

REVIEW **OPEN**

A focus on adolescence to reduce neurological, mental health and substance-use disability

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Globally, there is a crucial need to prioritize research directed at reducing neurological, mental health and substance-use disorders in adolescence, which is a pivotal age for the development of self-control and regulation. In adolescence, behaviour optimally advances towards adaptive long-term goals and suppresses conflicting maladaptive short-lived urges to balance impulsivity, exploration and defiance, while establishing effective societal participation. When self-control fails to develop, violence, injury and neurological, mental health and substance-use disorders can result, further challenging the development of self-regulation and impeding the transition to a productive adulthood. Adolescent outcomes, positive and negative, arise from both a life-course perspective and within a socioecological framework. Little is known about the emergence of self-control and regulation in adolescents in low- and middle-income countries where enormous environmental threats are more common (for example, poverty, war, local conflicts, sex trafficking and slavery, early marriage and/or pregnancy, and the absence of adequate access to education) than in high-income countries and can threaten optimal neurodevelopment. Research must develop or adapt appropriate assessments of adolescent ability and disability, social inclusion and exclusion, normative development, and neurological, mental health and substance-use disorders. Socioecological challenges in low- and middle-income countries require innovative strategies to prevent mental health, neurological and substance-use disorders and develop effective interventions for adolescents at risk, especially those already living with these disorders and the consequent disability.

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Adolescent neurological, mental health and substance-use (NMS) disorders in low- and middle-income countries (LMICs) must be addressed to ensure optimal development of ‘human capital’ for the future¹. Adolescents, defined by the World Health Organization (WHO) as those between 10 and 19 years of age, represent an estimated 1.2 billion of the world’s population². During these years, cognitive development continues to unfold, socioemotional development advances dramatically, and a constellation of NMS disorders reaches a peak during adolescence and early adulthood^{3,4} (Fig. 1). Research and practice in LMICs have focused on children under five years old, whereas adolescents are rarely prioritized.

Indeed, more than 15% of disability-adjusted life years (DALYs) are attributable to adolescents and young adults (20–24 years old), with DALY rates in Africa 2.5 times that of high-income countries⁵. Globally, the primary causes of years lost due to disability (YLD) for adolescents include neuropsychiatric disorders (45%), unintentional injuries (12%) and infectious diseases (10%)⁵. Up to 20% of young adults have a disabling mental illness, and up to 50% of adult mental health disorders experience their onset in adolescence⁶. Adolescence has received more attention since being made a high priority by the United Nations programme UNICEF and other agencies^{1,7}, facilitating opportunities for prevention of NMS disorders and support for adolescents already living

with these conditions (Box 1).

Adolescence is a crucial period of brain development that leads to increased self-regulation. However, concomitant impulsiveness can lead to risky behaviours that result in impaired cognitive or emotional development, lifelong disability and even death. These behaviours and challenging environmental exposures often interact over time, compounding their effects. For example, early initiation of substance misuse might lead to impaired cognitive and affective development, later addiction, brain injury and other health-related disorders such as HIV/AIDS⁸.

The impact of NMS disorders on adolescents is best understood from a life-course perspective. In this Review, we highlight only the causes of NMS disorders that tend to first appear during adolescence. We consider risk and resilience through a socioecological model in which an adolescent with a particular genome undergoes physical and hormonal transformations within the context of a family, peers, school, work, community and culture all of which can be instrumental in determining adolescent NMS outcomes. Few studies have been conducted using parallel methods across high-income countries and LMICs, and since it is not clear to what extent findings in high-income countries can be generalized to LMICs, we suggest that there is a need for comparative research using parallel methods. This Review focuses on research priorities to reduce the most important threats to

