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. Not enough is done to avoid and alleviate the suffering and disadvantages linked with depression, 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-rooted 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 so-called perfect storm that requires responses at multiple levels. The consequences of the pandemic thus emphasise 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, depression is a heterogeneous entity experienced with various combinations of signs and symptoms, severity levels, and longitudinal trajectories. The term depression is used broadly in this Commission and does not relate to any one diagnostic system or category: we use the terms "major depression" and "depressive disorder" when referring to specific classifications. We cover depression in this Commission as well as symptoms of depression causing distress or social impairment. However, we do not cover depression as occurring in the specific diagnostic context of bipolar disorder.

Third, core features of the condition have been described over thousands of years, long before the advent of contemporary classifications, and in diverse communities and cultures. History thus belies the myth that depression is a modern condition, an invention of biomedicine, or is 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 recognising the human brain and mind as an interface connecting our conscious selves to the world around us. Such recognition requires going beyond a brain-based or a social-environmental paradigm and recognising that biology is inseparable from environment across the human life course.

Fifth, at the individual level, detecting and diagnosing depression early in its course, on the basis of recognising the signs and symptoms of illness and functional impairment over time, is a crucial first step to recovery. A clinical formulation co-designed by the person with lived experience, caregivers as appropriate, and clinicians, sets the foundation for person-centred care. A formulation accommodates the heterogeneous presentations and unique personal stories, and will vary in complexity depending on the individual and family needs, the resources available, and the platform of care. Adopting a staged approach to prevention and care is a pragmatic strategy for reaching clinical decisions about interventions that are evidence-based and proportional. The staged

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Key messages

1 Depression is a common but poorly recognised 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 families and on society. However, these impacts are neither well understood nor acknowledged, and there is an insufficient response at local and international levels. Many factors regarding the prevention and treatment of depression remain unknown—for example, what works for whom and why—and further scientific discovery is required as well as better implementation of current management strategies to transform the lives of the millions of people and their families and communities who face these challenges.

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 civilisation. Depressed mood, loss of interest, and fatigue are common features of the condition across populations. However, 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 globally

Social and economic actions are needed across society to mitigate the effects of adversities and inequities early in life and across the 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 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 risk and resilience factors. A frequent and complex association exists between depression and physical health. No two individuals share the same life story and constitution, which ultimately leads to a particular experience of depression and different requirements for help, support, and treatment in recovery.

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

Most people with depression globally do not receive effective care due to a range of demand and supply barriers. Empowering individuals, families, and communities to work with professionals who can learn from their experiences 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 personalise care

Detection and diagnosis of depression on the basis of symptoms, function, and duration should be accompanied by a clinical review or formulation for each person, which takes into account individual values and preferences, life stories, and circumstances. Formulation identifies characteristics aiding personalised treatment. The complexity and sophistication of the formulation can 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 but proportional to the severity of the condition. This approach 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 Increased investment with whole-of-society engagement is a priority to translate current knowledge into practice and policy and to upgrade the science agenda

Although much remains unknown about depression, for which we advocate a cutting-edge science agenda, current knowledge and strategies are not optimally used; the most important immediate imperative is to invest in translation of this rich body of knowledge for practice and policy.

*This term encompasses 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 Commission.

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 intermediate interventions. Collaborative care models offer an evidence-based way for health systems to implement the staged approach to prevention and care, realising a vision of personalised interventions for delivery at scale.

Sixth, most individuals with depression recover from an episode if they obtain adequate support and treatment, even though for a minority there are recurrences. We call on communities and professionals to support the empowerment of people with lived experience of depression. The active role of people with this experience, alongside families, practitioners, policy makers, and civil society, is essential in ensuring that the unacceptably high amount of unmet need is addressed, through sharing their experiences 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, considering 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, and harm to future generations, given the known impact of parental depression on the development of offspring. Preventive and health promoting actions at the population level and individual level have a crucial 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 death by suicide. Collectively, these interventions can substantially contribute towards promoting the health of individuals, families, and communities, and achieving the Sustainable Development Goals in each country around the world.

We encourage health-care practitioners to consider depression as a condition that affects people of all ages in several 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, policy makers, and researchers need to integrate depression prevention and care into their broader agendas. The inclusion of mental health as a central aspect of universal health coverage, and recognition of the need for policies and interventions across sectors, beyond the health sector alone, are vital. Researchers should be encouraged to adopt a life course perspective to understanding depression and devise novel methods to optimise 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 Commission 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. The Commission emphasises the need to move beyond health care to consider what is required across societies to reduce the burden of depression. Economic arguments are presented alongside evidence derived from clinical, scientific, and lived experiences to reflect on and recommend actions across policy, research, and practice.

Although 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 used optimally. Therefore, investing in translation of knowledge into practice is imperative. There is abundant evidence for the efficacy of preventive and therapeutic interventions for depression. However, most communities do not benefit, and most people affected by this condition globally do not receive these interventions because of a range of demand and supply barriers. An adequate 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 has this ambitious agenda been as urgent or necessary.

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Introduction

> "When you have other diseases, they are considered normal. Why is depression not considered a normal disease?"
>
> *Vidushi Karnatic, age 20 years (Haldwani, India)*

Over the past decades, much has been achieved in the field of global mental health.[1] The consequences of mental health problems are recognised globally and promising strategies have been devised to address them, even in low-resourced settings. 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.

However, 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 most people affected by mental health problems do not receive appropriate interventions.

No mental health condition captures the complexity of these challenges as emphatically as does 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. These terms reflect 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. However, use of these definitions and systems can sometimes 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.

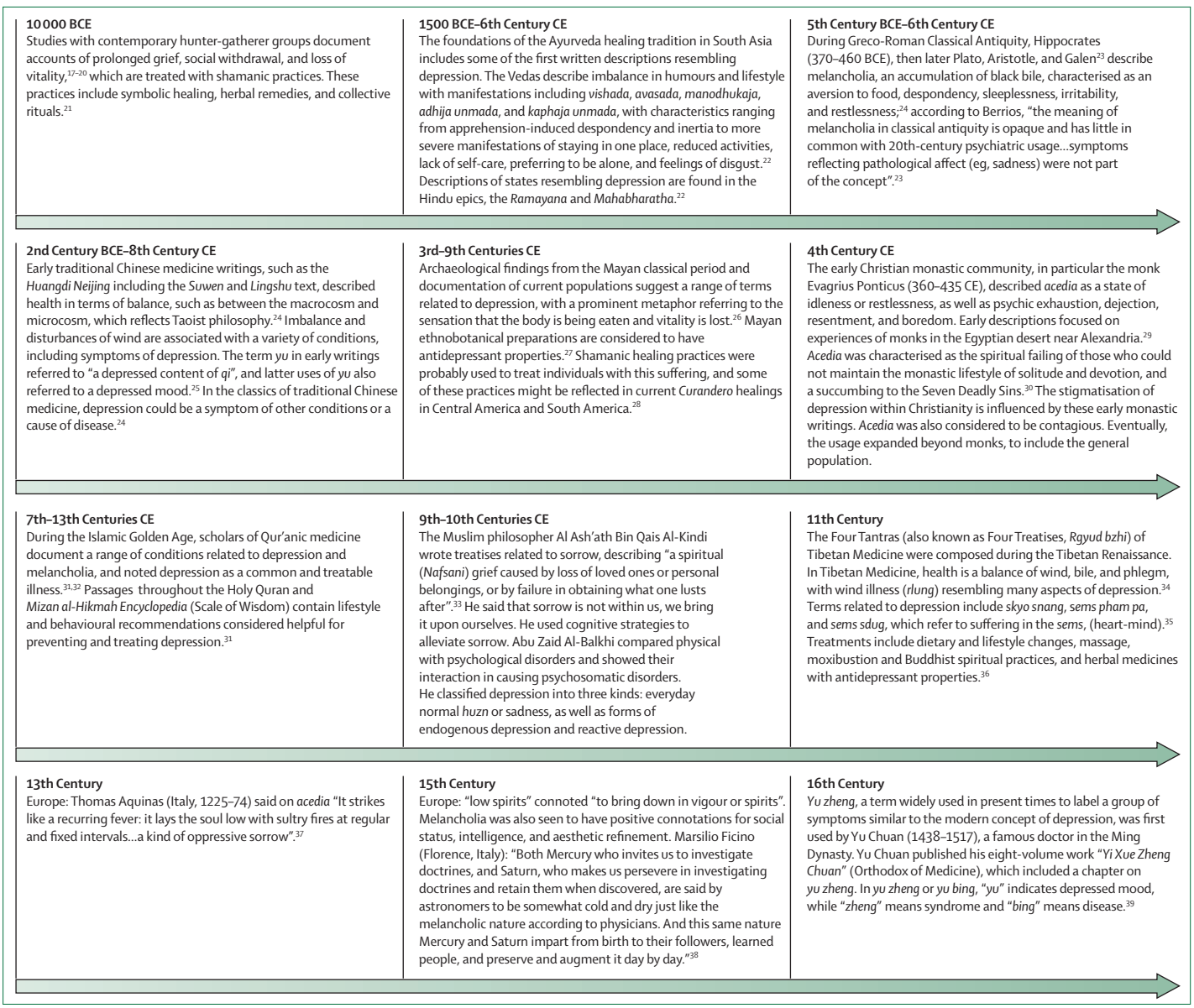
The concept of depression as used in medicine and health care refers to a condition that arises from multiple constellations of factors that operate in various ways with widely different outcomes. Different combinations of factors predispose to and precipitate the onset of an episode; lead to different 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 strategy works better for whom and in which circumstances. In this Commission we use two expressions to denote the lived experience of depression—people with depression and patients. The term patients refers to people with clinical encounters and constitutes a subgroup of people with depression.

Several core features of depression are identified across various geographies and cultures. However, the heterogeneity is evident from the multiple ways in which symptoms combine to produce a variety of clinical phenotypes.[6] In extreme circumstances, 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 to determine a single cause for depression has been unsuccessful. Approaches to understanding the multi-causal origins of the condition analogous to those used in other non-communicable diseases have been much more useful and appropriate.[9] Although the biological underpinnings of depression must be acknowledged, and depression can be conceptualised ultimately as an illness of the brain,[10] recognising the tangible and intangible environmental influences on brain development and function across the lifespan are essential. For example, research on childhood abuse and neglect 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 manifests. 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 challenges and multi-faceted 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 an 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 effects on public health and society, asserting that depression is everybody's business and a global health priority is important. Yet, despite the abundant evidence reviewed later in this Commission 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 importance as a biomedical condition, and how depression should be managed. There is a tension between depression constituting a 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 pathologised.[13] Critics 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] Other critiques question the extent to which



(Figure 1 continues on next page)

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, also indicating the grey areas and knowledge gaps requiring further research. Audiences include people with the lived experience of depression and their families, clinical and public health practitioners, researchers, and policy makers. 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, 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. Recognising 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 recognition improves the ability to communicate information about the disorder to a broader audience,[16] enhancing understanding and reducing stigma. The

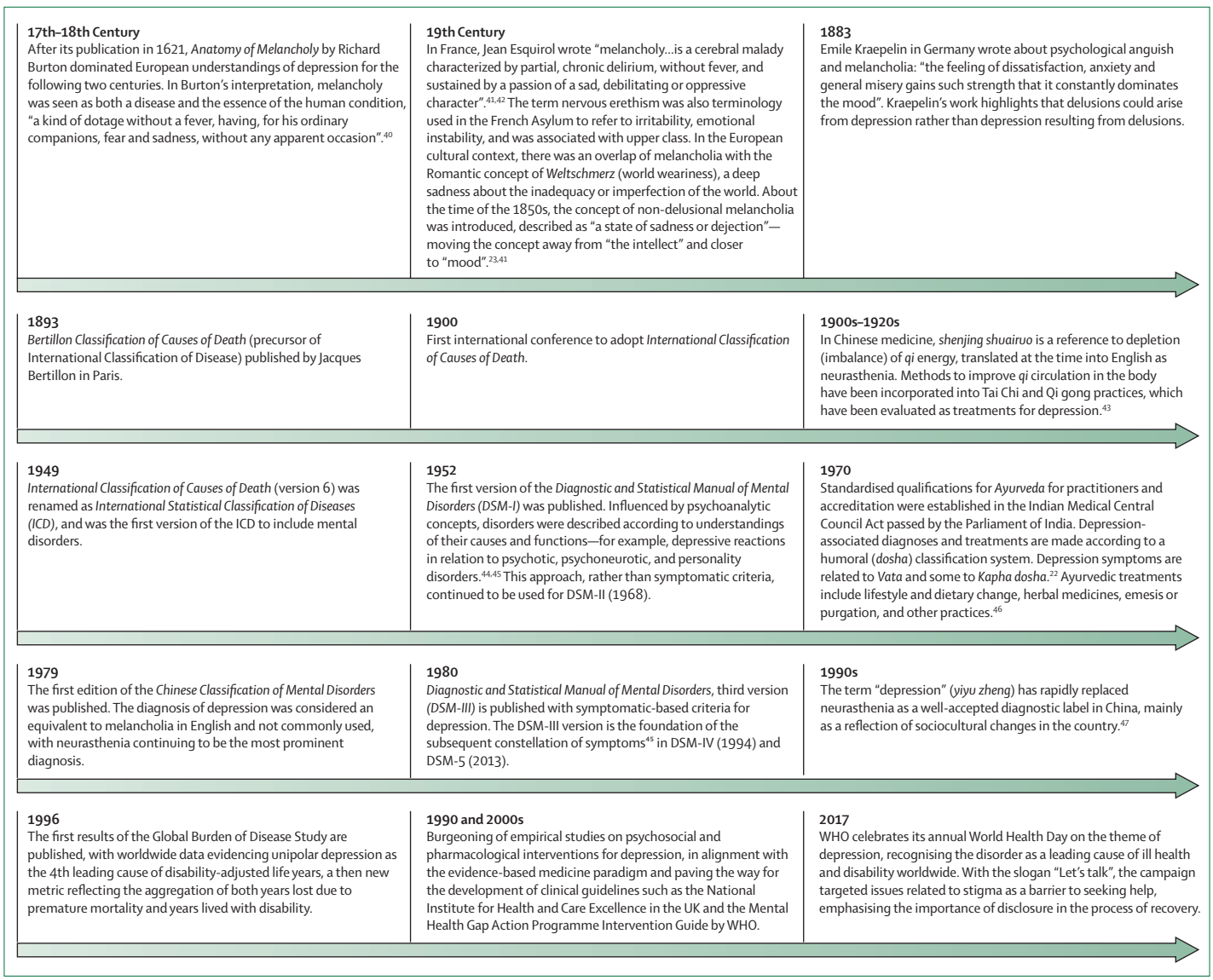


Figure 1: **Historical timeline of depression across the ages**

Commission emphasises the prospect of prevention and access to collaborative care strategies, even in resource-limited settings. Thus, the Commission marks a historic opportunity for united action by all stakeholders across sectors, to work together and reduce the global burden arising from depression.

