TIME FOR UNITED ACTION ON DEPRESSION: A LANCET-WORLD PSYCHIATRIC ASSOCIATION COMMISSION

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EXECUTIVE SUMMARY

Depression is a disorder of mood, so mysteriously painful and elusive in the way it becomes known to the self—to the mediating intellect—as to verge close to being beyond description. It thus remains nearly incomprehensible to those who have not experienced it in its extreme mode.
William Styron, *Darkness Visible,* 1990

Evidence has accumulated over decades that depression is a leading cause of avoidable suffering in the world. Yet too few people in communities, governments, and the health sector understand or acknowledge depression as distinct from the other troubles that people face. Too little is done to avoid and alleviate the suffering and disadvantage linked with it. And few governments acknowledge the brake that depression places on social and economic development.

By aligning knowledge about depression from many fields, this Commission has synthesised evidence from diverse contexts and, in consultation with people with lived experience, generated action-oriented recommendations for a variety of stakeholders: communities and those affected by depression and their families; clinicians and public health practitioners, and researchers who work to understand and address it; policy makers and financiers of health and long-term care; and those responsible for motivating decision makers and politicians to act on the evidence. Our aim is to promote concerted and united action to reduce the burden of depression and ensure that greater attention is paid to the millions of people who live with it across the globe.

Our task has never felt more urgent. The potentiation by the COVID-19 pandemic of adverse societal factors such as deep-seated structural inequalities and personal impacts such as social isolation, bereavement, sickness, uncertainty, impoverishment, and poor access to health care has had negative impacts on the mental health of millions of people. It has generated a "perfect storm" that requires responses at multiple levels. This underscores the need to make the prevention, recognition, and treatment of depression an immediate global priority, which we address through a number of key messages and recommendations.

First, depression is a common health condition. It is distinct from the sadness experienced by most people from time to time and from the misery or despair experienced by people in adversity. It brings profound suffering to individuals and families, impairs social functioning and economic productivity, and is associated with premature mortality from suicide and physical illnesses.

Second, even though biomedicine uses a single word to designate this condition, depression is a heterogeneous entity experienced with various combinations of signs and symptoms, severity levels, and longitudinal trajectories. We consider depressive disorders (or simply "depression") in this report as well as symptoms of depression causing distress or social impairment (although depression as experienced by people diagnosed with bipolar disorder is outside the scope of the report).

Third, core features of the condition have been described over thousands of years, well before the advent of contemporary classifications, and in diverse communities and cultures. This belies the myth that depression is a modern condition, an invention of biomedicine, or restricted to certain cultural groups.

Fourth, depression is the result of a unique combination of factors for each person affected. Proximal adversities act as triggers for the onset of an episode. They typically interact with genetic, environmental, social and developmental vulnerabilities and resilience factors. Embracing the complexity of the disorder involves recognizing the human brain/mind as an interface connecting our conscious selves to the world around us. This requires going beyond a brain-based or a social-environmental paradigm and recognizing that our biology is inseparable from our environment across our life course.

Fifth, at the individual level, detecting and diagnosing depression early in its course, based on recognising the signs and symptoms of illness and functional impairment over time, is a crucial first step. A clinical formulation co-designed by the person with lived experience, caregivers as appropriate, and clinicians sets the foundation for person-centred care. This accommodates the heterogeneous presentations and unique personal stories. A formulation will vary in complexity depending on the individual and family needs, the resources available, and the platform of care. Adopting a staged approach to treatment is a pragmatic strategy for reaching clinical decisions about interventions that are evidence-based and proportional. The staged approach encompasses low-intensity, early interventions aimed at interrupting an emerging episode of depression, long-term multi-modal care for people with recurrent or persistent depression, and a range of interventions in between. Collaborative care models offer an evidence-based way for health systems to implement the staged approach to prevention and care, realizing a vision of personalized interventions for delivery at scale.

Sixth, the great majority of individuals with depression recover from an episode if they obtain adequate support and treatment, even though for a significant minority there are recurrences. We call on communities and professionals to support the empowerment of people with the lived experience of depression. The active role of people with this experience, alongside families, practitioners, policymakers and civil society, is essential in ensuring that the unacceptably high levels of unmet needs are addressed: through sharing their experience to reduce stigma; supporting others with information about the condition and possibilities for help; and advocating for greater resources for evidence-based approaches.

Seventh, a public health approach to depression is needed, taking into account both its social structural determinants and the severity, breadth, and (for many people) durability and persistence of its consequences. The consequences include the loss of lives and the diminution of educational and work opportunities and social connections, even extending to harms to future generations. Preventive and health promoting actions at population and individual levels have a critical role in lowering the prevalence of depression. Early detection and sustained care as needed for people experiencing depression are essential to reducing distress, disability, and suicide. Together these interventions can contribute substantially towards both promoting the health of individuals, families, and communities, and achieving the Sustainable Development Goals for a country.

We encourage health care practitioners to consider depression as a condition that affects people of all ages in a number of different ways. It frequently accompanies other multifactorial illnesses such as diabetes, heart disease, cancer and dementia, and infectious diseases such as HIV and COVID-19, and is likely to complicate and prolong the course of these associated conditions. Practitioners will be rewarded by efforts to integrate depression care with their practice, leading to better outcomes, giving priority to the therapeutic alliance, and addressing the rights and needs of people with depression and their families.

Public health practitioners, policymakers, and researchers need to integrate depression prevention and care into their broader agendas. It is vital to make mental health a central aspect of universal health coverage, and to recognize the need for policies and interventions across sectors, beyond the health sector alone. Researchers should be encouraged to adopt a life course perspective to understanding depression and devise novel methods to optimize prevention, care and recovery, using approaches that are accessible in diverse resource contexts. Decision makers must respond appropriately using the best available evidence and acting on the knowledge that depression has especially profound effects on people living in poverty and adversity. All these stakeholders must also strive to actively engage people with lived experience of depression, including families and caregivers, in the design and implementation of services, policies, and research.

The multi-disciplinary contributions to this report and its synthesis of evidence across fields generate a new focus on several aspects of the experience of depression. The heterogeneity of depression, the universality of the experience even while influenced by culture and context, the uniqueness of the experience for each person, the importance of intervening early, and the consequent need to stage and personalise care are described and justified. We emphasise the need to move beyond health care to consider what is required across societies to reduce the burden of depression. Economics arguments are presented alongside evidence derived from clinical, scientific, and lived experience to reflect on and recommend actions across policy, research and practice.

While there remains much that we do not know about depression, for which we advocate a cutting-edge science agenda, there is much that we *do* know, and which is not utilized optimally. The imperative is, therefore, to invest in translation of knowledge into practice. There is abundant evidence for the efficacy of preventive and therapeutic interventions for depression. However, most communities still do not benefit and most people affected by this condition globally still do not receive these interventions because of a range of demand and supply barriers. Our response to depression will require whole-of-society and whole-of-government engagement, with united action to reduce exposure to adversity and enhance protective factors as well as engage with one of the most private of all human experiences in its diverse aspects, and to ensure that people needing help can find it. Never before has this ambitious agenda been as urgent or necessary.

Panel 1. Key messages of the Lancet WPA Commission on Depression[a]

1. Depression is a common but poorly recognized and understood health condition

Depression can cause profound distress, impair social functioning and economic productivity, and lead to premature mortality; it has substantial impacts on significant others and on society. Yet these impacts are neither well understood nor acknowledged, and there is an insufficient response at local and international levels. There is still a lot we don't know about the prevention and treatment of depression, about what works for whom and why, and we need further scientific discovery as well as better use of what we know if we are to transform the lives of the millions and their families and communities held back by it.

2. Depression is a heterogeneous condition

Although usually classified as a binary disorder, depression has a diversity of clinical presentations, severity levels, and longitudinal courses; it extends beyond the boundaries imposed by current classifications and commonly overlaps with other conditions.

3. Depression is universal, but culture and context matter

Depression has been described across the aeons of human civilization. Depressed mood, loss of interest, and fatigue are common features of the condition across populations. At the same time, there is also considerable variability in types and prevalence of depressive symptoms and signs among cultures and contexts.

4. Prevention is essential to reducing the burden of depression

Whole-of-society strategies are required to operate on adversities early in life and across the subsequent life course. Interventions are also needed at the individual level, focusing on current life habits and risk factors. More efficient prevention of depression is likely to have powerful impacts on the Sustainable Development Goals for a country and the health of individuals and families.

5. The experiences of depression and recovery from it are unique for each individual

Depression is the result of a set of factors, typically the interaction of proximal adversities with genetic, social, environmental and developmental vulnerability and resilience factors. There is a frequent and complex association between depression and physical health. No two individuals share the exact same life story and constitution, which ultimately lead to a particular experience of depression and different needs for help, support, and treatment in recovery.

6. Closing the gap requires engagement of people with lived experience

Preventive efforts across the world are rarely used to best effect and the vast majority of people with depression globally do not receive effective care due to a range of demand and supply barriers. Empowerment of individuals, families, and communities, to work with professionals who can learn from their experience and help demand the implementation of known preventive and therapeutic strategies and to hold health care systems and decision makers accountable is vital.

7. A formulation is needed to personalize care

Detection and diagnosis of depression based on symptoms, function, and duration should be accompanied by a clinical review or formulation for each person that takes into account individual values and preferences, life stories, and circumstances. Formulation identifies characteristics aiding personalised treatment. The complexity and sophistication of the formulation may vary depending on the context of care and availability of resources.

8. A staged approach to care addresses the heterogenous nature of depression and its impacts on individual, family and community functioning

A staged approach offers a pragmatic tool to translate the heterogenous clinical nature of depression for management and to ensure that interventions are comprehensive and yet proportional to the severity of the condition; this facilitates a focus on intervening early in the course of the condition and graduating the intensity of interventions, tailored to the specific needs of the person and the stage of illness.

9. Collaborative delivery models are a cost-effective strategy to scale up depression interventions in routine care

Collaborative care offers an evidence based approach for the delivery of interventions by diverse providers, tailored to the specific stage of the illness, and always including participatory decision

making with patients and engagement with families and communities, greatly increasing the chances of quality rights-based care and remission and recovery.

10. Higher investment with whole-of-society engagement is a priority to translate what we already know into practice and policy and to upgrade the science agenda

While there remains much that we do not know about depression for which we advocate a cutting-edge science agenda, there is much that we do know, and which is not utilized optimally; the most important immediate imperative is to invest in translation of this rich body of knowledge into practice and policy.

[a] Encompassing depressive disorders as well as symptoms of depression causing distress or social impairment. Depression as experienced by people diagnosed with bipolar disorder is outside the scope of the report.

INTRODUCTION

When you have other diseases, they are considered normal. Why is depression not considered a normal disease?
- Vidushi Karnatic, 20, Haldwani, India

Over the past decades, much has been achieved in the field of global mental health.[1] The suffering consequent on mental health problems is recognised globally, and promising strategies have been devised to address them, even in low-resourced contexts. The value of mental health and its interconnections with sustainable development are better understood. Mental health is central and intrinsic to overall health, exemplified by the inclusion of mental health in the UN Sustainable Development Goals.[1] Innovative ways of engaging communities and implementing services hold promise for expanded health promotion, prevention and treatment opportunities around the world.

But many challenges remain. Despite robust evidence of the effectiveness of several intervention strategies at multiple levels of promotion, prevention, treatment and support, poor understanding of mental health and mental ill-health and high levels of stigma and discrimination continue to hamper public action. There is no compelling evidence of a reduced burden of these conditions in any society, and the vast majority of persons affected by mental health problems do not receive appropriate interventions.

No mental health condition captures the complexity of these challenges as emphatically as depression, the leading mental health contributor to the Global Burden of Disease.[2] Metaphors such as "low spirits"[3] or "sadness and dejection"[4] have been used throughout human history to describe the experience of depression. This reflects the omnipresence of the experience, as well as the difficulty in a narrow, discrete framing of the features associated with a condition comprising diverse sets of deeply personal experiences.[5] Operational definitions and classification systems have been essential in creating a common language for science and practice. Using these definitions and systems nonetheless can be seen to deflect attention from the unique journey of each individual affected by the disorder and to give insufficient weight to the voices of people with lived experience.

The concept of depression as used in medicine and health care refers to a condition that arises from multiple constellations of factors that operate in various ways with widely different outcomes. Different combinations of factors predispose to and precipitate the onset of an episode; lead to different experiences and clinical presentations of the disorder with diverse trajectories; and respond to a wide range of prevention and treatment strategies, although with little indication so far of which works better for whom and in what circumstances. In this report we use two expressions to denote the lived experience of depression—"people with depression" and "patients"—the latter designating persons in clinical encounters and, therefore, constituting a subgroup of the former.

Several core features of depression are identified across various geographies and cultures. The heterogeneity is evident, however, from the multiple ways in which symptoms combine to produce a variety of clinical phenotypes.[6] At the extreme, two individuals can meet criteria for a diagnosis of major depressive disorder without sharing any single symptom.[7] Such variability leads to the question of whether depression is one disorder with shades of severity and multiple presentations, or whether it is a common name for a number of loosely related problems.[8] This diversity is further complicated by the fact that many of the core features of depression are also

part of the normative human response to adversity, without a clear defining line between everyday sadness or distress and the clinical condition.

Unsurprisingly, the quest for a mono-causal aetiology for depression has been unsuccessful. Approaches to understanding the multi-causal aetiology of the condition analogous to those used in other non-communicable diseases have been much more fruitful and appropriate.[9] While the biological underpinnings of depression must be acknowledged, and depression can be conceptualised ultimately as an illness of the brain,[10] it is essential to recognize the tangible and intangible environmental influences on brain development and function across the lifespan. Recent research on childhood abuse and neglect, for instance, emphasises the lasting effects on the risks for depression not only in childhood and adolescence, but also later in life and in subsequent generations.[11] These results make it clear that the pathways to experiencing depression can begin many years before the condition is manifest. The journey almost always involves environmental influences on neurodevelopment, psychological functioning and neural circuits and networks, which in turn mediate the specific phenomena associated with the condition.[12]

Researchers, practitioners, and those with lived experience have long worked to build a knowledge foundation for our understanding of this complex and heterogeneous human experience. Depression has profound effects on a person regardless of sex, background, social class, or age. It is associated with suffering and multifaceted disability, with the early age of onset contributing to difficulties in adult functioning. A proportion of those affected have a recurrent or persistent course, frequent co-occurrence of other health conditions, and an elevated risk of premature death from a range of causes including suicide. Beyond the individual, depression can have a significant impact on families and communities and is an important barrier to the sustainable development of nations. Given the degree of individual suffering and the deleterious impacts on public health and society, it is reasonable to assert that depression is everybody's business and a global health priority. Yet, despite the abundant evidence reviewed later in this report that much can be done to prevent depression and facilitate recovery, only a small minority of the world's population benefits from this knowledge. In this regard, depression is a global health crisis.

This crisis is due in part to the controversies that rage around the nature of depression, its significance as a biomedical condition, and how depression should be managed. There is a tension between depression constituting a *bona fide* medical entity and a leading cause of disability worldwide versus the construct of depression as an extreme of the normative emotional experience that should not be pathologized.[13] Critical voices question the application of the concept of depression and associated treatment science, mostly developed in European contexts, in diverse cultural settings around the world.[14] Still other critiques question the extent to which conceptualising depression as a biological disorder with implications for use of medications is simply a ploy for reification of normal human suffering under a medical model and promotion of the pharmaceutical industry.[15]

Recognising depression as a central yet neglected global health problem led to the creation of this Commission. This Commission has a mandate to present a unifying and balanced view of the available evidence on these and other core questions, indicating also the grey areas and knowledge gaps requiring further research. Its audiences include people with the lived experience of depression and their families, clinical and public health practitioners, researchers, and policymakers. The Commission aims to advance understanding of the nature of depression, laying to rest nihilistic debates — such as the idea that depression is simply sadness or that it

is a creation of biomedicine or that its roots are either biological or social — and providing evidence that depression can be prevented and treated if we move beyond a "one size fits all" approach, which does not work well for depression nor a range of other health conditions. Recognizing the subtleties of each person's experience of depression and the varying patterns in different population groups and cultural settings across the world is an essential step. This in itself improves the ability to communicate about the disorder to a broader audience,[16] enhancing understanding and reducing stigma. It brings the prospect of facilitating prevention and access to collaborative care strategies, even in resource-limited settings. In doing so, we stand on the edge of an historic opportunity for united action by all stakeholders, across sectors, to work together and reduce the global burden of suffering due to depression.

WHAT IS DEPRESSION?

People have described forms of suffering that resemble depression over thousands of years. Across cultures that developed written medical text—Chinese medicine, Ayurveda, Q'uranic medicine, Western classical antiquity—symptoms of depression are described and remedies outlined. These are underpinned by varied concepts of causation and vulnerability (Figure 1).

Figure 1. Depression across the ages

10,000 BCE
Studies with contemporary hunter-gatherer groups document accounts of prolonged grief, social withdrawal, and loss of vitality,[17-20] which are treated with shamanic practices. These practices include symbolic healing, herbal remedies, and collective rituals.[21]

1500 BCE – 6th Century CE
The foundations of the *Ayurveda* healing tradition in South Asia includes some of the first written descriptions resembling depression. The Vedas describe imbalance in humours and lifestyle with manifestations including *vishada, avasada, manodhukaja, adhija unmada,* and *kaphaja unmada*: with characteristics ranging from apprehension-induced despondency and inertia to more severe manifestations of staying in one place, reduced activities, lack of self-care, preferring to be alone, and disgust feelings.[22] Descriptions of states resembling depression are found in the Hindu epics, the *Ramayana* and *Mahabharatha*.[22]

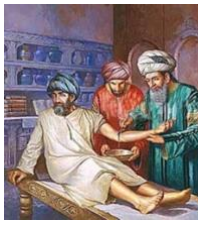
5th Century BCE – 6th Century CE
During Western Classical Antiquity, Hippocrates (370-460 BCE), then later Plato, Aristotle, and Galen[23] describe melancholia, an accumulation of black bile, characterized as an aversion to food, despondency, sleeplessness, irritability, restlessness[24]; according to Berrios, "the meaning of melancholia in classical antiquity is opaque and has little in common with 20th-century psychiatric usage (…) Symptoms reflecting pathological affect (e.g. sadness) were not part of the concept."[23]

2nd Century BCE – 8th Century CE
Early Traditional Chinese Medicine writings, such as the *Huangdi Neijing* including the *Suwen* and *Lingshu* text, described health in terms of balance, such as between the macrocosm and microcosm, which reflects Taoist philosophy.[24] Imbalance and disturbances of 'wind' are associated with a variety of conditions, including symptoms of depression. The term *yu* in early writings referred to "a depressed content of *qi*", and latter uses of *yu* also referred to depressed mood.[25] In the classics of Traditional Chinese Medicine, depression could be a symptom or other conditions or a cause of disease.[24]

3rd – 9th Centuries CE
Archaeological findings from the Mayan Classical Period and documentation of current populations suggest a range of terms related to depression, with a prominent metaphor referring to the sensation that the body is being eaten and vitality is lost.[26] Mayan ethnobotanical preparations are considered to have antidepressant properties.[27] Shamanic healing practices were likely used to treat individuals with this suffering, and some practice may be reflected in current *Curandero* healings in Central and South America.[28]

4th Century CE
The early Christian monastic community, in particular the monks Evagrius Ponticus (360-435 CE), described *acedia* as a state of idleness or restlessness, as well as psychic exhaustion, dejection, resentment, and boredom. Early descriptions focused on experiences of monks in the Egyptian desert near Alexandria.[29] *Acedia* was characterized as spiritual failing of those who could not maintain the monastic lifestyle of solitude and devotion, and a succumbing to the Seven Deadly Sins.[30] The stigmatization of depression within Christianity is influenced by these early monastic writings. Acedia was also considered to be contagious. Eventually, the usage expanded beyond monks, to include the general public.

7th – 13th Centuries CE
During the Islamic Golden Age, scholars of Q'uranic medicine document a range of conditions related to depression and melancholia, depression is a common and treatable illness.[31,32] Passages throughout the Holy Q'uran and *Mizan al-Hikmah Encyclopedia* (Scale of Wisdom) contain lifestyle and behavioural recommendations considered helpful for preventing and treating depression.[31]



9th– 10th Centuries CE
The Muslim philosopher Al Ash'ath Bin Qais Al-Kindi wrote treatises related to sorrow, describing "a spiritual (*Nafsani*) grief caused by loss of loved ones or personal belongings, or by failure in obtaining what one lusts after.''[33] He said that sorrow is not within us we bring it upon ourselves. He used cognitive strategies to alleviate sorrow. Abu Zaid Al-Balkhi compared physical with psychological disorders and showed their interaction in causing psychosomatic disorders. He classified depression into three kinds: everyday normal *huzn* or sadness, as well as forms of endogenous depression and reactive depression.

11th Century
The Four Tantras (also known as Four Treatises, *Rgyud bzhi*) of Tibetan Medicine were composed during the Tibetan Renaissance. In Tibetan Medicine, health is a balance of wind, bile, and phlegm, with wind illness (*rlung*) resembling many aspects of depression.[34] Terms related to depression include *skyo snang, sems pham pa, sems sdug*, which refer to suffering in the *sems*, (heart-mind).[35] Treatments include dietary and lifestyle changes, massage, moxibustion and Buddhist spiritual practices, and herbal medicines with anti-depressant properties.[36]

13th Century
Europe: Thomas Aquinas (Italy, 1225 to 1274) on *acedia:* "It strikes like a recurring fever: it lays the soul low with sultry fires at regular and fixed intervals… a kind of oppressive sorrow."[37]

14th Century
Europe: After surviving the Black Death, Julian of Norwich (England) became an anchorite. Her writings based on Christian theology had resonance for people devastated by death and turmoil from war, rebellion and plague. She was visited by travellers from across Europe — "all shall be well, and all shall be well and all manner of thing shall be well."

15th Century

Europe: "low spirits" connoted "to bring down in vigour or spirits." Melancholia was also seen to have positive connotations for social status, intelligence, aesthetic refinement. Marsilio Ficino (Florence, Italy): "[B]oth Mercury who invites us to investigate doctrines, and Saturn, who makes us persevere in investigating doctrines and retain them when discovered, are said by astronomers to be somewhat cold and dry just like the melancholic nature according to physicians. And this same nature Mercury and Saturn impart from birth to their followers, learned people, and preserve and augment it day by day."[38]

16th Century
Yu Zheng, a term widely used in present times to label a group of symptoms similar to the modern concept of depression, was first used by Yu Chuan (1438-1517), a famous doctor in the Ming Dynasty. Yu Chuan published his 8-volume work "Yi Xue Zheng Chuan" (Orthodox of Medicine), which included a chapter on "Yu Zheng." In Yu zheng or yu bing, "Yu" indicates depressed mood, while "zheng" means syndrome and "bing" means disease.[39]

17th-18th Century
After its publication in 1621, *Anatomy of Melancholy* by Richard Burton dominated European understandings of depression for the following two centuries. In Burton's interpretation, melancholy was seen as both a disease and the essence of the human condition, "a kind of dotage without a fever, having, for his ordinary companions, fear and sadness, without any apparent occasion."[40]

19th Century
In France, Jean Esquirol wrote "melancholy (…) is a cerebral malady characterized by partial, chronic delirium, without fever, and sustained by a passion of a sad, debilitating or oppressive character."[41,42] The term "nervous erethism" was also terminology used in the French Asylum to refer to irritability, emotional instability, also

association with upper class. In the European cultural context, overlap of melancholia with Romantic concept of *Weltschmerz* (world-weariness), a deep sadness about the inadequacy or imperfection of the world. Around the 1850s, the concept of nondelusional melancholia was introduced, described as "a state of sadness or dejection" – moving the concept away from "the intellect" and closer to "mood." Delusions were no longer considered the primary symptom in melancholia; the lack of knowledge regarding physiological aspects of the brain/mind led to the proposal of a classification of diseases according to the faculties involved, pushing melancholia away from disorders such as dementia and monomania. After 1860, having established melancholia as a mood disorder, scholars had to propose an explanation for the emergence of delusions in some individuals, and suggested that emotional alterations entailed alterations in intellectual functioning, i.e., the mood disorder spread to other faculties. Delusions would be the consequence, not the cause, of the depressed feeling.[23,41]

1883
Emile Kraepelin in Germany writes about melancholia that "psychological anguish" arises from "the feelings of dissatisfaction, anxiety and general misery gains such strength that it constantly dominates the mood." Kraepelin's work highlights that delusions could arise from depression rather than depression being a result of delusions.

1893
Bertillon Classification of Causes of Death (precursor of International Classification of Disease) published by Jacques Bertillon in Paris.

1900
First international conference to revise *International Classification of Causes of Death*.

1900s - 1920s
In Chinese Medicine, *shenjing shuairuo* is a reference to depletion (imbalance) of qi energy and was translated at that time as neurasthenia in Western medical terms. Ancient methods to improve qi circulation in the body have been incorporated into Tai Chi and Qi gong practices, which have been evaluated as treatments for depression.[43]

1949
International Classification of Causes of Death (Version 6) renamed as *International Statistical Classification of Diseases (ICD)*, and was the first version of the ICD to include mental disorders.

1952
First version of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-I)* published. Influenced by psychoanalytic concepts, disorders were described according to understandings of their causes and functions: e.g., "Depressive reactions" in relation to psychotic, psychoneurotic, and personality disorders.[44,45] This approach, rather than symptomatic criteria, continued to be used for DSM-II (1968).

1970
Standardized qualifications for Ayurveda for practitioners and accreditation established in Indian Medical Central Council Act passed by the Parliament of India. Depression-related diagnoses and treatments are made according to a humoral (*dosha*) classification system. Depression symptoms are related to *Vata* and some to *Kapha dosha*.[22] Ayurvedic treatments include lifestyle and dietary change, herbal medicines, emesis/purgation, and other practices.[46]

1979
The first edition of the Chinese Classification of Mental Disorders is published. The diagnosis "depression" was considered an equivalent of melancholia in English and not commonly used, with neurasthenia continuing to be the most prominent diagnosis.

1980
Diagnostic and Statistical Manual of Mental Disorders, third version *(DSM-III)* is published with symptomatic based criteria for depression. The DSM-III version is the foundation of the subsequent constellation of symptoms[45] in DSM-IV (1994) and DSM-5 (2013).

1990s
The term "depression" (*yiyu zheng*) has rapidly replaced neurasthenia as a well-accepted diagnostic label in China, mainly as a reflection of sociocultural changes in the country.[47]

Current diagnostic approaches

The World Health Organization's 11th revision of its International Classification of Diseases and Related Health Problems (ICD-11)[48] conceptualizes depression as a syndrome, i.e., a clinically recognizable set of reported experiences (symptoms) and observed behaviours (signs) associated with distress and interference with personal functions.[49] For a diagnosis of depression, at least five out of a list of 10 symptoms/signs have to be present most of the day, nearly every day, for at least two weeks (Table 1). The presence of either the first or the second symptom/sign is mandatory. The mood disturbance should result in significant functional impairment ("if functioning is maintained, it is only through significant additional effort"). The symptoms/signs are not a manifestation of another medical condition (e.g., a brain tumour), are not due to the effect of a substance or medication, and are not better explained by bereavement.

Table 1. ICD-11 and DSM-5 diagnostic criteria for depressive episode

ICD-11	DSM-5
Depressed mood as reported by the individual (e.g., feeling down, sad) or as observed (e.g., tearful, defeated appearance). In children and adolescents, depressed mood can manifest as irritability.	**Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)**
Markedly diminished interest or pleasure in activities, especially those normally found to be enjoyable to the individual. The latter may include a reduction in sexual desire.	**Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).**
Reduced ability to concentrate and sustain attention to tasks, or marked indecisiveness.	Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)..
Beliefs of low self-worth or excessive or inappropriate guilt that may be manifestly delusional.	Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation (with or without a specific plan), or evidence of attempted suicide.	Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
Significantly disrupted sleep (delayed sleep onset, increased frequency of waking up during the night, or early morning awakening) or excessive sleep.	Insomnia or hypersomnia nearly every day.
Significant change in appetite (diminished or increased) or significant weight change (gain or loss).	Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
Psychomotor agitation or retardation (observable by others, not merely subjective feelings of restlessness or being slowed down).	Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

Reduced energy, fatigue, or marked tiredness following the expenditure or only a minimum of effort.	Fatigue or loss of energy nearly every day.
Hopelessness about the future.	

The presence of at least one of the symptoms in bold is required for a diagnosis according to both ICD-11 and DSM-5. The DSM-5 also states that: at least five symptoms have to be simultaneously present for 2 weeks, and represent a change from previous functioning; the symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning; and the episode is not attributable to the physiological effects of a substance or to another medical condition.

