurological disorders and to reduce stigmatization and the impact and burden of these conditions.

1 A child meets established milestones for physical, cognitive and socio-emotional development at the rate expected for their age.
These mandates address some aspects of brain health in early life, such as early childhood development, neurodevelopment and neurodevelopmental disabilities as well as neurological disorders (see Glossary for definitions of terms, their commonalities and differences). They value, promote and protect brain health throughout the life course.

In 2022, WHO issued a position paper that included a conceptual framework for optimizing brain health for all throughout the life course by addressing interconnected determinants of brain health (1) (see Fig. 1). In making a case for brain health for all, the position paper shows that improving brain health will have wider health, societal and economic benefits.

Fig. 1.
A conceptual framework for optimizing brain health

Traditionally, child development has been measured using proxies such as stunting and extreme poverty. Stunting is an excellent direct measure of undernutrition and is widely used in combination with extreme poverty as a proxy measure of (neuro)development to estimate the proportion of children at risk of not reaching their developmental potential (14). Use of stunting as a proxy measure is based on quantitative estimates from studies that showed negative associations between stunting (i.e. height-for-age z-score < 2 standard deviations below WHO growth standards) at age 2 years and diminished schooling and economic performance. Similarly, positive associations are seen between linear growth...
and cognitive development (15). Data on stunting and poverty are relatively easy to obtain and understand and can be used at scale in global policies (16). As stunting and poverty are only proxy measures for brain health, they lack validity and provide little insight into the underlying mechanism by which they negatively affect neurodevelopment or imply causality. Evidence for their predictive power for future outcomes suggests that the effects may be mediated through neurodevelopment, and more recent studies have questioned their correlation with child development (see MAL-ED study (17)). While there are overlapping risk factors and interventions for stunting and neurodevelopment (e.g. undernutrition, nutritional supplementation), there are also distinct risk factors and interventions (responsive care, stimulation) that affect only child development (9). Lastly, as these proxy measures primarily estimate growth as an indirect approximation of brain health they fail to reflect the various domains of brain function and neurodevelopment.

The Early Childhood Development Index 2030 (ECDI2030), developed by the United Nations Children’s Fund, is the official measure for monitoring achievement of Sustainable Development Goal 4.2.1. The 20-item instrument is used to measure the developmental status of children aged 24–59 months and can be used at scale in population-based surveys to determine the proportion of children in a population “on track/not on track” for developmental potential. This instrument facilitates data collection and can be used in large standardized surveys, such as multiple indicator cluster surveys and demographic and health surveys, which allow cross-country, regional and urban–rural comparisons. Some of the shortcomings of the ECDI2030 include the limited age range (no measurement before 2 years or after 5 years) and lack of specificity for developmental domains, as it measures only health, learning and psychosocial well-being but not the multiple domains of brain health.

Investment in brain health and advocacy for its inclusion in the global public health discourse and broader political agendas, however, require accurate measurement of brain health at population level. To date, there is no simple, direct or global measure of brain health throughout the life course (I). Because of the multiple dimensions of the concept, it is difficult to capture the full spectrum of brain health in all domains of brain functioning (cognitive, language, sensory, social–emotional, behavioural and motor domains) and the wide range of determinants (aspects of physical health, including prenatal, healthy environments, learning and social connection, safety, security and access to high-quality services) (1). While several psychometric measures have been proposed for quantifying aspects of brain health, most measure cognitive function and not all the domains of brain functioning. Furthermore, there is no single, reliable metric that can be used at all ages as a proxy for brain health at population level (1). Advances in psychometrics, neuroimaging and neuro-modelling could be used to develop an integrated global metric of brain health that would allow both measurement of brain health and use of the measure to predict outcomes later in life and to evaluate interventions to optimize child development and brain health throughout the lifespan. For development of such a global brain health metric, an integrated measurement framework is necessary, with the individual components to be combined into a metric, which could subsequently be tested and validated.
2. The meeting

2.1 Overview

The meeting was attended by 53 stakeholders and experts (see Annex 1 for list of participants). The goal was to identify the components of a measurement framework for brain health with a focus on early life that is robust and versatile and can be used in various settings and models. Such a framework could be used to combine current work on measuring (directly and indirectly) brain structure and brain function across multiple domains into a single metric that would also account for different brain health outcomes and determinants. The resulting metric could be used to track progress in reaching global policy goals, as a basis for resource allocation (government expenditure on health and education; product development) and to provide evidence on what children need to reach their neurodevelopment potential. While the focus was on the first 5 years of life, the life course was kept in perspective, as brain health in early life affects health and social outcomes throughout life. Individual and population interventions may affect brain health at different times of life and also accumulate over time. Ultimately, efforts to develop a unified brain health metric would need to be extended to cover the entire lifespan.

The 53 experts who attended the meeting represented all six WHO regions and included WHO staff. Of the 53, 31 were female and 22 male, and 44% of the participants (excluding the secretariat) were from low- and middle-income countries. All the external participants completed declarations of interest as per WHO’s policy. Interests were declared by 23 external experts, of which none was deemed to constitute a conflict of interest for the purpose of the meeting. The participants had diverse expertise, including child health and development, neuroimaging, maternal health, epidemiology, computer science and neuroscience. Representatives of other United Nations agencies and multilateral organizations (i.e. the United Nations Children’s Fund, the United Nations Educational, Scientific and Cultural Organization and the World Bank) provided input.
2.2 Objectives

The objectives of the meeting were:

- to map current work to operationalize and measure brain health in early life;
- to outline the components of a measurement framework for brain health;
- to understand the requirements and modelling strategies for integrating individual brain health measures into population metrics; and
- to identify synergies with existing initiatives and datasets and to discuss gaps and needs for future development of metrics.

2.3 The case for a new, integrated framework for measuring brain health

Meaningful progress in improving brain health for all can be achieved only by including brain health in public health and global policy discourse once the latent construct “brain health” becomes measurable. This would ideally be done with a single, integrated metric for brain health starting from early childhood that could predict distal life-course outcomes and could be incorporated into population models.

A comprehensive framework is necessary to develop an integrated metric of brain health, built on the strengths of existing proxy measures but with a stronger focus on direct, multimodal features in order to measure individual components of brain health (see Box 1). An integrated framework for measuring brain health should also account for the impact of determinants including but not limited to early-life adversity and nutrition, and their role in early prevention and health promotion. Inclusion of both proximal and distal outcomes of early brain development in the framework would increase its predictive utility and allow development of stronger investment cases and economic arguments.
Box 1.  
**A measurement framework for developing a brain health metric**

**Framework:** A measurement framework for brain health and its determinants is a structure that combines individual components and measures into a single metric. For the purposes of this report, the framework would be a theoretical construct to operationalize brain health and the individual facets of brain functioning and brain structure.

**Model:** Once developed, the framework must be tested in models to confirm the measures selected and to determine the best combination of complementary measures for arriving at a single metric that explains most of the variance in the underlying construct of “brain health”.

**Metric:** A brain health metric will result from the framework after combination of individual measures. The single metric can then be used to measure brain health at population level, monitor the impact of interventions and inform policy decisions. If proven useful, especially for predicting later-life outcomes, a single brain health metric could also be used as an indicator or component of other indices, for instance, replacing proxy measures of child development such as stunting.

The proposed integrated measurement framework for brain health will be relevant for:

- policy (e.g. in population surveys, national health statistics; see Box 2) and better monitoring of global commitments to sustainable development;
- evaluation of the impact of programmes and products (e.g. for evaluating changes to a national early childhood development curriculum or nutrition interventions); and
- research, e.g. for measuring long-term impacts of iron supplementation in pregnancy on early outcomes.
Box 2.
Relevance of promoting and measuring brain health in early life – a policy perspective from Norway

The term “brain health” was first used officially in Norway in 2016. Now, it is frequently used by the public, professionals and even by politicians. The first steps towards the Norwegian Brain Health Strategy were taken in 2014 by the Norwegian Brain Council, a collaboration of over 60 patient organizations, medical professional associations and scientific institutions, which advocated with health authorities for more research, better treatment and rehabilitation for neurological disorders, and greater equity within health services.