Section 1: what is depression?

People have described different forms of suffering that resemble depression over thousands of years. Across cultures that developed written medical text—Chinese medicine, Ayurveda, Qur'anic medicine, and Greco-Roman Classical Antiquity—symptoms of depression are described and remedies outlined. These are underpinned by varied concepts of causation and vulnerability (figure 1).

Current diagnostic approaches

WHO's 11th revision of its International Classification of Diseases and Related Health Problems (ICD-11)[48] conceptualises depression as a syndrome (ie, a clinically recognisable 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 of a list of ten symptoms or signs have to be present most of the day, nearly every day, for at least 2 weeks (panel 1). The presence of either the first or the second symptom or sign is mandatory. The mood disturbance should result in substantial functional impairment (ie, functioning is only maintained through substantial additional effort).[48] The symptoms and signs should not be a manifestation of another medical condition (eg, a brain

Panel 1*: ICD-11 and DSM-5 diagnostic criteria for depressive episode

International Classification of Diseases and Related Health Problems, 11th revision (ICD-11)

- Depressed mood as reported by the individual (eg, feeling down, sad) or as observed (eg, tearful, defeated appearance). In children and adolescents, depressed mood can manifest as irritability.
- Markedly diminished interest or pleasure in activities, especially those normally found to be enjoyable to the individual (eg, a reduction in sexual desire).
- Reduced ability to concentrate and sustain attention to tasks or marked indecisiveness.
- Beliefs of low self-worth or excessive or inappropriate guilt that might be manifestly delusional.
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation (with or without a specific plan), or evidence of attempted suicide.
- Substantially disrupted sleep (delayed sleep onset, increased frequency of waking up during the night, or early morning awakening) or excessive sleep.
- Substantial change in appetite (diminished or increased) or substantial weight change (gain or loss).
- Psychomotor agitation or retardation (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.
- Hopelessness about the future.

American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)

- Depressed mood most of the day, nearly every day, as indicated by either subjective report (eg, feeling sad, empty, or hopeless) or observation made by others (eg, appears tearful). In children and adolescents, this mood can manifest as irritability.
- 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).
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
- Feelings of worthlessness or excessive or inappropriate guilt (which might 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 without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- Insomnia or hypersomnia nearly every day.
- Substantial weight loss when not dieting or weight gain (eg, a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. In children, this can manifest as an inability to make expected weight gain.
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Fatigue or loss of energy nearly every day.

*The presence of at least one of the first two bullet points for each list of criteria 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.

tumour), should not be due to the effect of a substance or medication, and should not be better explained by bereavement.

The list of symptoms and signs in panel 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 of more than 75 in differentiating people with a diagnosis of depression versus those without 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 those with depression from those without depression.[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 (ie, the individual's mood does not improve even temporarily in response to positive stimuli), anger, irritability, psychic anxiety, and somatic concomitants of anxiety (eg, headaches and muscle tension)—also discriminated between people with depression and people without depression, but performed less well than did 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 (ie, conditions characterised 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, which appears to be qualitatively different from other forms of depression, with more common vegetative symptoms, higher frequency of suicide attempts, and higher risk for depression in siblings. 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 substantial 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 melancholia being the most severe manifestation of depression.

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

The need to establish a threshold for subsyndromal depression 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 (ie, either depressed mood or loss of interest or pleasure), most of the time for at least 2 weeks.[62] Notably, 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,[63] although the time frame suggested is within the past month. An alternative has been to experience any two depressive symptoms most of the time for at least 2 weeks, associated with evidence of social dysfunction.[64]

The different levels of severity of depression also remain to be validly characterised. 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 and 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 instead assess 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.[65] Even in clinical trials, there is 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 4-point Likert scale. Scores can be interpreted as a continuous measure of severity or categorised into degrees of severity of depression; scores less than 5 signify absence of depression or sub-threshold depression. A meta-analysis[69] reported that sensitivity and specificity was maximized at a cutoff score of 10 or more in studies using a semi-structured diagnostic interview (29 studies, 6725 participants; sensitivity 0·88; specificity 0·85). Furthermore, using only 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 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 cutoffs.[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 aforementioned approaches, the severity of depression is evaluated by adding up the scores for the individual depressive symptoms and signs. However, 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 might 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 might also need to be considered. Relevant to this issue is the concept of complicated versus uncomplicated depression, in which complicated depression is characterised by at least one of the following symptoms or signs: psychomotor retardation, psychotic symptoms, suicidal ideation, and sense of worthlessness or guilt. The complicated or uncomplicated status was found to

predict the severity of depression significantly better than did 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 example, the choice of pharmacotherapy versus cognitive behavioural psychotherapy.[74]

Psychopathological oversimplification?

A concern voiced by both mental health and social science researchers[75,76] is that the previous translation of the concept of depression into operational terms might have involved a psychopathological oversimplification. This line of thought argues that the subjective experience of people with depression 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 people with depression 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] ("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, and exhausted), do suggest that the nature of the subjective experience of depression might not be fully conveyed by current diagnostic systems, and might involve a more substantial somatic component than currently maintained.

The aforementioned descriptions potentially might not be relevant to all or most people with depression, but only to a subgroup (ie, those with melancholia). However, a systematic review of qualitative studies done on depression worldwide[78] found that several somatic symptoms—namely headaches, general aches and pains, problems connected with the heart (eg, palpitations, heavy heart, and 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 (ie, palpitations, tremors, blurred vision, and sweating) to be one of the most central symptoms in the depression network, showing strong connections with other somatic complaints (limb heaviness, pain, and 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 suggested that depressive, anxiety, and somatic symptoms might be different presentations of a common latent phenomenon[80] and might 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 might instead be part of an externalising spectrum, also including anger attacks, aggression, substance abuse, and risk-taking behaviour.[83]

This characterisation 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 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 that are 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 can be subtle or might be concealed by the patient, and the boundary between delusions and persistent depressive ruminations or sustained preoccupations might 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 and ICD approach of 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 others are not.[58,86]

Since depression occurring within bipolar disorder does not seem to have distinct presenting features, the history of past manic or hypomanic episodes should be investigated 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] For example, a diagnosis of bipolar disorder can imply 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 (ie, a depressive syndrome accompanied by symptoms or signs of thought, motor or behavioural overactivation interpreted as contrapolar). DSM-5 defines "major depressive disorder with mixed features" as a depressive episode with at least three typical manic symptoms or signs such as expansive mood, inflated

self-esteem, or increased involvement in risky activities, present on most days. By contrast, in the ICD-11 characterisation, 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. In ICD-11, recurrent depressive disorder is defined by a history of at least two depressive episodes separated by several months without substantial mood disturbance. Both diagnostic systems acknowledge that the remission after a depressive episode might be considered either partial or full. ICD-11 provides a qualifier indicating that the current depressive episode is persistent (ie, diagnostic requirements have been met continuously for at least the past 2 years), whereas in DSM-5, persistent depressive disorder is a separate diagnostic entity. Dysthymic disorder is yet another variant characterised by persistent depressed mood and accompanied by typical symptoms of depression that never meet the diagnostic requirements for a depressive episode.

Age and gender

Depression among preschool children was not recognised until the early 2000s. 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] However, depressive symptoms might be part of the fluid and non-specific clinical picture that 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 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 could manifest in adolescence as a decline in academic performance or an inability to complete school assignments. Adolescents with depression are often primarily irritable and unstable, with frequent anger outbursts, sometimes without provocation, which can result in a deterioration of their interpersonal relationships.[94,95] Moreover, they might 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 can be the focus of relatives' or teachers' complaints. Suicidality and self-injurious behaviours are particularly sensitive concerns in young people. A further complication concerning young people is that 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 older people is often under-recognised or minimised. It is often ascribed to normal ageing, to losses, or to 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 older people is more commonly associated with cognitive impairment (particularly memory disturbances, impaired executive functions, or 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 age 12 years, and has been found to peak in adolescence, at age 16 years.[98] Whether the gender gap decreases or not during older age is currently debated.[99] The clinical picture is reported to be similar in women and men except that, as noted earlier, externalising features are now recognised as more common in men.[83] Additionally, appetite changes, fatigue, and poor sleep can 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 generalisability of depression to the global context is that most 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 (figures 1 and 2) suggest that while several core features of depression are clearly identified across geographies and cultures, substantial variations remain. For example, 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]

Cross-national studies using standardised diagnostic tools such as the Composite International Diagnostic Interview show that many of the ICD and DSM symptoms occur across cultures and populations.[103] However, contextually grounded research draws attention to other symptoms that are not routinely evaluated even though they might be salient for people presenting with depression and their health-care providers (eg, 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,

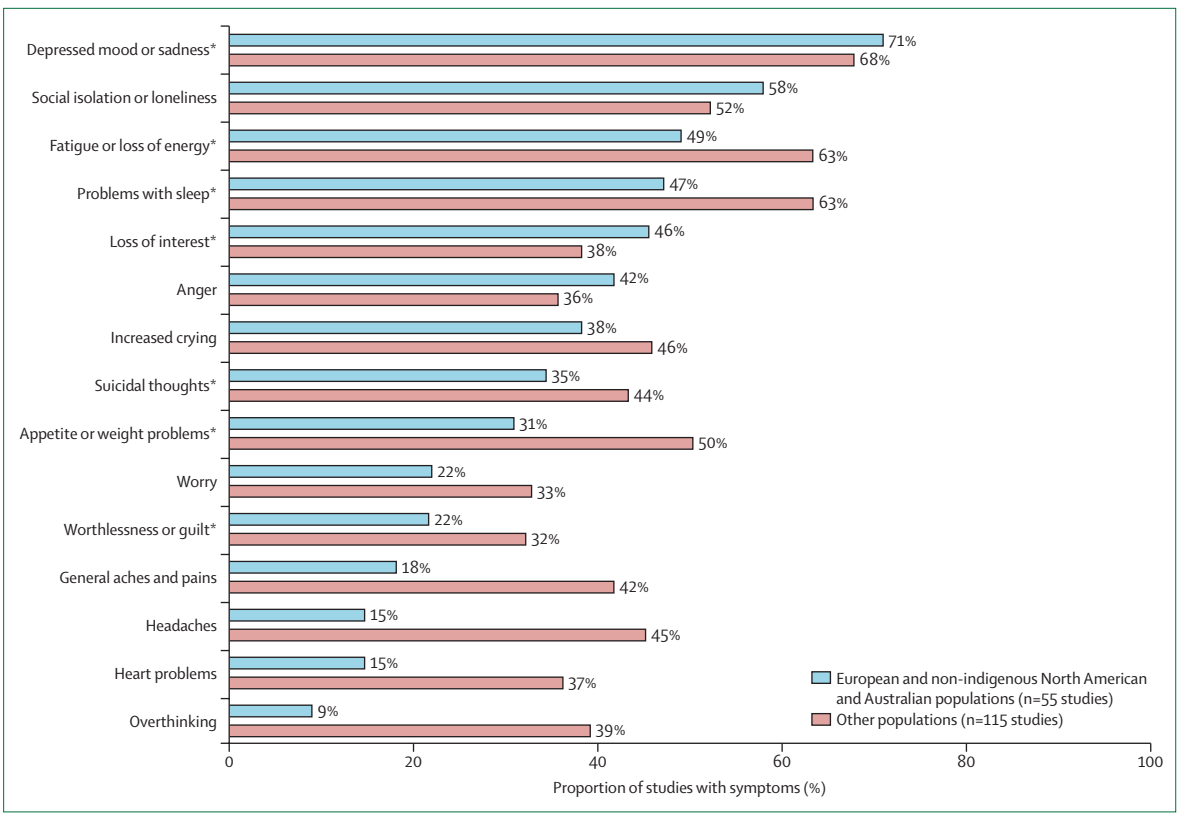


Figure 2: **Depressive symptoms in diverse global populations**
Data from Haroz and colleagues,[78] from 170 study populations and 76 nationalities or ethnicities. 55 populations were European or non-indigenous North American and Australian. Other populations included sub-Saharan Africa (38 study populations), South Asia (25 study populations), Latin America (21 study populations), East Asia (seven study populations), Southeast Asia (ten study populations), the Middle East and North Africa (11 study populations), and Australian, European, and North American Indigenous populations (three study populations). No studies were identified from Central Asia or Russia. Refugee and immigrant populations were categorised under the countries of origin. Other populations excluded Australian, European, and North American non-native populations. ICD=International Classification of Diseases and Related Health Problems. DSM=American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders. *ICD or DSM major depressive episode symptoms.

and Pacific Islander people and indigenous populations from North America, Europe, and Australia (figure 2),[78] might be associated with several factors. Even though somatic complaints are rarely documented in studies, they might be discussed more readily than are cognitive and emotional challenges.[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 suggested that depression was a relatively weak risk factor for suicidal ideation, plans, and attempts in low-income and middle-income countries, with a strong relationship between suicidality and depression found in high-income countries.[111]

Cultural idioms of distress have been evaluated for similarities with ICD or DSM classifications of depression. These idioms include *hwa-byung*, *shenjing shuairuo*, and *phiên não tâm thân* 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 or DSM depression categories observed that people endorsing these idioms had 7·55 greater odds than did others of meeting the ICD or 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] Use of 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 stigmatisation.[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 rarely been studied. To date, some studies have

suggested that symptoms such as appetite or weight changes do not distinguish between people with depression and people without depression outside of affluent high-resource settings, as shown by studies in Nigeria, Nepal, and Turkey.[122–124] Subjective experiences of loneliness are distinctive aspects of the phenomenology of depression among youth across cultural groups in high-income, low-income, and middle-income countries.[124–126]

Depression and grief

The effect of grief is different from a depressed mood. It consists of feelings of emptiness and loss, but 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 might 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 typical 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, in which the threshold for the diagnosis of depression is the same in bereaved and non-bereaved people.