The list of symptoms and signs in Table 1 – almost identical to that proposed by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) since its 3rd edition (DSM-III)[50]—is based on the best available evidence. In a sample of people attending outpatient clinics with a range of clinical diagnoses, all symptoms included in the DSM had a positive predictive value above 75%, in differentiating patients with a diagnosis of depression vs. non-depression, with the first two symptoms on the list having the highest values.[49] "Hopelessness about the future," the only symptom included in the ICD-11 but not in the DSMs, performed more strongly than about half of the DSM symptoms and signs in differentiating depressed from non-depressed subjects.[51] A further symptom, "diminished drive," outperformed almost all those that are currently listed, and should probably be added to the list.[51] Other symptoms and signs not included in these definitions – such as lack of reactivity of mood (i.e., the individual's mood fails to rise even temporarily in response to positive stimuli), anger, irritability, psychic anxiety, and somatic concomitants of anxiety (e.g., headaches, muscle tension) – also discriminated between depressed and non-depressed subjects, but performed less well than the symptoms and signs listed in the DSMs and ICD-11.[51]

"Continuous" or "categorical" and the question of severity

More controversial than the list of symptoms and signs defining depression has been the number of symptoms or signs required for diagnosis in both the DSM and the ICD (at least five, one of which must be either depressed mood or diminished interest or pleasure). Several studies[52,53] have reported that subthreshold depressions (i.e., conditions characterized by the presence of less than five depressive symptoms or signs) did not differ from diagnosable depression with respect to variables such as the risk for future depressive episodes, the family history of mental illness (including depression), psychiatric and physical comorbidity, and functional impairment. Nor has the clinical utility of the five-symptom threshold in predicting response to treatment been confirmed.[54,55]

Most studies applying latent class analysis[56] support the notion of a continuity between subthreshold and diagnosable depression. A possible exception is a "nuclear depressive syndrome,"[57] broadly resembling the melancholic subtype of depression (described later), which does seem to be qualitatively different. Whether melancholia represents a distinct disease entity or corresponds to the most severe manifestation of depression (in which further neural circuits are possibly recruited, so that the clinical picture becomes more complex and with a more significant "biological" component) remains open to debate. However, the fact that several people with recurrent depression experience some episodes which are melancholic and some others which are not[58] seems to argue in favour of the latter option.

The notion that depression is "continuous" rather than "categorical" does not solve the threshold issue. Should we extend the concept of depression up to include "normative sadness," i.e., "the sorrow that visits the human being when an adverse event hits his precarious existence"?[59] This does not seem reasonable, because on the one hand it would reinforce current complaints about the medicalization of "normal sorrow," driving inappropriate and unnecessary treatment,[60] and on the other it may mislead people who are really depressed, who could regard their condition as a "normal response to adversity," thus being discouraged from finding appropriate help.

The need to establish a "threshold" for subsyndromal depression in order to distinguish it from "ordinary feelings of sadness" has been widely acknowledged, and different solutions have been proposed.[61] The most frequently adopted option has been to require at least one "core" depressive symptom (i.e., either depressed mood or loss of interest or pleasure), most of the time for at least two weeks.[62] Of note, this option is endorsed in the "depression identification questions" of the Guidelines for the Treatment of Depression of the UK National Institute for Health and Care Excellence (NICE),[63] although the time frame suggested there is "the last month." An alternative has been to experience any two depressive symptoms most of the time for at least two weeks, associated with evidence of social dysfunction.[64]

The different levels of severity of depression also remain to be validly characterized. The descriptions provided in the current diagnostic systems, based on the number and intensity of symptoms and the degree of functional impairment, are somewhat generic and lack empirical validation. In fact, the ICD/DSM definitions of "mild," "moderate," and "severe" depression are rarely used in ordinary clinical practice worldwide. Clinical trials also do not use these definitions, and assess instead the severity of depression on the basis of the global score on a rating scale, usually the 17-item version of the Hamilton Depression Rating Scale (HAM-D).[65] Even in clinical trials, there is a variability in how the different levels of severity of depression are defined.[66,67]

The use of a measurement instrument — such as the 9-item version of the Patient Health Questionnaire (PHQ-9),[68] based on DSM criteria — has been proposed as a practical approach to addressing the questions of the "threshold" for subsyndromal depression and the assessment of the severity of depression. The PHQ-9 is a brief self-report questionnaire that can be completed by the user in just a few minutes and then rapidly scored by the clinician. It is the most widely used (in the global context) questionnaire for the assessment of nine symptoms of depression, each scored on a four point Likert scale. Scores can be interpreted as a continuous measure of severity or categorized into degrees of severity of depression; scores below 5 signify absence of depression or sub-threshold depression. A recent meta-analysis[69] reported that sensitivity and specificity was maximized at a cut-off score of 10 or above in studies using a semi-structured diagnostic interview (29 studies, 6,725 participants; sensitivity 0·88; specificity 0·85). Furthermore, using just the first two items which assess the core phenomena of depression (low mood and anhedonia), followed by the remaining questions only if either is endorsed, is associated with similar levels of sensitivity and specificity. 0·85).[69] Nonetheless, there is some evidence of variation in these psychometric properties across contexts and it is recommended that the instrument, like any other measure of depression, undergo systematic translation and adaptation followed by validation to establish appropriate local cut-offs.[70] The PHQ-9 has been proposed for routine assessment of depression in primary care settings[71] and shown to be sensitive to treatment response.

In the above-mentioned approaches, the severity of depression is evaluated by adding up the scores for the individual depressive symptoms/signs. However, recent research based on the network perspective on psychopathology (which understands mental disorders as complex networks of interacting symptoms) suggests that the various symptoms and signs may not have the same weight in determining the severity of depression: "depression sum-scores don't add up."[72] Therefore, the nature of the depressive symptoms and signs may also need to be considered. Relevant to this issue, for instance, is the concept of "complicated" vs. "uncomplicated" depression, the former characterized by at least one of the following symptoms or signs: psychomotor retardation, psychotic symptoms, suicidal ideation, and sense of worthlessness or guilt. The complicated/uncomplicated status was found to predict the severity of depression significantly better than the standard number-of-symptoms measures.[73] The nature of the depressive symptoms and signs, in addition to their overall intensity might also inform the selection of treatment—for instance, the choice of pharmacotherapy vs. cognitive-behavioural psychotherapy; this is discussed later.[74]

Psychopathological "oversimplification"?

A concern voiced by both mental health and social science researchers[75,76] is that the recent translation of the concept of depression into operational terms may have involved a psychopathological "oversimplification." This line of thought argues that the subjective experience of depressed persons is different from "normal forms of negative mood such as despair or sadness."[76] Some support for this argument has come from the few studies in which depressed persons were asked to describe their current experience in their own words, or to select from lists of adjectives those which best depicted their state. The most common descriptions provided in one of these studies,[77] (e.g., "a feeling that the subject was coming down with a viral illness, either influenza or glandular fever, along with descriptions of aches and pains"; "a sense of detachment from the environment"; "a specific inability to summon up effort, a feeling of being inhibited or an inability to envisage the future"), as well as the adjectives they most commonly endorsed (dispirited, sluggish, wretched, empty, washed out, awful, dull, exhausted), do suggest that the nature of the subjective experience of depression may not be fully conveyed by current diagnostic systems, and may involve a more significant "somatic" component than currently maintained.

It remains possible that those descriptions are not relevant to all or most people with depression, but only to a subgroup (i.e., those with melancholia). However, a systematic review of qualitative studies on depression conducted worldwide[78] found that several somatic symptoms—namely headaches, general aches and pains, problems connected with the heart (e.g., palpitations, heavy heart, heart pain)—were among the features most frequently reported by people with depression across populations. A study based on the "network approach"[79] also found "sympathetic arousal" (i.e., palpitations, tremors, blurred vision, sweating) to be one of the most central symptoms in the depression network, showing strong connections with other somatic complaints (limb heaviness, pain, headaches).

"Higher-order" dimensions and "specifiers"

Depression often co-exists, at different levels of severity, with anxiety and bodily distress. Studies in primary care settings have indeed suggested that depressive, anxiety, and somatic symptoms may be different presentations of a common latent phenomenon[80] and may require common therapeutic approaches,[81] leading some to propose a higher-order category of "common mental disorders."[82] However, in a subpopulation (more frequently in men), depression may instead be part of an "externalizing" spectrum, also including anger attacks, aggression, substance abuse and risk-taking behaviour.[83]

This characterization should also consider what current diagnostic systems regard as "specifiers" or "qualifiers" to the diagnosis of depression, such as the presence of melancholic, atypical or psychotic features, a peripartum onset, or a seasonal pattern of occurrence of depressive episodes. In some instances, these features have specific treatment implications, for example, use of antipsychotics in the presence of psychotic features or the use of light therapy in seasonal depression.[84] In the ICD-11, the qualifier "with melancholia" applies when several of the following symptoms have been present during the worst period within the past month: pervasive anhedonia, lack of emotional reactivity, terminal insomnia, depressive symptoms worse in the morning, marked psychomotor retardation or agitation, marked loss of appetite or loss of weight. The qualifier "with psychotic symptoms" applies when either delusions or hallucinations are present during the episode. Psychotic symptoms may be subtle, they may be concealed by the patient; and the boundary between delusions and persistent depressive ruminations or sustained preoccupations may not be clear. The latest edition of the DSM (DSM-5)[85] also includes the specifier "with atypical features" (absent in the ICD-11), which pertains to people who have increased appetite, weight and sleep, as opposed to lack of appetite and insomnia.

The DSM/ICD approach, considering melancholic and psychotic features as "specifiers" or "qualifiers" to the diagnosis of depression, rather than assuming that melancholia and psychotic depression are distinct diagnostic entities, is also supported by the evidence that, in many people with recurrent depression, some episodes are either psychotic or melancholic and some others are not.[58,86]

Since depression occurring within bipolar disorder does not seem to have distinct characteristic features, the history of past manic or hypomanic episodes should be explored in every person presenting with a depressive episode. Bipolar depression' is different from unipolar major depression in several important respects, including treatment needs and prognosis. Ascertaining this history can considerably affect the management plan.[87] It represents for instance an increased risk of postpartum psychosis in the initial weeks after birth in women.[88]

An issue which remains controversial is that of "mixed" depression, i.e., a depressive syndrome accompanied by symptoms/signs of thought, motor or behavioural overactivation interpreted as "contrapolar." DSM-5 defines "major depression with mixed features" as a depressive episode with at least three typical manic symptoms/signs – such as expansive mood, inflated self-esteem or increased involvement in risky activities – present on most days. On the contrary, in the ICD-11 characterization, the most common "contrapolar" features are irritability, racing or crowded thoughts, increased talkativeness and psychomotor agitation, in line with both the classic[89] and recent[90] literature on this issue.

Both the ICD-11 and DSM-5 provide different codes for "single episode depressive disorder" and "recurrent depressive disorder" (the latter defined in the ICD-11 by a history of at least two depressive episodes separated by several months without significant mood disturbance). Both diagnostic systems acknowledge that the remission after a depressive episode may either be "partial" or "full". The ICD-11 provides a qualifier indicating that the current depressive episode is "persistent" (i.e., diagnostic requirements have been met continuously for at least the past two years) whereas in the DSM-5, "persistent depressive disorder" is a separate diagnostic entity. "Dysthymic disorder" is yet another variant, characterised by persistent depressed mood, accompanied by typical symptoms of depression but which never meet the diagnostic requirements for a depressive episode.

Age and gender

Depression among preschool children has been recognized only recently; and, although less common than at other ages, preschool-onset depression can display a persistent course through late adolescence, with multiple negative outcomes.[91] Considering adolescents, there is a widespread notion that moodiness, feelings of loneliness, interpersonal sensitivity and negative self-perception are relatively common. This perception has contributed to the neglect or even the denial of the problem of youth depression, despite its importance as a signal of the possibility of recurrent depression throughout the life course.[92] On the other hand, depressive symptoms may be part of the fluid and nonspecific clinical picture which has been described as a prodromal stage of the development of several mental disorders.[93]

In the ICD-11 and DSM classifications, the only emphatic difference in the clinical picture of depression among children and adolescents compared with that in adults is that "depressed mood can manifest as irritability." Beyond that, the ICD-11 text notes that the reduced ability to concentrate or sustain attention may manifest in adolescence as a decline in academic performance or an inability to complete school assignments. Indeed, depressed adolescents are often primarily irritable and unstable, with frequent anger outbursts, sometimes without significant provocation, which may result in a deterioration of their interpersonal relationships.[94,95] Moreover, they may not report sadness, but complain of feelings of disquiet and malaise that are overwhelmingly painful.[95] Ruminations about being unable to live up to school demands or about feeling different from others are common. In many cases, conduct problems, eating disorders, substance abuse or inattention at school may be the main focus of relatives' or teachers' complaints. Suicidality and self-injurious behaviours are particularly sensitive concerns in young people. Complicating the picture in a young person, depression usually precedes mania in bipolar disorder, so that the index presentation of this disorder in youth is often depression.[96]

As in adolescents, depression among the elderly tends to be under-recognized or minimized. It is often ascribed to normal ageing, or to losses or physical illness. The clinical picture of depression in older people, compared with that in middle-aged adults, includes a higher frequency of somatic symptoms, anxiety, psychomotor retardation or agitation, and psychotic features. Moreover, depression in the elderly is more commonly associated with cognitive impairment (in particular memory disturbances, impaired executive functions and slowed information processing), painful conditions, and physical disability.[97]

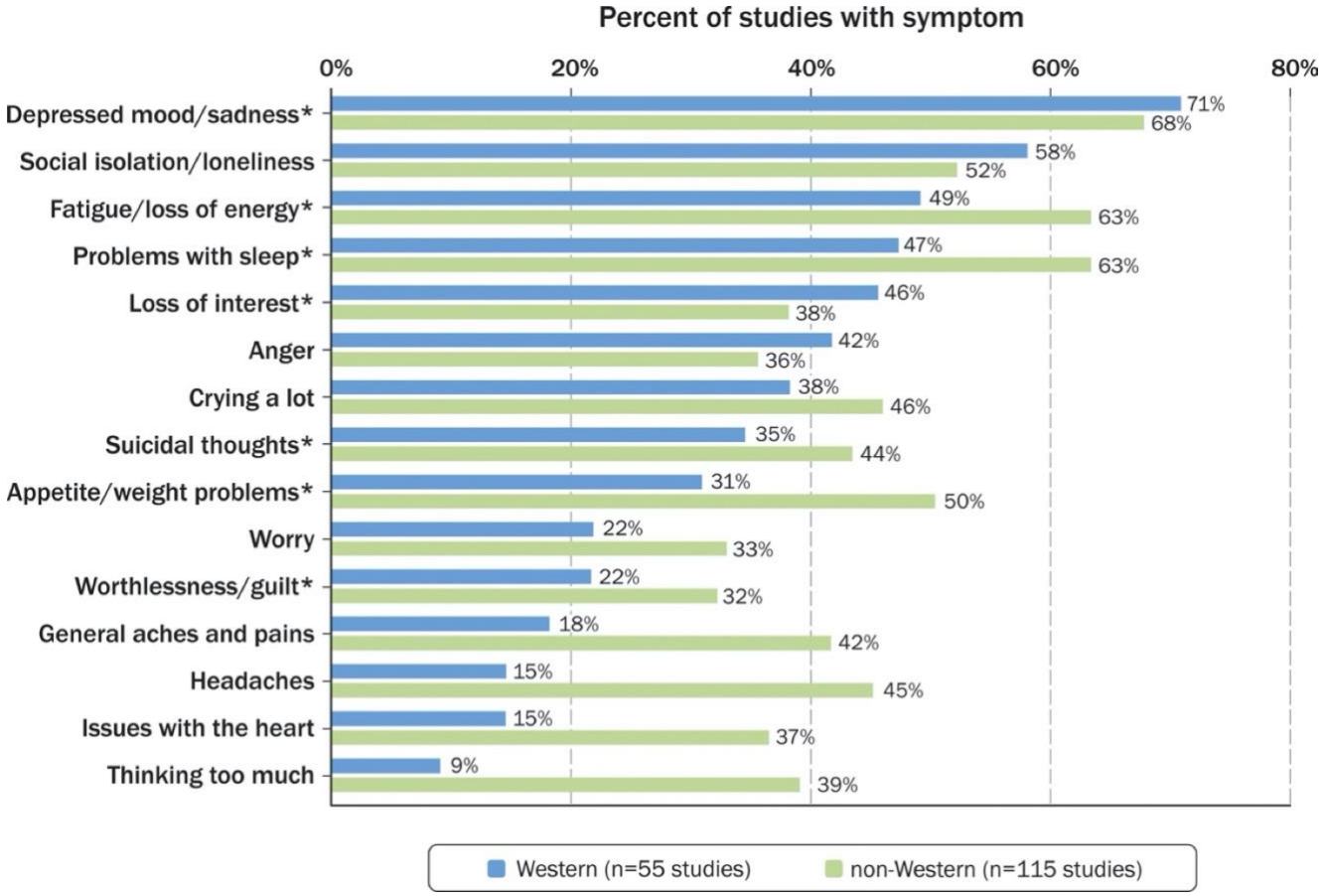
Depression is consistently found to be more common in women than in men. This gender difference is first apparent at about 12 years of age, and has been found to peak in adolescence, at about age 16.[98] Whether the gender gap decreases or not at older age is currently debated.[99] The clinical picture was reported until recently as similar in women and men although, as noted earlier, "externalizing" features are now recognised as more common in men.[83] In addition, appetite changes, fatigue, and poor sleep may be associated with pregnancy and the post-partum, and are less discriminating for depression during the perinatal period.[100]

Culture and depression

A challenge to understanding the generalizability of depression to the global context is that the vast majority of research has come from high-income, predominantly English-speaking countries. Some authors critique that the concept of depression conveyed by the ICD is biased towards these populations. Studies of depression across history and cultures (see Figures 1 and 2) suggest that while several core features of depression are clearly identified across

geographies and cultures, there remain significant variations. For instance, the prominence of sadness might not be universal, emotions are expressed in differing ways, and there is overlap between the concepts of social suffering and depression as a biomedical construct.[101,102]

Figure 2. Depressive symptoms in diverse global populations



Based on analyses by Haroz et al.[78] of data from 170 study populations and 76 nationalities/ethnicities. Study populations categorized as Western included North American/European/Australian non-native populations (55 study populations). Non-Western population included Sub-Saharan Africa (38 study populations), South Asia (25 study populations), Latin America (21 study populations), East Asia (7 study populations), Southeast Asia (10 study populations), the Middle East/North Africa (11 study populations), and North American/European/Australian Indigenous populations (3 study populations). No studies were identified from Russia or Central Asia. Non-Western populations excluded Northern American/European/Australian non-native populations. *ICD/DSM major depressive episode symptoms.

Cross-national studies using standardized diagnostic tools such as the CIDI support the prevalence of many of the ICD/DSM symptoms across cultures and populations.[103] However, contextually grounded research draws attention to other symptoms that are not routinely evaluated even though they may be salient for people presenting with depression and their healthcare providers. Examples are loneliness, anger, and headaches. The higher prevalence of somatic symptoms, such as headaches and general aches and pains, among African, Asian, Caribbean, Central and South American and Pacific Islander peoples and Indigenous populations from North America, Europe, and Australia (Figure 2),[78] may relate to a number of factors. Even though somatic complaints are rarely documented in studies, they may be discussed more readily than cognitive and emotional ones.[104,105] Irritability and anger are also not included within DSM criteria for adults but are frequently noted across diverse cultural groups.[78,106,107] The subjective experience of loneliness is also a hallmark symptom in many cultural groups;[78,108,109] for example, among Aboriginal men in Australia, loss of social

connection was a central feature of the depression experience with less salience of hopelessness and somatic complaints.[110] One notable finding contrasts depression as a relatively weak risk factor for suicidal ideation, plans and attempts in low- and middle-income countries with the strong relationship between suicidality and depression in high-income countries.[111]

Cultural idioms of distress have been evaluated for similarities with ICD/DSM classifications of depression. These idioms include *hwa-byung*, *shenjing shuairuo,* and *phiền não tâm thần* in East and Southeast Asia; tension and heart-mind problems in South Asia; *kufungisisa*, *kusuwisia*, and *yo'kwekyawa* in Sub-Saharan Africa; and *susto*, *coraje,* and *nervios*-related conditions in Latin America. A meta-analysis examining the association of these concepts with ICD/DSM depression categories observed that persons endorsing these idioms had 7·55 greater odds than others of meeting the ICD/DSM depression criteria.[4] The idiom "thinking too much" denotes a broader mental health syndrome, with manifestations such as sadness, lack of motivation, poor concentration, sleep difficulties and irritability, perhaps similar to the construct of 'common mental disorders'.[112-117] Using these idioms and other cultural concepts has been central to the development and adaptation of psychological interventions for depression that are culturally acceptable and reduce risk of stigmatization.[118-121] Use of the idioms can also be paired with depression screening tools to reduce screening time and improve accuracy of detection.[122]

Unfortunately, cultural influences on the experience of depression among children and adolescents have received very limited attention. To date, some studies have suggested that symptoms such as appetite or weight changes do not distinguish between depressed and non-depressed outside of affluent high-resource settings, as evidenced by studies in Turkey, Nigeria, and Nepal.[122-124] Subjective experiences of loneliness are distinctive aspects of the phenomenology of depression among youth across cultural groups in high-income and low- and middle-income countries.[124-126]

Depression and grief

The affect of grief is different from depressed mood. It consists of feelings of emptiness and loss. Self-esteem is usually preserved. Dysphoria tends to occur in waves, usually associated with thoughts or reminders of the deceased, rather than being persistent.[56] However, both the ICD-11 and the DSM-5 acknowledge that depression may occur in some bereaved people. The ICD-11 provides a higher threshold for the diagnosis of depression; a longer duration of the depressive state is required (a month or more following the loss, with no periods of positive mood or enjoyment of activities), as well as the presence of some symptoms which are unlikely to occur in "normal" grief (extreme beliefs of low self-worth and guilt not related to the lost loved one, psychotic symptoms, suicidal ideation, or psychomotor retardation). This approach, present in the DSM-IV, has been abandoned in the DSM-5, where the threshold for the diagnosis of depression is the same in bereaved and non-bereaved persons.

The ICD-11 has also introduced the new category of "prolonged grief disorder," including abnormally persistent and disabling responses to bereavement.[127] Following the death of a person close to the bereaved, there is a persistent and pervasive grief response characterized by longing for the deceased or persistent preoccupation with the deceased, accompanied by intense emotional pain. Symptoms may include sadness, guilt, anger, denial, blame, difficulty accepting the death, feeling that the person has lost a part of his or her self, an inability to experience positive mood, emotional numbness, and difficulty in engaging with social or other activities. This response must clearly exceed expected social, cultural, or religious norms and, to attract the diagnosis, it must persist for more than six months following the loss. There is

evidence that prolonged grief disorder, characterized as a stress disorder in DSM-5, responds well to a specific type of psychotherapy tailored for the condition.[128]

Although the symptoms of prolonged grief disorder are observed across cultural settings,[129] grief responses may manifest in culturally specific ways, with wide diversity in the expected norms for duration of grieving.[130-132] Of note, studies of cultural concepts of grief among refugees demonstrate that the terms and explanatory models for prolonged grief are distinct from cultural concepts of depression.[133]

EPIDEMIOLOGY AND BURDEN

Depression doesn't hand you an itinerary.
- Ishita Mehra, 22, Delhi, India

It is estimated that 4.7% (95% uncertainty interval: 4.4-5.0%) of the world's population have an episode of depression in any 12-month time period.[134] Only about half as many people have depression at a point in time given that average episode duration is about 6 months, although there is wide variation around this average.[135] Higher estimates have been reported for 12-month and 30-day prevalence of depressive episodes which include those due to bipolar disorder;[136] up to 20-33% of depressive episodes at a point in time is associated with a history of bipolar spectrum disorder.[137] This high proportion of bipolar involvement in current depressive episodes exists despite lifetime prevalence of bipolar disorder being much lower than that of depression because depressive episodes are much more persistent and recurrent among people with bipolar disorder than among individuals with depression.[138]

Estimates of depression prevalence within world regions pooled across available data sources were created by the World Health Organization (WHO) for 2015.[139] These estimates suggest that 12-month prevalence among women was somewhat higher in Africa and the Americas (5·8%) and somewhat lower in the Western Pacific (4·2%) than in the remaining regions of the world (5%). Among men, estimated prevalence was highest in Africa (4·8%), lowest in the Western Pacific (2·8%), and intermediate in other regions (3·5-3·8%). More recent estimates of depression point prevalence in differently defined world regions were created by the Institute for Health Metrics and Evaluation as part of their Global Burden of Disease (GBD) Study 2019.[140] The estimated point prevalence among both women and men was highest in North America (4·4 and 2·5% respectively) and lowest in the Western Pacific (2·3 and 1·3%); it was intermediate in other world regions both for women (2·8-3·6%) and men (1·9-2·0%). The exact reasons for such variations are yet to be understood. They are likely attributed mostly to the varying distribution of risk or protective factors. Methodological aspects, such as differential response to questions assessing depressive symptoms, may also account for some of the variability.

Most estimates of lifetime prevalence of depression are based on retrospective reports and need to be interpreted with caution as they are likely to underestimate true lifetime prevalence.[141] Retrospectively-reported lifetime prevalence of depression from community epidemiological surveys with adults aged 18-74 years in 28 countries[135] averaged 10·6% across countries (interquartile range of 6-14%). Prospective epidemiologic studies report much higher lifetime prevalence of major depression in the range of 30-40%.[141]

Course and outcome

The higher epidemiological estimates of lifetime prevalence than 12-month prevalence suggest that 33-50% of the people with a lifetime history of depression experience a depressive episode in a year. These estimates are broadly consistent with follow-up studies in clinical and community samples. However, this naturalistic course is diverse. Most depressive episodes remit within one year. The prevalence of persistent depression (i.e., an episode lasting more than 12 months) is estimated to be as low as 12% in people meeting criteria for a diagnosis of depression in community surveys; but it can be as high as 61% among those receiving treatment for depression in primary and secondary care settings (Table 2).[142] The diversity of the naturalistic course in depression is also apparent in rates of recurrence after recovery. Among individuals who seek treatment, depression is often an intermittent recurrent disorder over the life course,[143] commonly with partial remission between episodes.[144] In primary or secondary care settings, follow-up studies of 5 years or more suggest that recurrence can be as high as 71-85%. However recurrence rates are much lower for people ascertained as having depression in community samples; between 27% and 45% report experiencing a recurrent episode over 20 years (Table 2).