In 2015, a request for a brain health plan was submitted to Parliament, which resulted in a unanimous vote to consider development of such a strategy. In 2016, the Minister of Health requested the Norwegian Directorate of Health to prepare a status report on brain health. The report was developed with patient representatives and medical professionals and published in February 2017. It concluded that brain health should be promoted, as it represents a major and increasing burden of disease. In late 2017, the Norwegian Brain Health Strategy 2018–2024 was launched by the Prime Minister and the Minister of Health. The strategy focuses on prevention and quality of life, especially lifelong brain health promotion, from pregnancy to end of life, including palliative care; increased user participation and peer-oriented health services; high-quality treatment for habilitation and rehabilitation; and stimulation of research, science and innovation.

A challenge for implementation of the strategy is the lack of concrete measures at all levels. For instance, measures of brain disease and brain health should be included in health statistics to ensure appropriate prioritization in policy-making and to increase public awareness. Similarly, better measures are needed that are not disease-specific but maintain a broad perspective on brain health, in line with the national strategy.

In June 2023, the Minister of Health announced publication of the Norwegian Brain Health Strategy 2.0 in 2025, after the current brain health strategy expires in 2024.

Einar Bryne, Norwegian Directorate of Health and Norwegian Brain Council
A new measurement framework must, however, overcome the limited availability of appropriate measures between birth and 5 years, reflect a continuum of development in multiple domains, and identify skills and behaviour that are similar among children over time and among countries. The framework should also recognize that “traditional” health measures (such as linear growth, meeting developmental milestones or norms) might not be the most important outcomes for children and their parents. Thus, inclusion of measures of function and well-being in the framework will ensure that the brain health metric is more meaningful and inclusive of children and their caretakers.

In summary, measurement of brain health on a global scale could transform the lives of children, but it also poses unique challenges. A new, integrated framework for measuring brain health will provide the basis for an accurate metric of early brain health and allow insights at population level for policy development and prioritization of interventions to benefit all throughout the lifespan.
3. Discussions

The issues raised during the 2-day meeting during plenary presentations, panel discussions and working groups are summarized below (see Annex 2 for the meeting agenda).

3.1 Determinants of brain health

Many factors affect brain health at different stages of life and lead to lifelong adaptations of brain function and structure. These determinants can be broadly divided into physical health, healthy environments, safety and security, lifelong learning and social connection and access to high-quality services (1) (Fig. 2). Brain health throughout life can be improved by minimizing risk factors, especially in early life, and by enhancing promotive and protective factors that build neuroplasticity, the brain’s ability to grow, create new connections and recover or compensate for injuries.

**Fig. 2.**
Determinants of brain health throughout the life course

<table>
<thead>
<tr>
<th>Physical health</th>
<th>Healthy environments</th>
<th>Safety &amp; security</th>
<th>Learning &amp; social connection</th>
<th>Access to quality services</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal health, intrauterine environment</td>
<td>Safe use of chemicals</td>
<td>Physical safety</td>
<td>Education</td>
<td>Integrated care at all health/social care levels</td>
</tr>
<tr>
<td>Genetic and epigenetic factors</td>
<td>Protection from radiation</td>
<td>Financial security</td>
<td>Lifelong learning</td>
<td>Skilled workforce and interdisciplinary teams</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Healthy and safe workplaces and agricultural practices</td>
<td>Humanitarian crises and emergencies</td>
<td>Nurturing care</td>
<td>Access to essential medicines, diagnostics and health products</td>
</tr>
<tr>
<td>Infections</td>
<td>Air and water quality</td>
<td>Social connection/social isolation</td>
<td>Social networks</td>
<td>Carer support</td>
</tr>
<tr>
<td>Noncommunicable diseases</td>
<td>Stable climate</td>
<td>Access to preserved nature and health-supportive built environments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health behaviours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic injuries</td>
<td></td>
<td></td>
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</tbody>
</table>

Source: WHO (1)
In considering determinants of optimal brain health, the group recognized the importance of the early life period as critical for laying the foundation for lifelong physical and mental health. Nearly all physical, cognitive and social skills are developed during early life. Although genes contribute to the basic blueprint of early brain development, the ultimate course of human development is influenced by experiences during the early years, when the pace of brain development is greatest (18–21), at a rate of generating more than one million synapses per minute between the late prenatal period and the second and third years of life (22,23). This synaptic exuberance is followed by synaptic pruning, whereby experience cultivates neural circuits, which in turn lead to a reduction in the number of synapses and the brain becoming increasingly more efficient (Fig. 3).

**Fig. 3.**
The neural network - slide presented by Charles Nelson during the meeting

**THE NEURAL NETWORK**
The brain begins developing 3 weeks after conception and achieves dramatic growth during the first 1000 days – indeed, by some estimates 1 million synapses are formed each second during these early years. Importantly, during this time experience “cuts both ways,” such that positive experiences can shift growth in a positive direction and negative experiences can shift growth in a negative direction.

**INTO ADULTHOOD**
The infant brain has many more synapses than the adult brain, but over time, pruning leads to a reduction in synapses until adult numbers are reached.

Note, though, that in a number of domains (e.g., learning and memory) new synapses can be added throughout the life course (experience-dependent synaptogenesis).

Source: Reproduced by permission of Charles Nelson, Harvard Medical School, Boston Children’s Hospital; Pat Levitt, University of Southern California, Children’s Hospital Los Angeles.
“Experience cuts both ways”, however. Thus, children’s exposure to positive experiences biases their development in a particular direction, whereas exposure to adverse experiences biases it in a different direction, which may be adaptive in the short term but less healthy in the long term. Experiences per se are not deterministic, which is also true of genes; rather, behavioural development is nearly always a product of a gene and environmental interaction. Millions of children around the world are exposed to various biological and psychosocial risks, from malnutrition to child maltreatment including polygenic risk, epigenetic changes, metabolism, nutrition, stress, neuroinflammation, trauma (psychological and physical), (blue) light pollution that affects circadian rhythms and sleep, social interaction, isolation, social media and physical activity. Although people can be exposed to risk and adversity at any time in their life, exposure during critical periods of brain development – many of which occur during the first 5 years of life – can put children at a particular disadvantage.

Much work has already been done to understand the determinants of brain health and child development. While the body of literature is large, the question remains how these measures can be integrated into a framework and which determinants should be prioritized. There is wide acknowledgement that the following issues should be considered in developing a brain health measurement framework:
• Some factors may confer relative protection and actively promote children’s brain health and development, regardless of concurrent risks. They include breastfeeding, sleep and mother–child interaction. These factors should be emphasized in preventive strategies for better brain health.

• Although some environmental factors are important for optimal early brain health, others may differentially determine risk or resilience in some geographical areas and contexts (21). A comprehensive measurement framework should allow assignment of weights according to the likelihood of exposure.

• Children with different heritage have different genetic contributions to risk and resilience. These should be considered explicitly in view of the inherent differences revealed by recent advances in understanding genetic variation in populations, particularly those of African ancestry (24).

• A new framework should include a strategy for addressing multicollinearity and interactions between the many risk and protective factors.

• The relative importance of different windows of time and how risk and protective factors may manifest differently in sensitive periods should also be considered.