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 characterised by longing for the deceased or persistent preoccupation with the deceased, accompanied by intense emotional pain. Symptoms might include sadness, guilt, anger, denial, blame, difficulty accepting the death, feeling that the person has lost a part of themselves, 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 6 months following the loss. There is evidence that prolonged grief disorder, characterised 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 can manifest in culturally specific ways, with diversity in the expected norms for duration of grieving.[130–132] Notably, 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]

Section 2: epidemiology and burden of depression

"Depression doesn't hand you an itinerary."

Ishita Mehra, age 22 years (Delhi, India)

About 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] About half as many people have depression at any 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 any point in time are 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 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 (5·0%). 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 Study 2019.[140] The estimated point prevalence among both women and men was highest in North America (4·4% for women and 2·5% for men) and lowest in the Western Pacific (2·3% for women and 1·3% for men); 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 probably attributed mostly to the varying distribution of risk or protective factors. Methodological aspects, such as differential response to questions assessing depressive symptoms, might 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% (IQR 6–14) across countries. A prospective epidemiological study reported a much higher lifetime prevalence of major depression in the range of 30–40%.[141]

Course and outcome

Epidemiological estimates of lifetime prevalence are higher than those of 12-month prevalence, suggesting that 33–50% of 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 1 year. The prevalence of persistent depression (ie, 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 can be as high as 61% among those receiving treatment for depression in primary and secondary care settings (table 1).[145] The

	Setting	Sample	Indicator	Follow-up	Estimate
Persistence					
Markkula et al, 2016 (Finnish Health 2011 study)[142]	Community-based	298 individuals with depression	Persistence: CIDI depression diagnosis at follow-up	11 years	21%
Rhebergen et al, 2011 (NEMESIS 1)[143]	Community-based	201 individuals with depression	Persistence: CIDI depression diagnosis at follow-up	7 years	29%
Ten Have et al, 2018 (NEMESIS 2)[144]	Community-based	242 individuals with depression	Proportion of participants with 2 years of continuous symptoms based on CIDI and life chart	6 years	12%
Verduijn et al, 2017 (NESDA)[145]	Mixed primary and secondary care	903 individuals with depression	Proportion of participants with 2 years of continuous symptoms based on CIDI and lifechart	6 years	34%
Penninx et al, 2011 (NESDA)[146]	Mixed primary and secondary care	903 individuals with depression	Persistence: CIDI diagnosis at follow-up	2 years	42%
Comijs et al, 2015 (NESDO)[147]	Mixed primary and secondary care	285 individuals with depression (age 60 years and older)	Persistence: CIDI diagnosis at follow-up	2 years	48%
Judd et al, 1998 (NIMH-CDS)[148]	Tertiary care	431 individuals with depression	Proportion of weeks with symptoms in 195 829 total follow-up weeks based on LIFE Psychiatric Rating Scale	12 years	59% of total weeks with depression symptoms; 15% of total weeks with (severe) depression symptoms
Recurrence					
Mattisson et al, 2007 (Lundby study)[149]	Community-based	344 individuals with remitted first-incident depression	SCID (DSM-IV) diagnosis at follow-up	40 years	40%
Eaton et al, 2008 (Baltimore Epidemiologic Catchment Area)[150]	Community-based	92 individuals with remitted first-incident depression	DIS (DSM-III) diagnosis at follow-up	23 years	45%
Hardeveld et al, 2013 (NEMESIS 1)[151]	Community-based	687 individuals with remitted depression	CIDI (DSM-III) diagnosis at follow-up	20 years	42%
Ten Have et al, 2018 (NEMESIS 2)[144]	Community-based	746 individuals with remitted depression	CIDI (DSM-IV) diagnosis at follow-up	20 years	27%
Gopinath et al, 2007 (depression relapse randomised controlled trial)[152]	Primary care	386 individuals with remitted depression	SCID (DSM-IV) diagnosis at follow-up	1 year	31%
Riihimaki et al, 2014 (Vantaa depression study)[153]	Primary care	92 participants with depression who remitted from index disorder during follow-up	SCID (DSM-IV) diagnosis at follow-up	5 years	51%
Conradi et al, 2017 (long-term INSTEL randomised controlled trial)[154]	Primary care	166 individuals with depression who remitted from index disorder during follow-up	CIDI (DSM-IV) diagnosis at follow-up	10 years	77%
Hardeveld et al, 2013 (NEMESIS)[155]	Mixed primary and secondary care	375 individuals with depression who remitted from index disorder during follow-up	CIDI (DSM-IV) diagnosis at follow-up	2 years	27% (primary care); 34% (secondary care)
Holma et al, 2008 (Vantaa depression study)[156]	Secondary care	142 individuals with depression who remitted from index disorder during follow-up	SCAN and SCID (DSM-IV) diagnosis at follow-up	5 years	71%
Ramana et al, 1995 (in-patient study)[157]	Tertiary care	57 individuals with depression who remitted from index disorder during follow-up	CID (DSM-III) diagnosis at follow-up	15 months	40%
Mueller et al, 1999 (NIMH-CDS)[158]	Tertiary care	380 individuals with depression who remitted from index disorder during follow-up	SADS (DSM-III) diagnosis at follow-up	15 years	85%
Paterniti et al, 2017 (tertiary care study)[159]	Tertiary care	65 individuals with depression who remitted from index disorder during follow-up	SCID (DSM-IV) diagnosis at follow-up	3 years	59%

CIDI=Composite International Diagnostic Interview. 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. LIFE=Longitudinal Interval Follow-up Evaluation. SCID=Structured Clinical Interview for DSM-IV. DSM=American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders. DIS=Diagnostic Interview Schedule. INSTEL=INterventie STudie Eerste Lijn. SCAN=Schedules for Clinical Assessment in Neuropsychiatry. CID=Clinical Interview for Depression. SADS=Schedule for Affective Disorders and Schizophrenia.

Table 1: **Persistence and recurrence of depressive disorders in community and clinical samples**

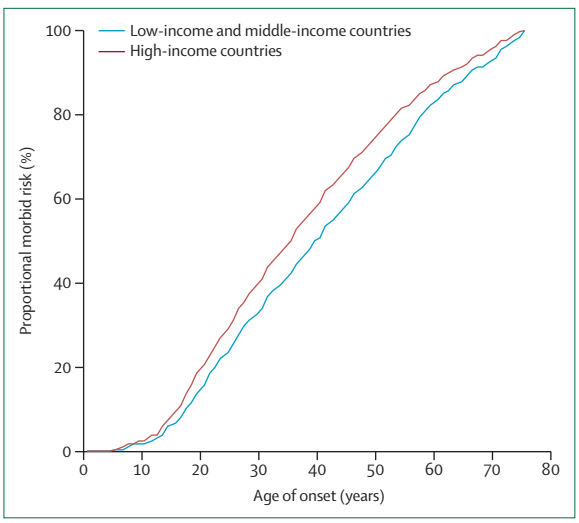


Figure 3: **Age of depression onset among the projected proportion of the population developing the disorder before age 75 years**
Data from 29 countries and provided by the WHO World Mental Health Survey Consortium. Morbid risk refers to the projected lifetime occurrence of major depression as of age 75 years estimated using actuarial methods with life tables. The term onset refers to lifetime first onset of a major depressive episode and does not consider the occurrence of subthreshold symptoms.

For more on **The World Mental Health Survey Initiative** see www.hcp.med.harvard.edu/wmh

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,[160] commonly with partial remission between episodes.[161] 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 1).

Age of onset

Retrospective reports have been used to reconstruct the distribution of age of onset—an alternative to the estimation of incidence.[162] In the World Mental Health surveys, median within-country depression age of onset was 26 years (IQR 17–37) in high-income countries and 24 years (17–35) in low-income and middle-income countries (figure 3). There was also a meaningful secondary peak for onset late in life.[163] These age of onset 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 age of onset 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 age of onset than many other common mental disorders. Lifetime prevalence (ie, 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 (ie, 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] On the basis of data from the World Mental Health surveys, the average morbid risk of depression at age 75 years is projected to be 19·6% (ie, 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 World Mental Health respondents with a lifetime history of depression at the time of survey. Furthermore, the median age of onset of depression among survey respondents is significantly lower than the projected median age of onset according to lifetime morbid risk calculations. The first reason for this difference is that early-onset cases are over-represented among those with a lifetime history at the time of survey. For example, fewer than half the survey respondents aged 18 years who will at some time in their life experience depression will have had that experience as of age 18 years. The second reason is survey bias of two types: loss of survey participants through early mortality of people with a history of depression, and under-representation in surveys of people older than age 85 years.

Sub-threshold depressive symptoms

Interest in expanding the definition of the depressive spectrum to characterise clinically significant manifestations that do not meet criteria for depression among people who might profit from early intervention is long standing.[167] Point prevalence of dysthymic disorder averages 1·5%,[168] but prevalence of sub-threshold syndromes of depressive symptoms with shorter duration (typically 2 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 might be the sequelae of partial remission of an episode of major depression.[173]

Comorbidities with other mental disorders

Comorbid anxiety or substance use disorders, or both, are found among most people diagnosed with depression, both in community epidemiological surveys[174] and in studies of primary care[175] or specialised 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 internalising and externalising disorders. The internalising disorders can also be divided into secondary dimensions of fear (eg, panic, phobia) and distress disorders (eg, major depressive episodes, generalised anxiety disorder, and post-traumatic stress disorder). 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 conceptualised as risk factors for the latent dimensions underlying these disorders.[178] For example, observed gender differences in depression prevalence became non-significant when controls were included for latent internalising and externalising dimensions.[179]

A cross-national analysis of this type, albeit based on retrospective age of onset reports obtained in cross-sectional community epidemiological surveys, followed on from World Mental Health 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 internalising and externalising variables. Depression was no more important than were several other internalising disorders (generalised anxiety disorder, obsessive-compulsive disorder, or 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 World Mental Health 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. The strength of these associations becomes weaker as the number of years since onset of the temporally primary disorder increases. Early-onset mood disorders were associated with especially high absolute risks of subsequent neurotic disorders (anxiety disorders and depression) over the next 5 years among both men (30·6%) and women (38·4%).

Comorbidities with physical disorders

Depression is 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 problem of spurious association, often unrecognised, when the same set of symptoms is double counted to arrive at both a psychiatric and a physical diagnosis. For example, in chronic obstructive pulmonary disease, somatic symptoms such as fatigue, decreased appetite, and weight loss might be simultaneously attributed to the physical and the psychiatric condition. Equally important to spurious association in a clinical setting is the misattribution of depressive symptoms to physical illness, resulting in failure to recognise depression and under-estimating the influence of depression on the course of physical illness.[182]

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] Additionally, a variety of unhealthy behaviours known to be linked to depression, such as an increased amount of smoking and drinking,[185] poor eating habits,[186] and unhealthy food intake, are simultaneous risk factors for physical disorders. On the basis of 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 appears to be the case for some disorders, comorbid depression is often associated with a worse course of the physical disorder,[187–190] with several mechanisms potentially involved. One of the most consistently documented mechanisms is the association of depression with non-adherence to treatment regimens.[191,192] Differential population-based clustering of depression with comorbid physical conditions on the basis of patterns of underlying negative social determinants of health is also now being modelled in the syndemics literature, built on the idea that comorbid conditions potentiate one another in certain social, economic, or cultural contexts.[193]

Depression is a major source of morbidity and mortality in older people, 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 could be a risk factor or a precursor; or dementia might be a risk factor or trigger for late-life depression; and the two conditions can be difficult to disentangle diagnostically. In the Framingham Heart Study cohort[194] a 50% increased risk of dementia was observed 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 (eg, hippocampal damage due to glucocorticoid cascade);[195] the cholinergic effect of tricyclic antidepressants;[196] and lifestyle factors such as poor diet, smoking, and reduced physical activity or social engagement, which are known to be associated with depression.[197] The co-occurrence of depression and diabetes appears to magnify the risk of developing dementia beyond that of either condition alone.[198] Depression often occurs at the early stages of dementia. Additionally, the depressive syndrome might be an early manifestation of an underlying neurodegenerative disease.[199] Alternatively, depressive symptoms might be a psychological response: a reaction to a person's growing awareness of the catastrophic consequences of their impending, irreversible, impairment.

Global estimates of excess mortality indicate more than 2·2 million excess deaths in people with depression, with particularly high rates of death among older individuals with cardiovascular disease.[200] A meta-analysis comprising 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 might 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 those aged 15–29 years and as the 15th most common cause of death at all ages worldwide.[201] A meta-review[202] reported an almost 20-fold risk of death by suicide for people with depression with a standardised mortality ratio of 19·7%. Depression is the most common psychiatric disorder reported in people who die by suicide, and psychological autopsy studies[203] estimate that depression is responsible for the largest proportion of the burden of disease attributed to suicide (as measured in disability-adjusted life years: 46%, 95% CI 28–61).[204] However, the relative contribution of depression to suicide is smaller in low-income and middle-income countries,[205,206] where a mood disorder was identified in 25% of people who died by suicide. Suicide attempts are 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 people with depression is significantly associated with previous suicide attempts, 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 people who have more than two depressive episodes.[212]

The impact of depression on functioning

The burden associated with depression increases sharply in the second and third decades of life (figure 4). This high score for the number of disability-adjusted life years 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 (eg, 0·582 for people living with HIV not receiving antiretroviral therapy and 0·569 for terminal cancer).[214]

Although there are several criticisms regarding the accuracy of disability weights,[215–217] 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 done as part of the World Mental Health Study.[220] Disorder-specific self-reported role impairment scores were compared across people who experienced each of ten chronic physical disorders and ten mental disorders in the year before interview. Depression and bipolar disorder were the mental disorders most often rated as 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 World Mental Health surveys, 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 or migraine, other chronic pain conditions, and cardiovascular disorders) and by far the highest proportion among the mental disorders.