Table 2. Persistence and recurrence of depressive disorders in community and clinical samples

Persistence					
Study	Setting	Sample	Indicator	Follow-up	Estimate
Finnish Health 2011 study[145]	Community-based	298 individuals with depression	Persistence: CIDI depression diagnosis at follow-up	11 years	21%
NEMESIS 1[146]	Community-based	201 individuals with depression	Persistence: CIDI depression diagnosis at follow-up	7 years	29%
NEMESIS 2[147]	Community-based	242 individuals with depression	% with 2 years of continuous symptoms based on CIDI and lifechart	6 years	12%
NESDA[142,148]	Mixed primary and secondary care	903 individuals with depression	% with 2 years of continuous symptoms based on CIDI and lifechart	6 years	34%
			Persistence: CIDI diagnosis at follow-up	2 years	42%
NESDO[149]	Mixed primary and secondary care	285 older (60+) individuals with depression	Persistence: CIDI diagnosis at follow-up	2 years	48%
NIMH-CDS[150]	Tertiary care	431 individuals with depression	% weeks with symptoms in 195,829 total follow-up weeks based on LIFE Psychiatric Rating Scale	12 years	59% of all weeks with depression symptoms; 15% of all weeks with (severe) depression symptoms
Recurrence					
Study	Setting	Sample	Indicator	Follow-up	Estimate
Lundby study[151]	Community-based	344 individuals with remitted first-incident depression	SCID (DSM-IV) diagnosis at follow-up	40 years	40%
Baltimore ECA[152]	Community-based	92 individuals with remitted first-incident depression	DIS (DSM-III) diagnosis at follow-up	23 years	45%
NEMESIS 1[153]	Community-based	687 individuals with remitted depression	CIDI (DSM-III) diagnosis at follow-up	20 years	42%

NEMESIS 2[147]	Community-based	746 individuals with remitted depression	CIDI (DSM-IV) diagnosis at follow-up	20 years	27%
Depression relapse RCT[154]	Primary care	386 individuals with remitted depression	SCID (DSM-IV) diagnosis at follow-up	1 year	31%
Vantaa Depression Study[155]	Primary care	92 depressed participants who remitted of index disorder during follow-up	SCID (DSM-IV) diagnosis at follow-up	5 years	51%
Long-term INSTEL RCT[156]	Primary care	166 individuals with depression who remitted of index disorder during follow-up	CIDI (DSM-IV) diagnosis at follow-up	10 years	77%
NEMESIS[157]	Mixed primary and secondary care	375 individuals with depression who remitted of index disorder during follow-up	CIDI (DSM-IV) diagnosis at follow-up	2 years	27% (primary care) 34% (secondary care)
Vantaa Depression Study[158]	Secondary care	142 individuals with depression who remitted of index disorder during follow-up	SCAN & SCID (DSM-IV) diagnosis at follow-up	5 years	71%
In-patient study[159]	Tertiary care	57 individuals with depression who remitted of index disorder during follow-up	CID (DSM-III) diagnosis at follow-up	15 months	40%
NIMH-CDS[160]	Tertiary care	380 individuals with depression who remitted from index disorder during follow-up	SADS (DSM-III) diagnosis at follow-up	15 years	85%
Tertiary care study[161]	Tertiary care	65 individuals with depression who remitted of index disorder during follow-up	SCID (DSM-IV) diagnosis at follow-up	3 years	59%

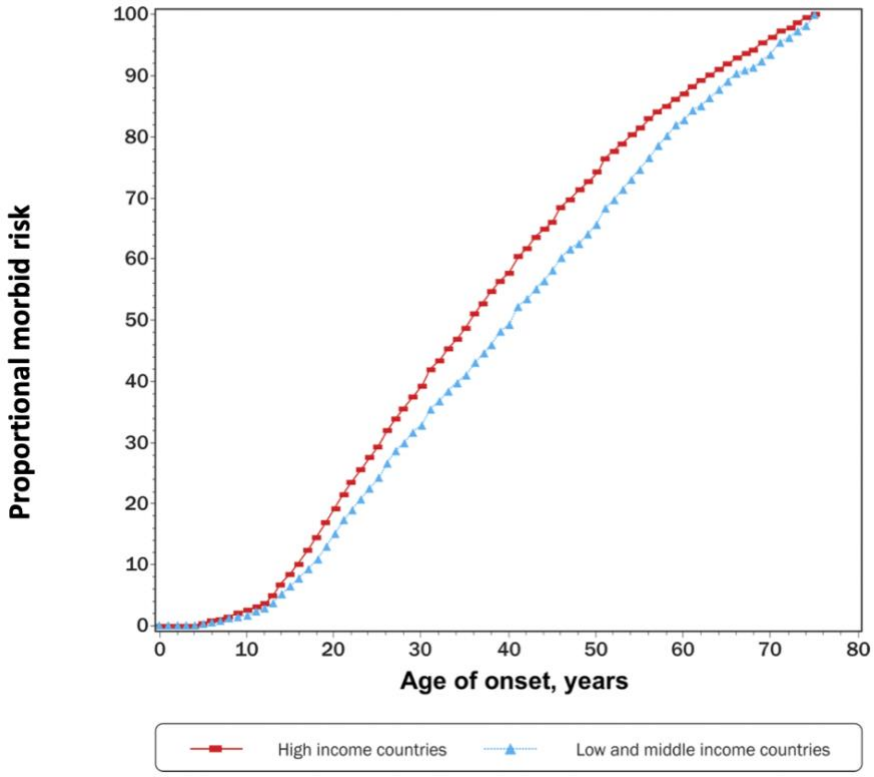
CIDI: Composite International Diagnostic Interview; DIS: Diagnostic Interview Schedule; SADS: Schedule for Affective Disorders and Schizophrenia; SCAN: Schedules for Clinical Assessment in Neuropsychiatry SCID: Structured Clinical Interview for DSM-IV; RCT: randomized controlled trial; Nemesis: The Netherlands Mental Health Survey and Incidence Study; NESDA: The Netherlands Study of Depression and Anxiety; NESDO: The Netherlands Study of Depression in Older Persons; NIMH-CDS: National Institute of Mental Health- Collaborative Depression Study.

Age of onset

Retrospective reports have been used to reconstruct the distribution of age-of-onset (AOO) – an alternative to the estimation of incidence.[162] In the World Mental Health (WMH) surveys, median within-country depression AOO was 26 (interquartile range 17-37) years of age in high-income countries and 24 (17-35) years in low- and middle-income countries. There was also a meaningful secondary peak for onset late in life.[163] These AOO distributions are later than for a number of other common mental disorders, such as anxiety disorders, and many cases of depression are comorbid with these other temporally primary disorders.[164] There is considerable interest in the possibility that AOO might be relevant for identifying depression subtypes, although this line of investigation is still at an early stage of development.[165]

There is an important implication of depression having a later AOO than many other common mental disorders. Lifetime prevalence (i.e., the proportion of the population who have experienced the disorder to date) is estimated directly from results of community epidemiological surveys. When a high proportion of first onsets occurs at ages later than those of respondents in the surveys, this estimate of lifetime *prevalence* will be lower than that of lifetime *morbid risk* (i.e., the projected proportion of the population who will experience the disorder at some time in their life), which is estimated using actuarial methods with life tables.[166] Based on data from the WMH surveys, the average morbid risk of depression at age 75 is projected to be 19·6% (i.e., it is estimated that almost one in five individuals around the world will have experienced depression by 75 years of age).[135] This is nearly twice as high as the proportion of WMH respondents with a lifetime history of depression at the time of survey. Also, as shown in Figure 3, the median AOO of major depression among the projected proportion of the population developing the disorder as of age 75 years—around the late 30s—is higher than the mean age-of-onset among people with a history of depression as of the time of survey. Two types of survey bias, early mortality of people with a history of depression and under-representation of the oldest old, likely lead these estimates to be conservative.

Figure 3. Age of depression onset among the projected proportion of the population (19·6%) developing the disorder as of 75 years of age



Results generated using data from 29 countries provided by the WHO World Mental Health Survey Consortium: www.hcp.med.harvard.edu/wmh. Morbid risk refers to the projected lifetime occurrence of major depression as of age 75 estimated using actuarial methods with life tables. "Onset" refers to lifetime first onset of a major depressive episode and does not take into account the occurrence of subthreshold symptoms.

Sub-threshold depressive syndromes

There has been a long-standing interest in expanding the definition of the depressive spectrum to characterize clinically significant manifestations that do not meet criteria for depression among people who might profit from early intervention.[167] Point prevalence of dysthymic disorder averages 1·5%.[168] But prevalence of subthreshold syndromes of depressive symptoms with shorter duration (typically two weeks) is as high as 17%.[61,169] These syndromes, sometimes labelled as 'minor depression', might also overlap with the construct of adjustment disorder with depressed mood. Unlike depression, the prevalence of minor depression is high among children[170] and adolescents,[171] and associated with substantial distress and impairment and with considerable medical and non-medical costs.[172] These syndromes constitute a risk factor for subsequent onset of depression, and may be the sequelae of partial remission of an episode of major depression.[173]

Comorbidities with other mental disorders

Comorbid anxiety and/or substance use disorders are found among most people diagnosed with depression, both in community epidemiological surveys[174] and in studies of primary care[175] or specialized care settings.[176] Numerous researchers have documented bivariate associations among hierarchy-free anxiety, mood, behaviour, and substance disorders that can be accounted

for by correlated latent predispositions to internalizing and externalizing disorders. The internalizing disorders can also be divided into secondary dimensions of fear (e.g., panic, phobia) and distress (e.g., major depressive episodes, generalized anxiety disorder, post-traumatic stress disorder) disorders. This structure is quite stable cross-nationally.[177]

Longitudinal data have been used to investigate temporal progression across lifetime comorbid mental disorders and whether risk factors for individual disorders are more accurately conceptualized as risk factors for the latent dimensions underlying these disorders.[178] As one example, observed gender differences in depression prevalence became statistically non-significant when controls were included for latent internalizing and externalizing dimensions.[179]

A cross-national analysis of this type, albeit based on retrospective AOO reports obtained in cross-sectional community epidemiological surveys, followed on from WMH surveys across 14 countries.[164] Almost all temporally primary lifetime anxiety, mood, disruptive behaviour, and substance disorders predicted the subsequent first onset of later disorders. Most time-lagged associations were explained by a model that assumed the existence of mediating latent internalizing and externalizing variables. Depression was no more important than several other internalizing disorders (generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder) in defining these latent variables.

An ambitious population-based cohort study with similar logic used information about age of first treatment of common mental disorders in health registries for the 5·9 million residents of Denmark born in that country between 1990 and 2015.[180] As in the retrospective WMH study, all temporally primary mental disorders included in this Danish study were associated with elevated risk of subsequent onset of all temporally secondary mental disorders. Time-related decays were found in these associations as a function of the number of years since onset of the primary disorders. Early-onset mood disorders were associated with especially high absolute risks of subsequent neurotic disorders (anxiety disorders and depression) over the next five years among both men (30·6%) and women (38·4%).

Comorbidities with physical disorders

It is well established that depression is significantly associated with a wide variety of chronic physical disorders, including arthritis, asthma, cancer, cardiovascular disease, diabetes, obesity, hypertension, cognitive impairment, chronic respiratory disorders, a variety of chronic pain conditions, and dementia.[181] These associations can reflect causal effects of physical disorders on depression, causal effects of depression on physical disorders, and effects of common antecedents, such as socioeconomic disadvantage or adverse lifestyle factors, which simultaneously affect both body and mind. There is also the often unrecognized problem of spurious association, when the same set of symptoms is double-counted to arrive at both a psychiatric and a physical diagnosis. In chronic obstructive pulmonary disease, for example, somatic symptoms such as fatigue, decreased appetite and weight loss may be simultaneously attributed to the physical and the psychiatric condition. This raises substantial risks of diagnostic confusion and potential for mismanagement in a situation where physical and psychiatric classifications fail to account adequately for each other, and the indications for treating depression need careful review.[182] Equally important in clinical situations is the misattribution of depressive symptoms and signs to physical illness and consequent failure to recognise depression that is having a substantial impact on suffering and the course of the physical illness.

Physical disorders are influenced by depression in at least two ways. First, to the extent that it is a causal risk factor, depression leads to an increased prevalence of these physical disorders. Consistent with this possibility, meta-analyses of longitudinal studies show that depression is a consistent predictor of the subsequent first onset of coronary artery disease, stroke, diabetes, heart attacks, obesity, osteoporosis and certain types of cancer.[183] A number of biologically plausible mechanisms have been proposed to explain the prospective associations of depression with these disorders, such as hypothalamic-pituitary-adrenal hyperactivity, autonomic dysregulation, and impaired immune function.[184] In addition, a variety of unhealthy behaviours known to be linked to depression, such as elevated rates of smoking and drinking,[185] poor eating habits,[186] and unhealthy food intake, are simultaneous risk factors for physical disorders. Based on these observations, there is good reason to believe that depression might be a causal risk factor for at least some chronic physical disorders.

Second, even if depression is more a consequence than a cause of chronic physical disorders, as it appears to be for some disorders, comorbid depression is often associated with a worse course of the physical disorder.[187-190] A number of mechanisms could be involved. One of the most consistently documented is the association of depression with non-adherence to treatment regimens.[191,192] Differential population-based clustering of depression with co-morbid physical conditions based on patterns of underlying negative social determinants of health is also now being modelled in the syndemics literature. This is built on the idea that co-morbid conditions potentiate one another under certain social, economic, or cultural context.[193]

Depression is a major source of morbidity and mortality in the elderly, with associated increases in public health burden, costs and use of services, and mortality, and reduced quality of life. In the case of dementia, depression may be a risk factor or a precursor; or else, dementia may be a risk factor or trigger for late-life depression; and the two conditions may be difficult to disentangle diagnostically among elderly people. In the Framingham Heart Study cohort[194] there was a 50% increased risk of dementia over a 17-year period among those with a diagnosis of depression at baseline compared with those without that diagnosis. Results were similar for those taking antidepressant medication. Hypotheses to explain this increased risk include chronic inflammatory and neurobiological changes (e.g., hippocampal damage due to glucocorticoid cascade),[195] the cholinergic impact of tricyclic antidepressants,[196] and lifestyle factors such as poor diet, smoking, and reduced physical activity or social engagement that are known to be associated with depression.[197] The co-occurrence of depression and diabetes appears to magnify the risk for dementia beyond that of either alone.[198] Depression often occurs at the early stages of the onset of dementia. This may be prodromal, with the depressive syndrome an early manifestation of an underlying neurodegenerative disease.[199] Alternatively, depressive symptoms may be a psychological response, a reaction to a person's growing awareness of the catastrophic consequences of his/her impending, irreversible impairment.

Global estimates of excess mortality indicate more than 2.2 million excess deaths in persons with depression, with particularly high rates of death among older individuals with cardiovascular disease.[200] A meta-analysis containing data from more than 1.8 million individuals in 35 countries confirms the presence of a significant association between depression and excess all-cause mortality, although this association may have been overestimated because of publication bias and low study quality.[190]

Suicidal behaviour

Suicide is ranked as the second leading cause of death among 15–29 year olds and as the 15th-most common cause of death at all ages worldwide.[201] A meta-review[202] reported an almost

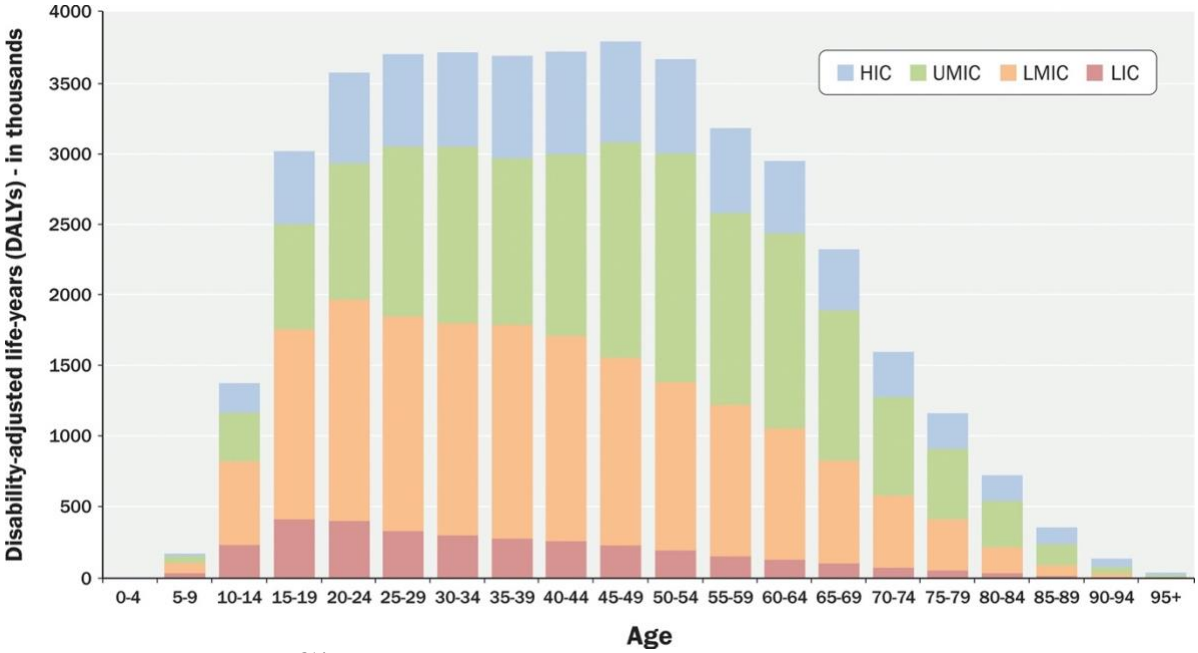
twenty-fold risk of suicide for persons with depression with a standardized mortality ratio (SMR) of 19·7%. Depression is the most common psychiatric disorder reported in people who die by suicide: from available psychological autopsy studies[203] it is estimated that depression is responsible for the largest proportion of the burden of disease attributed to suicide (as measured in DALYs: 46%; 95%CI 28% to 61%).[204] That said, it appears that the relative contribution of depression to suicide is smaller in low- and middle-income countries[205,206] where a mood disorder was identified in 25% of people who died by suicide. Suicide attempt is also far more common in people with depression.[207] A meta-analysis of suicide attempts in individuals with depression found a lifetime prevalence of 31% (95%CI: 27-34%) and confirmed that suicide attempts were common in individuals with depression across the world.[208]

Meta-analytic evidence[209] indicates that the risk of suicidal behaviour in persons with depression is significantly associated with previous suicide attempt, severe depression, anxiety, hopelessness, family history of psychiatric disorder, comorbid substance abuse disorder, personality disorder,[210] and sleep disorders, particularly nightmares and insomnia.[211] Deaths from suicide among those with a current depressive episode occur mostly (75%) during the first episode, 19% in the second episode and 7% in persons with more than 2 depressive episodes.[212]

The impact of depression on functioning

The burden associated with depression increases sharply in the second and third decades of life, and is mostly carried by the populations in middle-income countries (Figure 4). This high score for the number of disability-adjusted life years (DALYs) is partly attributable to the high estimated disability weight ranging from 0·145 (mild) to 0·396 (moderate) and 0·658 (severe), with the highest of these weights equivalent to those of the most severe physical conditions (e.g., 0·682 for AIDS not receiving antiretroviral therapy, 0·569 for terminal cancer).[213]

Figure 4. The burden of depression across the life course according to country income



Updated from Kieling et al.[214] using Global Burden of Disease 2019 data. HIC: high-income countries; UMIC: upper-middle income countries; LMIC: low-middle income countries; LIC: low-income countries.

While there are a number of criticisms about the accuracy of disability weights[215-217] it is doubtlessly true that depression is a highly burdensome condition and other studies have confirmed that the disability is experienced as one of the most severe of all health conditions. Community surveys examining the comparative effects of diverse diseases on various aspects of role functioning[218,219] typically show that musculoskeletal disorders and depression are associated with the highest levels of disability among all commonly occurring disorders. The most compelling study of this sort was based on 15 national surveys carried out as part of the WMH Study.[220] Disorder-specific self-reported role impairment scores were compared across people who experienced each of 10 chronic physical disorders and 10 mental disorders in the year before interview. Depression and bipolar disorder were the mental disorders most often rated "severely impairing" in all countries. None of the physical disorders considered, including cancer, diabetes and heart disease, had impairment levels as high as those for depression or bipolar disorder. Depression is also associated with the highest number of days out of role at the societal level of any physical or mental disorder. In the WMH surveys, for example, 62,971 respondents across 24 countries were assessed for a wide range of common disorders and for days out of role in the 30 days before interview.[221] Depression was associated with 5·1% of all days out of role, the fourth highest population attributable risk proportion of all the disorders considered (exceeded only by headache/migraine, other chronic pain conditions, and cardiovascular disorders) and by far the largest among the mental disorders.

The WHO World Health Surveys of nearly one-quarter of a million respondents across 60 countries examined the comparative decrements in perceived health associated with different chronic disorders.[136] A consistent pattern was found across countries and socio-demographic subgroups within countries: the association between depression and the decrement in perceived health was larger than for any of the four physical disorders considered (angina, arthritis, asthma, diabetes). A related study in the WMH surveys compared depression with 18 other disorders, physical (e.g., cancer, cardiovascular disorders, diabetes) and mental (e.g., bipolar disorder, panic disorder, post-traumatic stress disorder) in predicting a summary measure of perceived health.[222] Depression was one of the three disorders associated with the highest decrements in perceived health, the other two being severe insomnia and a group of neurological disorders that included epilepsy, Parkinson's disease, and multiple sclerosis.

Depression affects a range of specific areas of functioning; this evidence is summarized below, with an emphasis on describing the effect of depression on life course outcomes (as opposed to the reverse pathway).

Education & employment: Early-onset mental disorders are associated with premature termination of education.[223-225] Depression is significantly associated, at least in studies conducted in high-income countries, and after adjusting for comorbid conditions, with about 60% elevated odds of failure to complete secondary school. A number of prospective studies document the impact of depression on occupational difficulties. For example, an analysis of WMH data showed that a history of depression as of the age of completing schooling predicted current (at the time of interview) unemployment and work disability.[226] These associations were significant only in high-income countries. This raises the possibility that the impairments associated with depression are influenced by contextual factors such as the complexity of work and the eligibility of depression for sickness-benefits or disability benefits.

Economic consequences: The personal earnings and household income of people with depression are substantially lower than those of people without depression.[227,228] However, as with unemployment, depression could be a cause, a consequence, or both.[229] Several prospective studies suggest that depression prior to completing education predicts substantially reduced income-earnings in adulthood after adjusting for level of educational attainment.[230,231] Epidemiological surveys have estimated the workplace costs of depression on low work performance while on the job;[232] in the US, the annual salary-equivalent human capital value of these losses has been estimated in the range of $30·1 billion[233] to $51·5 billion.[234]

Intimate relationships: While most of the literature on intimate relationships refers specifically to marriage, it is plausible that this evidence may generalize to other types of intimate relationships. Early-onset mental disorders predict low probability of ever marrying. For people who marry, these disorders may be positively associated with early (before age 18) marriage,[235] which is known to be associated with a number of adverse life course outcomes. These associations are largely the same for men and women and across countries. Depression is one of the most important pre-marital mental disorders in these respects. A pre-marital history of mental disorders also appears to predict divorce,[236] again with associations quite similar for husbands and wives across all countries and depression among the most important disorders in this regard.[237] Marital dissatisfaction and discord are strongly related to depressive symptoms,[238,239] with an average correlation between marital dissatisfaction and depressive symptoms of approximately r = 0·4 across studies and very similar patterns for men and women.[240] Longitudinal studies show that this association is bidirectional,[241,242] but with a stronger time-lagged association of marital discord predicting depressive symptoms than vice-versa.[243] Fewer studies have considered the effects of clinical depression on marital functioning,[244,245] but those consistently document significant adverse effects.

Intimate partner violence (IPV): IPV is partly a consequence of pre-existing mental disorders.[246] The WMH surveys[247] found that the association between premarital history of depression and subsequent intimate partner violence disappears after controls are introduced for disruptive behavioural disorders and substance use disorders, suggesting that depression might be a risk marker rather than a causal risk factor. However, a large sibling control study[248] reported that men with depressive disorder had a higher risk of perpetrating IPV against women than their unaffected full siblings. The risk was further elevated when there was comorbidity with alcohol use disorders, drug use disorders, or personality disorder.

Parental functioning and offspring outcomes: Both maternal and paternal depression have an impact on the offspring, but the impact of maternal depression may be larger.[249] The negative effects can include low birth weight, poor school performance, relatively high rates of physical health complications, and depression, anxiety, substance abuse and suicidal behaviour, with substantial, persistent, wide-ranging economic impacts.[250] Effects on their offspring are sustained when parents experience persistent depression, live in poverty, or both.[251] These adverse effects may be mediated by the association of both maternal[252] and paternal[253] depression with negative parenting behaviours. These associations are found throughout the age range of children, but are most pronounced for the parents of young children. Both laboratory and naturalistic studies of parent-infant micro-interactions have documented subtle ways in which depression in a parent leads to maladaptive interactions that impede infant affect regulation and later child development and increase risk of subsequent psychopathology.[254]

Experience of caregiving: For family members, the experience of caring for a depressed child or older adult is usually demanding and frequently an isolating experience. Most informal

mental health carers are women family members. They frequently have a double role caring for children and an older person living with depression. They may lose employment and contact with friends and outside activity, and even other members of the family. Family carers have heightened risk of becoming depressed or anxious themselves.[255]

THE ROOTS OF DEPRESSION

Three key observations have shaped our understanding of why some people become depressed. First, depression tends to run in families, often jointly with bipolar disorder, substance use, and anxiety disorders. Children of parents with depression or bipolar disorder, in particular, have an elevated risk of developing depression themselves even when they are not raised by their biological parents. But many children of affected parents do not manifest the syndrome, and most people with depression have unaffected parents. Second, onset of depression in adolescents and adults is in most cases preceded by childhood-onset disorders, such as attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders. However, most children with ADHD or anxiety disorders will not end up developing depression as adults. Third, most early episodes of depression have an onset shortly after a stressful life event, in particular one involving loss, disappointment or humiliation, especially in people primed by early loss, neglect or trauma. Nevertheless, all people encounter stressful life events at some point in their lives and most do not develop depression in the aftermath. While these three observations point to genetic, developmental, and environmental origins of depression respectively, they also suggest that no single factor provides a complete explanation of why depression develops. Ultimately, it is the unique interplay of these factors, operating at different points of the life course, which constitutes the roots of depression in any individual.

Predisposing and protective factors

With systematic follow-up of large representative samples from childhood to adulthood, it has become apparent that the onset of a major depressive episode is not typically the first manifestation of psychopathology. In most cases, depression is preceded by childhood symptoms or disorders, including oppositional-defiant disorder, ADHD, and anxiety disorders.[256] The prospective association between anxiety and depression is particularly strong and well established.[257] The prospective association between ADHD and depression is more complex and may be particularly relevant for early-onset depression. Depression that manifests in childhood or early adolescence may be related to genetic liability to ADHD and other neurodevelopmental disorders [258] as well as environmental risk factors. Childhood ADHD and anxiety disorders also both strongly predict bipolar disorder, which can start as adolescent-onset depression.[259]

Among the offspring of parents with depression, the risk of developing depression by early adulthood is 40%, a more than two-fold increase compared with offspring of parents without mood disorders.[260] Analysis of an entire country's population, including individuals raised by their biological families and individuals raised by adoptive families, suggests that familial risk for depression is due to approximately equal contributions of genetic and environmental factors that are shared within families.[261] The genetic risk of depression is likely due to small effects of hundreds or thousands of common genetic variants, with overrepresentation of genes affecting brain development, inflammation, bioenergetics and neuronal signalling. The large number of common variants involved[262-264] entails that every individual carries some risk variants for depression, and a polygenic score (indexing the individual's load of risk variants) predicts the genetic liability to depression better than any specific genetic variant.[265] In

addition, the predictive power of molecular genetic information falls far short of estimates from family and twin analyses, indicating that the contribution of genetic variants to depression also depends on the environmental context.[12]

Much research has been done on early childhood adversities, suggesting that they are associated with an increased vulnerability to depression (as well as other psychopathology and somatic illnesses) in adulthood in the presence of stressful life events. Substantial evidence supports the idea that experiencing maltreatment during critical periods early in life increases a person's predisposition to a subsequent/later depressive episode.[266] Moreover, convincing evidence indicates that experiencing maltreatment in childhood increases the likelihood of exhibiting an unfavourable course of illness, with higher rates of recurrence and persistence in adulthood.[267] Maladaptive personality traits (which themselves have a variety of genetic and environmental roots) are also associated with increased vulnerability to depression. For example, the construct of neuroticism or negative affectivity has been shown to be associated with an increased probability of experiencing stressful life events and of subsequently responding to these events with depression.[268] Cognitive models propose that individuals at risk for depression exhibit biases in information processing, privileging interpretations that are pessimistic and self-critical, leading to "depressogenic" cognitive styles.[269] Variables related to an individual's interpersonal style might also represent risk factors for developing depression, possibly due to their contribution to stressful conflict and loss events.[270] Indeed, the modal clinical presentation of people with personality disorders is a complaint of depression[271,272] and significant proportions of people with depression have a comorbid personality disorder.[273] Such comorbidity has adverse prognostic and therapeutic implications.

Lifestyle habits have also been consistently associated with depression. Meta-analytic evidence supports an association of low levels of physical activity[274] and unhealthy dietary patterns with an increased risk of developing depression.[275] Prior use of substances has been shown to increase the predisposition to depression; for example, adolescent cannabis consumption has been associated with increased risk of developing the disorder in early adulthood.[276] A meta-analysis reported an association between tobacco smoking and increased risk of depression in cross-sectional studies, with the relationship maintained across several moderators.[277] It is noteworthy, however, that the overall strength of associations is variable, and limited evidence is available to indicate the direction of causality between most lifestyle factors and depression, with a strong probability of bidirectional causation in most cases.