• While large studies have been conducted in the global North, less is known about the risks for intellectual and developmental disabilities in other countries. Prospective studies conducted in the past decade have shown that perinatal factors, nutrition (including iron-deficiency anaemia), infections such as HIV and malaria, environmental stimulation and interaction, psychosocial factors and nurturing care may all impact brain development (12,25–27). Social and gender inequalities may further amplify developmental differences. Building on this work, more data are necessary to tailor interventions to promote the best potential for child brain health and well-being.

3.2 Measures to quantify aspects of brain health

Rapid neurodevelopment in the early years presents two conundra. First, the limited cognitive and behavioural repertoire available in the early years means that measures are often difficult to obtain and/or are unreliable. Secondly, cognitive and behavioural measures alone do not capture the actual biological mechanisms of changes in function.

Participants discussed valid, scalable cognitive and behavioural measures and other candidate neurobiological and imaging measures, their use in research and the lack of evidence on their implementation at group and population levels. There have been recent leaps and scientific innovation in the measurement of brain development in early life (see Table 1).
### Table 1.
Available measures, with examples, for quantifying brain health in early life (non-exhaustive list)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Examples</th>
<th>Resource and training needs</th>
<th>Domain of brain health measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive and behavioural</td>
<td>GSED</td>
<td>Basic equipment; training for more in-depth assessments; caregiver report and direct observation</td>
<td>Cognitive, motor, language, executive function, psychosocial, behavioural, developmental function, D-score</td>
</tr>
<tr>
<td></td>
<td>ECDI2030</td>
<td></td>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Neurobiological structure and function</td>
<td>MRI, ultrasound, functional near-infrared spectroscopy, EEG</td>
<td>Equipment; modality-specific expertise for acquisition, processing and interpretation</td>
<td>Brain structure and function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological and physiological</td>
<td>General observations (physiology) e.g. heart rate, sleep, hearing, vision</td>
<td>Basic equipment</td>
<td>Holistic view of brain health as part of general physical health and bi-directional effects, with sensory function (e.g. hearing and vision)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participation and function</td>
<td>Quality of Life and participation questionnaires</td>
<td>Limited training needed</td>
<td>Influence of function on activities in the home, community and other settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quality of life of child</td>
</tr>
</tbody>
</table>

Brain electrical activity can be measured on an electroencephalogram (EEG) in both high- and low-resource settings to both understand cognitive and emotional function and predict clinical outcomes, such as by measuring maturing visual evoked responses in infants (28). The structure and function of the developing brain can be safely measured with tools such as functional near-infrared spectroscopy and high-field magnetic resonance imaging (MRI). Recently, portable low-field MRI equipment has been used in low-resource settings and is being tested in many global contexts, which could transform access to neuroimaging (29). Methods such as eye tracking provide precise, inexpensive behavioural and physiological markers of cognitive and brain health. Standardized behavioural measures, such as the recently launched Global Scales for Early Development (GSED) are available in an open-access package to measure development of children up to 36 months of age (30, 31). The GSED measures child development holistically through a common unit, the developmental score (D-score).

Technological advances can therefore be used in developing a measurement framework for a global brain health metric. Technology has several potential advantages over behavioural measures. First, it is less likely to be sensitive to cultural and linguistic variation and may thus
The participants noted that cognitive and behavioural assessments of early childhood development could be strengthened by using emerging technologies in developmental cognitive neuroscience.

provide more objective indicators of development. Secondly, to track development over time, it is important that the same technology can be used at different ages; if different methods are used, true developmental change may be difficult to differentiate from measurement error. Thirdly, the new technology may be more sensitive not only to chart the course of development but, in the context of intervention, also more sensitive for distinguishing developmental change from change due to an intervention. It is therefore important to extend and improve the technology used to index brain and behavioural development.

The participants noted that cognitive and behavioural assessments of early childhood development (e.g. GSED or ECDI2030 used to monitor Sustainable Development Goal 4.2.1) could be strengthened by using emerging technologies in developmental cognitive neuroscience. This will require scalable tools and a measurement and interpretation framework adapted to the availability of resources and understanding of cultural and national differences in the lived experience of children.

In drafting a measurement framework for brain health, the following challenges and considerations should be taken into account:

- Measures proposed for inclusion should have robust psychometric properties (i.e. be reliable and valid in diverse local cultural, socioeconomic and linguistic contexts). Tools must be usable and scalable in both high-resource and low-resource settings, be low-cost and scalable to group and population levels if they are to be used in public health.

- Despite the diversity of measures and datasets in the field of cognitive neuroscience, lack of harmonization of standards for data collection and variation in data quality currently limit the (research) questions that can be investigated.

- There must be common understanding of the interpretation of brain health data among countries and cultures. If brain health includes adaptation to challenges in the environment, measurements (with tools for measuring specific outcomes) will differ by country and cultural context with different resources and opportunities. Thus, scientists and practitioners must interpret brain health by considering within-context challenges to growth and demands.

- Different measures can and should capture different aspects of brain health in order to account for the multidimensionality of the construct. The proposed measures should maximize the variance explained in the underlying construct (i.e. brain health) to enhance accuracy and to fine-tune the resulting metric.
3.3 Early markers of outcomes in later life

Early neurodevelopment influences proximal factors, such as school readiness, cognitive function and abilities, social–emotional competence and behavioural regulation (32–34). These outcomes may in turn positively affect more distal outcomes, such as academic performance and health outcomes, social interactions and economic success in adulthood (35–37). Thus, strong neurodevelopmental foundations enhance the brain capital, increasing an individual’s brain health and brain skills for emotional, cognitive and social resources. These proximal and distal effects therefore contribute to long-lasting personal and societal impacts.

For instance, longitudinal birth cohort studies such as COHORTS (38) and the Pelotas study (39) track the intelligence quotient of individuals over time, with standardized assessments to evaluate cognitive abilities, language skills and social–emotional development. Other studies have demonstrated the long-term cognitive effects of early childhood adversity with use of psychological testing, such as the Montreal Cognitive Assessment Test (40). Positive early neurodevelopment is associated with greater economic mobility and a reduced reliance on social support systems. Conversely, individuals who experience neurodevelopmental challenges
The longer the delay to intervention, the more effort will be required to shift the brain in a positive direction, and more effort generally translates into higher costs.

may face difficulties in education and employment, resulting in lower earnings and increased social costs, although other factors, such as socioeconomic background and access to resources, also shape economic outcomes.

Understanding the significant influence of early neurodevelopment on proximal and distal outcomes highlights the importance of investing in early childhood interventions and creating supportive environments to foster optimal neurodevelopment, ultimately promoting positive outcomes in various domains of life. Given that brain plasticity decreases with age, children exposed to hazardous environments in their early years do best if they receive interventions or services during this period. The longer the delay to intervention, the more effort will be required to shift the brain in a positive direction, and more effort generally translates into higher costs. Thus, as economists often remark, “pay now or pay more later”. The cost of redirecting neurodevelopment in a healthy direction is greater the older a child is and/or the longer they must wait for services. For instance, in the Newborn Hearing Screening Program in Cuba, the earlier the detection of hearing loss the better school performance (41, 42). Interventions such as that used in the High Scope Perry Preschool study, which offered pre-school and parental support for at-risk children by home visits (43), had positive long-term results, including better educational performance and future earnings, lower rates of teenage pregnancy and fewer crimes, arrests and prison time in adulthood (44).

Together, the evidence suggests that brain health is a mediating factor between positive and adverse early exposures and later outcomes. For instance, the alterations in brain structure, function and connectivity resulting from early adversity can have cascading effects on cognitive abilities, social–emotional functioning and overall well-being (18). Only a few studies, however, have assessed the causal effect of early adversity mediated by the brain on proximal and distal outcomes statistically. An exception is the Barbados Nutrition Study, which showed that early malnutrition in the first year of life affects cognitive outcome 45 years later and is mediated by brain dysfunction, as demonstrated by quantitative electroencephalography (45).