The WHO World Health Surveys of 245 404 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, and diabetes). A related study in the World Mental Health surveys compared depression with

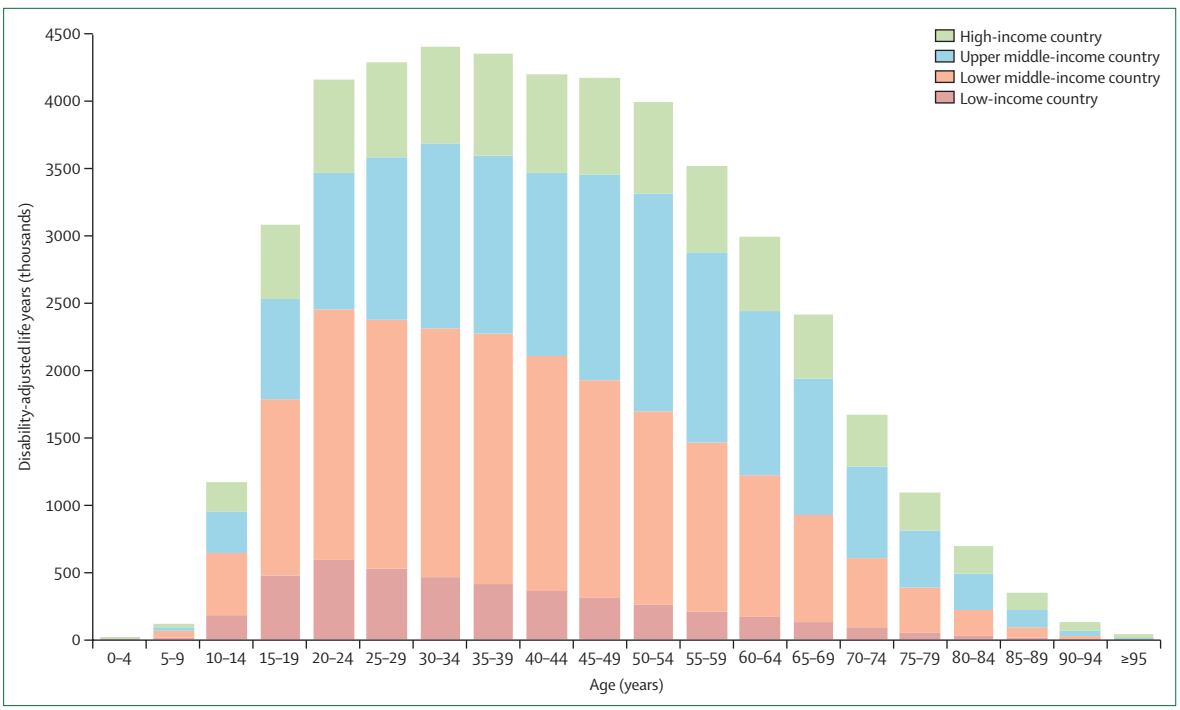


Figure 4: **The burden of depression across the life course according to country income level**
Adapted from Kieling and colleagues[233] using Global Burden of Disease 2019 data,[140] by permission of Elsevier.

18 other disorders, physical (eg, cancer, cardiovascular disorders, diabetes) and mental (eg, 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, along with 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 with evidence summarised in the following sectors, with an emphasis on describing the effect of depression on life course outcomes (as opposed to the effect of life events on depression).

The first sector is education and employment. Early-onset mental disorders are associated with premature termination of education.[223–225] Depression is significantly associated, at least in studies done in high-income countries and after adjusting for comorbid conditions, with about a 60% increased odds of not completing secondary school. Several prospective studies document the effect of depression on occupational difficulties. For example, an analysis of World Mental Health data showed that a history of depression as of the age of completing schooling (regardless of the exact age) predicted current (at the time of interview) unemployment and work disability.[226] The fact that these findings were significant only in high-income countries 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.

The second sector is 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 the onset of depression before the completion of 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 related to low work performance while on the job;[232] in the USA, the annual salary-equivalent human capital value of these losses has been estimated to range from USD$30·1 billion[233] to $51·5 billion.[234]

The third sector is intimate relationships. Although most of the literature on intimate relationships refers specifically to marriage, this evidence might generalise to other types of intimate relationships. Early-onset mental disorders predict a low probability of marriage. For people who marry, these disorders might be positively associated with early (before age 18 years) marriage,[235] which is known to be associated with several adverse life course outcomes. These associations are largely the same for men and women and across countries. Depression is one of the most important premarital mental disorders. A premarital 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 rather than depressive symptoms predicting marital discord.[243] Few studies have considered the effects of clinical depression on marital functioning,[244,245] but consistently document significant adverse effects.

The fourth sector is intimate partner violence. This type of violence is partly a consequence of pre-existing mental disorders.[246] The World Mental Health 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 intimate partner violence against women than did their unaffected full siblings, although absolute rates were low. The risk was further elevated when there was comorbidity with alcohol use disorders, drug use disorders, or personality disorders.

Another sector is parental functioning and offspring outcomes. Both maternal and paternal depression have an effect on the offspring, but the effect of maternal depression might be greater than the effect of paternal depression.[249] The negative effects can include low birth weight, poor school performance, relatively high rates of physical health complications, depression, anxiety, substance abuse, and suicidal behaviour, with substantial, persistent, and wide-ranging economic effects.[250] Effects on their offspring are sustained when parents experience persistent depression, live in poverty, or both.[251] These adverse effects can 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 hinder affect regulation in infants, hamper later child development, and increase risk of subsequent psychopathology.[254]

The final sector is caregiving. For family members, the experience of caring for a child or older adult with depression is usually demanding and frequently an isolating experience. Most informal mental health carers are female family members. They frequently have a double role caring for children and an older person living with depression. They might lose employment and contact with friends and outside activity, and even other members of the family. Family carers have a heightened risk of becoming depressed or anxious themselves.[255]

Section 3: 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 have an elevated risk of developing depression themselves even when they are not raised by their biological parents. However, 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 develop depression as adults. Third, most early episodes of depression have an onset shortly after a stressful life event, especially one involving loss, disappointment, or humiliation, particularly in people primed by early loss, neglect, or trauma. Nevertheless, all people encounter stressful life events and most do not develop depression in the aftermath. Although these three observations might suggest genetic, developmental, and environmental origins of depression, they also suggest that no single factor provides a complete explanation of why depression develops. The unique interplay of these factors, operating at different points of the life course, constitute the roots of depression in any individual.

Predisposing and protective factors

With systematic follow-up of large representative sample groups from childhood to adulthood, 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 might be particularly relevant for early-onset depression. Depression that manifests in childhood or early adolescence might 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 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 probably 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] Additionally, 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 susceptibility 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 or 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] Personality traits (which themselves have a variety of genetic and environmental roots) are also associated with increased susceptibility 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, resulting in interpretations that are pessimistic and self-critical, leading to so-called 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] The modal clinical presentation of people with personality disorders is a complaint of depression[271,272] and a large proportion 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] Previous 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] However, the overall strength of associations is variable, and few data are 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 that 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 to be consistently positively associated with the risk of depression, with most of the available evidence from high-income countries.[283] The relationship between poverty and depression is complex and likely to be characterised by both social causation (ie, social and economic adversities increase the risk of depression) and social selection (ie, 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 between a third and half of refugees and internally displaced populations meeting criteria for depression on self-report questionnaires.[284] Following the evidence regarding the effect of natural and built environments on physical health, emerging data suggest the relevance of biophysical factors such as air pollution, persistent organic and heavy metal pollutants,[285] and ambient noise in increasing the risk for developing depression.[286]

Conversely, some personal characteristics, interests, skills, and social support variables might constitute strengths that mitigate the effect of depression. Protective factors increase a person's resilience (ie, 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 or community support have been identified as contributing to resilience and enabling at-risk individuals to adapt or respond well to stressors. Resilience can be context-specific and time-specific, and might not be present

across all life domains;[288] individuals might be resilient to one environmental hazard but not to others, and might 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 coping process of the individual in a culturally meaningful way is also of utmost importance.[291] An adequate clinical assessment should not only investigate mental phenomena potentially relevant to overcome negative circumstances, but also explore past situations in which the individual and his or 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-victimisation (eg, bullying), loss of employment, and separation or divorce. There is substantial evidence corroborating the precipitating role of such proximal environmental influences in the development of depression. However, a large proportion of individuals are apparently less vulnerable to these experiences. Childhood sensitisation through trauma or neglect can play a role in influencing each person's level of vulnerability or resilience. Additionally, individuals with depression have an increased propensity to experience acute stressors compared with those without a history of depression. This perpetuating pattern of designated stress generation[293] is particularly relevant for interpersonal events. Other factors contributing to the recurrence and persistence of depression include substance use, behavioural patterns such as social withdrawal, and cognitive biases in attention, memory, and interpretation. A ruminative response style (characterised by an over-analysis of problems) tends to intensify negative, self-focused thoughts, and to hamper problem-solving, perpetuating symptoms of depression.[294] Identifying maintaining factors for any one person might help achieve sustained recovery.

Integrative models of pathogenic mechanisms

Discrete risk or protective factors associated with the onset and continuity of depression account for 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 (indirectly or distantly and less specifically related to onset) influence more downstream proximal factors (affecting the individual closer to the onset of the condition and often more directly). The understanding 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]

Although theories emphasising one aspect of causation have been applied with a modest degree of success (eg, 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 conceptualisations that fulfil these requirements are variants of the so-called 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 them sensitive to the stressor will develop depression. The vulnerability could have both biological (eg, genetic, endocrine, inflammation, or brain connectivity) and psychological (eg, temperament, personality, or beliefs) features.[295] Each person can carry a number of vulnerabilities that might add on to an overall diathesis or might result in sensitivity 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 might develop depression even with a mild stressor, and a person with a low degree of vulnerability might 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 diathesis-stress model can now be considered proven beyond reasonable doubt.[12,296]

More developmentally informed models, referred to as transactional models, also account for the fact that vulnerability can change over time due to biological events (eg, menarche or childbirth) and changes in the external environment.[297] For example, exposure to adverse environments earlier in life or even in utero might not be sufficient to cause depression, but could create a vulnerability that will render the individual more likely to develop depression following a further stressful experience. Furthermore, the same characteristic might make an individual sensitive to negative effects of adverse experiences and beneficial effects of positive experiences. This more inclusive conceptualisation 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, consideration of individually stable and changeable aspects of vulnerability separately is useful. 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 facilitate the study of 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 reconceptualisation of the diathesis-stress model to incorporate the inter-dependence of stressor and vulnerability.[301] Gene-environment interaction occurs when a genetic variant makes an individual more sensitive to the effect of an environmental exposure. Incorporation of gene-environment interactions improves the prediction of depression compared with 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] Genetic factors that render individuals more sensitive to both negative and positive environmental exposures can be measured, in the form of a polygenic score. This polygenic sensitivity score predicts greater negative and positive responses to adverse and beneficial exposures, supporting the differential-susceptibility 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, raising the question of how non-genetic vulnerability factors remain active over long time periods. Psychological and personality development theories might account for this observation. Equally, epigenetic modifications provide a suitable mechanism for such long-term memory. Exposure to adverse environments early in life could lead to modifications of the genome, such as DNA methylation, which will continue to affect the expression of genes for prolonged periods of time without altering the genetic sequence. Although 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 amount of systemic inflammation.[306] The long-term increase of inflammatory activity might 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.[307] Animal models have shown 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 neuroinflammation,[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, despite the importance of genetics and the environment, the final pathways of depression pathology occur in multiple but mutually interactive areas of the human brain (figure 5).

Over the past 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 early findings that have been replicated most consistently—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 (eg, frontal hypermetabolism). Increasing recognition of these individual differences, probably masked by the focus of earlier studies on group effects, assists the understanding of clinical heterogeneity in depression.[315,316]

Other limbic (amygdala, insula, and cingulate) and subcortical (basal ganglia, thalamus, periaqueductal grey, dorsal raphe, and lateral habenula) abnormalities have also been reported, especially with the introduction of resting and task-based functional MRI 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

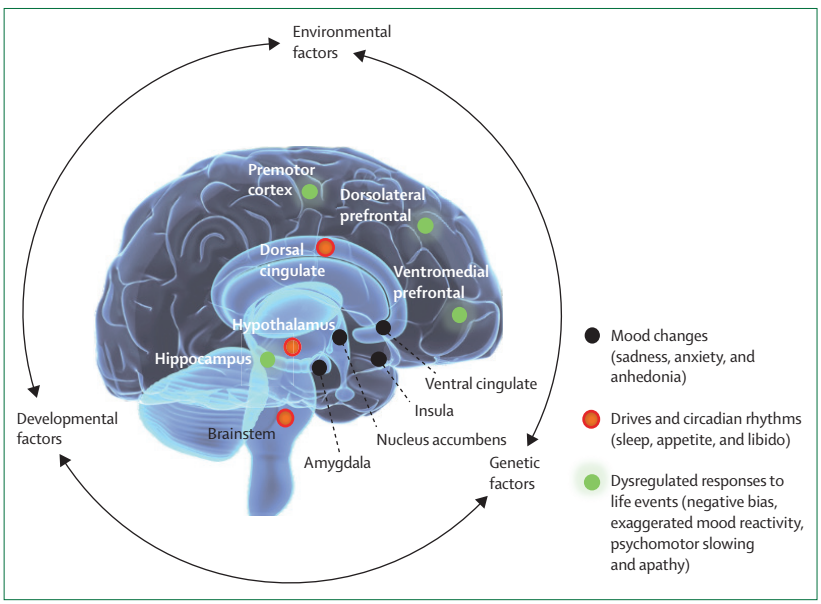


Figure 5: **Neural underpinnings of depression**
Depression results from an interaction between multiple risk and protective factors that is unique for each person. Regardless of the distal origins of the causal pathways, they converge during brain development and function and are expressed in multiple brain regions that interact to mediate various depressive features. These brain patterns are highly variable, probably reflecting aetiological differences; variations in the degree of illness severity and persistence; and the heterogeneous expression of mood, motor, cognitive, and vegetative symptoms among individuals.

of clinical symptoms among those tested might contribute to the observed variance,[317,318] although there is so far no consensus on the explanation 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 ineffective 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 integrated pathways and distributed neural networks. Technological and analytical 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.