The importance of social determinants suggests that a perspective beyond the individual level is also required to deal with factors influencing depression. Population health science focuses on structural factors and on how they shape the health of individuals within and across populations.[278] Many of the Sustainable Development Goals such as reducing gender and other inequities, and effective climate action align closely with factors which affect the risk of depression.[279] There is now a large evidence base that intimate partner violence and sexual abuse, which are endemic globally, are major risk factors for depression, particularly in women,[280,281] who are more likely to experience such violence, including coercive controlling behaviours.[282] Income inequality has been shown consistently as positively associated with the risk of depression (most of the available evidence coming from high-income countries).[283] The relationship between poverty and depression is complex and likely to be characterized by both social causation (i.e., social and economic adversities increase the risk of depression) and social selection (i.e., people with depression drift into poverty) mechanisms. The experience of forced displacement due to conflict, climate change, and other causes is associated with high prevalence of depression, with numerous studies identifying one-third to half of refugees and

internally displaced populations meeting criteria for depression on self-report questionnaires.[284] Following the evidence regarding the impact of natural and built environments on physical health, there are emerging data suggesting the relevance of biophysical factors such as air pollution, persistent organic and heavy metal pollutants,[285] and ambient noise in terms of increasing the risk for developing depression.[286]

Conversely, some personal characteristics, interests, skills, and social support variables may constitute strengths that mitigate the impact of depression. Protective factors increase a person's resilience, i.e. the ability to maintain or regain mental health in the face of adversity or to bounce back from hardship and trauma.[287-289] Factors such as history of secure attachment, cognitive abilities, self-regulation abilities, and positive peer/community support have been identified as contributing to resilience and enabling at-risk individuals to adapt or respond well to stressors. Resilience may be context- and time-specific, and may not be present across all life domains[288]: in other words, individuals might be resilient to one environmental hazard but not to others, and may exhibit resilience at one period in their lifetime but not at other points.[290] From a systemic point of view, the capacity of the physical and social environments to facilitate the process of coping by the individual in a culturally meaningful way is also of utmost importance.[291] An adequate clinical assessment should therefore not only investigate mental phenomena potentially relevant to overcome negative circumstances, but also explore past situations in which the individual and his/her environment dealt with adversity, as previous successes might be relevant for current and future challenges.[290]

Precipitating and perpetuating factors

Precipitating factors occur shortly before the onset of depression, possibly interacting with predisposing factors to trigger the disorder. Many studies[292] adopt the overarching term "stressful life events" to encompass experiences such as bereavement, separation, life-threatening situations, medical illnesses, being subjected to violence, peer-victimization (e.g., bullying), loss of employment, and separation/divorce. There is substantial evidence corroborating the precipitating role of such proximal environmental influences in the development of depression. A large proportion of individuals, however, are apparently less vulnerable to these experiences. Childhood sensitisation through trauma or neglect may play a role in parsing vulnerability versus resilience. While acute life events might precipitate the onset of depression in vulnerable persons, research has also shown that individuals with depression have an increased propensity to experience acute stressors in comparison to those without a history of depression. This perpetuating pattern, designated stress generation,[293] is particularly relevant for interpersonal events. Other factors contributing to the recurring and persistent nature of depression include substance use, behavioural patterns such as social withdrawal, and cognitive biases in attention, memory and interpretation. A ruminative response style (characterized by an over-analysis of problems) tends to intensify negative, self-focused thoughts and to hamper problem-solving, therefore perpetuating symptoms of depression.[294] Identifying maintaining factors might be of special relevance, as they might be suitable to target to achieve sustained recovery.

Integrative models of pathogenic mechanisms

The search for discrete risk or protective factors associated with the onset and continuity of depression captures only a small proportion of the complexity of this condition. Multiple factors are likely to operate through a probabilistic chain that is conditioned by timing, dosage, and context, in which upstream distal factors (more precocious and less specific) influence more downstream proximal factors (affecting the individual closer to the onset of the condition and often more directly). The picture is further complicated by the evidence that no risk factor

appears to be either necessary or sufficient, that the same risk factor might confer increased risk for various mental disorders, and that many individuals exposed to risk factors do not develop depression.[12]

While theories emphasizing one aspect of causation have been applied with a modest degree of success (e.g., monoamine hypothesis, cognitive theory, interpersonal theory), a broadly applicable model of depression will need to incorporate genetic, developmental, and environmental factors and allow for heterogeneity of causation across individuals. Most conceptualizations that fulfil these requirements are variants of the "diathesis-stress" model (alternatively referred to as vulnerability-stress model). The diathesis-stress model posits that, following an acute stressor, a person who carries a diathesis (or vulnerability) that renders him/her sensitive to the stressor will develop depression. The vulnerability may have both biological (e.g., genetic, endocrine, inflammation, brain connectivity) and psychological (e.g., temperament, personality, beliefs) features.[295] Each person may carry a number of vulnerabilities that may add on to an overall diathesis, or may make a person sensitive to different types of stressors. There is probably a complementary relationship between the degree of vulnerability and the severity of the stressor: a person with a high degree of vulnerability may develop depression even with a mild stressor, and a person with a low degree of vulnerability may only become depressed if encountering a stressor of extraordinary severity. With the accrual of studies on the joint effects of genetic and environmental factors in the causation of depression, the general stress-diathesis model can now be considered proven beyond reasonable doubt.[12,296]

More developmentally informed models, referred to as "transactional," also account for the fact that vulnerability can change over time due to both biological events (e.g. menarche, childbirth) and changes in the external environment.[297] For example, exposure to adverse environments earlier in life or even *in utero* may not be sufficient to cause depression, but may create a vulnerability that will render the individual more likely to develop depression following a further stressful experience. Furthermore, the same characteristic may make an individual sensitive to both negative effects of adverse experiences and beneficial effects of positive experiences. This more inclusive conceptualization of personal vulnerability and potential has been described as the "differential susceptibility" model.[298]

The diathesis-stress and differential susceptibility models raise questions about the nature of individual vulnerability. To distinguish cause and effect, it is useful to consider individually stable and changeable aspects of vulnerability separately. Genetic variation provides an unbiased source of information about vulnerability, because genetic sequence is believed to remain unchanged from conception and throughout the life of an individual. Therefore, specifications of the diathesis-stress model that involve genetic measurement allow for stronger conclusions about causality. These genetic models include gene-environment correlation and gene-environment interaction.[292]

Gene-environment correlation occurs when a genetic variant makes an individual more likely to be exposed to a particular aspect of the environment. Some recently identified gene-environment correlations challenge the assumption that genes and environment are separate primary causal factors. Individuals with a high loading of depression-related genetic variants report more stressful life events, even life events that are typically thought to be relatively independent of the individual.[299] For example, polygenic scores for depression, lower intelligence, and greater body weight predict whether an individual will be bullied.[300] These findings stimulate a reconceptualization of the diathesis-stress model to incorporate the

interdependence of stressor and vulnerability.[301] In turn, gene-environment interaction occurs when a genetic variant makes an individual more sensitive to the impact of an environmental exposure. Incorporation of gene-environment interactions improves the prediction of depression over the polygenic risk score approach.[302] Stressful life events are more likely to lead to depression in individuals who have a higher load of genetic risk variants.[303] It is also possible to measure genetic factors that render individuals more sensitive to both negative and positive environmental exposures, in the form of a polygenic score. This "polygenic sensitivity score" predicts greater negative and positive responses to adverse and beneficial exposures respectively, supporting the differential-sensitivity model.[304]

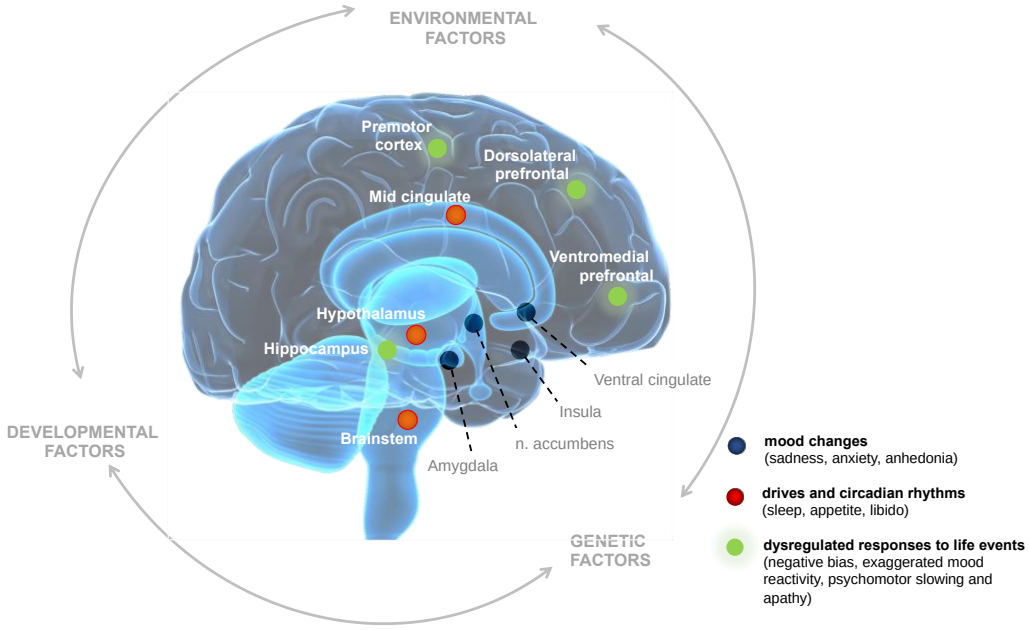
Some of the most powerful environmental factors are far removed in time from the actual onset of depression. For example, childhood maltreatment and bullying are associated with increased vulnerability to depression lasting for the individual's lifetime. This raises the question of how non-genetic vulnerability factors remain active over long time periods. Psychological and personality development theories might account for this phenomenon. Equally, epigenetic modifications provide a suitable mechanism for such very long-term memory. Exposure to adverse environments early in life may lead to modifications of the genome, such as DNA methylation, that will continue to affect the expression of genes for prolonged periods of time without altering the genetic sequence. While specific epigenetic modifications have been associated with experimental exposures in animal models, finding a reproducible epigenetic signature of adversity in humans has been challenging.[305] Exposure to adversity in childhood has also been found to increase the level of systemic inflammation.[306] The long-term increase of inflammatory activity may well play a role in the pathogenesis of depression, as symptoms of depression overlap with those of inflammatory disease.

The present models of depression are being challenged by factors that do not easily fit into the gene-environment dichotomy. One such factor is the gut microbiome, the ensemble of bacteria living in the human digestive tract, which is individually variable and is affected by human genetic makeup, diet and other aspects of the environment. The fact that the microbiome is itself genetic in nature opens a host of possibilities, including complex interactions between human and bacterial genomes. Gut bacteria can produce neuroactive substances, including gamma-aminobutyric acid (GABA) and serotonin, which can affect the brain of the human host. Intriguingly, the presence of these bacteria has been linked to depression in their human hosts.[307] Animal models have illustrated that a depressive phenotype can be transferred to a non-depressed animal by microbiome transplants from a depressed donor, and that depressed animals can have the phenotype removed by transplant from a non-depressed donor.[308]

The neural pathways of depression

The hundreds of genetic variants associated with depression, each of very low effect, are most concentrated among genes that are expressed in the prefrontal cortex and the anterior cingulate.[263] These same brain areas show accelerated breakdown of monoamine neurotransmitters,[309] increased neuro-inflammation,[310] reduced grey matter,[311] and heightened reactivity to mood-relevant stimuli[312] in individuals with depression. This convergence of evidence leaves little doubt that, while genetics and the environment are the primary movers, the final pathways of depression pathology occur in multiple but mutually interactive areas of the human brain (Figure 5).

Figure 5. Neural underpinnings of depression



Depression results from an interaction between multiple risk and protective factors that is unique for each person. Regardless of the distal origins of the causal pathways, they converge on brain development and function and are expressed in multiple brain regions that interact to mediate various depressive features (shown in blue, red, and green). These brain patterns are highly variable, likely reflecting etiological differences, variations in the degree of illness severity and persistence, and the heterogeneous expression of mood, motor, cognitive and vegetative symptoms among individuals.

Over the last 30 years, brain imaging has leveraged a conceptual shift in depression research. The dominant psychological and neurochemical theories of the past have been reframed to accommodate complementary genetic, developmental, molecular, and brain circuit models. The best replicated of early findings — frontal hypometabolism and hippocampal atrophy[313,314] — remain foundational to current models of depression, although they are not pathognomonic. A conspicuous contradiction is that many individuals do not show these core changes, or demonstrate opposite patterns (e.g., frontal hypermetabolism). Increasing recognition of these individual differences, likely masked previously by the focus of earlier studies on group effects, assists the understanding of clinical heterogeneity in depression.[315,316]

Other limbic (amygdala, insula, cingulate) and subcortical (basal ganglia, thalamus, periaqueductal grey, dorsal raphe, lateral habenula) abnormalities have also been reported, especially with the introduction of resting and task-based functional MRI (fMRI) and functional connectivity analyses. These findings are similarly variable. Differences among subgroups of people with depression, as well as variations in the degree of illness severity and duration, and the heterogeneous expression of clinical symptoms among those tested may contribute to the observed variance,[317,318] though there is so far no consensus on the bases for these results.

The investigation of neural mechanisms sub-serving depression pathogenesis and progression continues based on the assumption that this is unlikely to be a disease of a single gene, brain region or neurotransmitter system. Depression is now modelled as a neural systems disorder.

A depressive episode is viewed as the net effect of failed network regulation in the context of emotional, cognitive or somatic stress.[315,319] Employing this contemporary interconnected view, studies extend beyond properties of individual brain regions to examine instead integrated pathways and distributed neural networks. Technological and analytic advances[319-322] including routine use of "big data" make it possible to acquire multiple neuroimaging data in the same individual in a single session. There is also increasing public availability of large multimodal imaging datasets.[322,323] Translational studies using cell-specific animal models of depression-relevant behaviours further inform the interpretation of multimodal imaging data in people at all stages of risk and illness.[324-326] Such studies have revealed subtle abnormalities of individual region and pathway structure and function.

Definitive precipitants or mediators of such "systems dysfunction" are not yet characterized. However, several factors appear to be strong contributors. In addition to acute and chronic life stressors, these include genetic vulnerability, affective temperament, developmental insults, and early childhood trauma.[327-329] Depression network models have also evaluated mediators and moderators of resilience. Such studies draw upon animal models of acute and chronic stress exposure.[330,331] Converging findings across species again point to the crucial role of cortico-limbic circuitry in the experience of depression, with different regional abnormalities emerging at different ages and developmental stages. A prominent observation is the involvement of distinct prefrontal cortical subregions and their connections to numerous subcortical structures, including the cingulate, hypothalamus, amygdala, hippocampus, nucleus accumbens, dorsal raphe and other brain stem nuclei.[324-326] Links of these cortico-limbic circuits to physiological functions common to both chronic stress exposure and depression have emerged, including disruption of circadian functions, affective states, drives, motivation, intention and action. All these disturbances logically contribute to symptoms of low energy, apathy, anhedonia, negative mood, and changes in appetite, sleep and libido. These circuit aberrations can also result in anxiety, rumination, negative cognition and maladaptive habits. In the animal stress models, structural alterations (i.e., atrophy and morphological changes in neurons and glia) and functional adaptations (i.e., changes in blood flow, metabolism and gene expression) are observed, paralleling abnormalities seen in imaging and post-mortem studies of people with major depression. Chronic stress has additional time-dependent influences on systemic physiology. Immune, neuroendocrine, autonomic, metabolic and molecular mediators have further influence on cortico-limbic function in a bidirectional manner. This cascade of reactions will likely have impacts on cellular structure and function, neural network dynamics, and peripheral organ function, with differential effects in resilient and susceptible individuals.

Understanding brain plasticity and adaptive mechanisms, including their time course and trajectory, can be critical to the effective timing and delivery of various interventions. These observations might have important implications for treatment and prognosis; for example, different treatments appear to modulate distinct network nodes and their local and distant connections, and response may depend on targeting specific biological abnormalities.[332] Furthermore, the cascade of chemical and molecular adaptations that occur with depression and stress exposure might have a range of consequences, including irreversible structural and molecular damage that may well underlie treatment resistance phenomena.[324] Imaging studies are now designed to explicitly develop biomarkers of treatment-specific subtypes that can guide optimal treatment selection for individual subjects as well as avoid treatment classes unlikely to be helpful.[333,334] Further, treatments are now being tested to target chemical as well as imaging biotypes.[335-338]

THE PUBLIC UNDERSTANDING OF DEPRESSION

Due to sheer ignorance about mental illness, I often found myself left behind. Low levels of self-esteem and the overall guilt, shame, burden and stigma of having depression… aggravated the state of my mental health. In my studies... I would miss classes and not attend fieldwork. Unfortunately, due to a lack of awareness, this was construed as a personal failing. I was told to my face that- "depression was nothing but an excuse", to "cheer up", and informed that: "Medicine was not the solution to depression."
- Richa Sharma, 25, Najafgarh, India

I thought people would only understand me if they lived what I was living, I felt that nobody could understand me. Only those going through what I was going through.
- João Veit Costa, 19, Porto Alegre, Brazil

Stigma & discrimination
Negative attitudes towards people living with depression, and stigma and discrimination, are associated across several world regions with negative outcomes: low help-seeking, poor treatment adherence and poor treatment outcomes, low quality of life, and risk of suicidal thoughts and behaviour.[339-341] The negative attitudes include blaming the person for the illness and expectations that someone with depression cannot perform familial and occupational roles nor cope with either hardships or the daily routine of life.[342,343] Stigma may be encountered as beliefs about the attitudes of others (perceived stigma), or as a person's own thoughts and beliefs about their own depression (personal or self-stigma). Both may be more marked among certain groups including people with less education and those who are more psychologically distressed.[344] The accompanying prejudices include unwillingness to work with persons with depression or to have someone with depression marry into the family, and easily result in discrimination. Those living with depression report fear of disclosing depression in the workplace.[345]

Longitudinal data on public attitudes toward depression are available for some high-income countries; disappointingly, no reduction in public stigma has been reported over recent times. For example, in one US sample,[346] in 1996 compared with 2006: 46% and 47% of the public respectively were unwilling to work closely with someone with depression; and 33% and 32% of the public respectively thought persons with depression were violent toward others. Those members of the public endorsing neurobiological models of depression were three times more likely than others to report that persons with depression were violent toward others.[346] In the UK, there were no changes from 1998 to 2008 in attitudes such as people with depression are a "danger to others," "they are to blame for their own illness," and they will never fully recover.[343] Repeated cross-sectional surveys of the Australian general population[347] between 1995 and 2011 noted a meaningful increase (from 39% to 74%) in the proportion of respondents correctly recognising depression from a vignette; however, even though the dominant causes for depression were cited as stress-related, 40% of respondents continued to endorse weakness of character. Although long-term longitudinal studies are lacking from low- and middle-income countries, cross-sectional studies in Brazil, China, and Ethiopia also demonstrate high-levels of public stigma toward depression. Studies in São Paulo, Brazil, show a public perception of depression as associated with dangerousness.[348] In Wuhan, China, public stigma against depression was greatest among men, older adults, and persons self-identifying as coming from well-functioning families.[349] In Arba Minch, Ethiopia, stigma against depression was associated with lack of formal education.[350]

Conversely, attitudes may be less negative in cultural contexts where the symptoms of depression are attributed predominantly to problems of the heart, or to loss of the soul or other spiritual beliefs, rather than to a brain dysfunction.[101,351] Youth, compared with older people, tend to report less negative attitudes towards depression[352]; though they also appear unwilling to disclose a diagnosis of depression to their peers. The causes of depression they most commonly report are stress, thinking patterns, and lack of willpower.[352]

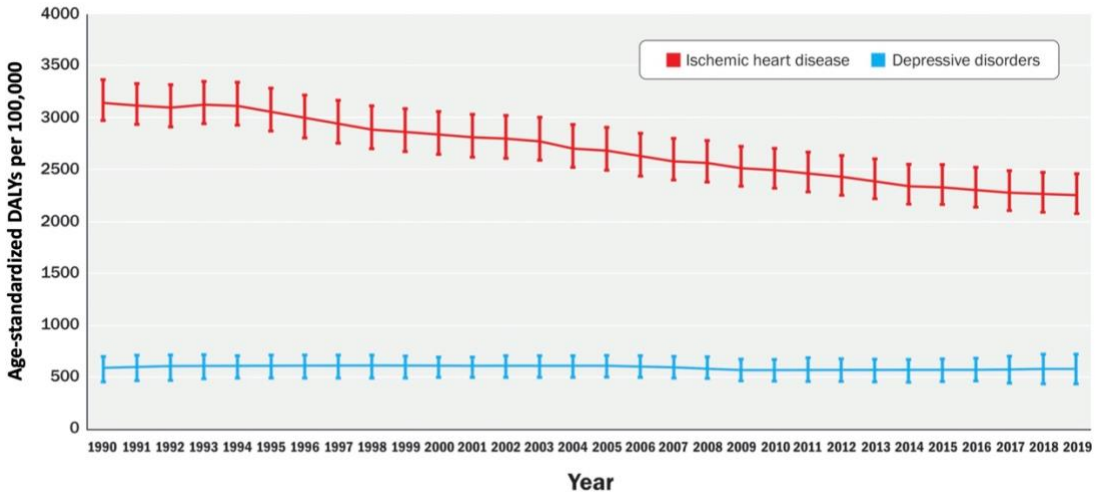
Depression literacy

Knowledge about strategies to attain and maintain good mental health and about depression and its treatments is referred to as depression literacy.[353] It is potentially an important determinant of help-seeking across age groups as well as relevant for public decision-makers. A meta-analysis (though only 15% of the studies were from low and middle income countries) reported a growing acceptance of treatments for depression over recent decades.[354] However, attitudes toward treatment seeking vary across countries; while 64% of persons with depression in high-income countries perceived the need for "treatment" as operationalized in the World Mental Health surveys, only 35% in other countries did so.[355] Lower levels of mental health literacy have been associated with a belief that one should use self-control to relieve depression rather than seek help.[356] Depression can be poorly recognized among elderly people because of a view that cognitive decline is "part of ageing." Young people and their parents may recognize depression although not seek help.

INTERVENTIONS TO REDUCE THE BURDEN OF DEPRESSION

In contrast to the reduction in the global burden of other medical conditions such as cardiovascular disease, largely driven by effective prevention strategies, there has been no reduction in the burden of depression over the past three decades (Figure 6). This contrast is apparent despite continuing efforts to address stigma and depression literacy, the robust state of the science of preventing and treating depression, and the evidence from population health science on the substantial effects possible from small changes in upstream macrosocial factors.

Figure 6. Global burden of ischemic heart disease and depressive disorders over time



Based on data from the Global Burden of Disease up to 2019. DALY: Disability-adjusted life-years.

Decreasing stigma and improving depression literacy

Strategies to decrease stigma and improve depression literacy are now seen by many as integral to national and international approaches to reducing the burden of depression. Evidence on how best to achieve these aims and the range of options is growing.

Advocacy

Advocacy to increase awareness of depression (and of mental ill-health more generally), decrease stigma and discrimination, and increase access to care has been evaluated in various contexts. Awareness campaigns have been mounted in many countries over the past two decades. An early review[357] found modest improvements in knowledge and awareness of depression in the short term, and improved attitudes towards persons with mental illness. However the promotion of the "Decade of the Brain" in the U.S., which aimed to promote treatability of depression and other conditions, evidently did not reduce stigma. Attributing depression to biological causes may have the unintended consequence of increasing stigma. A meta-analysis of etiological attribution for mental illness, including depression, found that neurobiological explanations promote stigma: manifest as more desire for social distance, more expectations of dangerousness, and lower expectations of treatment outcomes.[358] Stigma specific to depression seems to be lowest when a combination of life stress, chemical imbalances and genetic abnormalities is endorsed rather than a single biological cause.[359] However, cultural context is also relevant, and biological and sociological explanatory models appear to contribute differentially to stigma based on cultural values.[360]

While sustained population-wide improvements in attitudes toward depression have not been demonstrated, social marketing seems to be effective in reducing the stigma of mental illness.[361] Certain initiatives such as mass media campaigns demonstrate positive attitudinal changes at least in the short-term.[362] Overall, the evidence suggests that mass media campaigns have small to moderate positive effects on community attitudes in their early aftermath. There is limited information available on long term follow-up, and mixed evidence on whether the campaigns result in increased use of care.[363]

Targeted interventions have also been evaluated. For people with mental illness, some group-level interventions show promise, while for students, social contact-based interventions usually achieve short-term attitudinal improvement.[361,362] Other strategies include Mental Health First Aid training for the general public and for specific groups such as police and health workers. This program has been introduced in several countries and subpopulations, but so far has not consistently produced stigma-reduction sustained beyond six months after the training.[364] There have been a few evaluations of stigma-reduction programs for primary care workers in low- and middle-income countries. These have also demonstrated up to now only short-term improvements in attitudes.[365,366] Initiatives designed to change attitudes toward depression among health professional students in low- and middle-income countries have had mixed results.[367]

Social contact

Social contact appears to be the most effective type of intervention to improve knowledge about and attitudes towards mental illness in the short term, though the evidence for depression specifically and for longer-term benefits is weak.[362,368,369] Investigation of workplace stigma-reduction initiatives is limited, and few of these specifically target depression.[345]

Interventions for depression literacy and stigma reduction in young people

Because the onset of depression frequently occurs early in life, mental health awareness and literacy are important for young people. A recent systematic review concluded that fewer than half of adolescents could recognize depression, with lower recognition rates in low- and middle-income countries (China, India, Jordan, Nigeria).[352] There was a preference overall for informal sources of help.[352] The impulse to handle problems on their own represents a significant barrier to treatment in this age group.[370] The chance of moving through pathways to appropriate treatment is also influenced by the way complaints to a primary care practitioner are framed[371] — as well as providers' reluctance to discuss the topic with adolescents[372] — two more reasons that interventions to improve mental health literacy are crucial.