Understanding the causal pathway between exposure and risk and protective factors in early life and their complex interactions with neurodevelopment and brain health and outcomes in later life is crucial for developing targeted interventions and support systems to mitigate the negative impact of early childhood adversity, promote positive developmental trajectories and influence later-life outcomes.
The meeting participants agreed that the effects of brain health in early life on proximal and distal life outcomes should be established as an indicator for health policies. The framework should therefore consider and address the following.

• Gaps in the current evidence include limitations and flaws in existing frameworks, use of proxy measures, lack of instruments for measuring outcomes, no longitudinal studies, no causal modelling and limited geographical and social diversity.

• To build on and extend this work, the framework should include more direct measures of brain structure and functional integrity, such as EEG or MRI, to establish an association with proximal (early-life) outcomes, such as school readiness, and a long-range life-course view and distal outcomes, particularly in adolescence.

• Although overemphasis should be avoided, it is important to recognize and reflect in the measurement framework that disorders that impact the nervous system can affect quality of life, educational and occupational outcomes and life expectancy.

• Current and new data should be used for precise predictions of and interventions for neurodevelopmental dysfunction and enhancement.

• Scalable programmes for measuring impact and specific mechanisms are essential to improve each individual's opportunities. A new framework for measuring brain health should reflect and be predictive of proximal and distal effects while allowing for scalability according to setting and context.

3.4 Leveraging and synthesizing data and cohorts

To explore the potential utility of existing datasets and brain health measures used in studies and cohorts conducted in low- and middle-income as well as high-income settings for inclusion in the measurement framework, a scoping survey was conducted before the meeting (Box 3). Further context was provided during a dedicated panel session on existing cohorts and datasets.
Box 3. Survey of cohorts and datasets

Over 60 studies on child brain health were found, including cohort studies, randomized controlled trials, registry studies and longitudinal and cross-sectional designs. The studies were conducted in all six WHO regions, and many covered several countries. Most addressed children under 10 years, although some covered the lifespan.

Various predictors of neurodevelopment were studied, including aspects of maternal mental and physical health, environmental factors, safety and security, learning and social connection and access to health care. Over 90% included neurocognitive psychometric testing, while over 50% included data from neuroimaging, physiological biomarkers and/or clinical or functional evaluation. A few assessed the microbiome, and about half included genetic and epigenetic data. In terms of outcomes, information on school readiness and neurological disorders was collected in 40–50% of the studies and on mental and physical health conditions in over 70%. Future income and crime (longer-term outcomes) were addressed in only a few studies.

The available studies include observational and interventional studies in early childhood, long-term cohort studies from early childhood into adulthood and population registries. The data from these studies cover determinants of brain health, such as prenatal and birth exposure, nutrition, parental education and socioeconomic factors; brain health measures such as anthropometry, various screening and diagnostic assessments of neurodevelopmental delays and impairments; and short-, medium- and long-term outcomes, such as school readiness and educational attainment, executive function, social–emotional functioning, mental health and adult income.

In view of the significant investment in these longitudinal cohorts and the rich multi-country datasets, it will be important to leverage them in developing brain health metrics. The cohort studies cover various periods and can be used to identify early-life predictors of brain health at various stages of life, from childhood to adolescence and adulthood. The studies of interventions provide data on their efficacy in improving brain health, which is useful for guiding policy and programme decisions. The fact that existing studies and cohorts cover wide geographies and therefore capture determinants and outcomes of brain health in various cultures and settings further supports the development of a universally applicable brain health metric. The datasets could therefore be used to test a new framework and to identify missing links and evidence gaps for future research. Key recommendations from the meeting can be summarized as follows.

- The datasets should be synthesized and harmonized for more comprehensive analysis. Because of the different objectives and designs of the studies, it will be important to account for bias.
• Synthesis could be facilitated by harmonizing measures, definitions and outcomes from the start. Further, inclusion of more objective measures of brain development and new tools (e.g. MRI, EEG and GSED) in ongoing longitudinal cohorts and interventional studies of children in different settings will refine and improve measures of brain health.

• Meta-analytical approaches could contribute to consolidating the evidence from studies to provide a more complete picture of determinants and outcomes, including similarities and differences among predictive factors globally. Modelling and machine learning techniques could be used to identify patterns, relations and predictive factors for inclusion in brain health metrics.

• Synthesis of the data should result in a comprehensive framework for brain health that could continue to be shaped by research. The harmonized dataset and the framework could be used to identify measures of brain health and to model neurodevelopmental outcomes in different populations and to optimize and select interventions.
3.5 Characteristics of a new framework

As outlined in section 3.2, brain health can be measured directly and/or indirectly with structural and functional neuroscientific methods, neurobehavioural assessments such as GSED or targeted experimental paradigms, and through biological measures, such as genetic risk scores. As for other organs, for which single tests or measurements do not provide a comprehensive picture of health, the participants concluded that a multi-modal measure is likely to be the most appropriate for indexing brain health. They therefore synthesized their discussions on determinants, measures and outcomes for development of a draft measurement framework that could be applied to policy, population monitoring, programme impact and research (Fig 4). The figure summarizes the deliberations of three working groups that are described in the following section.
Fig 4. Components of a draft measurement framework for early-life brain health

**KEY BRAIN HEALTH MEASURES**

**Key measurement criteria and attributes**
- Robust psychometric properties incl. predictive power
- Sensitivity and responsiveness to change/interventions
- Cultural and contextual fairness
- Feasibility and scalability

**Key data requirements**
- Explore existing datasets, incl. cohorts and administrative health databases for relevant data
- Explore inclusion and combination of relevant measures in ongoing prospective studies/cohorts

**Brain structure**

**Brain function**

- **Cognitive/behavioural measures, e.g.** screening assessments
  - GSED, ECDI2030
  - measures of discrete brain functions

- **Neuroimaging, e.g.**
  - MRI
  - EEG

- **Biological/neurophysiological measures, e.g.**
  - hearing and vision, eye-tracking
  - core physiology measures such as sleep and activity
  - polygenic risk scores, saliva, blood

- **Functional measures, e.g.**
  - parent-report participation and quality of life measures

**KEY BRAIN HEALTH OUTCOMES**

**Proximal outcomes**

**School readiness** culturally appropriate measure of cognitive, behavioural and social functioning at school entry

**More distal outcomes**

**Well-being**

**Mental health/conditions** in later life, including cognitive function

**Physical health/conditions** absence of certain diseases and sensory dysfunctions

**Social and economic measures** such as educational attainment and employment
The selection of direct and indirect measures of brain health that 1) can capture the multiple dimensions of brain health, 2) account for different stages of development and different purposes of measurement, and 3) can also predict relevant later-life outcomes should be guided by several considerations.

### 3.5.1 Key measurement criteria

The proposed attributes of measures to be included in the framework are as follows.

- **Reliability, validity and predictive power.** To be considered for inclusion, measures in any multi-modal metric should have sound psychometric properties that, in combination, yield the best estimate of brain health. These include reliability, validity and predictive power of later-life outcomes. As stressed throughout the meeting, brain health in early life can affect later-life outcomes, such as general health, psychosocial well-being, school readiness, educational attainment, employment and life expectancy. A measurement framework should therefore include early-life markers that can predict (a selected group of relevant) outcomes later in life.