Additionally, public availability of large multimodal imaging datasets is increasing.[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 regions and pathway structure and function.

Definitive precipitants or mediators of such so-called systems dysfunction are not yet characterised. However, several factors (including those described earlier in this Section) appear to be strong contributors. In addition to acute and chronic life stressors, these factors 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 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 (ie, atrophy and morphological changes in neurons and glia) and functional adaptations (ie, 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 probably affects 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 crucial 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 might 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 could underlie treatment resistance.[324] Nowadays, imaging studies are designed to explicitly develop biomarkers of treatment-specific subtypes that can guide optimal treatment selection for each person and signify treatment classes that should be avoided because they

are unlikely to be helpful.[333,334] Furthermore, treatments are now being tested to target chemical as well as imaging biotypes.[335–338]

Section 4: 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, age 25 years (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, age 19 years (Porto Alegre, Brazil)*

Negative attitudes towards people living with depression, and stigma and discrimination, are associated with negative outcomes across several world regions, including an insufficient amount of help-seeking, poor treatment adherence and 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 might be encountered as beliefs about the attitudes of others (perceived stigma), or as one's own thoughts and beliefs about their own depression (personal or self-stigma). Both can 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 people 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; however, evidence for widespread reduction in public stigma over recent decades is scarce. For example, in one US sample,[346] in 1996, 46% of the public were unwilling to work closely with someone with depression, compared with 47% in 2006; and 33% thought people with depression were violent towards others in 1996, compared with 32% in 2006. Members of the public who endorsed neurobiological models of depression were three times more likely than were others to report that people with depression were violent toward others.[346] In the UK, there were no changes from 1998 to 2008 in attitudes towards depression, including the opinions that 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 associated with stress, 40% of respondents continued to endorse weakness of character. Although long-term longitudinal studies are few from low-income and middle-income countries, cross-sectional studies in Brazil, China, and Ethiopia show a high amount of public stigma toward depression. Studies in São Paulo, Brazil, show a public perception of depression as associated with dangerousness.[348] In Wuhan, China, increasing age was correlated with greater perceived and personal stigma. Higher personal stigma was also reported by men, unemployed people, and those self-identifying as coming from families with high levels of cohesion, affection, and communication.[349] In Arba Minch, Ethiopia, stigma against depression was associated with a lack of formal education.[350]

Conversely, attitudes might be less negative in cultural contexts in which the symptoms of depression are attributed predominantly to problems of the heart or spiritual beliefs, rather than to a brain dysfunction.[101,351] Young people, compared with older people, tend to report less negative attitudes towards depression;[352] although 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]

Knowledge about strategies to attain and maintain good mental health and about depression and its treatments is referred to as depression literacy.[353] Depression literacy is potentially an important determinant of help-seeking across age groups as well as public policy decisions. For example, policy makers in Australia and Canada have targeted improvement of mental health literacy with the objective of facilitating greater public engagement in prevention and treatment.[353] A meta-analysis (with 15% of the studies from low-income and middle income countries) reported a growing acceptance of treatments for depression over previous decades.[354] However, attitudes toward treatment seeking vary across countries; while 64% of people with depression in high-income countries perceived the need for treatment as operationalised in the World Mental Health surveys, only 35% in other countries did so.[355] An insufficient knowledge of mental health literacy has been associated with a belief that one should use self-control to relieve depression rather than seek help.[356] Depression can be poorly recognised among older people because of a view that cognitive decline is part of ageing, and young people and their parents might recognise depression but not seek help.

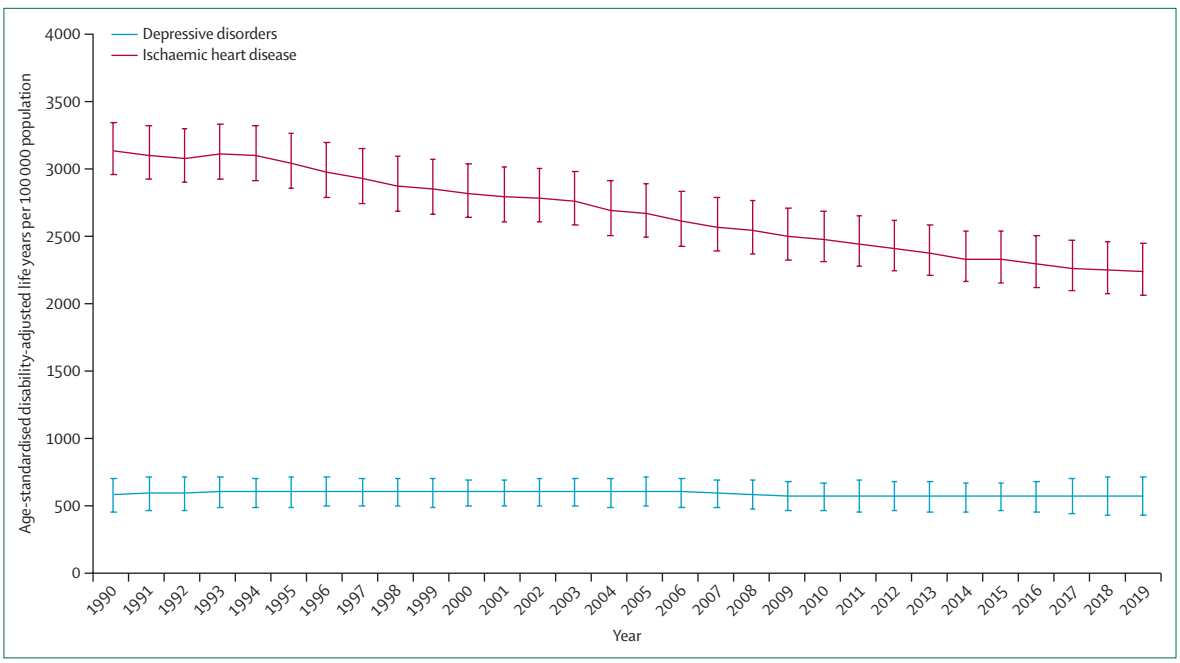


Figure 6: **Global burden of ischaemic heart disease and depressive disorders over time**
Data from Global Burden of Disease 2019.[140]

Taken together, these findings suggest that biomedical approaches to raising awareness about depression, focused on genetics and concepts of chemical imbalances, have been unsuccessful in reducing public stigma and improving treatment seeking. Alternative strategies in the following sections, such as social contact interventions, have shown greater benefit by facilitating empathy and engagement with people living with depression. Future research, interventions, and policies should prioritise partnering with the people with lived experience of depression to raise awareness about and increase acceptance of evidence-based interventions.

Section 5: 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 improve 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.

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 implement the range of options is increasing.

Advocacy and social contact

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 initiated in many countries over the past two decades. A 2009 review[357] found modest improvements in knowledge and awareness of depression in the short term, and improved attitudes towards people with mental illness. However, the promotion from 1990 to 1999 of the "Decade of the Brain" in the USA, a government-led initiative that had among its aims enhancing public awareness of the benefits from brain research, did not reduce stigma. Attributing depression to biological causes might have the unintended consequence of increasing stigma. A meta-analysis of causal attribution for mental illness, including depression, found that neurobiological explanations promote stigma expressed as more desire for social distance, more expectations of dangerousness, and lower expectations of treatment outcomes.[358] Stigma specific to depression appears 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 on the basis of cultural values.[360]

Although sustained population-wide improvements in attitudes toward depression have not been shown, 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. Information available on long term follow-up is scarce, and evidence on whether the campaigns result in increased use of care is mixed.[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 public and for specific groups such as police and health workers. This programme has been introduced in several countries and subpopulations, but so far has not consistently produced stigma-reduction sustained beyond 6 months after the training.[364] There have been a few evaluations of stigma-reduction programmes for primary care workers in low-income and middle-income countries. These have demonstrated only short-term improvements in attitudes.[365,366] Initiatives designed to change attitudes toward depression among health professional students in low-income and middle-income countries have had mixed results.[367]

Social contact appears to be the most effective type of intervention to improve knowledge about and attitudes towards mental illness in the short term, although the evidence for depression specifically and for longer-term benefits is weak.[362,368,369] Investigation of workplace stigma-reduction initiatives is rare, and few of these studies 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 2019 systematic review concluded that fewer than half of adolescents could recognise depression, with lower recognition rates in low-income and middle-income countries (such as China, India, Jordan, and Nigeria).[352] Adolescents across countries preferred informal sources of help for those who appeared to have depression.[352] The impulse to handle problems on their own represents a substantial barrier to treatment in this age group.[370] The chance of access to appropriate treatment is also influenced by the way complaints to a primary care practitioner are framed,[371] as well as the health professional's readiness to discuss the topic with adolescents[372]—two more reasons showing 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 US national survey correctly identified a vignette of childhood depression as something more than daily troubles, described it as a mental illness,[373] and recognised the necessity of intervention. However, another study suggests that parents' responses to adolescent depression are compromised by their own stigmatised attitudes towards and lack of knowledge about depression.[374]

Universal school-based programmes have been undertaken either with a focus on promoting mental health awareness,[375] or as depression and suicide prevention programmes with depression and suicide literacy as a core component.[376–380] The programmes have resulted in inconsistent changes in help-seeking behaviours and intentions.[376,381,382] One specific depression awareness and literacy training programme has demonstrated positive results: The Youth Aware of Mental Health intervention was developed by the World Psychiatric Association Global Child Mental Health Programme in collaboration with WHO and the International Association of Child and Adolescent Psychiatry and Allied Professionals. Youth Aware of Mental Health was associated with a reduction in suicide attempts up to 12 months following intervention when further developed for the Saving and Empowering Young Lives in Europe programme. The 5-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 who to contact for advice) 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 them) to take action to seek help for themselves or to support a peer finding help. Youth Aware of Mental Health was compared with gatekeeper training in a randomised trial and found to be more effective in preventing suicide ideation and attempts.[383]

Treatment preferences

Treatment preferences have remained relatively stable across age groups over recent decades. Multiple systematic reviews describe a consistent preference among both the public and people diagnosed with depression for counselling and other psychotherapy interventions over antidepressants.[384–386] Older 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 previous experience with psychological treatments and more severe symptoms of depression.[386,389] Explanations for the preference include the assumption that psychotherapy is better than is 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 medication

use signals greater severity of depressive symptoms.[388] In some contexts, medication is considered irrelevant as depression is not seen as a medical condition, and self-help is preferred.[391] Another study records a perception that many people are misdiagnosed with depression and given antidepressants unnecessarily.[392] This result echoes some academic critiques which state that current psychiatric practice is medicalising 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 stigmatised 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) might be effective in reducing depression and high rates of suicide among physicians and nurses.[395] Teaching physicians to recognise depression in themselves and their colleagues and to find solutions that work for them can also be expected to result in benefits to their patients.[396]

Health workers across the world, including those in low-income and middle-income countries, acknowledge stigma toward people with depression.[339,397] This stigma is associated with low rates of depression recognition[398,399] or poor quality of care. Physicians with stigmatising attitudes often do not offer appropriate physical health care to a person with documented depression, a practice known as diagnostic overshadowing.[397] Furthermore, stigma can contribute to bias, firstly, toward presentation of somatic complaints by patients and, secondly, toward health workers treating the somatic concerns without investigating associated mental health problems such as depression.[400] This bias overlaps with earlier constructs of masked depression.[401]

Prevention

The approach to prevention is two-fold: prevention science[402] considers the interaction of risk and protective factors for individuals across the life course; and population health science[278,279,403,404] 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. This two-fold approach is grounded in an ecological understanding of the interactions of individuals with their proximal contexts (eg, schools and family) and more distal contexts (eg, social attitudes and economic policies) in a dynamic manner over the life course.

We describe depression prevention through universal interventions (offered to an entire population rather than specific groups), selective interventions (targeted to individuals or groups at a 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 categorised 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 discussed when considering interventions for remission and recovery from episodes of depression and the principles of care.

Proximal interventions for the prevention of depression

Randomised controlled trials investigating the prevention of 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 standardised mean difference [SMD] 0·16, 95% CI 0·07–0·26[410,411]), with smaller effects as expected for the trials of interventions designed as universal prevention programmes. 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.[412] Overall, on the basis of these findings, the efficacy of specific psychological and educational interventions can be considered as relatively small, but meaningful.

A recent meta-analysis[413] of randomised controlled trials 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 1 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 with people in the control group.

Such interventions, even if requiring modest health system investments, provide savings that often accrue elsewhere in the health system or wider economy. However, implementation can bring economic challenges: savings from effective prevention might not accrue for many years, nor benefit the health-care sector, creating resource disincentives to take action.[414,415] We now examine the evidence on prevention across specific life course stages.