In a rare study of the awareness in adults of childhood and adolescent depression, most parents in a U.S. national survey correctly identified a vignette of childhood depression as something more than daily troubles, labelled it a mental illness,[373] and recognized the necessity of intervention. Other work suggests, however, that parents' responses to adolescent depression are compromised by their own stigma towards and lack of knowledge about depression.[374]

Universal school-based programs have been undertaken either with this focus,[375] or as depression and suicide prevention programs with depression and suicide literacy as a core component.[376-380] Once more, however, there are conflicting results on changes in help seeking recommendations and intentions.[376,381,382] One specific depression awareness and literacy training program reveals other significant outcomes. The Youth Aware of Mental Health (YAM) intervention grew out of the WPA Global Child Mental Health Program in collaboration with the WHO and the International Association of Child and Adolescent Psychiatry and Allied Professions. This was further developed in the context of the Saving and Empowering Young Lives in Europe (SEYLE) program, which was associated with a reduction in suicide attempts up to 12 months following intervention. The five-hour intervention included an awareness raising booklet covering six topics (awareness of mental health, self-help advice, stress and crisis, depression and suicidal thoughts, helping a troubled friend, and getting advice – who to contact) and lessons addressing these topics. Although not specifically assessed, there were numerous indications (such as students carrying the booklets 12 months later) that the students were directly empowered by these booklets and the brief role play sessions based on these: to take action for self or to support a peer finding help. YAM was compared to gatekeeper training in a randomized trial and found to be more effective.[383]

Treatment preferences

These have remained relatively stable across age groups over recent decades. Multiple systematic reviews describe a consistent preference among both the general public and people diagnosed with depression for counselling and other psychotherapy interventions over antidepressants.[384-386] Elderly people with depression in Europe are among the few populations with an equal preference for medication, psychotherapy, and talking to friends and family as treatment options.[387] The preference for psychotherapy is marked among adolescents, young adults, women, and minority ethnic groups,[385,386,388] as well as those with prior experience with psychological treatments and more severe symptoms of depression.[386,389] Explanations for the preference include the assumption that psychotherapy is better than antidepressant medication at resolving the causes of depression.[390] Negative attitudes towards antidepressant use are linked with views that depression is a sign of emotional weakness or reflects one's inability to deal with personal problems, or fears that it signals greater severity of depression symptoms.[388] In some contexts, medication is considered irrelevant as depression is not seen as a medical condition, and self-help preferred.[391] Another study records a perception that many people are

misdiagnosed with depression and given antidepressants unnecessarily.[392] This echoes some academic critiques that current psychiatric practice is medicalizing sadness in the name of treating depression, leading ultimately to a loss of sadness and grief as ordinary, acceptable emotional reactions.[60,393]

Importance of depression literacy for health workers

Depression remains stigmatized in the medical community.[394] It is receiving increasing attention in some countries in campaigns addressing physician burnout and wellbeing: a combination of strategies (anonymous screening, outreach, education, peer support, and emergency mental health care access) may be effective in reducing depression and high rates of suicide among physicians and nurses.[395] Teaching physicians to recognize depression in themselves and their colleagues and to find solutions that work for them can also be expected to repay as benefits to their patients.[396]

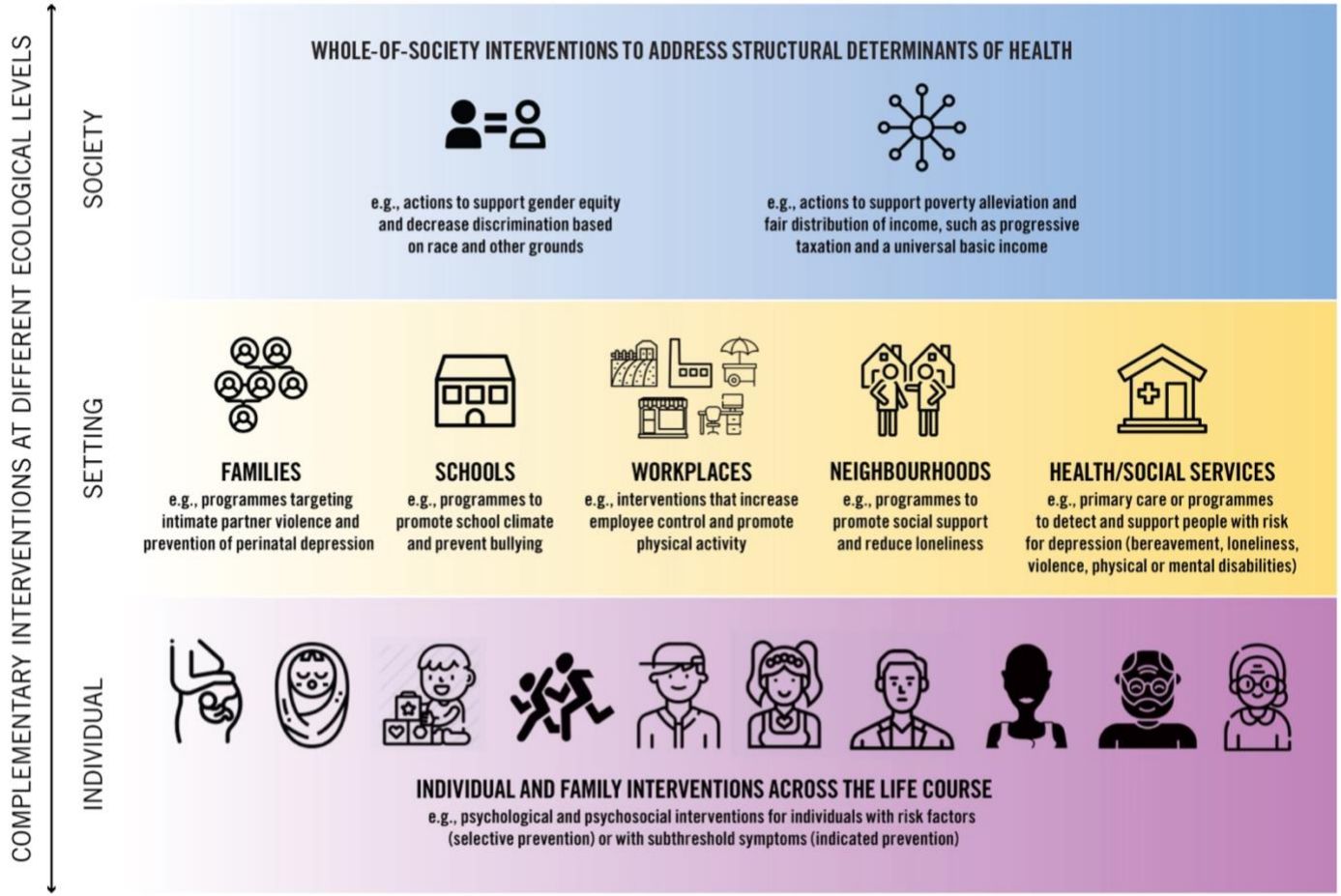
Health workers across the world, including those in low- and middle-income countries, acknowledge stigma toward people with depression.[339,397] This is associated with low rates of depression recognition[398,399] or poor quality of care. Physicians with stigmatizing attitudes often fail to offer appropriate physical health care to a person with documented depression, a practice known as diagnostic-overshadowing.[397] Stigma may contribute to a bias, first, toward presentation of somatic complaints by patients and, second, toward health workers' treating the somatic concerns without exploring associated mental health problems such as depression.[400] This overlaps with earlier constructs of masked depression.[401]

Prevention

The approach to prevention is two-fold: population health science[278,279,402,403] provides the basis for mobilising and measuring changes in the health status of populations, through policies and other interventions that influence the structural determinants of health (or macrosocial factors) such as income inequality and gender inequity; prevention science[404] considers the interaction of risk, protective and other factors for individuals across the life course. This two-fold approach is grounded in an ecological understanding of the interactions of individuals with their proximal contexts (e.g., schools, family) and more distal contexts (e.g., social attitudes, economic policies) in a dynamic fashion over the life course.

We describe depression prevention through universal (offered to an entire population rather than specific groups), selective (targeted to individuals or groups at higher-than-average risk for depression) and indicated interventions (targeted to individuals showing signs of subthreshold depression) within the multi-level ecological framework: with the levels broadly categorized as structural, settings-based, and individual (Figure 7). To be effective, interventions need to be adapted with local experts and communities for selected settings at the appropriate ecological level. The prevention of the recurrence of an episode of depression is subsequently covered when considering interventions for remission and recovery from episodes of depression and the principles of care.

Figure 7. Opportunities for the prevention of depression across the lifecycle



Whole-of-society preventive interventions (conceptually these are *universal interventions*) address structural determinants of depression. Interventions shown in the second and third rows represent the more immediate or proximal ecological levels of settings and individuals. These interventions can (i) be categorised as *universal*, *selective* or *indicated* depending on the focus of the work (e.g. all children in a school vs children with learning or emotional difficulties; noting that whole school programs may include a mix of these intervention types); and (ii) focus on risk and protective factors at different points across the lifecycle, within the various social contexts.

Proximal interventions for the prevention of depression
Randomised controlled trials for preventing depression have examined interventions that use adapted versions of psychological treatments for depression delivered in a range of settings and population groups – schools, general medical care, pregnancy-related settings,[405] and, increasingly, digital settings.[406-409] They include universal, selective and indicated interventions. A meta-analysis of 156 trials reported small effects (pooled SMD of 0·16 [0·07–0·26]),[410] with smaller effects as expected for the trials of interventions designed as universal prevention programs. For cognitive behavioural therapy (CBT)-based preventive eHealth interventions, a pooled mean difference of 0·25 for short-term outcomes has been reported; however, no effect was detected on long-term incidence rates.[411] All in all, based on these findings, the efficacy of specific psychological and educational interventions may be considered as relatively small, but meaningful.

A recent meta-analysis[412] of RCTs included participants from high risk groups, of all ages, but without a diagnosis of depression at baseline. Each of the included studies assigned participants to a preventive psychological intervention or a care-as-usual or comparable control group, and ascertained incident cases of depression at follow-up with a diagnostic interview. The analysis reported an incidence risk ratio of 0·81 one year after the preventive intervention. Given the average control event rate of 28%, 19 people had to participate in the intervention to prevent one depressive episode compared to people in the control condition.

Such interventions, even if requiring modest health system investments, provide savings that often accrue elsewhere in the health system or wider economy. There are, however, economic challenges to implementation: savings from effective prevention may not accrue for many years, nor benefit the healthcare sector, creating resource disincentives to take action.[413,414] We now examine the evidence on prevention across specific life course stages.

The perinatal period: A recent US Preventive Services Taskforce review[415] reports convincing evidence that pregnant or postpartum women who are at increased risk for depression — based on sub-threshold symptoms, history of depression, and/or socio-economic and demographic factors including recent intimate partner violence or other negative life events — would benefit from counselling (CBT or interpersonal psychotherapy [IPT] adapted for this purpose). The Taskforce also reviews evidence on non-psychological interventions. It concludes, consistent with an earlier systematic review on exercise,[416] that while the evidence base on exercise and social interventions to prevent antenatal depression in mothers is growing, it remains insufficient to support implementation and points to a prominent area of research need.

There is also a growing evidence base on the depression prevention effects of parental interventions in the perinatal period. These are designed to promote healthy parenting and family bonding, and include[417,418] social programs addressing depressive symptoms; substance use counselling and treatment; screening for risks to the development of a child; attention to the behavioural needs of children with chronic medical disorders; and parent education programs. For many of these strategies, there is strong evidence of cost-effectiveness. [419] While this evidence comes mainly from high-income countries, a peer-delivered psychological intervention (The Thinking Healthy Programme) in India and Pakistan has been shown to have a moderate effect on remission from perinatal depression as well as low-cost to deliver and cost-saving through reduced health service use and productivity losses.[420,421] A key delivery strategy during the perinatal period addresses perinatal health care concurrently with risk factors for depression, such as intimate partner violence, and preventive interventions.

Collaborative care (described in detail later) enables obstetricians, nurses, primary health care practitioners, social workers and mental health practitioners to provide integrated care in a single setting.[403] An enduring and cost-saving preventive effect on postnatal depression was achieved in one study of a universal intervention[422] that trained health visitors (community health professionals) in identifying depression and psychological intervention methods.[423]

Several strategies devised to support the mental health of parents[403] are successful and relevant in preventing adverse mental health outcomes in their offspring (see also below). However, the focus on pregnancy may not be early enough to prevent intergenerational transmission of depression. There is emerging evidence that poor mental health in the preconception period can be associated with poor mother infant bonding[424] and with infant reactivity, a marker of future mental health problems.[425] This raises the possibility of predicting perinatal depression from adolescence and before conception and investing in the future through promotion of education for girls, and addressing gender equity through societal interventions such as preventing child marriage, delaying marriage beyond adolescence and other measures.[426,427]

Children and adolescents: Most depression prevention trials have been conducted with children and adolescents.[410] The focus is warranted given the substantial emergence of mental disorders in the first decades of life and the potential for shaping current and future generations.[427] Nine out of 10 reviews of these trials report significant reductions in depressive symptoms,[428-436] generally with small effect sizes. Four reviews analysed the incidence of depressive disorders as an outcome, and all reported reductions in incidence.[430-432] Subgroup results from a meta-analysis[412] of psychological intervention trials indicate an incidence risk reduction of 0·71 (95% CI: 0·51–0·99) among high-risk children and adolescents without depression at baseline one year after the intervention. Given the average control event rate of 25%, 14 individuals had to participate in the intervention to prevent one additional episode of depressive disorder compared with the control group outcome.

Educational institutions, from schools to universities, offer unique opportunities for preventive interventions. Bullying at school (and in other settings) is an important target for interventions to avert a strong lifetime risk for depression.[436] A large meta-analysis focused solely on school-based CBT detected small effects for depression prevention in the short- and medium-terms, with a small long-term benefit.[431] Another meta-analysis of school-based depression prevention programmes highlighted 81 RCTs with positive but small effect sizes.[434] The SEHER trial from India is one of the few examples of a school-based intervention in a low-resource setting. It reported benefits from a lay counsellor-coordinated intervention targeting the social environment (school climate), with large and incremental effects (with time) in reducing bullying and depression symptom severity.[437] A systematic review of 68 prevention programs for college, graduate and professional students in 15 countries[438] reported moderate reductions in symptoms, regardless of delivery format or prevention level.

While economic evaluations suggest that depression prevention strategies in children and adolescents are cost-effective,[439] many actions are initiated outside the healthcare sector (e.g. in schools). The costs of doing so might be a disincentive, even though interventions such as social and emotional learning programmes and anti-bullying initiatives offer strong economic pay-offs over quite long periods.[440-442] Many lifestyle risk factors and risk pathways for depression and non-communicable diseases are shared from childhood and adolescence onwards. This makes common preventive approaches attractive for targeting these factors. There are compelling reasons to target depression specifically in such shared approaches. Not only is depression an important negative health outcome in its own right, and its avoidance an

immediate incentive for young people and their families, but it is also likely to mediate the effects of many risk factors on other diseases.

Adults: Employment is demonstrated to reduce the risk of depression,[443] possibly by providing a greater sense of autonomy, improved socioeconomic status, and avenues for personal development.[444] Workplace interventions that increase employee control and promote physical activity appear to be associated with mental health benefits;[445] those using CBT-based techniques typically report small benefits.[446] A systematic review and meta-analysis reports small to medium effects for indicated preventive interventions in the workplace, targeting persons with sub-threshold depressive symptoms with either CBT-based (six studies) or other psychosocial interventions (two studies).[447] There is also moderately strong evidence that CBT is cost-saving in workplace settings.[448]

Many trials of prevention through psychological interventions in group or individual format have been conducted in other settings, covering both selective and indicated prevention approaches. A meta-analysis of 32 RCTs (6,214 participants) of psychological interventions of various types among adults found that the chance of developing a depressive disorder was 21% lower than in the control groups.[449] The authors concluded that prevention of depression seems feasible and psychological intervention may be an effective way to delay or prevent the onset of depressive disorders. Small reductions in depressive symptoms after psychological and educational interventions have been reported for primary care patients.[450]

The evidence base is growing for preventive interventions targeting the lifestyle factors of smoking and physical activity. Quitting cigarette smoking is associated with improved anxiety and depression.[451] There is meta-analytic evidence that exercise may have antidepressant effects[452,453] and preventive benefits.[454,455] A meta-analysis of prospective cohort studies reported a protective effect of physical activity against the emergence of depression across age groups and across geographical regions.[274] There is strong evidence that exercise during pregnancy can reduce the risk of postpartum depression.[456] The potential of diet as a modifiable variable to include in depression prevention programs has been examined with no clear findings to date.[457]

Prevention of depression needs to take into account sexual and intimate partner violence and abuse given their association.[281] Many health practitioners in primary and secondary care do not routinely enquire about intimate partner violence in routine health care consultations, nor do they all know how to respond safely to disclosures.[458-460] When practitioners are trained to ask sensitively and safely about abuse and have clear referral pathways, clinical encounters can be opportunities for identification and referral for help, contributing to prevention of depression. This is demonstrated in a cluster trial in primary care[461] and suggested by a pilot study in secondary mental health care.[459] Training for competencies in gender-based violence assessment and treatment in health care settings has been developed by the World Psychiatric Association.[462]

Older adults: Preventing late-life depression is likely to reduce the risk of suicide, dementia and age-related disability. The potential to prevent depression in the context of a chronic medical condition is illustrated by studies of depression and the use of antidepressant medicines after stroke. Meta-analytic findings indicate that antidepressant prophylaxis following acute stroke is likely to reduce the incidence of depression and improve motor and neurological function.[463] Prevention trials have explored Vitamin D insufficiency and inflammation, using supplementation[464] and low dose aspirin[465] respectively, without any evidence of efficacy.

Loneliness is associated with the development of depressive symptoms, especially later in life.[466] Simple signposting services—assessment of needs to help identify opportunities for participation in local social activities, based in primary care or community facilities—are both effective[467] and cost-effective[442] in reducing social isolation and loneliness. Other strategies such as those addressing maladaptive social cognition exhibit promising results.[468] The changes in lifestyle imposed by the physical distancing policies in many countries as a response to the COVID-19 pandemic represent a disproportionate challenge to older adults. They exacerbate the increase in rates of social isolation and loneliness that have concerned communities and governments in several parts of the world in recent years. In this context, the use of technology[469] (ranging from traditional telephone calls to internet-delivered interventions) to promote social support and a sense of belonging may be a significant help, as well as broader befriending and community inclusion initiatives in the longer term.[468,470]

Only one randomized controlled trial of indicated prevention specifically focused on older adults has been conducted in a low- or middle-income country.[71,471] The DIL intervention ("Depression In later Life" and also signifying the Konkani word for "heart") was delivered by lay counsellors to older persons at primary care clinics in Goa, India. It was grounded in problem solving therapy and also included brief behavioural treatment for insomnia, education in better self-management for common medical disorders like diabetes, and assistance in navigating medical and social services. Over one year, the intervention led to a significant reduction in incident episodes of depression compared to enhanced care as usual (4·4% versus 14·4%). The DIL intervention appeared to build resilience in the form of active coping, behavioural activation, and persistence, especially for dealing with health-related problems and their attendant threat to independence and degrading the quality of life.

Tackling structural determinants of health across the life cycle

While much of the empirical evidence on prevention has focused on proximal determinants described above, attention is also needed to address more distal structural factors of significance, which influence the inequitable distribution of proximal determinants, in particular poverty, income inequality, gender inequity, historic marginalization and displacement. This is consistent with a shift from cultural competency to "structural competency," which emphasizes the need for social and health services and planners to be knowledgeable about the context and resources of their communities and service users, and actively draw upon resources to mitigate social and structural determinants of mental illness.[283] Promoting structural competency is likely to provide dividends not only for prevention, but also for the treatment and care of individuals with depression.

Addressing structural factors through policy-based interventions that reach all parts of the population has the greatest potential impact on preventing depression.[1,403,472-474] This approach, grounded in population health science, is equivalent to the use of public policy to change population patterns of diet, exercise and tobacco use in prevention of cardiovascular disease. These interventions lie figuratively at the base of the health impact pyramid devised by Frieden[475] to describe the impact of different types of public health interventions; and tend to be the most effective, rapid, equitable, cost-effective and sustainable forms of prevention.[476] How many people in a country live in conditions conducive to healthy development and to health and productivity across the life span, which is a fundamental human right,[279,403] depends critically on public policy and planning.

Most countries have witnessed a dramatic increase in income inequality in the past three decades. On top of this, the COVID-19 pandemic has destabilised economies worldwide and the climate emergency and environmental degradation continue apace, fuelling this and other inequities. A recent systematic review demonstrates a greater risk of depression in populations with higher income inequality relative to populations with lower inequality.[283,477] It proposes an ecological framework, with mechanisms operating at the national level (the neo-material hypothesis), neighbourhood level (the social capital and the social comparison hypotheses) and individual level (psychological stress and social defeat hypotheses) to explain this association. The authors conclude that policy makers should actively promote actions to support the fair distribution of income, such as progressive taxation policies and a universal basic income. As one example, in Malawi's scaled-up *Social Cash Transfer Program*,[478] a program aimed at reducing poverty, hunger and improving school attendance, that reached 330,000 impoverished households, depressive symptomatology in youth was reduced by 15 percentage points. The reduction in young women was partially explained by increased social support, reiterating the importance of giving attention to peer support strategies and evidence of the synergistic impact of diverse sectors, through increased school attendance. Indeed, policies that reduce gender inequities and systematic disadvantages experienced by women, income inequities such as through universal health coverage and expanding opportunities for educational attainment, and racial or ethnic inequities linked in part to racism and discrimination can be potentially powerful preventive strategies.

The gender disparity in depressive disorders — as women are nearly twice as likely as men to report the experience of depression — may relate to inequalities beyond the level of health policies.[479] It is likely that inequality may impact on depression through several different mechanisms — one such pathway being lack of access to financial resources, making it difficult for women to leave relationships where there is intimate partner violence.[479-481]

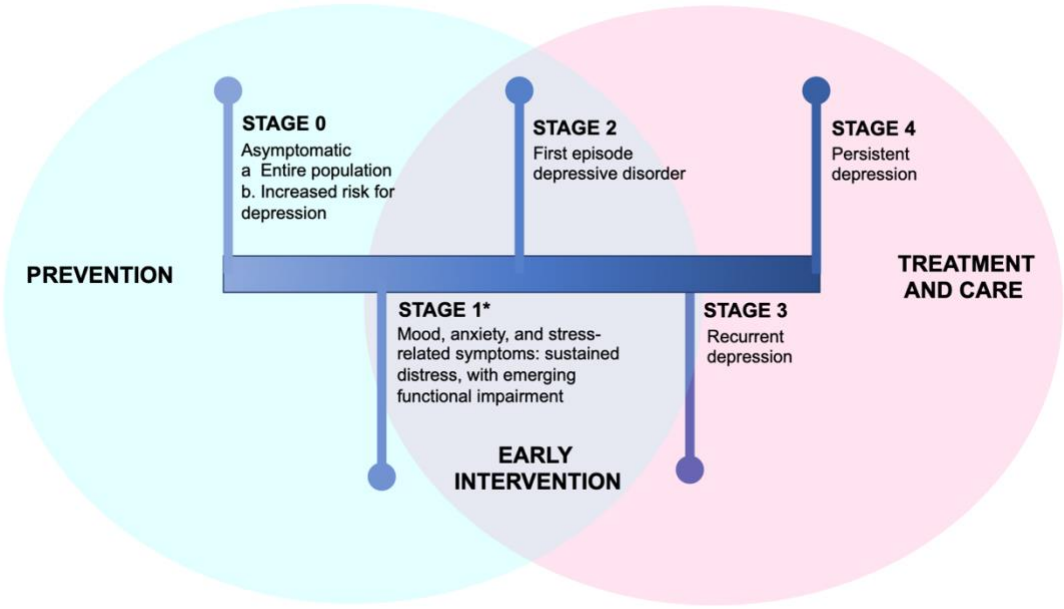
Evidence exists to take pre-emptive action to halt the potentially damaging effects of poverty, income inequality, violence and other social inequities on the mental health of populations.[283] A number of evidence-based strategies across the life course at individual and community levels can be used as well to mitigate the risks of depression arising from the more proximal adversities and risk factors noted above. There is, nonetheless, a need to learn more about the mechanisms of change and strengthen the evidence base through refined interventions and evaluation of broad public health programs and policies. Health professionals should ally themselves with other stakeholders in government, civil society and communities more generally to champion such policies, and the need for greater investments in proven interventions for the prevention of depression.[283] A whole-of-society approach to the prevention of depression is justified, linked to measures such as those implemented to curtail alcohol consumption and overlapping with successful actions by many countries to reduce the prevalence of coronary heart disease and several forms of cancer.[482]

Staged approaches to early intervention, treatment and care

Staging models as used across healthcare[483] offer a pragmatic guide to managing the heterogeneity of depression. They identify where an individual lies along a continuum of risk for illness progression (of the depressive illness or its underlying pathophysiology) and extension (additional complications beyond the syndrome of depression)[484,485] (Figure 8) and aid in reviewing the person's needs for intervention, including early intervention. They acknowledge the transdiagnostic nature of psychopathology, assuming that illnesses begin with distressing symptoms and emerging functional impairment, at first, at least, below a clinically

significant threshold. Illness states may not progress from one stage to the other, and may change in the opposite direction as well, especially from stage 4 to 3. This may occur in the natural course of the condition or as a result of clinical or non-clinical interventions, so that people frequently reach partial or full remission.[486] However, staging provides a model for responding to the state people are in and for seeking to reduce the risks of progression to a more advanced stage.

Figure 8. A clinical staging framework for depression



*Also described as "subsyndromal" or "subthreshold"; includes transdiagnostic presentations that could benefit from interventions.

The extent and rate of progression from one stage to the next — and whether this occurs — will differ between people. For example, most people with sub-clinical symptoms do not progress and frequently recover. Others show rapid progression to severe depression and do not come to clinical attention for the first time until they are very unwell and suicidal: especially when mental health literacy and help seeking are poor or weak, or access to care is difficult. Some of these people do not respond to first-line treatments and the situation calls for a staged care approach to allocating more intensive treatments. Ideally, this is best managed by a multidisciplinary collaborative care team (described below), particularly when comorbidity or complications are present.

Staged approaches to intervention for depression include: universal and selective preventive interventions (stage 0) and indicated prevention of depression (stage 1); interventions early in the course of a depressive disorder, from its first episode (stage 2), comprising the delivery of evidence-based first-line interventions for acute episodes of clinical-threshold depression; and the provision of second line or more complex interventions for people who do not respond to the first-line interventions or who present with or graduate to recurrent or persistent depression (stages 3 and 4).[487]

Intervening early in the course of the disorder

Clinical staging provides a framework for planning and recommending interventions from the earliest point that a need for care emerges in the course of a depressive illness (indicated prevention). The illness presentation is highly variable at the point a person's distress first comes to professional attention — whether this be in an educational, welfare or workplace context, or in a primary care or other clinical setting. The need, mode and most appropriate setting for intervening in the first stages of illness can vary according to the level of distress and disability, the availability of resources, as well as the help-seeking behaviour of the affected person. For example, indicated prevention can be offered as self-help, or as online or school-based interventions. It can also be offered in clinical settings (as in primary care or linked frontline community-based mental health programs).

The first episodes of depression may provide the next critical opportunity for early intervention. Recalling that deaths from suicide among those with a current depressive episode occur most often (75%) during the first episode underscores the urgent need to identify and treat adequately the very first major depressive episode. In addition, the risk of recurrence after the first two episodes is substantially less than after the third and subsequent episodes, indicating an early potential for recovery on which interventions should capitalise.[488] Consistent with this, structural brain changes are minimal during the first episode of depression, but become more evident with recurrence.[489,490] This has led to suggestions that depression can be itself neurotoxic, and that recurrence is associated with an active process of neuroprogression[491]: that is, the experience of depression causes brain changes that make depression more likely in the future.[492] Early episode depression is less likely to be complicated overall (despite the risk of suicide) than depression later in the course of the illness. People with first or early episodes of uncomplicated depression can usually be cared for, at least initially, in primary care settings. The net benefit of early intervention, given that some episodes are self-limited without treatment, is an urgent priority for research investment.

Episodes of depression early in life affect critical developmental processes and life domains, particularly during adolescence and early adulthood, posing a major threat to lives and future potential. This includes developmental tasks, creating a stable identity, completing education, commencing work, establishing intimate relationships, and starting a family. Successful navigation of these tasks establishes a trajectory through adulthood, while failure to do so compounds over many decades, and even trans-generationally. Enhanced primary care for youth mental health – where young people can refer themselves, or be referred by family, educators, or primary care doctors – represents an important innovation to reach young people very early in the course of emerging mental ill-health.[493] Innovative models of integrated youth health care, known as 'headspace' centres in Australia, have spread to a number of countries.[494] Care is holistic and integrative, and alongside treatment for depression, intervention is provided for physical health, substance use, education, employment, and other developmental and social needs.

Risk-factors such as sexual trauma and bullying are common to a wide range of mental health problems,[495,496] and should be addressed as part of early preventive efforts. The trans-diagnostic perspective[497] recognises that emerging mental ill-health is fluid, made up of a range of clinical presentations which ebb and flow prior to distillation into more stable subsequent phenotypes later in the course of the illness. Early interventions (especially psychosocial interventions, but also including judicious use of medications such as selective serotonin reuptake inhibitors) may thus have beneficial effects across a range of syndromes.[497]

Interventions for remission and recovery from depressive episodes

When I'm depressed, I feel dead inside, like a shell of a person going through the motions… I can't stop crying, even when positive things are going on around me.
- Annika Sweetland, 44, United States

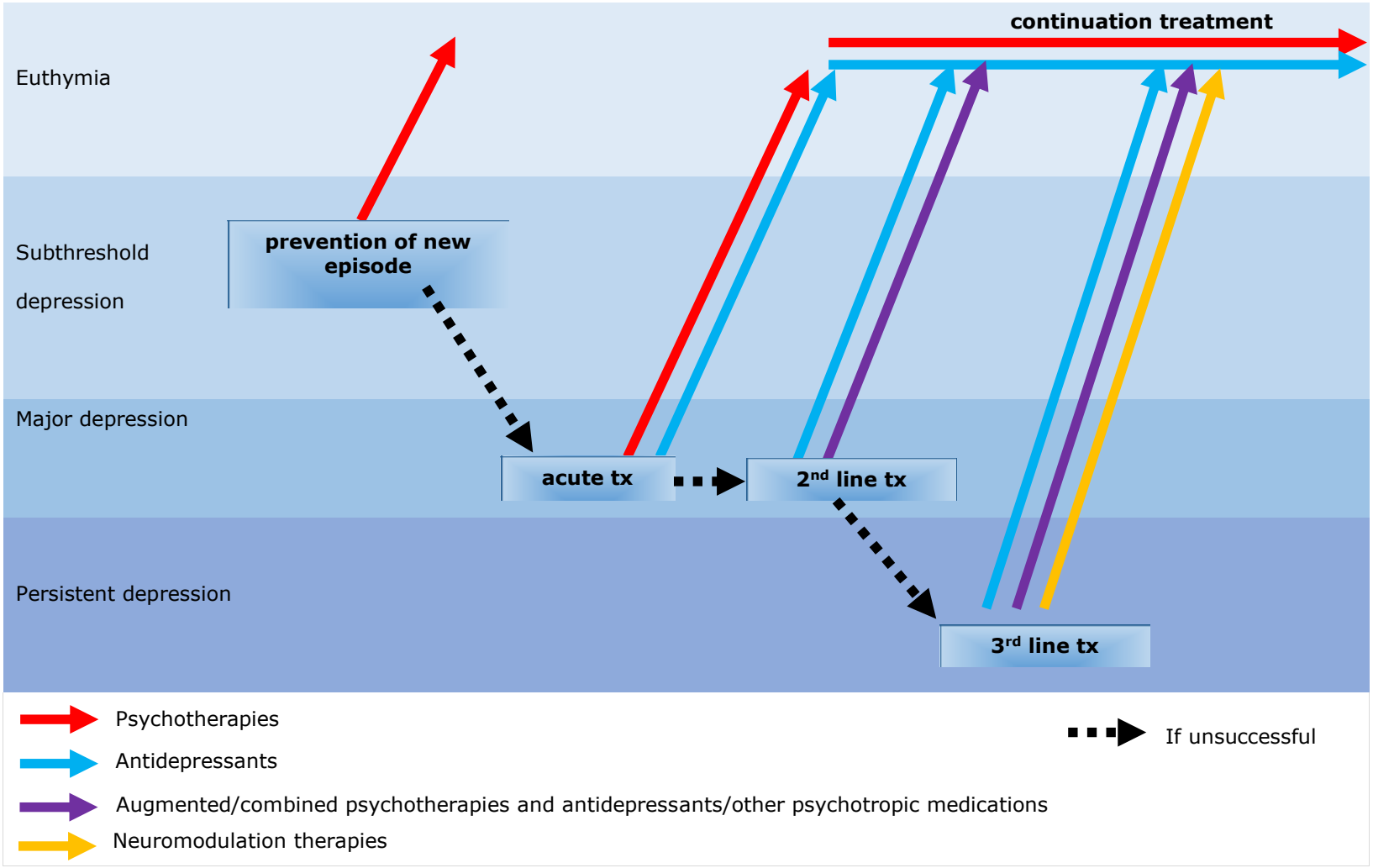
Sometimes the simplest things are the ones that make me feel alive... When I go to bed thinking about the breakfast I'm going to prepare the next day, I know I'm not depressed anymore.
- Nacho Guevara, 47, Costa Rica

Here we consider the treatment of depressive episodes that meet clinical severity threshold criteria (other than episodes experienced as part of bipolar disorder). A number of the principles of care apply to all forms of depression, and to mental ill-health in general. However, there are important variations in the care for people with bipolar disorder that we do not address here.