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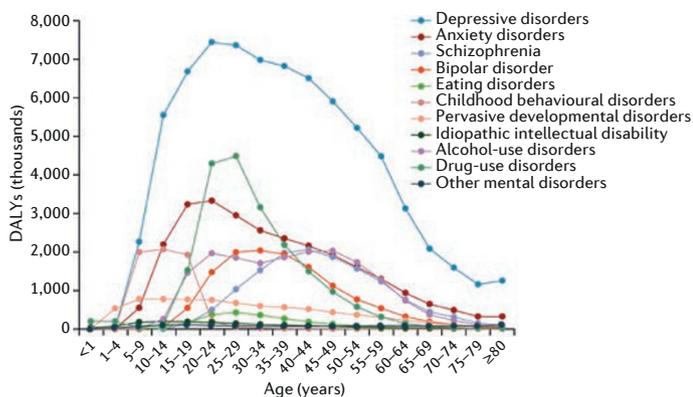


Figure 1 | Disability-adjusted life years (DALYs) for each neurological, mental health and substance-use (NMS) disorder in 2010 by age*. Note the rise of NMS disorders in late childhood and adolescence, particularly depression, anxiety, alcohol and other drug-use disorders. Reprinted with permission from ref. 4.

adolescents in LMICs and contains suggestions to improve methodology and a brief list of high-impact research priorities (Box 2). We also suggest a range of broader research opportunities, priorities and challenges, including research capacity building (Supplementary Table 1).

NEURODEVELOPMENT AND NMS DISORDERS

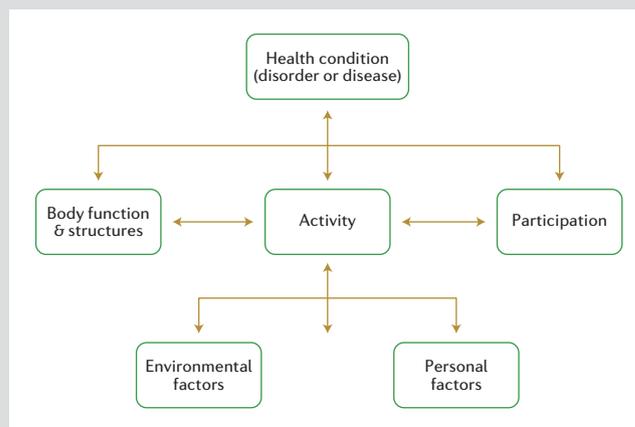
Adolescence is a time of profound change as young adults cope with increasing independence and the growing importance of social and sexual relationships, while simultaneously developing and exercising self-control. It is unknown whether hormonal, cognitive, affective and societal transitions from childhood to adolescence occur in a similar time frame and sequence in LMICs as they do in high-income countries, or whether any differences in timing or sequencing affect neural development. The likelihood that an adolescent will develop a specific NMS-related disability depends to some extent on the balance between higher order cognitive function (known as executive control) and environmental pressures, societal expectations and impulsivity, and the way in which the individual processes emotional, social and behavioural cues⁹⁻¹² (Fig. 2). The impact of adolescent NMS disorders can be exacerbated by early exposure to risk factors that are more prevalent in LMICs (for example, malnutrition, infectious disease, abuse, neglect, internal conflict or war, early pregnancy and marriage, and adolescent labour). Consequently, adolescents in LMICs may be at a higher risk than their counterparts in high-income countries.

The recent Well-Being of Adolescents in Vulnerable Environments study used identical methods to study adolescents from disadvantaged areas in five cities: Baltimore, Shanghai, Delhi, Ibadan and Johannesburg. Neighbourhood physical and social exposures were associated with adolescent disorders in LMICs and high-income countries, although patterns and degree of association varied. The authors concluded that “for young people growing up in poverty, residency in a high-income country may matter far less than the immediate social contexts within which they develop and grow”¹³. There is also evidence¹⁴ that in settings where socioeconomic disparities are great that depression is especially high compared with places where poverty is almost universal. Such findings illustrate the need for longitudinal and cross-sectional multi-country studies using comparable methods across differing levels of economic and social development.