The first important life course stage is the perinatal period. A 2019 US Preventive Services Taskforce review[416] showed convincing evidence that pregnant or postpartum

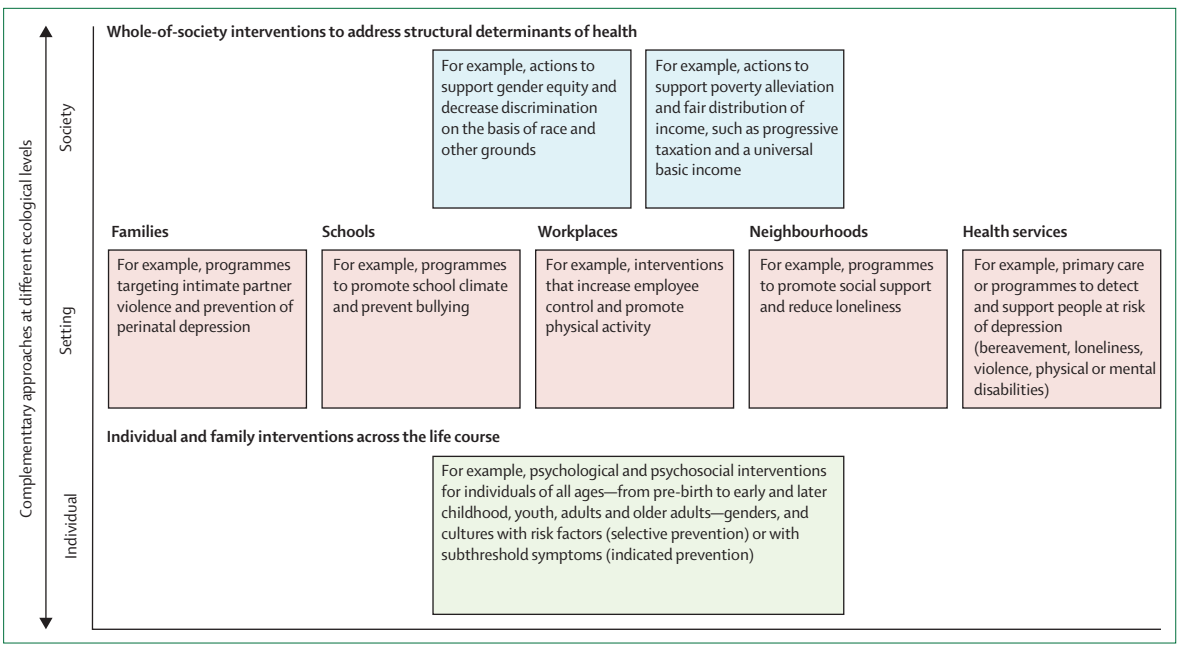


Figure 7: **Opportunities for the prevention of depression across the lifecycle**
Whole-of-society preventive interventions (conceptually these are universal interventions) address structural determinants of depression. Interventions shown in the second and third rows represent the more immediate or proximal ecological levels of settings and individuals. These interventions can: (1) be categorised as universal, selective, or indicated depending on the focus of the work (eg, all children in a school *vs* children with learning or emotional difficulties; noting that whole-school programmes can include a mix of these intervention types); and (2) focus on risk and protective factors at different points across the lifecycle, within the various social contexts.

women who are at increased risk for depression—based on sub-threshold symptoms, history of depression, or socio-economic and demographic factors including recent intimate partner violence or other negative life events—would benefit from counselling (CBT or interpersonal psychotherapy adapted for this purpose). The Taskforce also reviewed evidence on non-psychological interventions. It concluded, consistent with an earlier systematic review on exercise,[417] that while the evidence on exercise and social interventions to prevent antenatal depression in mothers is increasing, it remains insufficient to support implementation and points to a prominent area of unmet research need.

There is also increasing evidence on the depression prevention effects of parental interventions in the perinatal period. These are designed to promote healthy parenting and family bonding, and include[418,419] social programmes 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 programmes. For many of these strategies, there is strong evidence of cost-effectiveness.[420] Although 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 a low delivery cost and cost-saving through reduced health service use and productivity losses.[421,422] 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 enables obstetricians, nurses, primary health-care practitioners, social workers, and mental health practitioners to provide integrated care in a single setting.[404] An enduring and cost-saving preventive effect on postnatal depression was achieved in one study of a universal intervention[423] that trained health visitors (community health professionals) in identifying depression and psychological intervention methods.[424]

Several strategies devised to support the mental health of parents[404] are successful and relevant in preventing adverse mental health outcomes in their offspring. However, the focus on pregnancy might not be early enough to prevent intergenerational transmission of depression. Emerging evidence suggests that poor mental health in the preconception period can be associated with poor mother–infant bonding[425] and with infant reactivity, a marker of future mental health problems.[426] This evidence emphasises the importance of identifying perinatal depression, and supports investment 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.[427,428]

The second important life course stage is childhood and adolescence. Most depression prevention trials have been done in 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.[428] Nine of ten reviews of these trials report significant reductions in depressive symptoms,[429–437] generally with small effect sizes. Four reviews analysed the incidence of depressive disorders as an outcome, and all reported reductions in incidence.[431–433] Subgroup results from a meta-analysis[413] 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 1 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.[437] A large meta-analysis, which focused solely on school-based CBT, detected small effects for depression prevention in the short-term and medium-term, with a small long-term benefit.[432] Another meta-analysis of school-based depression prevention programmes highlighted 81 randomised controlled trials with positive but small effect sizes.[435] The SEHER trial[438] 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. A systematic review of 68 prevention programmes for college, graduate, and professional students in 15 countries[439] reported moderate reductions in symptoms, regardless of delivery format or prevention level.

Although economic evaluations suggest that depression prevention strategies in children and adolescents are cost-effective,[440] many actions are initiated outside of the health-care sector (eg, 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 payoffs over quite long periods.[441–443] Many lifestyle risk factors and risk pathways for depression and non-communicable diseases are shared from childhood and adolescence onwards. Knowledge of these shared risks and pathways 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, 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.

The third stage of the life course is adulthood. In adults, employment has been shown to reduce the risk of depression,[444] possibly by providing a greater sense of autonomy, improved socioeconomic status, and avenues for personal development.[445] Workplace interventions that increase employee control and promote physical activity appear to be associated with mental health benefits,[446] while those using CBT-based techniques typically show small benefits.[447] A systematic review and meta-analysis showed small to medium effects for indicated preventive interventions in the workplace, targeting people with sub-threshold depressive symptoms with either CBT-based (six studies) or other psychosocial interventions (two studies).[448] There is also moderately strong evidence that CBT is cost-saving in workplace settings.[449]

Many trials of prevention through psychological interventions in group or individual formats have been done in other settings, covering both selective and indicated prevention approaches. A meta-analysis of 32 randomised controlled trials (6214 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.[450] The authors concluded that prevention of depression seems feasible and psychological intervention might 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.[411]

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 can 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 programmes has been examined with no clear findings to date.[457]

Prevention of depression should consider 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. Improved identification and referral to advocacy services has been demonstrated in a cluster trial of training and support interventions for intimate

partner violence in primary care[461] and suggested by a pilot study in secondary mental health care.[459] The World Psychiatric Association has developed a training programme for competencies in gender-based violence assessment and treatment in health-care settings to facilitate the implementation of initiatives in this area.[462]

The final stage of the life course is late adulthood. In 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 shown by studies of depression and the use of antidepressant medication 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 investigated vitamin D insufficiency with supplementation,[464] and inflammation with low dose aspirin,[465] 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[443] 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 social isolation and loneliness that has concerned communities and governments in several parts of the world in previous 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 is important, as well as broader befriending and community inclusion initiatives in the longer term.[468,470]

Only one randomised controlled trial of indicated prevention, specifically focused on older adults, has been done in a low-income or middle-income country.[71,471] The Depression In later Life intervention (DIL; also signifying the Konkani word for heart) was delivered by lay counsellors to older people at primary care clinics in Goa, India. It was grounded in problem-solving therapy and included brief behavioural treatment for insomnia, education in better self-management for common medical disorders such as diabetes, and assistance in navigating medical and social services. Over the course of 1 year, the intervention led to a significant reduction in incident episodes of depression compared with enhanced care-as-usual (4·4% *vs* 14·4%). The DIL intervention appeared to build resilience in the form of active coping, behavioural activation, and persistence in dealing with health-related problems and their attendant threat to independence and diminishing the quality of life.

Tackling structural determinants of health across the life course

Although much of the empirical evidence on prevention has focused on the aforementioned proximal determinants, 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 marginalisation, and displacement. Giving attention to distal structural factors is consistent with a shift from cultural competency to structural competency, which emphasises 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.[1,404,472–474] 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 effect of different types of public health interventions, and tend to be the most effective, rapid, equitable, cost-effective, and sustainable forms of prevention.[476] The number of people in a country that live in conditions conducive to healthy development and to health and productivity across the life span, which is a fundamental human right,[279,404] crucially depends on public policy and planning.

Most countries have witnessed a dramatic increase in income inequality in the past three decades. Additionally, 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 showed a greater risk of depression in populations with higher income inequality than in populations with lower income inequality.[283] The authors proposed an ecological framework,[283,477] with mechanisms operating at the national level (the neo-material hypothesis), neighbourhood level (the social capital and the social comparison hypotheses), and the individual level (psychological stress and social defeat hypotheses) to explain this association. The authors concluded that policy makers should actively promote actions to support the fair distribution of income, such as progressive taxation policies and a universal basic income. For example, in Malawi's scaled-up Social Cash Transfer Program,[478] a programme 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

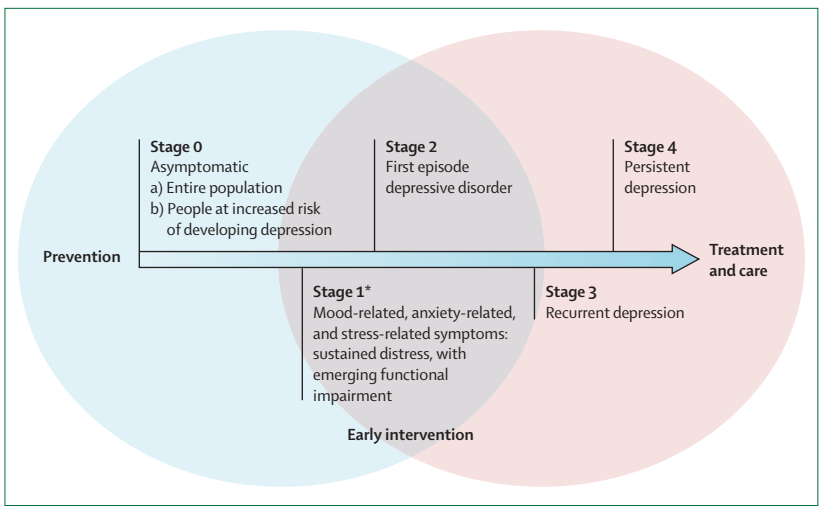


Figure 8: **A clinical staging framework for depression**
*This stage is also described as subsyndromal or subthreshold and includes transdiagnostic presentations that could benefit from interventions.

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 effect of diverse sectors (through increased school attendance). 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—women are nearly twice as likely as are men to report the experience of depression—might relate to inequalities beyond health policies.[479] Inequality could potentially result in depression through several different mechanisms—with one such pathway being lack of access to financial resources, making it difficult for women to leave relationships in which they experience 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] Several evidence-based strategies across the life course at the individual-level and community-level can be used to mitigate the risks of depression arising from the more proximal adversities and risk factors. However, learning more about the mechanisms of change and strengthening the evidence base through refined interventions and evaluation of broad public health programmes and policies is mandatory. Health professionals should ally themselves with other stakeholders in government, civil society, and communities 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

Staging models as used across health-care services[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] and aid in reviewing the individual's need for intervention, including early intervention (figure 8). These models acknowledge the transdiagnostic nature of psychopathology, and assume that illnesses begin with distressing symptoms and emerging functional impairment that is, at least initially, below a clinically significant threshold. Illness stages do not necessarily progress from one stage to the other, and might even progress in the opposite direction, especially from stage 4 to stage 3. Improvement can 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 needs of the individual and reducing the risks of progression to a more advanced stage.

The extent and rate of progression from one stage to the next—and whether this progression 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 type of care is best managed by a multidisciplinary collaborative care team, 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 (stage 3 and stage 4).[487]

Early intervention 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 time when 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 intervention in the first stages of illness can vary according to the level of distress and disability, the availability of resources, and the help-seeking behaviour of the affected individual. 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 (such as primary care or linked frontline community-based mental health programmes).

The first episodes of depression can provide a crucial opportunity for early intervention. The fact that deaths by suicide among those with a current depressive episode occur most often (75%) during the first episode emphasises the urgent need to identify and treat adequately the very first major depressive episode. Additionally, 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.[488] Consistent with this potential for early recovery, structural brain changes are minimal during the first episode of depression, but become more evident with recurrence.[489,490] This finding has led to suggestions that depression can be neurotoxic, and that recurrence is associated with an active process of neuroprogression;[491] 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 death by suicide) than is 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-limiting without treatment, is an urgent priority for research investment.