The WHO's mhGAP guidelines[498] based on a review of the effectiveness of first-line treatments for depression and the feasibility of their delivery in routine care settings have recommended either of two treatments for any individual: antidepressant medication (in particular SSRIs) or brief, structured psychological treatments based on CBT or IPT (including variants of these treatments such as behavioural activation, problem-solving therapies, mindfulness, acceptance and commitment therapy). A significant proportion of people will remit even with no treatment ("spontaneous remission"), and there are no aggregate differences in effects or in effect modifications between the two primary monotherapies for an acute episode of depression. Our current state of knowledge therefore precludes precision medicine approaches to predict who will respond to 'watchful waiting' or to a specific first-line treatment so that we can confidently allocate individuals to any of these specific interventions (i.e. the 'optimum' intervention for an individual). Clinicians may recommend, as throughout health care, a period of watchful waiting for those with a mild condition, for further assessment and monitoring, relationship building and shared decision-making. Other initiatives used in this period may include brief interventions such as psychoeducation and lifestyle interventions, particularly exercise, that may also promote remission. These interventions may be employed also as adjuncts to the two primary monotherapies. Insomnia is increasingly considered as a comorbid condition rather than an accompanying symptom of depression, and treatments targeted at insomnia may improve[499] and prevent depression.[500]

Non-responders to antidepressant medication may show additional benefit from switching to or augmentation with other medication. Alternatively, combined treatment (psychotherapy plus medication) works better than either alone. Non-responders to these second line treatments may benefit from neuro-modulation therapies such as electroconvulsive therapy (ECT) and brain stimulation. Effective treatment leads to improvements in a range of outcomes, beyond depression alone, including improved physical well-being, function and reduced suicidal behaviour, all of which are often prioritized by patients. Thus, depression treatment works very well because of the enormous variety of treatments, but it is often necessary to go through a sometimes protracted process of trial and error to find the right treatment for the right person. This is especially true for people receiving treatment for the first time, who have no past experience about what worked for them on a previous occasion. Figure 9 depicts the steps in the management of an episode of depression. We now briefly review the evidence in support of these treatment options.

Figure 9. Clinical interventions for depression



Effectiveness of self-help and social interventions on depression outcomes
Guided self-help (internet-based or not), which encompasses interventions based on effective psychological therapies, but designed to be entirely or mostly self-delivered, is as effective as individual, group or telephone psychotherapies, with moderate effect sizes (Cohen's d range 0·51-0·69) compared with care as usual.[501] Unguided self-help can also have smaller but significant effects[502]; moreover, it has an advantage that it does not require contact with a helping person. However, individuals with depression seem to benefit more when there is at least a modicum of human interaction, especially in more severe depression.[503] There is less consistent evidence in support of lifestyle interventions, with higher quality studies generally showing small effects, as for exercise[453] or quitting smoking, or null effects as for omega-3 fatty acids and Vitamin D. While the evidence base on the effectiveness of social interventions, ranging from structural interventions such as housing and income support to social support interventions such as peer support, is less well studied, there are indications that these are also potentially important strategies for persons who are experiencing such adversities.[504]

Effectiveness of first-line treatments on depression outcomes
Some 750 trials with over 30,000 participants provide evidence for various psychotherapies for the acute treatment of major depression,[505] and more than 500 trials involving over 110,000 participants provide support for the efficacy of antidepressants.[506] Efficacy is comparable in magnitude to therapy for common medical disorders.[507] When measured against the common comparator, pill placebo, CBT had an SMD of 0·20 (0·01 to 0·38)[508] and antidepressants an SMD of 0·30 (0·26 to 0·34).[506] Given the average placebo response rate of 40%,[509] the SMD of 0·3 or 0·2 would translate into NNTs of approximately 9 and 13, respectively.[510-512]

We now have a relatively clear understanding of possible differences in efficacy among active antidepressants,[506] optimal dosing of new generation antidepressants[513,514] and delivery formats for psychotherapies.[501] Among adults, direct comparisons of antidepressants reported that several specific antidepressants were more effective than other antidepressants (range of ORs for response 1·19–1·96), whereas others were in a least efficacious group (0·51–0·84),[506] There have been no discernible differences detected so far among different psychotherapies.[505] On average, pharmacotherapies and psychotherapies are similarly efficacious.[515] There is no evidence that personal treatment preferences, particularly in people with no prior treatment exposure, moderate symptomatic outcomes.[516]

In children and adolescents, CBT and IPT may be seen as first-line treatments, with medicine added if these therapies are not successful.[517] A recent systematic review[518] suggests anti-depressant medicine—specifically fluoxetine— alone or in combination with CBT is the most efficacious treatment in moderate-to-severe depressive disorder. However, the quality of the evidence is low. This is set in the context of the evidence of smaller effects in children and adolescents, than in adults and older adults, of both antidepressants and psychotherapy compared with placebo.[519] Treatment choices need to take this into consideration, together with the risk of suicidality with or without treatment (even as that remains to be elucidated).

Limitations of first-line treatments
The use of antidepressants is associated with a number of unwanted effects. While a number of specific side effects are commonly reported with use of SSRIs, for example, nausea, dry mouth, headache, diarrhoea, tremor, dizziness, anxiety, nervousness, agitation, insomnia, constipation,[520] and sexual side effects, none of these except for increased risk of osteoporosis[521] are associated with enduring impacts.[522] A recent umbrella review of systematic

reviews examined 120 putative associations of antidepressant medication and adverse outcomes and observed that while there were some associations, none of them remained after sensitivity analyses adjusting for confounding by indication and the authors concluded with no absolute contraindication to antidepressants.[523]

Of concern is the so-called discontinuation syndrome or withdrawal syndrome[524,525] upon abrupt or gradual discontinuation of SSRIs and SNRIs. Withdrawal symptoms have been reported to occur typically within a few days and persist for a few weeks; but many variations are possible including later onset and longer duration.[526] One review reports incidence rates ranging from 27% to 86% (weighted average of 56%) based on individual reports in surveys[524] and another at 31% based on RCTs employing a withdrawal symptom scale.[527] While gradual and hyperbolic tapering may mitigate the symptoms,[528] there is a paucity of adequate research to guide their management.[529] The question of withdrawal may be related to increases in prolonged prescription in some countries.[530,531]

Second and third-line treatments

Partial or non-response to depression treatment is common in clinical practice. Close to half the people treated for major depression fail to achieve symptomatic remission during initial acute or short-term treatment. The expression "treatment-resistant depression" is commonly used in the literature to describe situations of failure to achieve a reduction in depressive symptoms, frequently defined as occurring after at least two courses of antidepressants.[532] This concept has been criticized for a number of reasons, including its inconsistent definition and sometimes limited consideration of psychosocial approaches to intervention. More recently, the notion of "difficult-to-treat depression" has been proposed to encompass the acute phase of treatment as well as sustained response and remission. It provides a more positive framing, aiming to address overall functioning and quality of life as well as depressive symptoms to enhance engagement of the patient and consideration of the whole range of interventions.[533]

Before concluding that a given treatment approach is not effective, it is important to consider the possible reasons for failure to respond, including: treatment adherence; diagnostic accuracy; co-occurring conditions, whether psychiatric or medical; and factors in the psychosocial context that complicate treatment or necessitate adaptation of clinical care to meet a person's needs.[67] There may be need for additional resources, social interventions or other support for adequate and personalized clinical care in the face of stressors or life events such as bereavement. People of different backgrounds may vary in their understanding of, and beliefs about, depression, and what constitutes acceptable, needed or appropriate care. Family member or carer support for engagement in treatment is a vital dimension of this social context.

In short-term trials of depression monotherapy, participants receive one medication or one psychotherapy for 8-16 weeks. Only a limited number of clinical trials is available to guide practice when people fail to respond to the initial treatment. Recent systematic reviews of pharmacotherapy studies identified seven trials for dose escalation,[534] four for switching of antidepressants,[535] 48 for various augmentation agents, or 25 studies for augmentation of pharmacotherapy with psychotherapies.[536] Reviews have found no evidence to support dose escalation but some evidence for the other strategies. In the Sequence Treatment Alternatives and Relieve Depression (STAR*D) study — a study designed to test treatments to achieve remission — by switching ineffective treatments after 8 weeks the remission rate reached 67% over one year among participants who remained in the study. Even if remission was reached after several trials, it was associated with better prognosis than for treatment as usual.[537] It is notable that some characteristics of depression linked to poor outcome of first line

antidepressant treatment may also predict good response to augmentation strategies. For example, profound loss of interest and reduced activity were associated with non-response to SSRI antidepressants, but good response to augmentation with aripiprazole.[538] In addition, some psychotherapies have been developed specifically for persistent depressive disorder.[539]

The efficacy of the choice among these strategies is not the only consideration, however; tolerability and safety outcomes are also essential. An example of a current comparative effectiveness trial for the pharmacotherapy of treatment-resistant depression is the US-based multisite trial, OPTIMUM, being carried out both in the specialty mental health sector and in primary care. OPTIMUM provides a stepped-care algorithm that specifies augmentation and switching strategies, such as aripiprazole, bupropion and lithium, on a platform of measurement-based care.[540] Combination of the first-line treatments is another promising strategy. Higher response rates can be achieved with combined treatment with medication and psychotherapy. The response rate of combined treatment compared with placebo is about twice as large as medication alone compared with placebo. While these differences underscore the advantages of combined treatment, it is not possible to conclude from evidence now available whether this is an additive effect of the two treatments or simply the result of personalized allocation of the optimum treatment.[515]

Depression with psychotic features is a severe form of the condition (discussed earlier) and one of the few depression subtypes for which specific pharmacotherapy is indicated. A systematic review of 12 RCTs (929 participants) reports no evidence of efficacy for monotherapy with an antidepressant or an antipsychotic, but superior efficacy of their combination over either monotherapy alone or placebo.[541]

Finally, a number of additional options are now available for treatment-resistant/refractory/difficult to treat or persistent depression. Neuromodulation therapies such as ECT or rTMS have been established as successful in the short term (with relatively large SMDs). The long-term stability of their efficacy is yet to be established.[542] Drugs that focus on the glutamatergic system (ketamine, esketamine, rapastinel), the GABAergic system (brexanolone, SAGE-217), the opioidergic system (buprenorphine, samidorphan), and the inflammatory system (minocycline) have been developed and trialled, with promising results for some.[543-545] However, the initial results for many novel treatments have not been replicated.[546] Novel psychological treatments based on the 'third wave' of cognitive behavioural interventions[547] include mindfulness-based CBT, acceptance and commitment therapy, and meta-cognitive therapy. A growing number of studies also show that transdiagnostic psychological interventions aimed at people with depression or anxiety or both are also effective in the treatment of depression.[548] Other psychological treatments derive from a mechanistic understanding of psychopathology based on experimental findings such as interpretation bias modification.[549]

Preventing relapse and recurrence

Achieving remission and recovering from an acute episode is insufficient given the high risk of relapse and recurrence.[550] Inter-episode wellness intervals tend to become progressively shorter, and the risk of treatment resistance increases with each succeeding episode. Thus, getting well is not enough, it is staying well that really counts. A growing evidence base provides an expanding set of treatment options for preventing relapse and recurrence. It is well demonstrated that once participants have recovered with antidepressant treatment, continued pharmacotherapy reduces the risk of relapse or recurrence by half, resulting in NNTs of approximately 4 to prevent a relapse within a year among people at high risk of relapse (for

example, those who have experienced multiple episodes).[551] These trials keep the dosage for continuation treatment at the level of the initially successful acute treatment.

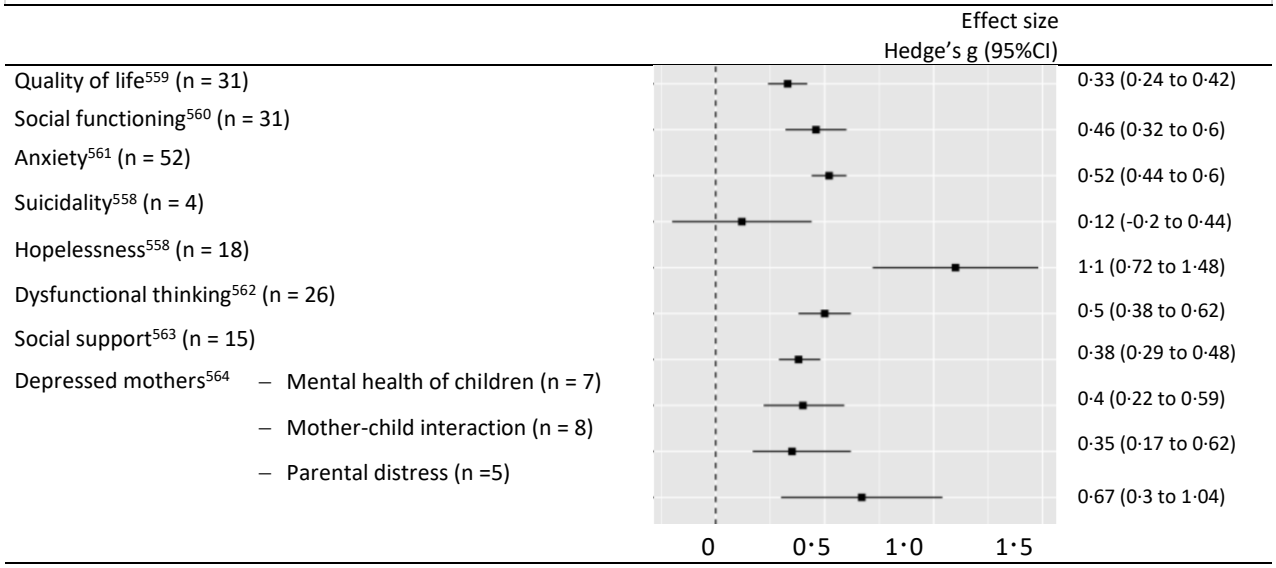
A recent network meta-analysis of 81 trials found that initiating the treatment of a depressive episode with psychotherapy, alone or added to pharmacotherapy, may increase substantially the chances of getting well and staying well for up to a year by 12-16 percentage points compared with initiating the treatment with drugs only.[552]Accumulating evidence from 30 trials also supports efficacy of mindfulness-based CBT, preventive CBT, and IPT in relapse prevention.[553] The results of a recent systematic review and meta-analysis indicate reduced risk of relapse and recurrence in patients remitted from a depressive episode when psychotherapy is sequentially integrated with antidepressant medication.[554]

For people recovering from psychotic depression, continuing the antipsychotic medication over several months at least is needed in order to prevent relapse and recurrence.[555] There is evidence that continuation ECT may also be effective in sustaining remission in people with refractory depression.[556]

Other impacts of first-line treatments

People with depression typically come into treatment with several problems and concerns.[557] The impact of treatments on other outcomes, in particular functional outcomes, is at least as important as on the mental health symptoms. Figure 10 shows that the psychological treatment of depression has considerable effects on quality of life, social functioning and social support: less evidence is available on the effects of antidepressant treatments on this range of outcomes. The question of whether the treatment of depression *per se* has a significant effect on suicidality does not have a definitive answer, largely due to low power of trials to detect rare outcomes, though there are real-world studies which suggest an association (discussed later).[558]

Figure 10. The effects of psychological treatment for depression on relevant outcomes



Psychotherapies include: acceptance and commitment; acceptance and commitment therapy with extensive email support; behavioural activation; body, mind, spirit psychotherapy; cognitive–behavioural therapy (CBT); coping with depression dialectical behaviour therapy skills training; guided self-help; interpersonal counselling; interpersonal psychotherapy; life review; mindfulness-based cognitive therapy and coping with depression; problem solving therapy; problem-solving treatment; psychodynamic psychotherapy; religious CBT, non-religious therapist; mindfulness based cognitive therapy; supportive psychotherapy.

Depression treatments have been tested in people diagnosed with depression comorbid with various somatic conditions. The studies show consistent improvements in depression status in all these groups. The treatment effect on somatic outcomes, however, has generally not been significant (Table 3). An exception to this is the positive effect of antidepressant treatment on glycaemic control in those with diabetes;[565] for which there is also strong evidence of cost-effectiveness. Other meta-analyses and large randomized trials found insufficient evidence for effects on survival or cardiac events. This could indicate that the strong epidemiological association between depression and somatic health is not directly causal, or that depression treatment does not target directly the pathology underlying the pathway from depression to somatic condition; or that it takes trials of longer duration and with larger samples to observe the impact of depression treatment on somatic outcomes.

The transgenerational effects of depression treatment on families and on future generations are fields of growing interest. Emerging evidence demonstrates that the effective treatment of persistent postnatal depressive symptoms in mothers is associated with improved child outcomes at 2 years of age.[566]

Table 3. The effects of depression treatment on general medical disorders

Study	Studies/sample	Intervention vs. Control	Results on depression symptoms	Results on somatic outcome(s)
Meta-analytic evidence				
Pizzi 2011[567]	4 RCTs in 734 patients with myocardial infarction and depression	SSRI treatment vs. placebo or no intervention	Reduction (SMD: –0·34 [–0·06 to –0·63])	No reduction of CHD readmissions (0·74 [0·44 to 1·23])
Cristea 2019[568]	7 RCTs in patients with diabetes and depression or depressive symptoms	Psychotherapy vs. TAU	Not presented	No difference in glycaemic control (change in HbA1C) (Hedges' g: –0·01 [–0·30 to 0·29])
Baumeister 2012[565]	4 RCTs in 441 patients with diabetes and depression	Psychological intervention vs. TAU	Reduction (SMD: –0·42 [–0·70 to –0·14])	No significant effect on HbA1c (pooled ES not shown)
Baumeister 2012[565]	5 RCTs in 238 patients with diabetes and depression	Antidepressant treatment vs. placebo	Reduction (SMD: –0·61 [–0·94 to –0·27])	Reduction in HbA1c (SMD: –0·4% [–0·6% to –0·1%])
Sharpe 2014[569] Walker 2014[570] Mulick 2018[571]	2 RCTs in 642 patients with cancer and depression	Multicomponent collaborative care for People with Cancer (DCPC) vs. TAU	Reduction in mixed cancer (SMD: –0·78 [–0·90 to –0·66]) Reduction in lung cancer (SMD: –0·38 [–0·58 to –0·18])	No difference in survival (HR: 0·92 [0·72 to 1·18])
Legg 2019[572]	2 RCTs in 2,829 patients with stroke and with(out) depression 3 RCTs in 3,245 patients for mortality outcome	SSRI vs. placebo	Reduction (SMD: –0·11 [–0·19 to –0·04])	No difference in disability score (SMD: –0·01 [–0·09 to 0·06]) No difference in mortality (HR: 0·99 [0·79 to 1·25])
Selection of individual randomized treatment studies (sample size>200)				
ENRICHD[573]	2,481 patients with MI and major/minor	CBT-based psychosocial intervention with SSRI	Reduction in HamD after 6 months: –10·1 in IntG,	No difference in event-free 4-year survival (75·9% vs. 75·8%)

	depression and/or low support	treatment when indicated vs. TAU	–8·4 in TAU	
MIND-IT[574]	331 patients with MI and depression	SSRI treatment vs. TAU	No difference in BDI after 18 months: 11·0 in IntG 10·2 in TAU	No difference in cardiac events after 18 months: 14% in IntG 13% in TAU
SADHEART[575]	369 patients with MI and depression	SSRI treatment vs. placebo	HamD change after 16 weeks: –8·4 in IntG –7·6 in placebo	No difference in cardiac safety measures (including change in LVEF)
Katon 2010[576]	214 patients with poorly controlled diabetes and/or MI plus depressive symptoms (PHQ9≥10)	Collaborative care vs. TAU	Reduction in 12-month SCL-20 score (SMD –0·41 [–0·56 to –0·26])	No difference in 12-month HbA1C: –0·56 % (–0·85 to –0·27%) Reduction in 12-month LDL cholesterol: –9·1 (–17·5 to –0·8) No difference in 12-month blood pressure: –0·4 (–6·9 to 0·1)
PROSPECT[577,578]	396 older patients with depression, 60-94 years	Algorithm-based care vs. TAU	% Reduction in HamD score after 4 months: 41% in intervention 24% in TAU RR=3·9 (1·8 to 8·5)	No reduction in 8-yr mortality in IntG vs. TAU (HR 0·76 [0·57 to 1·00])
Naik et al. 2019[579]	225 patients with uncontrolled diabetes and depression (PHQ9≥10)	Telephone intervention with collaborative goal-setting and behavioural activation vs. enhanced usual care	Reduction: PHQ-9 after 12 months (SMD: 2·14 [0·18 to 4·10])	No reduction in HbA1c after 12 months (mean difference: –0·06% [–0·61% to 0·50%])

RCT: Randomized controlled trial; TAU: Treatment as usual; SMD: Standardized mean difference; MI: myocardial infarction; depression: major depressive disorder; CHD: coronary heart disease; SSRI: selective serotonin reuptake inhibitor; SMD: standardized mean difference; TAU: treatment as usual; IntG: intervention group; DCPC: depression care for cancer patients; HamD: Hamilton Depression Scale; BDI: Beck Depression Inventory; LVEF: left ventricular ejection fraction; PHQ: Patient Health Questionnaire HbA1c: haemoglobin A1c.

Translation to clinical practice

RCTs and their meta-analyses are considered the gold standard for assessing the effects of treatments. Bias is a significant problem, however, as for RCTs in all fields. The failure to publish negative trial results, as demonstrated for drug trials[580] and psychotherapy trials,[581] leads to overestimating effect sizes in meta-analyses. These problems are diminishing, thanks to concerted efforts across a number of countries to regulate trial registration and reporting.[582] Belief in the superiority of an intervention, or researcher allegiance,[583] has been associated with stronger observed effects of therapies, particularly in psychotherapy research.[584] The risk of bias was rated as low in only 18% of trials in a meta-analysis of 500 drug trials in depression[506] and in only 23% studies in a meta-analysis of almost 300 psychotherapy trials.[585]

The generalizability of trial evidence to practice is also compromised by the fact that over 90% of trials are conducted in countries covering 10% of the world's population. Furthermore, most trials recruit participants attending mental health facilities. These participants do not represent people experiencing depression in the population[586]: they are more likely to have had prior treatments and to have complicated or persistent episodes of depression and high levels of personality disorder comorbidity[587] that may dampen the effects of the active treatment. They are also more likely to have high awareness of their depressive condition and to be accessing other therapies (including informal support) that enhance the effects of the control arm. It has been estimated that only 12 to 34% of people in routine outpatient care are eligible for participation in a pharmacotherapy trial: others are ineligible because of comorbidities or failing to meet the minimum severity threshold.[588] Although this problem is smaller in psychotherapy research,[589,590] and the efficacy of psychotherapies appears of similar magnitude between high- and low-/middle-income countries when they are tested in randomised trials,[585] generalizability of research to practice needs attention in this area too. Evidence on cost-effectiveness (for *any* therapy) does not readily transfer from one country to another because of differences in health and other systems, in the availability and relative salaries of care professionals, and in funding arrangements that alter incentives to deliver treatment and the associated unit costs. It is especially dangerous to assume that economics evidence from a high-income country will be relevant in low- or middle-income countries.

An important and desirable aspect of randomised trials is the need for participants to be blind to, or unaware of, the condition to which they are assigned. This is impossible for trials of psychotherapy. Although it is possible in drug trials, participants often discern from noticeable side effects when they receive active drug rather than placebo.[591] The use of waiting list control groups as often the case in psychotherapy research may lead to an overestimation of the effects of treatment.[592,593] The nature of care as usual or treatment as usual depends heavily on the health care system of the country and the study setting, ranging from (almost) no care to specialised mental health care by well-trained professionals.[594] This contributes to extensive heterogeneity between trials.[595] The choice of non-specific treatment, such as non-specific counselling, as a control condition is also a problem for a depression trial. These therapies can result in good outcomes, comparable for example to those recorded for CBT.[596] Ultimately, the choice of a control condition depends on the research question that is to be answered.

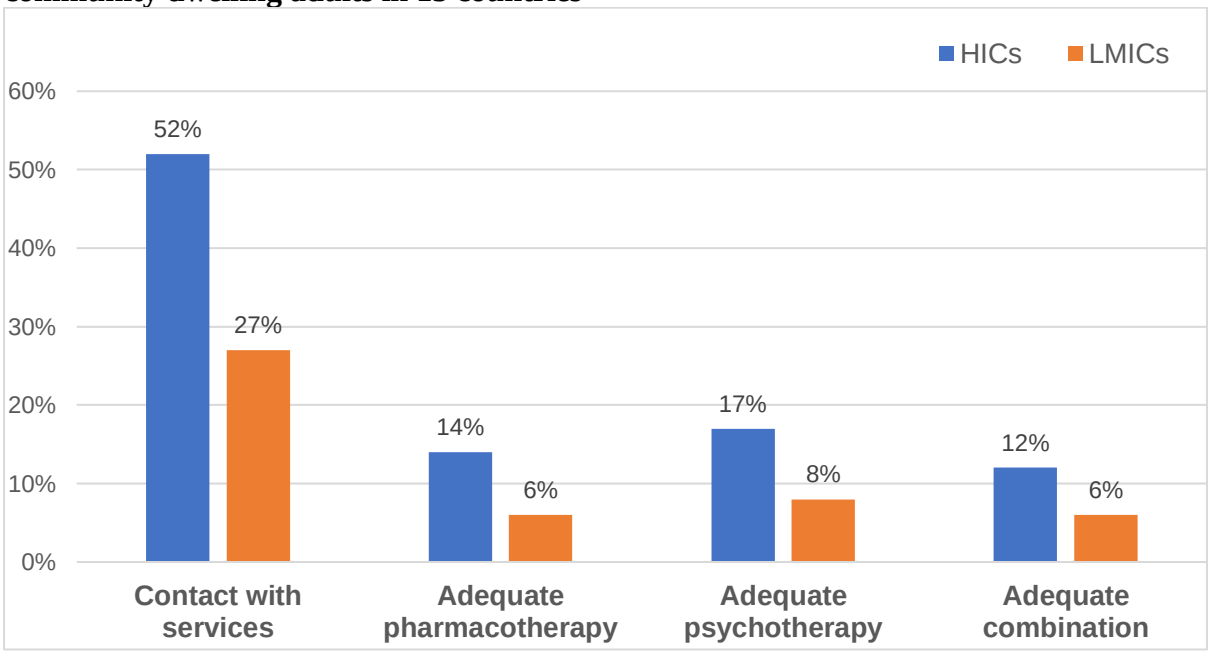
Finally, we must recognize the challenge of reconciling the relatively modest effect sizes of the two first-line treatments for depression with the experience of clinical practice. There is an outstanding need for practice research on how best to apply, combine or sequence one or more of the approaches to first-line treatment in primary health care.[597] The most obvious reason for the dissonance is that many people recover without treatment. Trials with a control group seek

to discern the treatment effects over and above spontaneous recovery, while in routine care the latter cannot be distinguished. Additionally, trial participants usually receive regular assessments and close attention, including many hours of clinical contact, and promise of alternate treatment at study completion. The short-term benefit from these personal contacts and conditions can diminish group treatment differences. Further, in short-term trials of depression monotherapy, participants receive only one medication or one psychotherapy for 8-16 weeks. In clinical practice, however, if an individual does not respond or responds partially, changes to the treatment plan are often made earlier. For example, in the Strategic Use of New generation antidepressants study, switching or augmenting mediations as early as 3 weeks was associated with an NNT of 10 in achieving remission by 9 weeks in comparison with standard length acute phase treatment.[598] Personalizing the second line treatment choice through machine learning identified a small group of individuals (around 8%) who would fare better if continued unchanged on their initial treatment.[599] As for some other clinical conditions, particular forms of treatment are more effective for some people than for others.