PREVENTION OF NMS DISABILITY

An overview of research priorities for prevention of NMS disability is presented in Supplementary Table 1. Adolescents and young adults experience the highest amounts of violence, both towards self (self-harm and suicide) and others (partner violence, delinquent behaviour, criminal acts and war-related trauma)². In addition, adolescents are at increased risk of a range of health problems that can lead to NMS disability

BOX 1 | HUMAN RIGHTS AND ADOLESCENT RESEARCH



Two major international conventions and a new classification system transformed opportunities to support optimal development for children and adolescents living with neurological, mental health and substance-use disorders and for the primary prevention of disabling disorders. The Convention on the Rights of the Child (which includes adolescents) and the Convention on the Rights of People with Disabilities hold nations responsible for ensuring optimal developmental outcomes for children and adolescents and guarantee rights for those living with disabilities. These rights also commit countries to support adolescents in social inclusion and participation in society, and reduce stigma.

The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) takes account of the interaction between the biology of a given individual and the specific external challenges or supports affecting an individual's ability to function. It also acknowledges societal structures (environmental factors) that decrease or increase barriers to participation and inclusion⁴⁷. The ICF-CY, outlined in the Figure, relies on concepts of disability rather than disorder-specific pathology or morbidity and incorporates a socioecological framework. This highlights the importance of environmental context alongside genetic risk as a child develops through adolescence to adulthood.

such as HIV/AIDS, meningitis, and trauma due to civil and interpersonal violence, as well as unintentional injury such as road traffic accidents⁵.

Gender inequality, education, pregnancy and violence

Increases in gender inequality during adolescence are evident in many LMICs, with a higher proportion of boys than girls completing secondary school. This directly results in a substantial gender gap in education and literacy rates² and indirectly in differential opportunities for the development of executive function, self-regulation and employability. Intimate partner violence (IPV) against women also peaks during adolescence and is a known risk factor for acquiring HIV as well as brain trauma, post traumatic stress disorder (PTSD) and depression. The WHO multicountry study found that in women aged 15-24 who have ever had a romantic or sexual partner, the prevalence of IPV experience before the age of 15 ranged from 19% to 64%, with most sites reporting that this occurred in more than 50% of participants. There is little information on NMS outcomes in adolescent women experiencing IPV in LMICs, although in high-income countries, PTSD, depression and substance misuse are frequently associated with IPV¹⁵. Girls are at higher risk of HIV and AIDS, whereas boys are more at risk of civil and interpersonal violence¹⁶.

Adolescent mothers in high-income countries are particularly at risk of developing depression: prenatal, postnatal and, in one study, long-term depression¹⁷, but we found no research on the impact of adolescent pregnancy on depression in LMICs. The impact of adolescent pregnancy on maternal cognitive development has not been studied in any context and represents a global research priority. This is especially relevant in LMICs where 20% of mothers have had their first child by the age of 18 and more than 20% of girls are married before age 18, despite a ban based on international conventions¹⁶.

Community and conflict-related violence and injury

Adolescence is a dynamic time of biological (brain and sexual maturation) and social development (differentiating self from others and appraising the self by forming self-control, self-esteem and self-efficacy). Adolescents are concomitantly more likely to break social rules and experience aggression towards self and others^{9–11}. The peak age of both committing and receiving violent acts is between 14 and 19 years old – adolescent males are more frequently the perpetrators and victims than are females².

In wars, despite international agreements and conventions to the contrary, child soldiers are pressed into service at a young age, experiencing disrupted social and emotional development and interrupted schooling. These adolescents are at risk of physical trauma with lasting disability, PTSD and addiction¹⁸. Similar outcomes are found from the impact of post-conflict displacement of adolescents, who are often separated from their family and community¹⁹. However, there is evidence that negative impacts can be mitigated by stable and supportive social environments. A study of 880 Bosnian adolescents demonstrated the need for better methodological approaches to unpack the multitiered pathways that lead to trauma in order to develop better interventions²⁰. A review of interventions providing mental health support to conflict-affected children and adolescents found that most were school-based programmes²¹. There were few family- or community-based programmes and only two multilevel programmes. A systematic review of interventions for refugee children found eight studies in LMICs (seven in refugee camps) that showed that treatments, including cognitive behavioural therapy (CBT) and narrative exposure therapy, were successful in reducing psychological problems such as depression and PTSD²².