Episodes of depression early in life can affect crucial 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 unsuccessful navigation compounds over many decades, and even across generations. Enhanced primary care for youth mental health—to which young people can refer themselves, or be referred to 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, interventions are 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 transdiagnostic perspective[497] recognises that emerging mental ill-health is fluid, made up of a range of clinical presentations which ebb and flow before settling into more stable subsequent phenotypes later in the course of the illness. Early interventions (especially psychosocial interventions, but also judicious use of medications such as selective serotonin reuptake inhibitors [SSRIs]) might 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, age 44 years, (New York, NY, USA)*

> "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, age 47 years, (San Jose, Costa Rica)*

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

WHO's Mental Health Gap Action Programme 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 a choice between two types of treatment for any individual. One option for those with mild depression is one of a set of brief, structured psychological treatments based on CBT or interpersonal psychotherapy (including variants of these treatments such as behavioural activation, problem-solving therapies, mindfulness, acceptance, and commitment therapy). Treatment with antidepressant medication (in particular SSRIs) is another option for those with moderate or severe depression and those who do not respond to psychotherapy. A substantial proportion of people will remit with no treatment (spontaneous remission), and there are no aggregate differences in effects or in effect

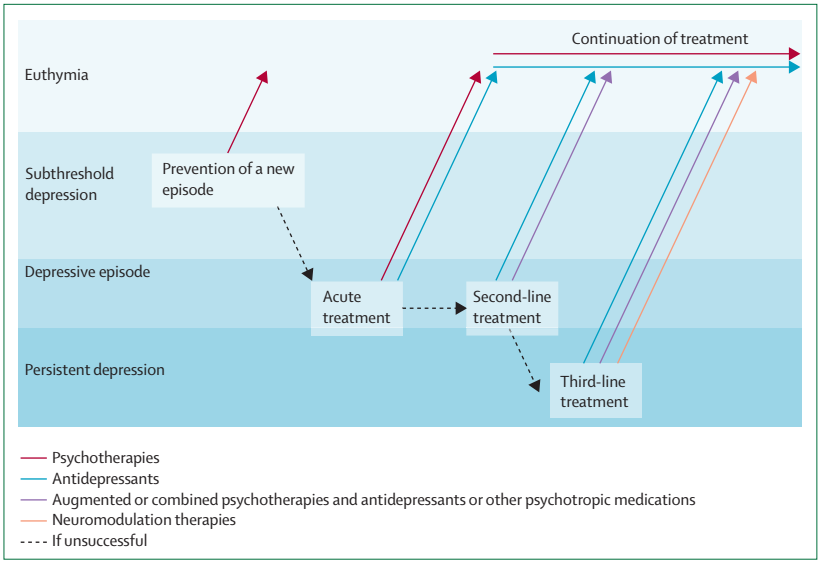


Figure 9: **Clinical interventions for depression**

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 so-called watchful waiting or to a specific first-line treatment so that we can confidently allocate individuals to any of these specific interventions (ie, the optimum intervention for an individual). Clinicians might recommend a period of watchful waiting for further assessment and monitoring, relationship building, and shared decision making for those with a mild condition. Other initiatives used in this period might include brief interventions such as psychoeducation and lifestyle interventions, particularly exercise, that could also promote remission. These interventions might also be employed 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 might improve[499] and prevent depression.[500]

Non-responders to antidepressant medication might show benefit from switching to or augmentation with other medication. Alternatively, combined treatment (psychotherapy plus medication) works better than does either treatment alone. Non-responders to these second-line treatments might benefit from neuromodulation 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, social functioning, and reduced suicidal behaviour, which are often prioritised by patients. Treatment for depression has the potential to be very beneficial for the patient due to the enormous variety of treatments, but a process of trial and error, to find the right treatment for the right person, is often necessary. This process of trial and error can particularly occur in those receiving treatment for the first time, who have no past experience of treatments that might have worked on a previous occasion. Figure 9 depicts the steps in the management of an episode of depression. The following subsections review the evidence in support of these treatment options.

Effectiveness of self-help and social interventions on depression outcomes

Guided self-help (including internet-based self-help), which encompasses interventions on the basis of effective psychological therapies but is designed to be entirely or mostly self-delivered, is as effective as are 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 the advantage that it does not require human support. However, individuals with depression, especially with severe depression, appear to show a greater improvement when there is at least a modicum of human interaction than none at all.[503] There is less consistent evidence in support of lifestyle interventions, with higher quality studies generally showing small effects, as shown for exercise[453] or quitting smoking, or null effects as shown for omega-3 fatty acids and vitamin D.[464] Although 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 people who are experiencing such adversities.[504]

Effectiveness of first-line treatments on depression outcomes

About 750 trials with more than 30 000 participants provide evidence for various psychotherapies for the acute treatment of major depression,[505] and more than 500 trials involving more than 110 000 participants provide support for the efficacy of antidepressants.[506] Efficacy is comparable in magnitude to therapies for common medical disorders.[507] When measured against the common comparator, pill placebo, CBT had an SMD of 0·20 (95% CI 0·01–0·38)[508] and antidepressants an SMD of 0·30 (0·26–0·34).[506] Given the average placebo response rate of 40%,[509] the SMD of 0·3 would translate into a number needed to treat of nine and the SMD of 0·2 would translate into a number needed to treat of 13.[510–512]

Clinicians and scientists in the field currently 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 among antidepressants have shown a more effective antidepressant group (range of ORs for response 1·19–1·96) and a less efficacious antidepressant group (range of ORs for response 0·51–0·84).[506] No discernible differences have been detected so far among

different psychotherapies,[505] and pharmacotherapies and psychotherapies have been found to be similarly efficacious.[515] There is no evidence that personal treatment preferences, particularly in people with no previous treatment exposure, moderate symptomatic outcomes.[516] A recent network meta-analysis has observed that psychotherapy might be the best initial treatment choice for depression with regards to the outcomes of sustained response or recovery.[517,518]

In children and adolescents, CBT and interpersonal psychotherapy can be seen as first-line treatments, with medication added if these therapies are not successful.[519] A 2020 systematic review[520] suggests that antidepressant 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 finding 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.[521]

Limitations of first-line treatments with antidepressant medication

The use of antidepressants is associated with several unwanted effects. Although a number of specific side-effects are commonly reported with use of SSRIs, (including nausea, dry mouth, headache, diarrhoea, tremor, dizziness, anxiety, nervousness, agitation, insomnia, and constipation),[522] and sexual side effects, none of these unwanted effects except for increased risk of osteoporosis[523] are long-lasting.[524] A 2019 umbrella review of systematic reviews examined 120 putative associations of antidepressant medication and adverse outcomes and showed 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.[525]

Of concern is the so-called discontinuation syndrome or withdrawal syndrome[526,527] upon abrupt or gradual discontinuation of SSRIs and serotonin noradrenaline reuptake inhibitors. 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 of these symptoms and longer duration.[528] One review reports incidence rates ranging from 27% to 86% (weighted average of 56%) according to individual reports in surveys[526] and another showed a 31% incidence rate according to randomised controlled trials that used a withdrawal symptom scale.[529] Although gradual and hyperbolic tapering might mitigate the symptoms,[530] there is a paucity of adequate research to guide their management.[531] In some countries, withdrawal might be associated with increased likelihood of patients being prescribed longer courses of drugs.[532,533]

Second-line and third-line treatments

A partial response or non-response to depression treatment is common in clinical practice. Almost half the people treated for major depression do not achieve symptomatic remission during initial acute or short-term treatment. The expression "treatment-resistant depression" is commonly used in the literature to describe situations in which a reduction in depressive symptoms is not achieved, frequently defined as occurring after at least two courses of antidepressants.[534] This concept has been criticised for several reasons, including its inconsistent definition and sometimes limited consideration of psychosocial approaches to intervention. The notion of difficult-to-treat depression has been proposed to encompass the acute phase of treatment as well as sustained response and remission, providing a more positive framing than that suggested by the expression "treatment-resistant depression" aiming to address overall functioning and quality of life as well as depressive symptoms to enhance engagement of the patient and consideration of a range of interventions.[535]

Before concluding that a given treatment approach is not effective, possible reasons for an absence in response should be considered, 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 the needs of the individual.[67] Additional resources might be required to elicit a response, or social interventions or other support for adequate and personalised clinical care in the presence of stressors or life events such as bereavement. People of different backgrounds might vary in their understanding and beliefs about depression, and what is deemed as acceptable, required, 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 type of medication or one type of psychotherapy for 8–16 weeks. Only a limited number of clinical trials are available to guide practice when people do not respond to the initial treatment. Systematic reviews of pharmacotherapy studies have identified seven trials for dose escalation,[536] four for switching of antidepressants,[537] 48 for various augmentation agents, and 25 for augmentation of pharmacotherapy with psychotherapies.[538] Reviews have found no evidence to support dose escalation, but some evidence for the other strategies. In the Sequence Treatment Alternatives and Relieve Depression study—designed to test treatments to achieve remission—after 8 weeks the remission rate reached 67% over 1 year among participants who remained in the study, by switching ineffective treatments. Even if remission was reached after several trials, it was associated with better prognosis than for treatment-as-usual.[539] Notably, some characteristics of depression that are linked to a poor outcome of first-line

antidepressant treatment might predict good responses to augmentation strategies. For example, profound loss of interest and reduced activity were associated with non-response to SSRI antidepressants, but with a good response to augmentation with aripiprazole.[540] Additionally, some psychotherapies have been developed specifically for persistent depressive disorder.[541]

The efficacy of the choice among these strategies is not the only consideration: 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, done 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.[542] Combination of the first-line treatments is another promising strategy, and higher response rates can be achieved with combined treatment of medication and psychotherapy. The response rate of combined treatment compared with placebo is about twice as high as medication alone compared with placebo. Although these differences underscore the advantages of combined treatment, concluding from the available evidence whether this is an additive effect of the two treatments or simply the result of personalised allocation of the optimum treatment is not possible.[515]

Depression with psychotic features is a severe form of the condition and one of the few depression subtypes for which specific pharmacotherapy is indicated. A systematic review of 12 randomised controlled trials (929 participants) showed no evidence of efficacy for monotherapy with an antidepressant or an antipsychotic, but superior efficacy of their combination compared with either monotherapy or placebo.[543]

Finally, several additional options are now available for treatment-resistant, refractory, difficult to treat, or persistent depression. Neuromodulation therapies such as ECT or repetitive transcranial magnetic stimulation 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.[544] Drugs that focus on the glutamatergic system (ketamine, esketamine, and 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 of these drugs.[545–547] However, the initial results for many novel treatments have not been replicated.[548] Novel psychological treatments based on the so-called third wave of cognitive behavioural interventions[549] include mindfulness-based CBT, acceptance and commitment therapy, and meta-cognitive therapy. An increasing 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.[550] Other psychological treatments derive from a mechanistic understanding of psychopathology based on experimental findings such as interpretation bias modification.[551]

Preventing relapse and recurrence

Achieving remission and recovering from an acute episode is insufficient as a treatment goal given the high risk of relapse and recurrence.[552] Inter-episode wellness intervals tend to become progressively shorter, and the risk of treatment resistance increases with each succeeding episode. Thus, recovery from an episode is not enough, individuals must maintain their recovery and avoid relapse. A growing evidence base provides an expanding set of treatment options for preventing relapse and recurrence. Evidence suggests that once participants have recovered with antidepressant treatment, continued pharmacotherapy reduces the risk of relapse or recurrence by half, resulting in a number needed to treat of approximately four to prevent a relapse within a year among people at high risk of relapse (for example, those who have experienced multiple episodes).[553] These trials keep the dosage for continuation treatment the same as 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, might substantially increase the chances of recovery and maintaining this recovery for up to a year by 12–16 percentage points compared with initiating the treatment with drugs alone.[517] Accumulating evidence from 30 trials also supports efficacy of mindfulness-based CBT, preventive CBT, and interpersonal psychotherapy in relapse prevention.[554] The results of a 2021 systematic review and meta-analysis indicate reduced risk of relapse and recurrence in patients who remitted from a depressive episode when psychotherapy was sequentially integrated with antidepressant medication.[555]

For people recovering from psychotic depression, continuation of antipsychotic medication over several months is required to prevent relapse and recurrence.[556] Evidence suggests that continuation of ECT might also be effective in sustaining remission in people with refractory depression.[557]

Other impacts of first-line treatments

People with depression typically begin treatment with several problems and concerns.[558] The effect of treatments on other outcomes, in particular functional outcomes, is considered as important as the mental health symptoms. The psychological treatment of depression has considerable effects on quality of life, social functioning, and social support, but less evidence is available on the effects of antidepressant treatments on these outcomes (figure 10). The question of whether the treatment of depression has a meaningful effect on the risk of death by suicide does not have a definitive answer, largely due to

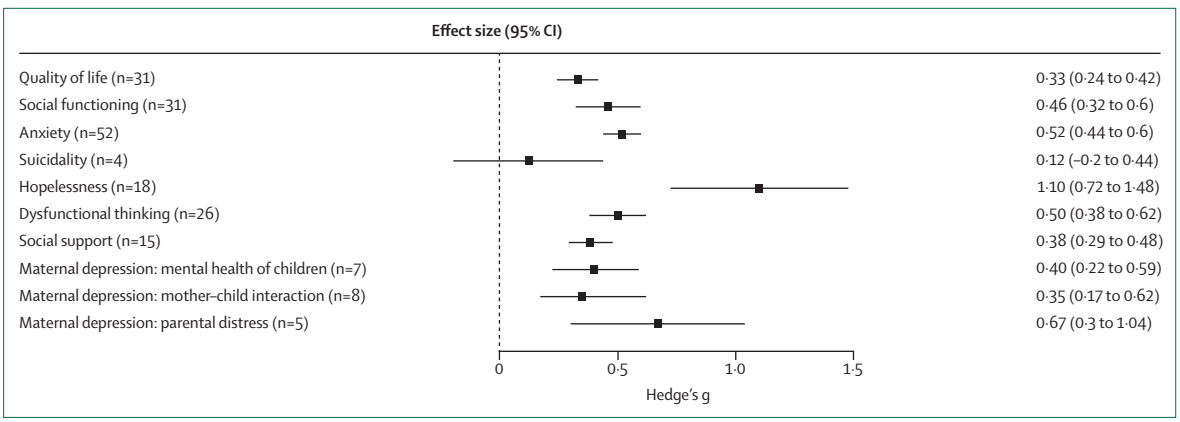


Figure 10: **The effects of psychological treatment for depression on other relevant outcomes**
Outcomes include: quality of life;[559] social functioning;[560] anxiety;[561] suicidality;[562] hopelessness;[562] dysfunctional thinking;[563] social support;[564] and maternal depression.[565]

the low power of trials to detect rare outcomes, although there are real-world studies that suggest an association.[562]