- **Sensitivity and responsiveness of measures.** In order to be widely applicable, a new measurement framework and resulting metric(s) should be both sensitive to distribution tails (e.g. extremes of sampling distribution, as those that most require accurate prediction are often the most unusual) and continuously valid, i.e. throughout the child development spectrum. The framework should also be sensitive to risk and resilience factors to ensure that individuals with difficulties due to either identifiable neurological conditions or neurodivergent functional needs are referred to and receive further help. In order for any new metric to be useful for programme evaluation, it should be responsive to change.

- **Cultural and contextual appropriateness.** Measures should also be suitable for resource-limited contexts and readily adaptable to cultural norms. For example, for measures that require administration of a test on tablets or an item kit, consideration should be given to whether the children’s experience with tablets or elements of the kit could influence the measurement.

- **Feasibility and scalability.** Key determinants of feasibility and scalability are availability, accessibility and affordability (low resource needs in terms of both costs and labour). Recent advances in neuroscience and technology have made both direct and indirect measurements of brain health more scalable and feasible during the past decade. In particular, behavioural measures such as GSED and tablet-based paradigms that do not require advanced training or qualifications and new technologies for measuring brain function (EEG) and brain structure (MRI) make their inclusion in a multi-modal index for brain health possible. In order to increase feasibility, a triaged approach would be optimal, whereby established scalable metrics, such as GSED, could be complemented by more advanced EEG or MRI in smaller but widely representative (research) samples or in subgroups identified after screening as requiring follow-up with several techniques, stratified by geographical representation or national gross domestic product.

### 3.5.2 Key measures to include in the framework

Suggestions for measures that could be tested for inclusion in an integrated metric fell into three main categories, although different groups assigned different importance to individual measures. The following were agreed to be important:
Discussions

- a broadly valid, scalable cognitive or behavioural measure such as GSED, measures of discrete brain functions (e.g. language, cognition, socio-emotional development and emerging executive functions, including attention and self-regulation) and measures for early identification of individuals with neurological or neurodevelopmental impairment to facilitate intervention;
- measures of neurobiological structure and function, such as MRI and EEG;
- more general measures of neurophysiological processes and health (e.g. hearing and vision, core physiology, such as sleep and activity, and polygenic risk scores);
- measures of levels of participation and function in society; and
- recognition that research on measurement is continuing and that measures will probably have to be updated as new methods emerge.

In considering the measures to be included, the three groups concluded that a new multi-modal metric should reflect and respond to various settings and scenarios. Therefore, a layered or tiered approach might be best suited to the requirements of population-based monitoring, programme or intervention evaluation and research. Depth and complexity would be added incrementally to the tiers (Fig. 5). The hierarchy of measures could be conceived as an inverse pyramid, with policy and population-relevant measures and clinically relevant screening at the top, the focus narrowing to programme level, including behavioural and then detailed, more resource-demanding neuroimaging measures. At deeper levels, more scalable measures should still be included to better calibrate and understand neuroimaging results. For example, research samples could include both gold-standard and scalable measures to link deep phenotyping findings with population-level readouts of brain health. Several participants and groups also stressed that any set of measurements must be compatible with modern computer modelling and machine-learning techniques.

Fig 5.
Proposed tiers of measurement

**POPULATION LEVEL:** Adequate representation in terms of geography, culture, sex, etc.

**INDIVIDUAL LEVEL:** In-depth understanding of underlying neurobiological processes in young children.

Note: Precision is greater at individual level, while coverage is greater at population level.
3.5.3 Key outcomes to be considered

The groups agreed that a proximal outcome of early brain health be included in the measurement framework, which would correspond roughly to the end of the main age range considered at the meeting (5 years). There was also strong agreement that any proximal outcome measure should itself be a reliable predictor of outcomes later in life. In view of the focus of the meeting on early life, the groups agreed that a culturally appropriate measure of cognitive, behavioural and social functioning at school entry was the most appropriate functional outcome measure for this period.

They noted, however, that additional factors of particular relevance to children and their caregivers should also be captured, including psychosocial well-being at both proximal and distal times. Other important downstream outcomes include physical health (such as absence of various noncommunicable diseases and sensory function, such as vision and hearing) and measures of mental health and cognition at older ages, when a more nuanced view of the range of domains is possible.
3.5.4 Key data requirements

The participants agreed that existing databases, including administrative health databases, could be explored for retrospective inclusion of brain health measures. Conceptual and statistical methods could be used to prioritize the measures that would be most useful and predictive at specific ages; however, studies should be identified that would be appropriate for potential inclusion in models that require harmonized data for key determinants, measures and outcomes.

Prospective studies with longitudinal GSED data and health-related, behavioural and short-term outcomes would be a key resource base. While it was recognized that existing cohorts (both past and current) should be the main source, ongoing cohorts in which children in the early life phase are still being seen should be prioritized in the short term to optimize harmonization of measures and potentially to add elements of particular interest for model testing (e.g. MRI). Moreover, in selecting statistical models, consideration should be given to balancing accuracy and complexity with ensuring that the metric can be interpreted by and has meaning for a non-expert public.

Recommendations for measuring brain health at any scale also require an ethical framework and infrastructure to guide the use and interpretation of brain measurements appropriately.
4. Conclusions and next steps

An integrated measurement framework with a tiered approach to selecting measures was favoured at the end of the 2-day discussions. Largely scalable measures could be used to inform "the bigger picture", while more resource-intensive and neurobiological methods could be used to validate the overall metric and to measure outcomes appropriately. As measurements and algorithms become more sophisticated, they should include the feasibility of scaling for global application, while retaining fidelity. In addition, ultimately, efforts to develop a unified brain health metric would need to be extended to cover the entire lifespan. However, for the purposes of this meeting and to manage the scope, the initial focus was on the first years of life.

Priorities for the next steps in development of a brain health metric for early life should include the following.

- Establish a community of practice. The experts expressed their appreciation of the interdisciplinary exchanges during the 2-day meeting and recommended continued collaboration to take the task forward. To facilitate continued exchange and collaboration, an extended community of practice could be established, reaching beyond the meeting participants for wider geographical representation. The community would contribute to building bridges among disciplines, facilitating collaboration, synergies and sharing of resources and for future policy development. The community might also be useful for completing the necessary activities.

- Comprehensively map available cohorts and datasets. Building on the survey, fully map existing cohorts and datasets, and extract measures, determinants and outcomes. Similar work has been conducted with the international family of ageing, health and retirement studies that are being conducted in many countries and whose data are available at the Gateway of global aging data (https://g2aqing.org/app/home) as important steps in harmonizing data.
• Create harmonized dataset(s) from available cohorts. Extract and harmonize relevant data from the cohorts through collaboration and data-sharing. Different legal frameworks and legislation on data-sharing in countries might require flexible inclusion of data and harmonized data spaces.

• Generate evidence gap maps on determinants and outcomes of child development. Collate evidence on the influence of specific determinants on domains of brain health and neurological and neurodevelopmental disability in children aged 0–5 years and on indicators at times when they are most relevant.

• Develop comprehensive data models to test the framework and its components, mainly by pooling existing and secondary data to the extent possible. The new metric should be validated against existing measures and datasets by stratifying data on an appropriate, diverse subsample of all measures, allowing for collection of data on sub-domains. Validation should also include establishing the predictive validity of the new metric, especially between very early childhood and school entry.

• Extend data collection protocols. The brain health of children aged 3–5 years should be assessed with measures that include higher cognitive function. These could include adaptation and modification of GSED protocols (which are restricted to children aged 0–3 years) to include broader, age-specific developmental norms and also neurodiversity.

• Develop equitable ethical and legal frameworks and requirements. The community of practice could recommend an ethical framework and infrastructure to ensure equity, data-sharing and use of existing data and also guide the use and interpretation of the brain measurements.