There is limited evidence that interventions developed in high-income countries can be transplanted successfully^{22,23}. It has been argued²⁴ that the most effective strategies for preventing violence should promote mental health and be delivered to all young people, thus avoiding stigmatization and attracting broad community support. Yet, the evidence base for effective programmes to prevent violence in LMICs is almost non-existent^{3,6}. A recent review of interventions to support street children found 12 studies in high-income countries, but did not find any adequately robust interventions in LMICs despite the plethora of programmes that are being implemented^{25,26}.

Road traffic accidents and other transport-related injuries are the leading cause of brain trauma and spinal cord injury, death and disability, disproportionately affecting young adults and accounting for about 5% of all DALYs, which is only exceeded by unipolar depression⁵.

Mental health and substance use

Difficulties in the development of executive control in adolescence can lead to a lack of balance in the regulation of cognition, emotions and behaviour when dealing with intrusive negative thoughts and feelings. This may result in depression or anxiety. Such affective disorders often have their onset in adolescence (Fig. 1) when these disorders are more likely to become severe and disabling⁹. The prevalence of depression in adolescent girls is substantially higher globally than that in boys⁵. There is some evidence from high-income countries that early intervention to reduce the duration of first episodes of depression can reduce later recurrence²⁷; this needs to be evaluated in LMICs.

The first onset of schizophrenia often arises in adolescence or

early adult life (Fig. 1). Early identification of psychosis by a range of non-specialists followed by intervention may mitigate the severity of the disease and the need for hospitalization²⁸. Family approaches have also shown promise for young adults at high risk²⁹. However, differences between high-income countries and LMICs in risk factors for, and the effective prevention and treatment of, psychoses are poorly understood³⁰.

Adolescents can be at increased risk of developing substance-use disorders owing to poor self-control and impulsiveness. Although not well studied in LMICs, substance-misuse is often initiated in adolescence and accounts for a substantial proportion of the disability burden faced by adolescents³¹. It also contributes to other major causes of disability such as unintentional injuries and violence⁵. Alcohol use, particularly binge drinking, has been shown to inhibit neuronal development in adolescence³² and has a greater impact on motor and executive impairment in adolescents than in adults, thus conferring greater risk of injury or risky behaviour in adolescents³³.

In Russia, excessive alcohol consumption is a major cause of premature death³⁴ and is associated with early initiation and frequent alcohol consumption in adolescence³⁵. Evidence-based interventions to delay onset of drinking and reduce binge drinking in adolescents in LMICs are a high priority. A related priority calls for the inclusion of measures of depression, violence and sexually transmitted diseases in research aimed at diminishing the impact of either early initiation of drinking or of binge drinking in adolescence.

Infectious diseases

Vaccine-preventable neurological disorders may result in cognitive disability, epilepsy, motor disorders, and hearing and/or vision loss. For example, meningitis A is prevalent in sub-Saharan Africa and targets adolescents and young adults, causing death, cognitive disability and hearing loss. WHO and PATH have developed a new vaccine against meningitis A that has been introduced in a number of African countries. More than 100 million doses have been delivered to people between 1 and 29 years of age, contributing to the lowest incidence of the disease in 10 years³⁶. The use of implementation science to further scale-up this intervention would eliminate a major cause of hearing loss and cognitive disability in African adolescents.