Principles of care

Care is provided across the world in various settings and with very different resources available to assess and plan and intervene. Whether the person needing care is met in their own home, a community setting, a primary care clinic, or a hospital or institutional setting, the principles of care are the same. She or he will ideally be offered the same standards of care or support as a person with a physical illness or injury, especially as the presentations of somatic and mental illnesses are often intertwined. This should include the opportunity to access and receive timely care at the onset of illness, still a major obstacle around the world. Data from the WMHS covering 15 countries indicate that, among community-dwelling adults meeting diagnostic criteria for depression, less than half had any contact with a general medical or specialist provider, and only 10% received effective care.[600] There was a consistent discrepancy between HICs and LMICs, with coverage estimates in the former on average double those in the latter: though even in HIC, less than a fifth of adults meeting criteria received effective care (Figure 11).

Figure 11. Contact with services and effective coverage for depression care for community dwelling adults in 15 countries[600]



Results generated using data from 15 countries provided by the WHO World Mental Health Survey Consortium: www.hcp.med.harvard.edu/wmh. Contact with services among representative samples of community dwelling adults defined as any contact with specialist mental health or general medical health provider for a mental health condition; adequate pharmacotherapy, as taking an antidepressant with adequate medication control and adherence; adequate psychotherapy, as complying with at least eight sessions from an adequate provider or still being in treatment after two visits; and adequate combination of pharmacotherapy and psychotherapy as adequate pharmacotherapy and/or psychotherapy for mild and moderate depression, and a combination of both adequate pharmacotherapy and psychotherapy for severe depression. All HICs vs LMICs comparisons $p < 0{\cdot}001$. HICs: high-income countries; LMICs: low- and middle-income countries.

In most countries and contexts, it is primary care and community health workers who provide the bulk of care for and have the most extensive contact with people living with depression and their families. The use of hybrid models of digital and in-person care is accelerating to become a feature of care in many parts of the world, blending with the use of guided self-help and tailored social interventions to support quality and rights-based care.

The United Nations Convention on the Rights of People with Disabilities (CRPD) establishes the rights of people with depression and other mental disorders to social inclusion and to choice of health care of the same quality as that offered to people with all health conditions, as close as possible to their homes and respecting their personhood and rights.[1] People needing treatment for depression face risks when stigma and discrimination surrounding mental disorders and their treatment prompt fear and exclusion. There is widespread agreement that coercive practices are over-used in depression care when it is delivered in institutional and also in some community settings. The WPA in common with WHO advocates for a pragmatic approach to implementing viable alternatives to coercion,[601] one of which is adopting a community-based collaborative care approach that includes shared or supported decision-making.

Diagnosis and formulation

Establishing the presence or absence of the disorder is an essential step in clinical care. Initial screening for depression can be reliably achieved with a brief validated measure such as the PHQ-9 or a diagnostic interview.[602] However a more detailed clinical assessment is required to inform whether treatment is recommended, and then which types of interventions are likely to be most acceptable and effective. Formulation aids in reaching the ultimate goal of shared or supported decision-making through identifying the person's values or preferences as well as the factors informing a clinician's personalised treatment recommendations (Panel 2).[603]

Panel 2. Factors relevant for clinical assessment and decision-making ("formulation")

- Age, gender, language, culture, family, history of violence or abuse, and living arrangements
- Severity of the clinical picture (e.g., syndromal vs. subsyndromal, global score on a rating scale)
- Staging of the disorder (including course features, such as first episode, persistence, relapse/recurrence)
- Current life stressors and presence/absence of support
- Suicide risk assessment
- Concomitant substance abuse, physical health
- History of manic/hypomanic episodes
- Presence of psychotic features
- Antecedent variables (e.g., family history, developmental history, early environmental exposures, previous psychiatric diagnoses)*
- Other concomitant variables (e.g., personality traits/cognitive schemas, religious and spiritual beliefs, psychiatric comorbidities, social functioning, neurocognition, maladaptive cognitive schemas, dimensions of psychological well-being)*

*Assessments recommended in specific circumstances, for example persistent or treatment resistant depression.

Formulation assists in choosing which medication, psychosocial or lifestyle approaches to treatment and care a person might need or expect, as well as identifying individuals at risk of suicide.[604] It can also mould expectations of therapy; for example, evidence suggests a history of childhood trauma and personality disorders might predict poorer response to initial interventions.[605] Formulation typically assembles five domains of information and understanding that are based on awareness of the factors shown in Panel 2 and critical in clinical decision-making: *presenting problems*, identifying what the clinician and the person with depression see as difficulties, or foci needing treatment; *predisposing factors* referring to potential biopsychosocial vulnerabilities; *precipitating factors* referring to salient circumstances preceding the onset or exacerbation of the presenting episode; *perpetuating factors*, which are situations or dynamics that serve to maintain or worsen the condition; and *protective/positive factors*, strengths or supports that may mitigate the impact of depression on a person's life. Formulation allows more informed discussion between the person and clinician about choices in treatment, care and life circumstances and prepares the way for personalised interventions concordant with the person's values and expectations.

Clinicians need to understand the meaning of a person's presentation with depression in the context of their developmental and previous history and current circumstances. It is fundamental first of all to know about developmental history, attachment styles and personality development, as well as prodromal and major depressive episodes – age of onset, number of such episodes, their severity, duration, functional consequences, effects on cognition, and duration of inter-episode intervals – or burden of residual inter-episode symptoms and dysfunction as the case may be. Family history of depression (and what treatments have helped), medical history, social support, religious and spiritual affiliations and beliefs, life circumstances and life events and previous treatment history provide further vital context for understanding the current need for treatment, and the types and duration of treatment likely to be helpful. Delineation of co-occurring psychiatric disorders and of somatic illnesses is necessary for treatment planning.

Collaborative care

Collaborative care is the best-evaluated approach for translating evidence from randomized trials and realizing the goals of staged approaches in practice.[606] Collaborative care integrates team-based health, social and support services. It offers a ready platform for reaching underserved populations, for engaging in task-sharing of mental health care with non-specialist providers, for mitigating the barriers posed by stigma, in that people receive care at home or where they want to receive it, for promoting engagement with family caregivers, for the implementation of measurement-based care, and for allowing the use of algorithms of care that better match intensity of services with the level of needs. Moreover, it is amenable to both treatment and prevention of depression.

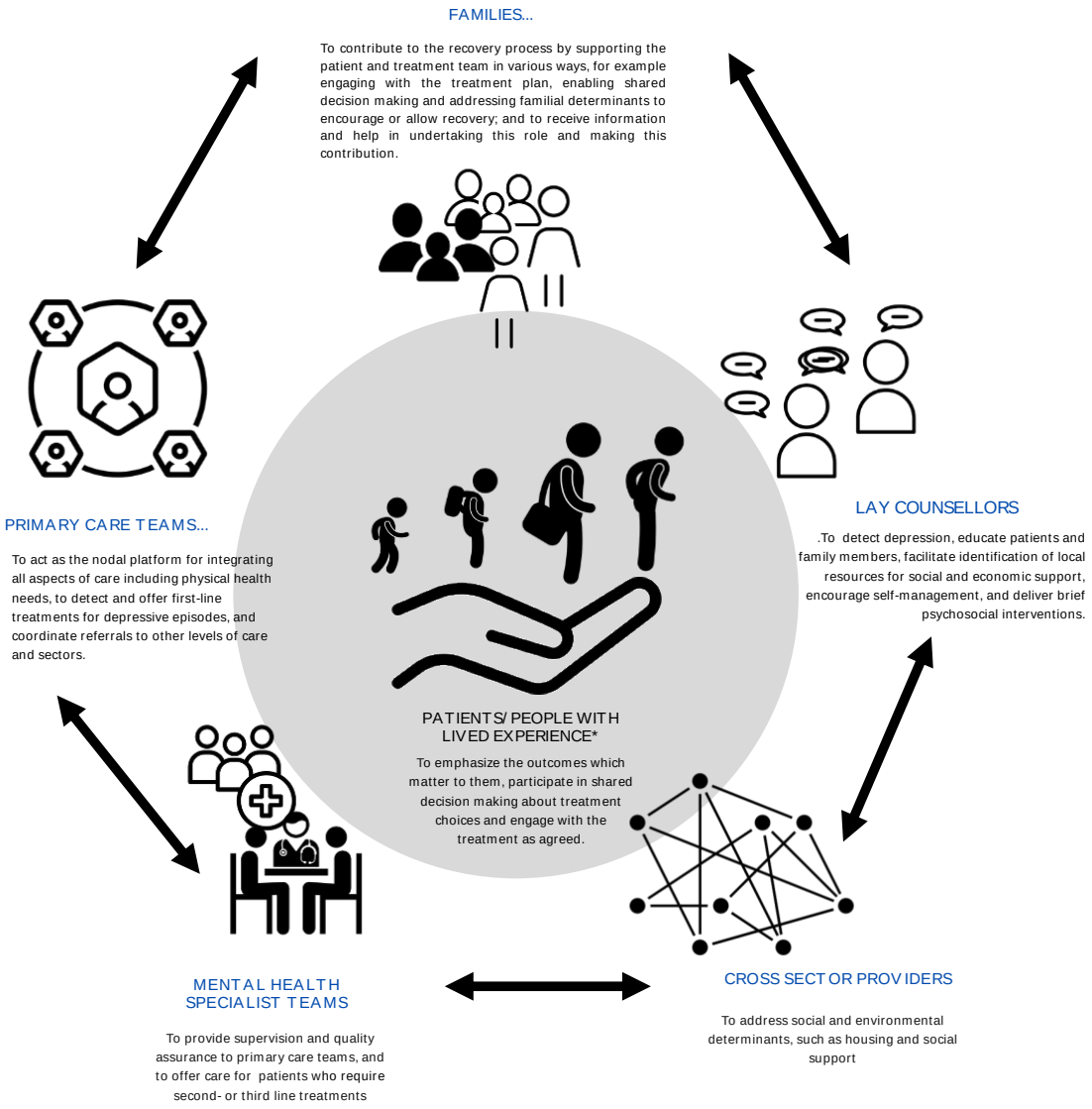
The aim of collaborative care is to consider the outcomes that matter most to people with depression and their caregivers. Critical to this goal is the use of shared decision making, giving primacy to the individual's perspective, as discussed later. Functional recovery is often as important as symptomatic recovery, and is a significant factor in predicting longer term prognosis.[607] Vocational recovery can be achieved with support from practitioners with educational and employment expertise.[608] Relationships in families and friendship groups are often disrupted and social support endangered when most needed. Collaborative care is usually family-centred as well as person-centred – recognizing that family caregivers are often demoralized, need information about depression and its treatment, and play a vital role in providing advice about their family member's background and condition, in forming part of a safety net to prevent suicide, and in encouraging treatment adherence. Recovery support includes specific attention to maintaining or retrieving positive social connections. Once people have recovered, the next challenge is to sustain the recovery, the support for which is typically neglected in crisis oriented acute service models. Self-help aided by technology and engaging a wider community of helpers including spiritual providers, may be highly relevant for some individuals.

Team configurations vary across and within countries. In well-resourced settings they generally include mental health specialists, primary care clinicians, and social workers, and ideally vocational and educational support workers, concerned with care management and working with broader systems (Figure 12). The mental health specialists may be co-located in primary care or in mental health facilities; the critical requirement is coordination between these sectors. Collaborative care may be enabled or enhanced in scarce-resource settings with the engagement of lay counsellors or community health workers.[609] Task sharing with lay community workers aims to confront the scarcity of specialised health and mental health workers and improve access to care and deliver brief psychosocial interventions.

Achieving and sustaining good quality of care and a rights-based approach in a collaborative care system is ideally integrated in the monitoring of standards and quality of care in the local health services, using the principles of quality improvement and considering outcomes that matter most to people with depression and their caregivers. Measurement-based care (MBC) may be used to assist clinicians to dynamically assess outcomes and initiate modifications in treatment plans accordingly. MBC includes standardized assessment of depressive symptoms, medication side effects, and adherence. It typically uses a multi-step decision tree (algorithm) in treatment planning to match level or intensity of care with the needs of individuals and assist with consistent follow-up. MBC shows promise of resulting in higher remission and recovery rates than does care as usual.[537,610]

Collaborative care also allows the integration of specific care for people at risk of suicidal behaviour and those with comorbid medical conditions. For people with comorbid conditions such as diabetes or heart disease, systematic reviews indicate that collaborative care can not only improve depressive symptoms,[611] but also has beneficial impact on self-management of chronic disease.[612] The COINCIDE trial, for example, tested the effectiveness and cost-effectiveness of collaborative care offered to people with depression and diabetes or cardiovascular disease by wellbeing practitioners and practice nurses. Care included behavioural activation, cognitive restructuring, graded exposure, lifestyle advice, management of drug treatment, and prevention of relapse. The intervention improved depression outcomes and increased self-management. Effect sizes were modest, but the intervention was delivered in the context of routine practice in areas of high deprivation.[613] Both clinical and cost effectiveness persisted at two years.[614] The recent INDEPENDENT trial replicated these findings in a low-resource setting (India).[615] The cost-effectiveness of collaborative care for depression in the UK[616] and in India has been demonstrated in recent years. Within public primary-care facilities in Goa, the engagement of lay health workers in the care of people with common mental disorders was not only cost–effective but also cost-saving.[617]

Figure 12. The collaborative care team



* Note on terminology: these terms are used interchangeably at different points in the report. We are aware of the strong preferences of people for either of these or alternate terms and use them respectfully.

\Personalized care

There are two distinct perspectives to personalized care for depression: one seeks to place the person at the centre of clinical decisions, prioritising outcomes that matter to the person and enabling the individual to make a fully informed decision about treatment. Such an approach explicitly addresses co-morbidities and social determinants. Importantly, outcomes that matter to individuals are not necessarily present in currently available instruments used to capture the construct of depression. Domains such as mental pain and overall functioning, for instance, despite being highly ranked by people with depression, informal caregivers, and healthcare professionals, are not covered by most depression rating scales used in clinical trials.[618] This perspective is synonymous with the concept of 'person-centred' care and central to collaborative care described above.

The second perspective of personalized care is aligned with precision medicine, and aims at identifying characteristics of an individual associated with the outcome of different treatment options in order to offer a good match between the individual and the treatment received.[190,603,619] While most treatments of depression have comparable effects at the group level with no or only small group differences, individuals with specific genetic, biological, psychosocial, and/or environmental characteristics, including moderators and prognostic factors might respond better to one treatment than to another. For example, preliminary research indicates that pharmacotherapy is probably more effective than psychotherapy in individuals with dysthymia and persistent depression,[620] and combined treatments are more effective than either treatment alone in older adults.[515] It has long been expected that the efficacy of pharmacological treatments could be improved with increasing knowledge of genotyping,[621] as about 50% of response to antidepressants can be attributed to genetic factors.[622] Applying a precision treatment algorithm to data from a trial comparing antidepressant medication vs CBT yielded an additional benefit on remission of 'matching' individuals to either treatment based on only five clinically sensible indices (personality disorder, marital status, employment status, number of prior medications trials, and number of precipitants).[623] Despite the promise of these preliminary studies, the current state of knowledge about moderators and prognostic factors is of limited significance in guiding individualized care.[624]

Machine learning techniques using big datasets offer a promising approach to developing personalized treatments of depression and prediction models for treatment outcomes.[599] Another promising area of research is the identification of neuroimaging patterns or biomarkers to predict illness vulnerability, discriminate depression subtypes, or guide treatment selection in individuals. Beyond treatment selection at initiation of treatment, such indicators are also needed to identify people likely to develop treatment resistance or those at risk for relapse. Recent studies implementing this general approach have identified several putative treatment selection brain biotypes with potential utility for choosing between psychotherapy and medication and for stimulation-based treatments such as transcranial magnetic stimulation and deep brain stimulation.[333,336] In parallel, others continue to search for biological or behavioural surrogates of such brain-based biotypes, with equivalent specificity but with more potential widespread availability.[516,625]

Digital strategies

The enhancement of treatment and care by leveraging digital technologies is a significant new frontier in health care. Digital strategies may extend the reach of other clinical interventions to underserved populations, or increase the period, intensity or quality of care for those already served. Internet CBT (iCBT) was one of the earliest attempts to take advantage of the emerging

digital technologies in depression care. It is now well-established that iCBT, when supported by human guidance, is as effective as face-to-face CBT and is superior to various control conditions.[501] There is also evidence of cost-effectiveness in primary care settings,[626] although a recent review concluded that face-to-face CBT had a higher probability of being cost-effective.[627] Unguided iCBT can also have smaller but significant effects.[502] Computer-based iCBT is rapidly being superseded by smartphone app-based iCBT and novel app-based approaches are emerging such as cognitive-emotional training.[628] None of the thousands of apps so far available, however, has yet obtained regulatory approval. A recent individual participant network meta-analysis was able to distinguish potentially helpful (e.g., behavioural activation), less helpful, or potentially harmful (e.g., relaxation) iCBT components. The study also showed a decrease in dropout rates when human encouragement to proceed with iCBT was combined with automated encouragement.[629]

Digital technologies also offer new possibilities for the way we screen, diagnose, assess, and monitor people with depression and the way we train mental healthcare personnel and monitor their care delivery. Computerised adaptive testing enables more efficient, flexible and precise administration of individual-reported outcome measures.[630] Digital technologies for workforce training[631] and monitoring of care include natural language processing of the services as they are delivered, and automatic feedback on adherence to quality indicators or indicators of individual improvement. Care delivery including collaborative care can be extended in various ways by the use of tele-medicine. This has been demonstrated in diverse contexts during the COVID-19 pandemic wherein digital technology has become the standard delivery platform for mental health care. Shared decision making (SDM) may be facilitated for individuals who prefer automatic, interactive display of information specific to their own characteristics and needs[632] on interactive web pages or smartphone apps.[633] Several trials are examining the feasibility and effects of such personalised interactive decision aids.[634] There is special interest in support for decisions regarding use of antidepressants in pregnancy.[635]

Technology offers the possibility that response to treatments will be monitored more closely through smart devices, so that timely and efficient adjustments in interventions can be implemented. Digital phenotyping, the "moment-by-moment quantification of the individual-level human phenotype in situ using data from personal digital devices"[636] takes advantage of unprecedented types and amounts of data including movement, pulse rate, blood pressure, and sleep, meals and other lifestyle patterns, in addition to repeated self-report and neurocognitive tests.[637] Such phenotyping may lead to support for differential diagnosis[638] and prediction of relapses or recurrences.[639] Systems have been developed that integrate digitally-assisted diagnostics, prognostics, decision-making, therapeutics and outcome assessments into an electronic health record (EHR) system, for example the Learning Healthcare System (LHS), to create a continual cycle of care improvement.[640] This interactive tool can empower both the individuals with depression and their health care providers in personalised and evidence-based decision making.

However, several barriers limit the coverage and impact of digital innovations. First, the perspectives of individuals are of paramount importance for all digital strategies. Experience shows that their uptake and sustained use by the intended users is low.[641] In one large pragmatic trial of unguided iCBT, the median number of completed sessions for two widely used programs was one out of eight and one out of six.[642] While the dropout rate from routine treatment, mainly through antidepressant pharmacotherapy, may also be high (e.g., in one claims database analysis we found that 28% never returned after the initial prescription and

55% dropped out within 3 months),[643] the rate of dropouts is greater for digital therapies than face-to-face routine treatments.[501]

Second, installing, updating and troubleshooting digital devices is not straightforward or easy for some individuals and professionals alike. While half the psychiatric outpatients surveyed reported a positive view of mental health apps, only one in four had ever downloaded an app and only one in ten was currently using an app.[644] Relying on digital interventions may widen inequalities in access to care due to the "digital divide." We may need "digital navigators" as members of the collaborative care team to help support both the patients and the clinicians in engaging with the digital world.[645] Third, we need innovative ways to assess and control the quality of the thousands of mental health apps already in the market, entering the market and being continually updated. The UK NHS has launched an Apps Library homepage listing evaluated applications. Fourth, the whole system must be accountable for privacy and ethical concerns.[646,647]

Care in specific contexts and populations

Preventing suicide in the context of caring for people with depression: While people living with depression have a much higher risk of suicidal behaviour than others in the population (see Epidemiology and Burden, "Suicidal behaviour"), most do not die by suicide or attempt suicide. Hence it is important for clinicians to aim to identify and intervene with those at higher risk. Interventions that are currently used for suicide prevention include counselling with patients and family care givers to reduce access to lethal means for suicide, together with the use of suicide-specific interventions (e.g., safety planning), and attention to contextual factors such as family discord and the need for social support. These and similar elements of re-engineering practice have been associated with reductions in suicide of up to 29% in clinical populations int the UK,[648] and with even more dramatic reductions associated with changes in the Henry Ford Health System in the U.S.[649] Using anti-depressants has a modest effect in reducing suicides[650] in adult and older populations with depression. Ecological studies in Europe[651] do indicate suicide rates have fallen in countries where there has been greater increase in the use of antidepressants; however, ecological studies even if consistent are no proof of causation. There is strong evidence that the use of lithium has added benefits for its unique anti-suicidal effects (although this effect may be specific to individuals with bipolar depression).[652] There is a body of early evidence for use of ketamine intravenously for rapid reduction of suicidal ideation;[653,654] however, the longer-term impacts are still unknown.[655] Some depressed suicidal individuals may require admission to hospital, but there is weak evidence to support suicide watch and the close monitoring prescribed by most guidelines.[656] Such workforce intensive protocols are potentially intrusive and unwelcome, and may be unwarranted given their questionable efficacy.[657]

Despite evidence gaps of these kinds there are very few cost-effectiveness studies on improving or optimising services to prevent suicide in people with depression, in hospital or community settings. One example is better training for primary care physicians to identify individuals at risk of suicide linked to moderate to severe depression in England. This was evaluated and found to be highly cost-effective.[658,659]

Nonetheless meta-analyses show that clinical judgments about suicide risk predict subsequent suicidal behaviours only weakly.[660] Based on this evidence, numerous attempts have been made to develop suicide prediction tools using patient self-report scales, neuropsychological tests, medical records, or some combination of these as predictors of suicidal behaviours. This

literature has been reviewed extensively.[661-663] Composite prediction strength for most such models is in the range considered either acceptable (AUC=0.7-0.8) or excellent (AUC=0.8-0.9).[664] However, given the rarity of suicidal behaviours, positive predictive value (PPV; prevalence of subsequent suicidal behaviour among patients predicted to be at high risk) is low even among the patients predicted to be at high risk and a substantial proportion of the patients who go on to engage in suicidal behaviours are predicted not to be at high risk. This has led many critics to argue that suicide prediction tools have no clinical value.[665] This negative evaluation has to be tempered, though, by two considerations.[666-668] First, no existing suicide prediction study has ever applied the full range of significant predictors found in the literature to a large heterogeneous sample of patients and used best-practices statistical methods to develop a stable prediction model. Second, even though PPV in such an optimal model would still be relatively low, the net benefit would likely be positive given that several suicide prevention interventions are cost-effective even at low PPV.[669,670]

Maternal depression: The general principles of treating depression in mothers are the same as those for adults more generally: with an additional concern relating to the potential risk of adverse outcomes from in utero exposure to psychotropic medications. Given that the effects of foetal exposure to SSRIs remain unclear, and given the suggested caution in their use during pregnancy,[671] an individualised collaborative risk-benefit analysis is a sensible option. This considers the consequences of untreated depression as well as the effects of antidepressants on both mother and infant. A national case series of suicides reveals that perinatal deaths of women from suicide are associated with depression that has not been actively treated with medication.[672] Although there are fewer studies on breastfeeding exposure, most SSRIs have been found to pass only minimally into breast milk.[673] Of course, psychological treatments do not carry any of these risks and can be offered as first-line treatments of maternal depression (other than in severe depression, for example with psychosis, when pharmacotherapy is indicated).

A recent systematic review reports effective psychosocial interventions for depression in women experiencing IPV in low and middle income countries.[674] Strong evidence supports the effectiveness of psychosocial interventions for perinatal depression delivered by non-specialist providers including those delivered by peers in these contexts.[675]

Remission of depression in a mother has positive effects on her school aged and adolescent children[564,676] for at least a year afterwards:[677] including the children of mothers treated with medication[676,678] or psychotherapy,[679-682] and varying with the severity of maternal depression.[683] Comorbid problems such as intimate partner violence (IPV) need to be addressed for immediate safety for the family and to reduce deleterious effects on children.[684]

Children and adolescents: Several general principles are key to successfully engaging young people in care. These include providing psychoeducation at a developmentally appropriate level and implementing person- and family-centred, shared decision-making initiatives. Practitioners must also contend with the definition of outcomes and the development and use of multidimensional and multi-informant measures.[685] These encourage the essential integration of multiple perspectives.[686] There is a growing evidence-base for providing collaborative care for depression, working not only in team-based and measurement-guided, but also in youth-driven, family-centred approaches.[687] In one randomized controlled trial that compared collaborative care with enhanced usual care, youth in the intervention group reported higher rates of clinical response (68% vs. 39%) and remission (50% vs. 21%), as well as satisfaction with care[688] — this model also seems to be cost-effective.[689] A meta-analysis[690] of

routine specialist mental health care suggests that between 33% and 40% of young people experiencing severe and complex depression showed measurable improvement. Several factors contributed to these results, including active supports in care delivery; involvement of parents and active outreach; and efforts to increase engagement with the young people, fostering a more open and empowering relationship between them and the practitioners. There is good evidence for the effectiveness of psychological therapies for depression in adolescents,[691] and emerging evidence for the use of modular, trans-diagnostic psychological treatments (compared with 'disorder' specific treatments).[692] Beyond clinical approaches, attention has been directed to more rigorous assessment of a variety of self-delivered and community approaches.[693] Children and adolescents spend an important proportion of their times in school settings in which assessment and interventions can take place. A recent example demonstrated the effectiveness of a brief, lay counsellor delivered, problem solving treatment for adolescents with common mental health problems in India.[694]

Older adults: The hallmark of major depressive disorder in older adults is co-occurrence with medical disorders, high rates of mild cognitive impairment, association with social determinants of well-being (e.g., bereavement, social role transitions, social isolation and loneliness, and depletion of social and economic resources), exposure to polypharmacy, and risk for suicide. Collaborative care involves the delivery of evidence-informed, late-life depression treatment and suicide prevention through coordinated medical, mental health and social services, offered within primary care. This is preferred by many to specialty mental health, because of less stigma and greater access, trust, and affordability. Pioneering studies, such as IMPACT[695] and PROSPECT,[577] have identified core "ingredients" of collaborative care: (1) virtual or actual co-location of mental health expertise within primary care settings (e.g., through telepsychiatry or placement of mental health specialists, such as social workers or psychiatric nurses, within clinics); (2) multidisciplinary teams; (3) measurement-based care to monitor treatment adherence, efficacy and tolerability; (4) engagement of family care-givers to respond to both person-focused and family-centred needs; and (5) evidence-informed provision of acute and continuation treatment modalities both to achieve remission and to maintain recovery and wellness. Collaborative care models also increasingly use community health workers and lay counsellors to facilitate outreach and task sharing in low-resource settings, in the service of both treatment and prevention of depression.[471]

Forced migrants, refugees, and other populations affected by humanitarian crises: More than 235 million people are living in settings of humanitarian crises.[696] The Inter-Agency Standing Committee, which includes UN institutions and a range of humanitarian response organizations, recommends that mental health services in humanitarian settings follow a tiered approach with promotion of basic services and security available to all individuals, followed by bolstering of community and family supports for those in particular risk groups or with moderate psychosocial distress.[697] The WHO mental health Gap Action Programme-Humanitarian Intervention Guide[498] recommends ruling out normal reactions to major loss, bereavement, and displacement when considering a diagnosis of depression, as well as consideration of other possible diagnoses such as prolonged grief disorder. The guidelines highlight the role of psychoeducation, stress management, and strengthening social support, in addition to referring to evidence-supported psychosocial interventions and prescription of antidepressant medication.

Most evidence on psychosocial interventions focuses on treatments which have been adapted from specialist-delivered interventions in high-resource settings, e.g., Trauma-Focused Cognitive Behavioural Therapy (TF-CBT). New psychological interventions have been

developed specifically intended for delivery by non-specialists to populations affected by humanitarian crises, e.g., Problem Management Plus (PM+).[698] Self-help plus (SH+) is also a new intervention developed for administration to large groups in humanitarian settings; SH+ requires limited involvement of facilitators and is built around audio recordings for guided learning of basic psychological skills for persons with mild to moderate psychosocial distress.[699] An umbrella review identifies moderate evidence for the benefit of these interventions for adults (but not to date for children) with depression in humanitarian settings, though weak strength of association for any specific treatment, such as CBT or IPT.[418,700]

RECOMMENDATIONS

This Commission has synthesized a large body of science, spanning disciplines ranging from neuroscience to global health, to generate an understanding of the nature of depression, its impact on people and communities, how it might be prevented and the pathways to recovery. By design, this is, for the most part, a narrative review scripted by a team of scholars and practitioners who were purposively chosen to reflect their individual and complementary leadership of this range of disciplines. That said, we believe that the science points to a number of specific key messages and actionable recommendation.