• Inform policies and decisions. A new metric for brain health in early life can be used to measure progress in reaching global policy goals for existing and potential new mandates and commitments, guide resource allocation (government expenditure on health and education; product development) and provide crucial support for children in reaching their neurodevelopmental potential.
References


Annex 1. List of participants

External participants

- Alexander, Daniel, University College London, London, United Kingdom
- Abubakar, Amina, Aga Khan University, Kilifi, Kenya
- Amso, Dima, Columbia University, New York City (NY), USA
- Bhutta, Zulfiqar, Institute for Global Health and Development, Agha Khan University, Karachi, Pakistan
- Bjørk, Marte-Helene, University of Bergen, Bergen, Norway
- Black, Maureen, University of Maryland, Severna Park (MD), USA
- Bringas Vega, Maria Luisa, Cuban Neuroscience Center, Havana City, Cuba
- Bryne, Einar, Norwegian Directorate of Health, Tonsberg, Norway
- Buss, Claudia, Charité Institute of Medical Psychology, Berlin, Germany
- Cousin, Ewerton, Institute for Health Metrics and Evaluation, Seattle (WA), USA
- Deoni, Sean, Bill & Melinda Gates Foundation, Seattle (WA), USA
- Donald, Kirsty, University of Cape Town, Cape Town, South Africa
- Eyre, Harris, Rice University, Houston (TX), USA
- Fair, Damien, University of Minnesota, Minneapolis (MN), USA
- Fortin, Alvaro, United Nations Children's Fund, Beirut, Lebanon
- Gakidou, Emmanuela, Institute for Health Metrics and Evaluation, Seattle (WA), USA
- Garbard-Durnam, Laurel, Northeastern University, Boston (MA), USA
- Gladstone, Melissa, University of Liverpool, Liverpool, United Kingdom
- Haas, Magali, Cohen Veterans Bioscience, New York City (NY), USA
- Helsby, Gaya, Bill & Melinda Gates Foundation, Seattle (WA), USA
- Hill, Sean, University of Toronto, Toronto (Ont), Canada, and Federal Institute of Technology, Lausanne, Switzerland
- Holla, Alaka, World Bank, Washington DC, USA
- Jafri Kaleem, Sidra, Agha Khan University, Karachi, Pakistan
- Janus, Magdalena, McMaster University, Hamilton (Ont), Canada
- Kakooza-Mwesige, Angelina, Makerere University College of Health Sciences, Kampala, Uganda
- Kumar, Aarti, Community Empowerment Lab, New Delhi, India
- Maalouf, Fadi, American University of Beirut, Beirut, Lebanon
- Martinus, Ammaarah, UNESCO Mahatma Gandhi Institute of Education for Peace and Sustainable Development, New Delhi, India
- Mullany, Erin, Institute for Health Metrics and Evaluation, Seattle (WA), USA
- Murray, Joseph, Federal University of Pelotas, Pelotas, Brazil
- Nelson, Charles, Boston Children's Hospital and Harvard Medical School, Newton (MA), USA
• Proctor, Joshua L., Bill & Melinda Gates Foundation, Seattle (WA), USA
• Ramírez-Zea, Manuel, Institute of Nutrition of Central America and Panama, Guatemala City, Guatemala
• Rao, Nirmala, The University of Hong Kong, Hong Kong, China
• Richter, Linda, University of the Witwatersrand, Johannesburg, South Africa
• Salam, Joseph, Bill & Melinda Gates Foundation, Seattle (WA), USA
• Sazawal, Sunil, Centre for Public Health Kinetics, New Delhi, India
• Scerif, Gaia, University of Oxford, Oxford, United Kingdom
• Stein, Aryeh, Emory University, Atlanta (GA), USA
• Steinmetz, Jaimie, Institute for Health Metrics and Evaluation, Seattle (WA), USA
• Swieboda, Pawel, EBRAINS, Brussels, Belgium
• Taneja, Sunita, Centre for Health Research and Development, New Delhi, India
• Valdes-Sosa, Pedro, Global Brain Consortium, Chengdu, China
• Weber, Ann, University of Nevada, Reno (NV), USA
• Wedderburn, Catherine, University of Cape Town, Cape Town, South Africa
• Williams, Steve, King's College London, London, United Kingdom

**WHO staff**

• Amuthavalli, Jothees, Technical Officer (epidemiologist), Ageing and Health unit, Maternal, Newborn, Child and Adolescent Health and Ageing
• Cao, Bochen, statistician, Monitoring, Forecasting and Inequalities unit, Data and Analytics
• Cavallera, Vanessa, Technical officer, Brain Health unit, Mental Health and Substance Use
• Daelmans, Bernadette, Unit Head, Child Health and Development unit, Maternal, Newborn, Child and Adolescent Health and Ageing
• Dua, Tarun, Unit Head, Brain Health unit, Mental Health and Substance Use
• Seeher, Katrin, Mental health specialist, Brain Health unit, Mental Health and Substance Use
• Servili, Chiara, Technical officer, Brain Health unit, Mental Health and Substance Use
Annex 2. Meeting agenda

The aim of this technical meeting was to bring together key stakeholders and subject matter experts to identify the key components of a measurement framework for brain health in early life that is robust and versatile and can be used in different scenarios and models.

Objectives

• to outline key components of a measurement framework for brain health
• to map current efforts to operationalize and measure brain health in early life
• to understand requirements and modelling strategies for integrating individual brain health measures into population metrics
• to identify synergies of existing initiatives and datasets and discuss gaps and needs for future metrics development

Expected outcomes

• draft measurement framework(s)
• a meeting report and an article in a peer-reviewed journal
• areas for future work.

Day 1

08:30–09:00 Registration and WHO security clearance

Session 1 Welcome and introductions

Objective: To welcome everyone, introduce participants and provide overall context and setting, describe the meeting objectives and expected outcomes and how efforts fit strategically into the overall vision and allow partners to present their ideas.

Session chair: Tarun Dua

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<thead>
<tr>
<th>Title</th>
<th>Presenter</th>
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<tbody>
<tr>
<td>09:00–09:10 Welcome</td>
<td>Tarun Dua</td>
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<td>09:10–09:20 Global context and setting the scene</td>
<td>Tarun Dua</td>
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<td>09:20–09:30 Brain health estimation in Global Burden of Disease</td>
<td>Emmanuela Gakidou</td>
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<tr>
<td>09:30–09:40 MNCH D&amp;T goals and aspirations for early neurodevelopment</td>
<td>Joseph Salama</td>
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<tr>
<td>09:40–09:50 Agenda and housekeeping</td>
<td>Tarun Dua</td>
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<tr>
<td>09:50–10:05 Overview of participants by expertise and contributions Introduction to the ice-breaker activity</td>
<td>Catherine Wedderburn and Jaimie Steinmetz</td>
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10:05–10:50 Tea/coffee
**Session 2**  
**What is brain health and what are the different ways of measuring it?**

**Session objective:** To summarize evidence on determinants and measurement of brain function and structure in early life by different approaches. The session will conclude with a panel on current understanding of effects of child neurodevelopment on later outcomes. In each panel, questions will be to the panelists, followed by a brief discussion.