Untreated HIV infection is associated with disabling cognitive impairment, depression and behavioural disorders in adolescence³⁷. Following the scale-up of antiretroviral (ARV) therapy, survival of perinatally infected children in sub-Saharan Africa has dramatically improved. The population of adolescents with HIV is now estimated at 2 million with more than 90% of those living in sub-Saharan Africa. Young adults infected with HIV are at increased risk of developmental and neuropsychological disturbances, which seriously undermine academic and social achievement^{37,38}. A study in South Africa evaluated a community participatory approach to adapt a family-based intervention (originally developed in the United States) to promote mental health awareness in adolescents receiving HIV ARV treatment³⁷. Short-term results showed improvements in mental health, behaviour and adherence to the drug regimen with a decrease in stigma experience³⁷. Peer-led programmes are now part of many large-scale initiatives to reduce HIV risk in young adults, and a systematic review found that they are effective in increasing knowledge, particularly of HIV prevention approaches and transmission routes and in increasing condom use in LMICs, but evidence of changes in sexual behaviour and STI rates are not conclusive³⁹. Research to determine the effectiveness, generalizability and the long-term impact of such interventions to support adolescent development is a priority.

Research in developing educational initiatives

An important challenge to adolescents' development in LMICs is the low rate of secondary education completion². A review of competencies needed by vulnerable young adults as a result of war, homelessness and child labour concluded that these are not the same as those

conventionally required in the education of adolescents in high-income countries, but posits that the process by which they are acquired is universal¹⁸. Research is needed for the development, evaluation and delivery of necessary competencies in secondary education in LMICs. Such innovative approaches would add to standard interventions to improve health, mental health and social outcomes. Such programmes would focus not only on the acquisition of skills and knowledge, but also on the development of cognitive and motivational skills that are central to the emergence of self-regulated learning.

ADOLESCENTS WITH DISABILITIES RESEARCH

There are few studies that evaluate the approaches that support LMIC adolescents living with disabilities. A systematic review of 22 school-based interventions in LMICs found promising support for mental health promotion and some evidence that interventions to prevent and to treat mental health disorders are effective⁴⁰. The study identified a series of research gaps that need to be filled to understand how to further evaluate and bring to scale these school-based interventions. These include the need to focus on current stressors such as social exclusion and domestic violence, and to test interventions as part of a multilayered societal programme with an emphasis on task shifting (use of trained mid-level researchers in place of clinical specialists).

A priority area for research is to develop and evaluate programmes to ensure that adolescents living with an NMS disability are not excluded from access to social, educational and health services that would reduce secondary and tertiary development of disability and ensure optimal development. Interventions that increase independence must also be developed and tested to protect adolescents from violence, and to ensure educational parity and an effective transition to adult services⁴¹.

METHODOLOGICAL ISSUES

It is often challenging to include adolescents in research. With the increasing independence of adolescents, their parents may not have accurate information regarding exposures and even outcomes. The home may no longer be a feasible setting for any study that requires either a physical examination or biological samples. However, recent studies have shown that providing support to carers and communities that assist vulnerable adolescents facing HIV infection can mitigate obstacles in reaching such groups^{37,42}. Studies based in schools are often used, although such approaches may only work for younger (10–13 year olds) populations because most LMICs adolescents are no longer in school. According to UNICEF² only 61% of boys and 49% of girls entered secondary school in LMICs. One successful approach to reach vulnerable or marginalized urban adolescents is respondent-driven sampling⁴³.

Disaggregation of age group

Researchers should collect data to allow disaggregation by age to facilitate, at low additional cost, age-specific estimates of exposures and outcomes. Often research data on adolescents are combined with either children or adults³. A systematic review, including studies from LMICs and high-income countries, demonstrated that the highest prevalence of intellectual disability was among children and adolescents compared with adults, and within LMICs compared with high-income countries⁴⁴. However, it was impossible to disaggregate adolescents from children or adults. As an example of the importance of disaggregation⁴⁵, a peer support-group intervention to reduce the impact of stigma in those living with epilepsy in Zambia found a significant effect in adolescents, but not in adults.

Promoting and funding longitudinal studies

Major birth cohort studies in high-income countries have provided information on risks and resilience across the life course, but these are not comparable for LMICs. There are several long-standing birth cohort studies in LMICs such as those in Guatemala, India, Brazil, the Philippines and South Africa⁴⁶. The cohorts in such studies should be supported over the life course and the studies should be further developed to

BOX 2 | RECOMMENDATIONS FOR RESEARCH

Recommendations for methodological priorities for research to reduce neurological, mental health and substance-use (NMS) disorders in adolescents in low- and middle-income countries (LMICs).