We present recommendations for action by four primary stakeholders: the general community and, in particular, persons with the lived experience of depression; practitioners who are in a position to prevent and treat depression; researchers who lead scientific endeavours to reduce the burden of depression; and decision-makers who design policies and finance their implementation (Panel 3).

Panel 3. Recommendations of the Lancet WPA Commission on Depression

Reducing the burden of depression requires united action by diverse stakeholders.

The general community, including people with lived experience of depression

1. *Seek help early. This increases the chances of preventing or recovering from an episode of illness.*
2. *Talk with family and friends if possible, taking confidence from the knowledge that depression is a common human condition experienced across the ages and across cultures.*
3. *Remain hopeful because most persons with depression will recover with the right support and treatment.*
4. *Ensure that treatment is informed by evidence-based practice, focused on your priorities, with decisions made collaboratively, and engaging where possible and appropriate with your family, friends, community, and peer supporters.*
5. *Find partners or groups to sustain you in educating yourself about the illness, practicing self-care to get well and stay well, sharing your experience and supporting others as a peer support worker or advocate; and look for opportunities to speak up as an expert or organise for the need for care, against discrimination, and for social changes that support mental health and reduce the risks of depression.*

Health care practitioners

1. *Learn about depression: about the variations in its origins, presentation and course, and about the lived experience of depression.*
2. *Pro-actively recognise and assess the risks of depression, the onset of the illness early in its course and at any stage in life, and its consequences.*
3. *Personalize your management approach to prevention, treatment and recovery in view of each person's needs, challenges and strengths, keeping in mind their socio-cultural context, family and developmental history and life circumstances, their own priorities, and the available resources.*

4. *Practice collaborative care and implement quality assurance and rights-based approaches, working with the person with depression to achieve optimal outcomes.*
5. *Prioritise the therapeutic alliance, continuity of care and the rights of people to receive care with dignity and choice, the needs of families where appropriate, and the obligation to reduce stigma associated with depression.*

Researchers and research funders

1. *Understand the aetiology and nature of the condition across the life course and evolve (urgently) a multidisciplinary and collaborative approach to reducing the burden of depression.*
2. *Engage people with lived experience of depression and their families, as well as practitioners and policymakers, in the conception, design, and implementation of research.*
3. *Identify under-used and novel prevention targets from social determinants to individual vulnerabilities, and engage with partners in evaluating program implementation and policy changes.*
4. *Design and test therapies addressing early intervention and novel mechanisms of disease.*
5. *Prioritise the development of precision medicine approaches to optimize prevention, care, and recovery.*

Decision makers

1. *Respond to the experience of people with depression and to the science, recognising that depression 1) has profound effects on people's health, social relationships, and economic and educational opportunities, and 2) affects people everywhere but is more likely to affect those living in poverty and adversity from historic or contemporary losses, injustices, and inequities.*
2. *Secure investment across society in prevention and health promotion, targeting determinants of health across the life course, in particular during childhood and emerging adulthood, and across the whole of society and the environment to tackle economic and social inequities.*
3. *Secure investment in depression care, including intervening early in the course of the disorder and sustaining care as needed, because existing treatments work, can reduce human suffering, and make economic sense from a societal perspective.*
4. *Support the sustainable implementation of rights-based depression care, including legal and collaborative care frameworks integrated across the health and social welfare systems, co-designed with people with lived experience of depression and their families.*
5. *Invest in research, including basic and practice and implementation science.*

The community/persons living with depression

The important thing in the process of recovery is to have small funs and to continue to have them. Small things you can enjoy in your everyday life: get in touch with the nature, get in touch with people, find your favourite music, find your favourite movies.
- Keigo Kobayashi, 41, Kyoto, Japan

Perhaps the central question that dominates the public understanding of depression is the boundary between depression as a health condition, as opposed to an extension of social suffering and the expected range of human responses to stress and loss. The evidence we present compellingly demonstrates that while the boundaries between these normative human emotional states and depression are not always clear, and that the experience of depression itself can take diverse forms, these two experiences are distinct in many ways, for example in their duration, impact on daily functioning, and long-term health consequences. Moreover, historical and cross-cultural evidence demonstrates that the condition has been described since ancient times and in diverse civilizations, and, although the experience of depression can take many forms, the core illness experience is very similar across cultures. Above all, depression can affect anyone, and is never the person's "fault" or a sign of psychological "weakness."

While depression can affect a person at any point in their lives, it is most likely to have its onset in young adulthood. While many persons will experience just one episode, others will have repeated episodes and a few may experience persistent distress for long periods.

Just as you would for other health concerns, you should find help for depression — and do so early, because the longer the illness lingers, the longer you suffer needlessly and the chances of recovery are diminished. There is a wide range of interventions which can promote recovery, from self-help (interventions based on psychological therapies designed to be learned independently by the person or used with only modest levels of guidance) and lifestyle changes to psychological therapies provided by legitimate workforces (including those engaged in task-sharing) in different settings, antidepressant medication, and more specialized therapies for those who continue to experience the illness despite trying these options. Most people who seek and find healthcare will recover with the aid of interventions recommended in primary care or community settings, through appropriately trained and supported community-based providers and primary care practitioners. There are a variety of evidence-based interventions that can provide relief to the great majority of people with depression, but no one intervention is right for everyone and multiple trials of different interventions may be needed to find what works for you. Therefore, keep in mind that recovery is a journey: if you do not strike gold on the first trial, persisting with alternatives will incrementally but continuously increase your chances of recovery.[701] Mental health professionals often work with primary care providers to support this work. They also provide direct care to a significant proportion of people who do not receive interventions in primary care or do not recover with those interventions. A relatively small number of people may need brief periods of care in hospital and other treatments.

Your role in the recovery process is central, using information from reliable sources and seeking help early to find what helps you the most. It is crucial that you are an active partner in decision-making, ensuring that your priorities and needs are being addressed. Your needs and priorities may range from relief for specific distressing symptoms (such as not being able to sleep or being tormented by ruminations) to social concerns (such as unemployment) or care for health conditions (such as diabetes). Addressing your ideas, concerns and expectations in a holistic manner is the hallmark of good quality primary care which is why this is the ideal first setting for you to seek help. And, if you and a healthcare provider decide together that medication or psychotherapy is likely to be helpful, always remember to engage with this agreed treatment for they are most effective when taken in the right dose (for e.g. the number of sessions of therapy), the right way (for e.g. practicing skills taught in sessions at home) and the right duration (for e.g. often up to a year for antidepressant medication). Upon recovery, remember that it is just as important to remain well through incorporating the skills you have learned in every-day life, engaging your family and friends and other community resources to support you through difficult times, and being sensitive to the signals which indicate you may be relapsing so that you can act quickly and reverse the slide.

When you recover, you may want to think about how your journey can help others who are also living with depression, the vast majority in silence, unable to get the appropriate support and care because of the lack of skilled providers or adequately resourced services, or because they are embarrassed to do so for the reasons we highlight earlier. Your lived experience makes you an ‘expert’ in understanding this condition and the pathways to recovery, and you may wish to play a role in sharing this expertise in your community, becoming involved with civil society groups as a peer support worker or advocate, and mobilizing your community to demand that policy makers invest in depression prevention and care (in particular, the

scientifically proven interventions which work). Your voice is crucial to effect policy change, to ensure that others in your community are able to access the care science has shown works.

Health Care Practitioners

A wide range of practitioners can provide treatments for depression, from community health workers delivering brief psychological therapies, to family doctors offering advice, support and/or antidepressant medication, to coaches guiding people engaged with internet-delivered psychotherapy, to mental health specialists offering the full range of interventions. The messages we have distilled apply to varying degrees to these diverse providers, but are most germane to non-specialist practitioners.

It is imperative that you give depression the same attention as you would to other common conditions, such as diabetes and hypertension, by learning all you need to know about depression, in particular about its diverse origins, presentations and course. Depression rarely occurs by itself; it occurs in a developmental, social, environmental and economic context, it is very often a companion to chronic medical conditions (such as diabetes) whose outcomes it worsens, and may co-occur with other mental health conditions too (such as harmful drinking). Depression can also profoundly affect the health of others in the family, most notably the child of a depressed parent. Depression can be brought to remission in the great majority of cases with evidence based and persistent treatment, but may require many trials of different treatments until a regimen is found that works; and upon recovery, it is important to bear in mind that depression may be recurrent in some people.

Although the varying presentations of depression often mean that its 'hallmark' features, such as sadness or loss of interest, may not be obvious in many people, it is important to detect depression and offer help as early as possible. Pro-active detection strategies can be used: asking a few questions about mood and ability to engage with and find pleasure in daily life would suffice. Do not overlook adolescents and young people whose clinical presentation may be changeable and mixed, and who may be more reticent to share their inner experiences. The admission of such symptoms should trigger a fuller inquiry to assess the range of other symptoms, their severity and duration. Simple screening tools like the PHQ-9 may be useful for this purpose. Bereavement is one particular life event which requires thoughtful inquiry to distinguish the normative response associated with grief from depression. Also, gender-based vulnerabilities which render women more likely to experience sexual abuse or intimate partner violence or abuse need to be addressed simultaneously with treating depression.

The diversity of depression histories and presentations means that you need to personalize your management approach in view of the individual's problems and strengths, keeping in mind their background, life circumstances, families, co-occurring medical conditions and priorities. While there are, as yet, no definitive individual characteristics which can guide practitioners on which intervention to use, offering a choice of the primary evidence-based treatments is the aspiration with the goal of meeting individual preferences. This range of strategies which call for a person-centred approach to depression care is more difficult for a provider working in isolation, and a collaborative care delivery model is the most effective one to integrate the diversity of depression into routine care. The collaborative care 'team' always includes the primary care practitioner and the person with depression, but also extends to the community health worker (who typically plays a range of roles, from supporting adherence to providing brief psychological treatments) and a mental health specialist (who typically provides guidance, consultation and referral for patients with severe and refractory conditions). For many people, engaging with their family members is also an important element. Family

members can support the recovery process, especially when recognised and included by the care team, but also experience relief from their own distress though a better understanding of the illness. Coordination with social welfare services, such as those which support women who are experiencing domestic violence, and with spiritual providers in certain contexts, enhances the chances of recovery. If you work in isolation, try to identify others who could work with you to build a team.

We emphasize the importance of collaborative care, the most cost-effective way to extend the effective coverage of known interventions to the wider population as a component of universal health care. The essence of this delivery model is empowering primary care to provide integrated care for multiple morbidities, often by sharing care with community workers, and addressing social determinants of health. Mental health specialists need to actively engage with the scaling up of collaborative care by supporting primary care practices in their geographic area, and offering guidance, consultation and clinical care for people with refractory or complex depression presentations.

Diagnosis-driven and evidence-informed treatment (on the one hand) and individual person-centred case formulation (on the other) are complementary and synergistic rather than antithetical. Persons living with depression benefit from shared or supported decision-making with clinicians that is informed both by the best available scientific evidence and by an empathic understanding of the specific risk and protective factors relevant for a given individual.[702] Available treatment guidelines need to be leavened by an understanding of individual-specific risk and protective factors and by an individual's preferences and expectations. We strongly recommend instituting quality assurance strategies, at the very least by keeping track of individual and aggregate metrics, such as the numbers and proportions of people with depression who are detected, initiated on evidence-based treatments, and have completed the treatment and recovered.

Remain persistent and hopeful in pursuing multiple sequential treatments when one has failed, and provide encouragement and support to people with depression to do the same. Finally, it is implicit that all practitioners must respect and champion the rights of individuals with depression to receive good quality care with dignity, on par with any other medical condition, and take responsibility for ensuring that the treatment setting is free from stigma towards people experiencing depression. In doing that, consider how your own attitudes towards people living with depression align with contemporary values in depression care. At the heart of this commitment is the therapeutic alliance and the principles of shared and supported decision making which emphasize that the patient's will and preferences are at the centre of treatment plans.

Researchers and research funders

An urgent priority for the depression research community is to evolve a multidimensional approach, incorporating the interplay of genetics, brain biology and experiences/stressors across the lifespan. The complex and heterogeneous nature of the condition poses particular challenges for researchers as the phenotype varies considerably, does not show distinct boundaries, and is the result of diverse pathways and leads to diverse outcomes. Such an effort will need "collaboration across disciplines and settings to form a community of mental health scientists inclusive of any discipline that uses evidence in a rigorous and transparent way to inform understanding of mental health"[703] and should involve a common set of research methods and metrics applied in diverse populations, in the spirit of data-sharing and capacity building. This, in turn, requires large scale consortiums and a parallel shift in the mind-set of

traditional research funding mechanisms which typically pit researchers into competition with one another and where the efficiency of substantive, consortium style, long-term funding, is diluted by multiple smaller grants.

There is a pressing need to enhance the effectiveness and impact of known interventions for the prevention and care of depression, and to evaluate the costs and effectiveness of their widespread implementation in diverse settings and across populations. Precision medicine approaches need to be applied for assessing differential response to first-line treatments and evaluating the combination and sequential allocation of diverse treatment approaches to enhance overall response rates.[554,597] Moreover there is a range of approaches beyond these biomedical treatments ranging from exercise, meditation and yoga[704] to community support that await further investigation for their utility as preventive, ameliorative and adjunctive measures. Social and economic policies need to be evaluated for their anticipated or unanticipated effects on risk factors and depression prevalence.[413]

Translation of discoveries in the domains of prevention and therapeutics into practice face formidable barriers limiting both the demand for care and access to quality care, and the implementation of practice and policy changes. While these barriers are experienced universally, far greater challenges are encountered in the least resourced communities and countries, and evidence does not necessarily generalise from one context to another. Elaborating these barriers and designing and evaluating innovative strategies to address them is essential if we are to achieve higher levels of effective coverage of evidence based interventions. The flourishing of 'frugal innovations' in global mental health, such as the use of task-sharing of brief psychological therapies, is one example of delivery science which can address some of these barriers.

Finally, we strongly recommend the engagement of persons with lived experience of depression and their families in all aspects of research: from defining the research priorities and questions, to advising on the methods, interpreting the findings and communicating the results to the community and decision-makers. In view of the magnitude of challenges that result from mental health stigma and discrimination, a concerted effort is needed for methodologically strong research that will provide robust evidence to support decisions on investment in interventions to reduce stigma.

Decision/Policy makers

There is arguably no other health condition which is as common, as burdensome, as universal and as treatable as depression which has attracted such little policy attention and so few resources. Despite the science showing that depression causes profound, enduring suffering and premature mortality, is associated with poor physical health, social and economic disadvantage and enormous loss of productivity for the country, opportunities are lost for prevention of much of the burden and the vast majority of people affected by the condition suffer in silence. Much of the inaction stems from myths about the condition, such as that it is not a 'real' health condition distinguishable from everyday misery, or that it is a concern only of affluent persons or contexts, or that it requires very expensive treatment programs, or that prevention and treatments don't work.

These myths also prevail amongst health care practitioners and the general community, restricting demand for interventions, and deflecting financial investments to build a robust, evidence-based, mental health care system and collaborations for prevention and care across education, health and other sectors. The singular focus on narrowly defined biomedical models

of care, based on binary diagnoses-driven algorithms and heavily reliant on mental health specialists, who are scarce in number or inequitably distributed within and between countries, is an additional structural barrier. There may be a perceived tension between the concept of 'scaling up' that requires a degree of standardization of 'packages' of care and the personal formulation approach which we advocate in this Commission; we think that these tensions can be navigated by distinguishing specific, evidence-based, guidelines which are standardized for implementation across all contexts from the approach in an individual clinical encounter, which needs to be tailored to the person, through a stepped collaborative care approach.

There is now sufficient evidence demonstrating the effectiveness of collaborative care models for delivering interventions across the diversity of depression presentations. Key members of the team are non-specialist providers, such as community health workers and peer support workers, who can deliver a significant proportion of front-line care. Utilizing such locally recruited, widely available and low-cost human resources not only addresses the formidable barrier of lack of skilled providers and constrained budgets, but also helps reduce stigma and cultural barriers, and aligns with person-centred integrated care. It is also consistent with the staged approach to depression care, enabling many persons with depression to quickly receive low-intensity interventions, freeing up and supporting scarce specialised services to address the relatively less common, complicated and refractory presentations. Of course, explicit in the concept of collaborative care is the seamless integration and mutual support of such front-line provision with primary and specialist care, and with social welfare services. Throughout this continuum of care, it is important to ensure that only evidence-based interventions are scaled up and those which have historically been neglected, such as psychological therapies, given particular attention. Some high-income countries have introduced programs providing improved access to psychological therapies[705] for persons with depression and anxiety symptoms detected in primary care, showing that this is feasible but needs further evaluation in terms of cost-effectiveness.

Challenges in scaling up this delivery model are the building of a community-based mental health workforce, because the orthodox models of training (typically expert-led workshops) and quality assurance (similarly, expert-led supervision) are not sustainable; and enabling seamless coordination of care across the platforms of delivery. Digital platforms offer a unique, and a very timely opportunity in the context of physical distancing policies, to build a mental health capable workforce and enable coordinated care. Digitally delivered training and delivery models, such as tele-psychiatry, will enable much larger numbers of providers to be trained and greatly increase the reach of experts; their relevance has greatly increased as a result of the pandemic. Still, many barriers remain, including formal recognition by payers and decision-makers that such collaborative and digitally enabled delivery formats represent good value for money, in both the short- and longer-term. Another threat is the risk of push-back from sceptics who claim such models of care represent low-quality; there is no evidence that this is the case, as long as such models are adequately resourced to ensure that that each worker has access to training and referral at a more expert level, and that quality improvement strategies are implemented. There are welcome signals that these approaches are being adopted; for example, mental health specialists in several countries are now reimbursed for their work in primary care settings, including remote consultation on clinical management under specified circumstances.

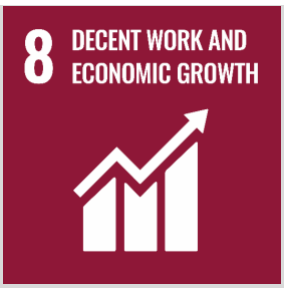
Prevention has been historically the most neglected aspect of depression. This is in part because most interventions are outside the health sector, targeting determinants in the salient environments of pregnancy and early childhood extending to emerging adulthood, including support for parenting, promoting school climate and building social and emotional

competencies, and from there to adult and later life, promoting economic equity, shared life chances and social connectedness. Measures to reduce violence in the family and bullying at school, workplace mental health promotion, and addressing loneliness, particularly in older adults, are key preventive interventions. Targeting key lifestyle determinants such as diet, physical activity, smoking and other substance misuse has resonances in prevention of other non-communicable disorders.

Thus, whole-of-government actions are required, well beyond the traditional health sector, to successfully realize the population-wide coverage of these interventions, with a particular emphasis on addressing existing disparities, for example by increasing allocations for poor and historically disadvantaged and dispossessed populations including indigenous societies around the world. Tackling the climate emergency and the continuing threats of pandemics and other global and regional emergencies that exacerbate existing inequities and threats to health are vital parts of global and national efforts to prevent depression. But whole-of-government approaches challenge the silo-budgeting conventions of public bureaucracies (especially those that are performance-managed) and require strong commitment to *long-term* cross-sectoral, solutions. Preventive efforts outside the state sector (e.g., in workplaces) may also be hard to incentivise. Even when preventive strategies or treatments appear cost-effective, there may therefore be economic and other structural barriers to implementation. Thus, budgetary allocations for preventive strategies need to be ear-marked from the relevant ministries which are concerned with these diverse sectors. Investing in depression prevention and care represents excellent value for money, not least due to the contribution they can make to the attainment of several of the SDGs (Figure 13).

Figure 13. Depression and the Sustainable Development Goals

How depression relates to this SDG	The SDG	Actions to prevent or treat depression that contribute to achieving the SDG
Being depressed impairs work performance and increases the risk of becoming unemployed, inadequately employed or inactive, and increases vulnerability to economic, social and environmental shocks and disasters. It is also associated with increased health care costs, often out-of-pocket in most countries with inadequate universal mental health coverage.	 End poverty in all its forms everywhere.	Increasing people's likelihood to find and hold a job, reducing disability associated with co-morbid medical conditions, less isolation and morbidity among family caregivers, decreasing health care costs, and increasing people's resilience when exposed to shocks and disasters.
Poor nutrition is a risk factor for depression, and depression is associated with unhealthy eating habits and obesity. Depression in mothers is strongly associated with childhood undernutrition and stunting.	 End hunger, achieve food security and improved nutrition and promote sustainable agriculture.	Enabling persons to take a more active hand in self-care, including provision and intake of adequate nutrition, and enabling parents to create a more nurturing environment for the healthy growth and development of children.

How depression relates to this SDG	The SDG	Actions to prevent or treat depression that contribute to achieving the SDG
Depression is, by itself, the single most burdensome mental health condition. It also increases the risk of a number of other health conditions, such as cardiovascular events, other mental health conditions such as substance use, and worsens their prognosis, contributing to premature mortality.	 Ensure healthy lives and promote well-being for all at all ages.	Promoting substantial improvement of health-related quality of life, with reduction in mortality risk from non-communicable diseases, including cancer-related deaths, and suicidal behaviour.
Maternal depression adversely affects offspring cognitive development and educational attainment; being depressed during childhood or adolescence has a negative impact on educational performance and outcome; depression reduces the access of adults to technical, vocational and tertiary education and reduces their chances for successful completion.	 Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all.	Enhancing educational attainment across the life course, ultimately contributing to the protection of cognitive reserve and brain health.
Depression disproportionately affects women, in part due to gendered disadvantages faced by girls and women, including interpersonal violence, fuelling further gender inequalities in education, health and income.	 Achieve gender equality and empower all women and girls.	Improving the health of girls and women, including reduced self-harm, increasing agency and self-efficacy, and reducing exposure to interpersonal violence.
Depression is a major drag on productivity and economic growth.	 Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all.	Improving productivity at work, contributing to greater economic performance of industry, and fostering equal opportunities of employment for those with depression. *The Economist* voted addressing the burden of depression as an economic best buy.

How depression relates to this SDG	The SDG	Actions to prevent or treat depression that contribute to achieving the SDG
Marginalised and disadvantaged communities are more vulnerable and income inequality is associated with higher risk of depression.	 . Reduce inequality within and among countries.	Reducing health inequalities (including premature mortality) and, ultimately, reducing income inequalities.
Person-centred urban spaces, for example with minimal noise/air pollution, green spaces, night lighting, pedestrian zones and bike lanes which encourage physical activity and attention to personal safety, reduce the risk of depression.	 Make cities and human settlements inclusive, safe, resilient and sustainable.	Promoting a positive cycle between more inclusive, safe and sustainable settlements and a psychologically resilient, socially connected and healthy population.
Extreme climate events and associated disasters lead to an increased risk for depression.	 Take urgent action to combat climate change and its impacts.	Strengthening resilience and adaptive capacity to climate change, preventing depression's sequelae, including grief over catastrophic loss of livelihood and life.
Wars, civil conflicts and socially fractured societies lead to trauma and stressors associated with threats to personal safety, loss, bereavement and displacement which increase the risk for depression.	 Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels.	Enabling persons and communities affected to better address and cope with the diverse stressors and tolerate diversity, ultimately contributing to the rebuilding of shattered lives and communities.

A final word for decision makers concerned with development assistance for health, such as the international aid departments of wealthier countries and foundations: the evidence we present clearly shows that depression is a health condition which hits the poorest people,

communities and countries the hardest. Much of the global unmet need for prevention and care is concentrated in these populations and this burden is expected to grow considerably following the COVID-19 pandemic, refugee crises and the climate emergency. Despite this, development assistance has almost entirely neglected mental health even though these countries need substantial external financial support to adequately resource their mental health care systems. It is time to change.

CONCLUSION

Depression is one of the leading causes of avoidable suffering and premature mortality in the world but has attracted little policy attention. Most countries are ill-equipped to deal with the burden of depression, not only because of the long-standing under-resourcing of mental health care systems and the massive paucity of skilled providers, but also because of the rigid silos that typically separate mental health expertise and mental health care from primary health care and community support sectors, and that separate health policy from other pertinent areas of public policy such as education, employment, migration and welfare benefits.

This Commission provides a message of hope, not only in the form of robust evidence on what can be done to prevent and treat depression, but also how such interventions can be delivered even in the least resourced contexts. This evidence offers us an historic opportunity for united action to transform mental health care systems globally. Investing in actions to reduce the burden of depression enables individuals to regain and maintain their well-being, hope for the future and the necessary cognitive capabilities to be effective in their work and personal lives. Collectively the impact will contribute to strengthening national economies and to the attainment of the Sustainable Development Goals. Paired with this, we urge decision-makers to consider seriously the call for a whole-of-society approach to the prevention of depression that can be expected to deliver benefits equivalent to those found in many countries from reducing the prevalence of coronary heart disease and several forms of cancer. We cannot think of a more important set of investments, now more than ever before.
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Contributors

HH, VP, CK, and CB drafted and revised the whole report. MB, PC, TAF, RCK, MM, PM, CFR, and MMW led the drafting of specific sections of the report. All authors contributed text to sections of the report, and all reviewed and revised the paper for intellectual content. HH, VP, CK, CB, PC, TAF, RCK, MM, CFR, CD, BAK, HM, and BP also contributed specific non-text items.

Declaration of interest

HH reports her role as President of the World Psychiatric Association during the period of preparing and submitting the report for publication and support through Australian National Health and Medical Research Council (NHMRC) Practitioner Fellowship. VP reports being a co-founder of Librum, a mental health consulting firm, and has consulted with Johnson & Johnson, with no fees received related to the submitted work. His research on depression is supported by the NIMH and the Wellcome Trust. CK is a *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq), Brazil, researcher and a UK Academy of Medical Sciences Newton Advanced Fellow. MB reports grants from NHMRC as Senior Principal Research Fellow, during the conduct of the study; personal fees from Servier, Lundbeck, Livanova, Grunbiotics, Otsuka, RANZCP, ANZJP, and Medisquire India, outside the submitted work; and three issued patents (Modulation of Physiological processes and agents useful for same, Modulation of diseases of the central nervous system and related disorders, and Xanthone-rich plant extracts or compounds therefrom for modulating diseases of the central nervous system and related disorders issued). CB reports travel support from Wellcome Trust and personal fees from the University of Melbourne and the World Psychiatric Association, during the conduct of the study. TAF reports grants and personal fees from Mitsubishi-Tanabe and personal fees from MSD and Shionogi, outside the submitted work; and patent 2018-177688 pending, as well as intellectual properties for Kokoro-app licensed to Tanabe-Mitsubishi. RCK was a consultant for Datastat, Inc., Holmusk, RallyPoint Networks, Inc., and Sage Pharmaceuticals. He has stock options in Mirah, PYM, and Roga Sciences. CR reports consultant fees from the Depression and Bipolar Support Alliance, Weill Cornell School of Medicine, UpToDate, The University of Maryland School of Public Health, Psychopharmacology Institute, and Merck, and an honorarium from the American Association for Geriatric Psychiatry, outside the submitted work; and royalties from the University of Pittsburgh and Oxford University Press. MMW in the last 3 years has received research funding from NIMH, Brain and Behavior Foundation, Templeton Foundation and the Sackler Foundation, and has received book royalties from Perseus Press, Oxford Press, and APA Publishing and royalties on the social adjustment scale from Multihealth Systems. DC is funded by the African Academy of Sciences, and is involved as the founder of Friendship Bench which supported by Boehringer Ingelheim. CD reports grants from National Institute for Health and Social Care (England), personal fees from World Organisation of Family Doctors, personal fees from iheed - Accredited Medical Education Online (Ireland), outside the submitted work; and as Chair of the Working Party for Mental Health of the World Organisation for Family Doctors, CD advocates for the central role of family doctors in the assessment and management of depression in primary care settings. LH reports funding from the South London and Maudsley NHS Foundation Trust/King's College London Biomedical Research Centre; the UKRI Collaborative Mental Health Network plus: Violence, Abuse and Mental Health: Opportunities for change (ES/S004424/1); NIHR HS&DR ESMI II: The Effectiveness and cost effectiveness of community perinatal Mental health services (17/49/38); and salary support from the South London NIHR Applied Research Collaboration. HM reports personal fees from Abbott Labs, outside the submitted work; and a patent US 2005/0033379A1 licensed to Abbott Labs. BP reports grants from Jansen Research, grants from Boehringer Ingelheim, outside the

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