**Session chair:** Emmanuela Gakidou

<table>
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<tr>
<th>Time</th>
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<tr>
<td>10:50–10:55</td>
<td>Panel introduction</td>
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<td>Emmanuela Gakidou</td>
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<td>10:55–11:40</td>
<td><strong>Panel 1:</strong> Determinants of childhood neurodevelopment</td>
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<td>• Brain development in the early years</td>
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<td>• Risk and protective factors in pregnancy and early childhood (determinants)</td>
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<td><strong>Moderator:</strong> Linda Richter</td>
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<td></td>
<td><strong>Panelists:</strong> Amina Abubakar, Fadi Maalouf, Charles Nelson, Gaia Scerif</td>
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<td><strong>Resource person:</strong> Catherine Wedderburn</td>
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<td><strong>Guiding questions for the panel:</strong></td>
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<td>• How does early brain development map onto functional outcomes?</td>
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<td>• What defines something as a risk or a protective factor for brain health? How are proxies of brain health, e.g. stunting, determined?</td>
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<td>• How can we best define the roles of risk/protective factors in early brain development, including as moderators or mediators, considering that they are often interrelated, multiple, simultaneous and accumulate over time?</td>
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<td>• How do we assess time-variable risk/protective factors in pregnancy and childhood?</td>
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<td>11:40–12:25</td>
<td><strong>Panel 2:</strong> Brain health measurements</td>
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<td>• Cognitive / behavioural / psychometric measures</td>
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<td>• Neurophysiological/biological measures</td>
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<td><strong>Moderator:</strong> Dima Amso</td>
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<td><strong>Panelists:</strong> Damien Fair, Laurel Garbard-Durnam, Angelina Kakooza-Mwesige, Ann Weber</td>
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<td><strong>Resource person:</strong> Kirsty Donald</td>
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Guiding questions for the panel:

• What are the key neurocognitive and neurophysiological measures, including leveraging emerging technologies? What are the most pressing gaps in evidence for comparative accuracy of such measures?

• What have you learnt about brain measurement from doing large studies on brain development? What are the most important factors to consider when selecting measures of brain health?

• How do we integrate information/data from multiple measures of brain health? What are the challenges involved in doing so and what are some examples?

• How can we best track trajectories of brain health, and what factors should we consider when doing so? How do we define a good brain health outcome/at risk/not on track?

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<tr>
<th>12:25–13:10</th>
<th>Panel 3: How childhood neurodevelopment affects later outcomes (health, social, and economic)</th>
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<tr>
<td>Moderator:</td>
<td>Pedro Valdes-Sosa</td>
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<td>Panelists:</td>
<td>Maria Luisa Bringas Vega, Alvaro Fortin, Magali Haas, Joseph Murray, Aryeh Stein</td>
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<td>Resource person:</td>
<td>Ewerton Cousin</td>
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Guiding questions for the panel:

• How does early neurodevelopment impact proximal (e.g. school readiness) and distal (e.g. employment) health, social, and economic outcomes? What are the key outcomes impacted?

• How are outcomes measured in existing studies?

• What evidence exists that neurodevelopment mediates the effects of adverse early exposures on later outcomes?

• What other mediators need to be considered, on top of early development?

• What is an example of quantifying the effect of early brain development on a later outcome?

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<thead>
<tr>
<th>13:10–13:15</th>
<th>Breakout group introduction: Katrin Seeher</th>
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<td>13:15–14:15</td>
<td>Lunch and group photograph</td>
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Session 3  Break-out groups

14:15–15:30  Session objective: To discuss in smaller groups the individual streams below and develop recommendations for inclusion of key elements in the framework

Stream 1: Determinants

Stream 2: Measures and biomarkers

Stream 3: Health, social and economic outcomes

For each stream, this session will be dedicated to, first, information gathering and appraising and establishing the status quo, and, secondly, on making a recommendation on what to propose for inclusion in the framework.

Session chair: Katrin Seeher

Stream 1: Determinants

Moderator: Claudia Buss


Rapporteur: Linda Richter

Resource person: Vanessa Cavallera

Guiding questions for the breakout group:

• Which are the most important/relevant risk and protective factors for early brain development from each of the determinant clusters during different developmental periods?

• How do these link to existing global mandates?

• Which brain health determinants should be included in the framework?

• How are these determinants measured within existing studies? How do we account for their interrelations?

Stream 2: Measures and biomarkers

Moderator: Steve Williams

Participants: Amina Abubakar, Dima Amso, Marte-Helene Bjørk, Maria Luisa Bringas Vega, Laurel Garbard-Durnam, Melissa Gladstone, Aarti Kumar, Pawel Swieboda, Pedro Valdes-Sosa

Rapporteur: Ann Weber

Resource person: Kirsty Donald
Guiding questions for the breakout group:

- What measures/metrics are the most informative for early brain development? What non-neurological biomarkers are most strongly correlated with early neurodevelopment?
- Which measures and biomarkers are most useful in different contexts? How can we apply new(er) techniques to existing (and future) data & learnings (including AI) from other fields for better brain health metrics?
- Which brain health measures should be included in the framework?
- How are these measures / biomarkers collected in existing studies?

Stream 3: Health, social and economic outcomes

Moderator: Nirmala Rao

Participants: Daniel Alexander, Damien Fair, Alvaro Fortin, Magali Haas, Sean Hill, Alaka Holla, Magdalena Janus, Ammaarah Martinus, Gaia Scerif, Aryeh Stein, Sunita Taneja

Rapporteur: Harris Eyre

Resource person: Jaimie Steinmetz

Guiding questions for the breakout group:

- What are the key early and later health outcomes (including school readiness and/or other mental or physical health) linked to early childhood development?
- What are the key early and later social and economic outcomes (e.g. human capital) linked to childhood development?
- Which health and non-health outcomes should be included in the framework?
- How are these outcomes measured in existing studies?

15:30–16:00 Tea or coffee

Session 4 Feedback and outlook for day 2

Session objective: Opportunity for participants to share and reflect on day 1

Session chair: Katrin Seeher

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:00–16:15</td>
<td>Working group reflections on Determinants</td>
<td>Claudia Buss and Linda Richter</td>
</tr>
<tr>
<td>16:15–16:30</td>
<td>Working group reflections on Measures and biomarkers</td>
<td>Steve Williams and Ann Weber</td>
</tr>
<tr>
<td>16:30–16:45</td>
<td>Working group reflections on Health, social, and economic outcomes</td>
<td>Nirmala Rao and Harris Eyre</td>
</tr>
<tr>
<td>16:45–17:30</td>
<td>Group discussion and main messages</td>
<td>Katrin Seeher</td>
</tr>
</tbody>
</table>

End of day 1
## Day 2

### Session 5  
**Overnight thoughts and welcome back**

**Session objective:** Reflect on day 1 and introduce day 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:30–08:40</td>
<td>Welcome back</td>
<td>Tarun Dua</td>
</tr>
<tr>
<td>08:40–09:15</td>
<td>Feedback from participants on day 1</td>
<td>Catherine Wedderburn</td>
</tr>
</tbody>
</table>

### Session 6  
**What data and indices exist, and how are they related to population metrics?**

**Session objective:** To summarize existing studies and data in the field of neurodevelopment, discuss how they may be used, and explore downstream uses (programme, policy and research) of neurodevelopmental population metrics.

**Session chair:** Emmanuela Gakidou

<table>
<thead>
<tr>
<th>Time</th>
<th>Panel 4: Existing cohorts and intervention studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:15–10:00</td>
<td>Discussion of existing cohorts, the data that is collected, including determinants of brain health, measures, outcomes; time intervals; gaps; and how studies might incorporate brain health measures in the future.</td>
</tr>
</tbody>
</table>

**Moderator:** Aarti Kumar

**Panelists:** Marte-Helene Bjork, Sidra Kaleem, Manuel Ramírez-Zea, Sunil Sazawal, Sunita Taneja

**Resource person:** Kirsty Donald

**Guiding questions for the panel:**

- What datasets/biobanks and national registries exist that can be used to answer research and/or programme impact questions related to brain metrics? What data do they collect in terms of measures of brain health, determinants, outcomes; time intervals; gaps – focusing on day 1 discussions?

- What statistical models are used in existing cohort/intervention studies? What machine learning approaches are available to better synthesise and harvest existing data across studies and how could they be applied?