- Disaggregate adolescent age group in both child and adult studies
- Promote, develop and fund longitudinal cohort studies in LMICs, including observational and follow-up of interventions over the long term
- Initiate cross-nation studies of interventions to promote resilience in adolescents
- Include constellations of exposures and outcomes in studies that involve adolescents and avoid focusing on a single exposure or outcome
- Use methodological approaches to explore multisectoral and multilevel pathways leading to NMS disorders in traumatized young adults
- Include measures of disability and participation in studies of adolescents
- Use new screening measures that include adolescence developed for national studies (UNICEF and Washington Group on Disability Statistics)
- Link development of research priorities to emerging findings from national studies
- Train mid-level researchers (nurses, teachers and others) to conduct research, including assessment of NMS disorders where shown to be effective

High impact priorities for research to reduce NMS disorders in adolescents in LMICs.

- Develop and evaluate strategies to provide mental health interventions for adolescents in community and school settings and address gaps
- Develop an evidence base for interventions designed to prevent violence in young adults
- Investigate the impact of early child bearing on adolescent mothers on development of executive function
- Develop innovative approaches to provide appropriate secondary education for all adolescents
- Develop innovative approaches to ensure inclusive education for those living with disabilities
- Develop and evaluate approaches to protect those living with disabilities from violence and to ensure participation in their communities and cultures
- Support evaluation of interventions to support the transition between adolescent and adult life for those living with NMS disabilities in LMICs

address the research questions that are central to preventing or reducing the impact of adolescent NMS disorders and their consequences.

Broadening outcomes measures

Since there is a constellation of exposures that put adolescents at risk of NMS disorders (many of which may simultaneously be NMS outcomes of other exposures), research into NMS disorders in adolescence should, ideally, not focus on a single exposure or outcome, but should measure multiple factors, whether exposure or outcome. In order to avoid too narrow a sectoral focus, researchers should include a summary measure of disability in addition to measures specific to their study question and consider environmental exposures across education, social development and health, using the framework of the International Classification of Functioning, Disability and Health for Children and