- What are some examples of research and programmatic questions related to brain metrics? How can we mine the current datasets/biobanks/registries to answer questions related to brain metrics?

- How can we incorporate different data collection methods into existing studies to inform population metrics / frameworks?
Panel 5: Downstream uses of neurodevelopmental population metrics across contexts and user perspectives

- Principles for including a measure into an index/population metric
- Examples of why and how proxy measures (e.g. stunting) have been integrated into metrics that are used to inform decision-making to evaluate which approach(es) are best for scaling up
- Understanding brain metric benchmarking and different user perspectives

Moderator: Melissa Gladstone
Panelists: Einar Bryne, Harris Eyre, Sean Hill, Pawel Swieboda
Resource person: Ewerton Cousin

Guiding questions for this panel:

- What are the principles for including a measure as an index/population metric? What aspects are important to inform metric utilization?
- What is the pathway from measure to downstream use across user perspectives (programme, policy, and research)?
- How can existing brain health measures translate into population metrics? How could we use a framework in our research, policy, programme and other intervention scenarios?
- How have other indices or proxy measures been integrated as population metrics and used to inform decision-making and policy?

Session 7 Sprint breakout session: Draft framework

Session objective: To brainstorm framework criteria and components in smaller groups and draft frameworks

Session chair: Catherine Wedderburn

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:15–11:30</td>
<td>What does the framework look like? Introduction to the sprint breakout groups</td>
<td>Catherine Wedderburn</td>
</tr>
</tbody>
</table>
Guiding questions for sprint breakout groups:

• What criteria or properties does this metric/collection of measures need?
  e.g. ability to measure trajectories, policy effects; scalability; validity

• What will give us the most relevant and fit-for-purpose measure of brain health/function?
  e.g. a global index or several measures or individual domain scores

• What were your top considerations in developing this framework?
  e.g. key determinants and health and non-health outcomes

• In what setting, and for what purpose, do you propose developing such a metric?
  e.g. modelling, research, programmes, policy

• What type of data / sources would you propose to use to validate these?
  e.g. different studies, consider standardization and comparability across settings

11:30–13:00

**Moderator:** Maureen Black  
**Participants:** Einar Bryne, Zulfi Bhutta, Claudia Buss, Damien Fair, Alvaro Fortin, Angelina Kakooza-Mwesige, Aarti Kumar, Ammaarah Martinus, Aryeh Stein, Pawel Swieboda, Sunita Taneja, Steve Williams  
**Rapporteur:** Melissa Gladstone  
**Resource person:** Erin Mullany

13:00–14:00  
**Lunch**
Session 8  Feedback: Bringing it all together

**Session objective:** to synthesize the discussions at this meeting and outline the scope of the next steps

**Session chair:** Kirsty Donald

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Presenter</th>
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</thead>
<tbody>
<tr>
<td>14:00–14:15</td>
<td>Group 1 presents draft framework</td>
<td>Maureen Black &amp; Melissa Gladstone</td>
</tr>
<tr>
<td>14:15–14:30</td>
<td>Group 2 presents draft framework</td>
<td>Danny Alexander &amp; Laurel Garbard–Durnam</td>
</tr>
<tr>
<td>14:30–14:45</td>
<td>Group 3 presents draft framework</td>
<td>Magdalena Janus &amp; Gaia Scerif</td>
</tr>
<tr>
<td>14:45–15:15</td>
<td>Plenary discussion on draft frameworks</td>
<td>Kirsty Donald</td>
</tr>
<tr>
<td>15:15–15:50</td>
<td>Bringing it all together and next steps</td>
<td>Kirsty Donald &amp; Emmanuela Gakidou</td>
</tr>
<tr>
<td>15:50–16:00</td>
<td>Close and thanks</td>
<td>Tarun Dua</td>
</tr>
</tbody>
</table>

End of meeting
Annex 3. Themes and proposed characteristics of a new measurement framework

Participants formed three groups to discuss the potential components of a new measurement framework. The emerging themes from those discussions are summarized below and formed the basis for Fig 4 in this document.

<table>
<thead>
<tr>
<th>Theme</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement criteria</td>
<td>Early years</td>
<td>Feasibility</td>
<td>Harmonization with metrics for older children</td>
</tr>
<tr>
<td></td>
<td>Trajectory: stable within the trajectory</td>
<td>Psychometrics (reliability)</td>
<td>Sensitivity to determinants of development (not easily confounded)</td>
</tr>
<tr>
<td></td>
<td>Valid across countries</td>
<td>Sensitivity to distribution tails</td>
<td>Scalable</td>
</tr>
<tr>
<td></td>
<td>Should screen and identify children with difficulties or the prevalence of children at risk of disability</td>
<td>Cultural appropriateness</td>
<td>Valid</td>
</tr>
<tr>
<td></td>
<td>Predictive validity</td>
<td>Predictive power</td>
<td>For programmes and research: Ability to separate domains of brain health in discrete measurements</td>
</tr>
<tr>
<td>Measures to be included</td>
<td>Child development</td>
<td>Gold standards:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GSED</td>
<td>Policy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• structural MRI</td>
<td>Behaviour test / holistic development (GSED)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• resting EEG</td>
<td>Functional measure / participation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• tablet tasks (e.g. baby toolkit)</td>
<td>Sensory test (hearing, vision) e.g. eye tracking</td>
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<tr>
<td></td>
<td></td>
<td>• polygenic risk scores (saliva/blood)</td>
<td>Language / cognitive / executive function</td>
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<tr>
<td></td>
<td></td>
<td>• sleep/activity (wearables)</td>
<td>Socioemotional development and self-regulation</td>
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<tr>
<td></td>
<td></td>
<td>Essential/core:</td>
<td>Screen for neurodevelopmental impairments / disorders (GSED +?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• GSED/tablet tasks</td>
<td>Programme:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• MRI and/or EEG</td>
<td>Electrophysiology (e.g. quantitative EEG, evoked potentials)</td>
</tr>
</tbody>
</table>
Measures of early-life brain health at population level - Report of a technical meeting

- polygenic risk scores (saliva/blood)

Research (into metrics for brain health):
- MRI to further improve metrics and interpretation of functional evidence
- D-score type with scores on different scales to create an Index
- different levels of measurement of the same constructs

<table>
<thead>
<tr>
<th>Outcomes of brain health (including human and social capital)</th>
<th>Pre-school:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition at age 18 in one data set</td>
<td>Developmental health / school readiness / performance</td>
</tr>
<tr>
<td>Predict school attainment</td>
<td>Emotional well-being</td>
</tr>
<tr>
<td>Well-being in adulthood</td>
<td>School:</td>
</tr>
<tr>
<td>Fewer noncommunicable diseases</td>
<td>Intelligence?</td>
</tr>
<tr>
<td></td>
<td>Function?</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
</tr>
<tr>
<td></td>
<td>Adult life:</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
</tr>
</tbody>
</table>

| Data requirements | |
|-------------------||
| Existing cohort studies already have relevant data | Use statistical and conceptual methods to prioritize the measure that is most useful and predictive at specific ages |
| Prospective studies with GSED over time, with health- and behaviour-related and short-term outcomes | Identify studies for collection of harmonized data for a glossary |
|                                                          | Develop glossary |
|                                                          | Improved, scalable gold standard |
|                                                          | Stratified, multi-scale approach |
|                                                          | Harmonizing and standardizing structural metrics assessment tools |

| Data requirements | |
|-------------------||
| Existing cohort studies already have relevant data | |
| Ethical infrastructure necessary for use of index readout | |
| Build brain measures into existing cohorts | |
| 5-min MRI ready to implement | |
| Statistical modeling (e.g. trade-off between interpretability and accuracy) | |
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