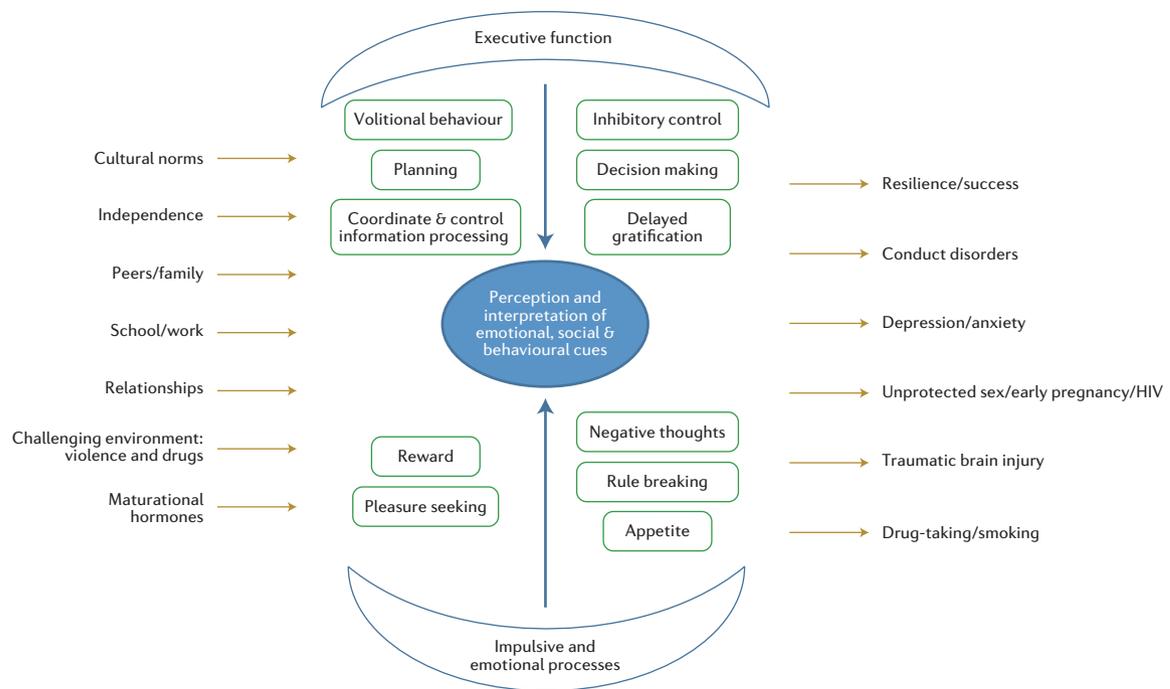


Figure 2 | The interaction between ‘top down’ executive function and ‘bottom up’ impulsive and emotional processes in regulating social, cultural and biological challenges of adolescent development with a range of outcomes^{9–12}.

Youth (ICF-CY)⁴⁷. To accomplish this cross-cultural age-appropriate measures of disability, environmental risk and social participation need to be developed and validated to assess the balance between the developing abilities of the adolescent within the context of the barriers faced in their own communities and culture.

Developing research capacity to measure adolescent NMS outcomes beyond mortality and conventional morbidity measures is essential. UNICEF and the Washington Group on Disability Statistics collaborated to extend internationally appropriate screening measures of disability to include the adolescents. The WHO has developed a child and adolescent form of the brief WHO Disability Assessment Schedule⁴⁸, which is designed to provide information regarding the function of young adults living with disabilities, including NMS disorders. This schedule uses the ICF-CY to provide information on external supports and barriers, and societal participation. It is a priority to include these measures in national surveys and in research studies, to provide both comparative data and population estimates of adolescent disability, which can inform national strategies.

CONCLUSION

Because of the range of environmental challenges that are more common in LMICs, adolescents are at particular risk of developing neurocognitive deficits and disabilities, and mental health problems that limit their reasoning abilities, life-management skills and employability. These are often related to the poor development of executive function or socioemotional development caused by traumatic brain injury due to war or interpersonal conflict, domestic violence or abuse, substance use, or infectious diseases. These largely unmeasured NMS disorders cannot be prevented or treated by an under-resourced health and educational infrastructure. Therefore, it is imperative to develop neurodevelopmental and psychiatric screening strategies to identify and assess these young adults. These will make it possible to evaluate the effectiveness of prevention and early intervention programmes for NMS disorders. Along with screening and clinical assessment for neurocognitive and neuropsychiatric disorders in adolescents at high risk, it is crucial to provide comprehensive access to effective rehabilitative neurocognitive and psychosocial interventions. A scaffold of universal

supports for those at high risk of NMS and with disability will also require evaluation of more intensive interventions for those with significant disorders.

The recent extension of screening measures to include NMS disability in adolescents for use in national or regional surveys provides new opportunities for prioritizing research and directing funding streams in LMICs, and provide the data on which programmes and policies can be based.

Adolescence is not simply a phase between childhood and adulthood. Research to prevent and ameliorate NMS disorders in LMICs must bring an understanding of the interlocking neurobiological and social factors that challenge young adults, and recognize that the patterns of risk and resilience may differ from those in high-income countries. Research must investigate approaches to prevent toxic exposures such as community violence, sex trafficking, drug addiction, poverty and the harm caused by war. Research should develop and evaluate interventions to prevent the emergence of disability from NMS disorders in adolescents in LMICs, as well as to develop and test interventions to support adolescents living with disability to ensure appropriate schooling, employment and the opportunity to become productive members of society, with a rewarding quality of life.

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SUPPLEMENTARY INFORMATION

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ADDITIONAL INFORMATION



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