Depression treatments have been tested in people diagnosed with depression and various comorbid somatic conditions. The studies show consistent improvements in depression status in all these groups. However, the treatment effect on somatic outcomes has generally not been significant (table 2). An exception to this finding is the positive effect of antidepressant treatment on glycaemic control in those with diabetes;[568] for which there is also strong evidence of cost-effectiveness. Other meta-analyses and large randomised trials found insufficient evidence for effects on survival or cardiac events. These results could indicate that the strong epidemiological association between depression and somatic health is not directly causal or that depression treatment does not directly target the pathology underlying the pathway from depression to somatic condition, or that trials of longer duration and with larger samples are required to observe the effect 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 shows that the effective treatment of persistent postnatal depressive symptoms in mothers is associated with improved child outcomes at age 2 years.[580]

Translation to clinical practice

Randomised controlled trials and their meta-analyses are considered the gold standard for assessing the effects of treatments. However, problems of bias can be a challenge for these trials in mental health as in all areas of medicine. The failure to publish negative trial results, as demonstrated for drug trials[581] and psychotherapy trials,[582] 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.[583] Belief in the superiority of an intervention, or researcher allegiance,[584] has been associated with stronger observed effects of therapies, particularly in psychotherapy research.[585] 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% of studies in a meta-analysis of almost 300 psychotherapy trials.[586]

The generalisability of trial evidence to practice is also compromised by the fact that more than 90% of trials are done 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;[587] they are more likely to have had previous treatments and complicated or persistent episodes of depression, in addition to a personality disorder or other comorbidities[588] that might diminish 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 group. Evidence shows that between 12% and 34% of people in routine outpatient care are eligible for participation in a pharmacotherapy trial and others are ineligible because of comorbidities or not meeting the minimum severity threshold.[589] Although representativeness is less of a problem in psychotherapy research,[590,591] and the efficacy of psychotherapies appears to be of similar magnitude in high-income and low-income or middle-income countries when they are tested in randomised trials,[586] generalisability of research to practice requires attention. Evidence on cost-effectiveness for therapies or treatments does not readily transfer from one country to another because of differences in health and other systems, the availability and relative salaries of care professionals, and funding arrangements that alter incentives to deliver treatment and the associated unit costs. Economic evidence from a high-income country should not be assumed to be generalisable to low-income or middle-income countries.[592]

	Studies and samples	Intervention *vs* control	Results on depression symptoms	Results on somatic outcomes
Meta-analytic evidence				
Pizzi et al, 2011[566]	Four randomised controlled trials in 734 patients with myocardial infarction and depression	SSRI treatment versus placebo or no intervention	Reduction (SMD −0·34, 95% CI −0·06 to −0·63)	No reduction of coronary heart disease readmissions (SMD 0·74, 95% CI 0·44 to 1·23)
Cristea et al, 2019[567]	Seven randomised controlled trials in patients with diabetes and depression or depressive symptoms	Psychotherapy versus treatment-as-usual	Not presented	No difference in glycaemic control (change in HbA_{1c}; Hedges' g −0·01, 95% CI −0·30 to 0·29)
Baumeister et al, 2012[568]	Four randomised controlled trials in 441 patients with diabetes and depression	Psychological intervention versus treatment-as-usual	Reduction (SMD −0·42, 95% CI −0·70 to −0·14)	No significant effect on HbA_{1c} (pooled effect sizes not shown)
Baumeister et al, 2012[568]	Five randomised controlled trials in 238 patients with diabetes and depression	Antidepressant treatment versus placebo	Reduction (SMD −0·61, 95% CI −0·94 to −0·27)	Reduction in HbA_{1c} (SMD −0·4%, 95% CI −0·6 to −0·1)
Sharpe et al 2014;[569] Walker et al, 2014;[570] Mulick et al, 2018[571]	Two randomised controlled trials in 642 patients with cancer and depression	Multicomponent collaborative care for People with Cancer (DCPC) versus treatment-as-usual	Reduction in mixed cancer (SMD −0·78, 95% CI −0·90 to −0·66); reduction in lung cancer (SMD −0·38, −0·58 to −0·18)	No difference in survival (HR 0·92, 95% CI 0·72 to 1·18)
Legg et al, 2019[572]	Two randomised controlled trials in 2829 patients with stroke and with or without depression; three randomised controlled trials in 3245 patients for mortality outcome	SSRI versus placebo	Reduction (SMD −0·11, 95% CI −0·19 to −0·04)	No difference in disability score (SMD −0·01, 95% CI −0·09 to 0·06); no difference in mortality (HR 0·99, 95% CI 0·79 to 1·25)
Individual randomised treatment studies (sample size >200 participants)				
Berkman et al, 2003[573] (ENRICHD)	2481 patients with myocardial infarction and major or minor depression and low support	Cognitive behavioural therapy-based psychosocial intervention with SSRI treatment when indicated versus treatment-as-usual	Reduction in HamD after 6 months (intervention group, −10·1; treatment-as-usual, −8·4)	No difference in event-free 4-year survival (75·9% *vs* 75·8%)
van Melle et al, 2007[574] (MIND-IT)	331 patients with myocardial infarction and depression	SSRI treatment versus treatment-as-usual	No difference in Beck Depression Inventory after 18 months (intervention group, 11·0; treatment-as-usual, 10·2)	No difference in cardiac events after 18 months (intervention group, 14%; treatment-as-usual, 13%)
Glassman et al, 2002[575] (SADHEART)	369 patients with myocardial infarction and depression	SSRI treatment versus placebo	Change in HamD after 16 weeks: intervention group, −8·4; placebo group, −7·6	No difference in cardiac safety measures (including change in left ventricular ejection fraction)
Katon et al, 2010[576]	214 patients with poorly controlled diabetes or myocardial infarction, or both, plus depressive symptoms (Patient Health Questionnaire-9 ≥10)	Collaborative care versus treatment-as-usual	Reduction in 12-month Symptom Checklist-20 score (SMD −0·41, 95% CI −0·56 to −0·26)	No difference in 12-month HbA_{1c} (−0·56%, 95% CI −0·85 to −0·27); reduction in 12-month low-density lipoprotein cholesterol (−9·1 mg/dL, 95% CI −17·5 to −0·8); no difference in 12-month blood pressure (−0·4 mm Hg, 95% CI −6·9 to 0·1)
Gallo et al, 2013;[577] Bruce et al, 2004[578] (PROSPECT)	396 older patients with depression, age 60–94 years	Algorithm-based care versus treatment-as-usual	Percentage reduction in HamD score after 4 months: intervention group, 41%; treatment-as-usual, 24%; RR 3·9 (95% CI 1·8 to 8·5)	No reduction in 8-year mortality in intervention group versus treatment-as-usual (HR 0·76, 95% CI 0·57 to 1·00)
Naik et al, 2019[579]	225 patients with uncontrolled diabetes and depression (Patient Health Questionnaire-9 ≥10)	Telephone intervention with collaborative goal-setting and behavioural activation versus enhanced usual care	Reduction in Patient Health Questionnaire-9 after 12 months (SMD 2·14, 95% CI 0·18 to 4·10)	No reduction in HbA_{1c} after 12 months (mean difference −0·06%, 95% CI −0·61 to 0·50)

SSRI=selective serotonin reuptake inhibitor. SMD=standardised mean difference. HbA_{1c}=haemoglobin A_{1c}. DCPC=depression care for cancer patients. HR=hazard ratio. HamD=Hamilton Depression Scale. RR=risk ratio.

Table 2: **The effects of depression treatment on general medical disorders**

An important and desirable aspect of randomised trials is the need for participants to be masked to the group or intervention to which they are assigned. However, masking is not possible for trials of psychotherapy. Although masking is possible in drug trials, participants often discern from noticeable side-effects when they receive active drug rather than placebo.[593] The use of waiting list control groups (common in psychotherapy research) might lead to an overestimation of the effects of treatment.[594,595] The nature and definition 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;[596] these differences contribute to extensive heterogeneity between trials.[597] The choice of non-specific treatment, such as non-specific counselling, as a control condition is also a challenge for a depression trial. These non-specific

therapies can result in good outcomes, which are comparable to those recorded for other therapies (eg, CBT).[598] Ultimately, the choice of a control condition depends on the research question.

Finally, the challenge of understanding the gap between the relatively modest effect sizes of the two first-line treatments for depression and the experience of clinical practice must be recognised. 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.[599] 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, treatment effects and spontaneous recovery 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. Furthermore, in short-term trials of depression monotherapy, participants receive only one medication or one type of psychotherapy for 8–16 weeks. However, in clinical practice, if an individual does not respond to treatment, or responds partially, changes to the treatment plan are often made earlier than in clinical trials. For example, in the Strategic Use of New generation antidepressants study,[600] switching or augmenting mediations as early as 3 weeks was associated with a number needed to treat of ten in achieving remission by 9 weeks in comparison with standard length acute phase treatment. Personalising the second-line treatment choice through machine learning identified a small group of individuals (about 8%) who would fare better if continued unchanged on their initial treatment.[601] Similar to other clinical conditions, particular forms of treatment for depression 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, 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. The individual 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. The standards of care should include the opportunity to access and receive timely care at the onset of illness; a basic need that remains unmet for most people around the world. Data from the World Mental Health Survey covering 15 countries indicate that, among community-dwelling adults meeting diagnostic criteria for depression, an average of less than half across countries had any contact with a general medical or specialist provider, and only about 10% received effective care.[602] There was a consistent discrepancy between high-income countries and low-income and middle-income countries, with coverage estimates in the high-income countries about twice as high as those in low-income and middle-income countries. However, even in high-income countries, less than a fifth of adults meeting criteria received effective care (figure 11).

In most countries and contexts, primary care workers and community health workers 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 UN Convention on the Rights of People with Disabilities 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. Agreement is widespread that coercive practices are overused in depression care when it is

For more on **The World Mental Health Survey Initiative** see www.hcp.med.harvard.edu/wmh

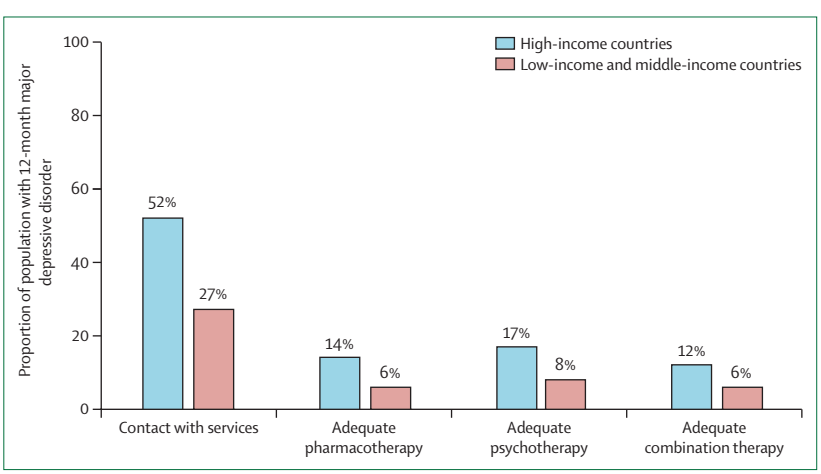


Figure 11: **Contact with services and effective coverage for depression care for community-dwelling adults in 15 countries**

Adapted from Vigo and colleagues,[602] using data from 15 countries provided by the WHO World Mental Health Survey Consortium, by permission of Cambridge University Press. Contact with services among representative samples of community-dwelling adults was defined as any contact with specialist mental health or general medical health provider for a mental health condition. Adequate pharmacotherapy was defined as taking an antidepressant with adequate medication control and adherence. Adequate psychotherapy was defined as complying with at least eight sessions from an adequate provider or still being in treatment after two visits. Adequate combination of pharmacotherapy and psychotherapy was defined as adequate pharmacotherapy or psychotherapy, or both, for mild and moderate depression, and a combination of both adequate pharmacotherapy and psychotherapy for severe depression.[602] All high-income countries versus low-income and middle-income countries comparisons were p<0·001.

***Panel 2*: Formulation—factors relevant for clinical assessment and decision making**

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

*Assessments recommended in specific circumstances such as persistent or treatment-resistant depression.

delivered in institutional settings and in some community settings. The World Psychiatric Association, in common with WHO, advocates for a pragmatic approach to implementing viable alternatives to coercion,[603] 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 Patient Health Questionnaire-9 or a diagnostic interview.[604] However, a more detailed clinical assessment is required to inform whether treatment is recommended, and which types of interventions are likely to be most acceptable and effective. Formulation aids in reaching the 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).[605]

Formulation assists in choosing which medication, psychotherapeutic, or lifestyle approaches to treatment and care a person might need or expect, as well as identifying individuals at risk of death by suicide.[606] It can also mould expectations of therapy; for example, evidence suggests that a history of childhood trauma or personality disorders might predict a poorer response to initial interventions than in people without such history.[607] Formulation typically assembles five domains of information and understanding that are based on awareness of the factors shown in panel 2 and are crucial in clinical decision making. The first is presenting problems, which is identifying what the clinician and the person with depression see as difficulties or foci needing treatment. The second is predisposing factors, which refers to potential biopsychosocial vulnerabilities. Third is precipitating factors, which refers to salient circumstances preceding the onset or exacerbation of the presenting episode. Fourth is perpetuating factors, which are situations or dynamics that serve to maintain or worsen the condition. The final domain is protective or positive factors, which are strengths or support systems that might 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 should understand the meaning of an individual's presentation with depression in the context of their developmental and previous history and current circumstances. Knowledge about developmental history, attachment styles, and personality development, as well as prodromal and major depressive episodes (age of onset and number of such episodes and their severity, duration, functional consequences, effects on cognition, and duration of inter-episode intervals or burden of residual inter-episode symptoms and dysfunction) is fundamental to effective care. Family history of depression (and which treatments have helped), medical history, social support, religious and spiritual affiliations and beliefs, life circumstances and life events, and previous treatment history provide further context for understanding the 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 most well-evaluated approach for translating evidence from randomised trials and realising the goals of staged approaches in practice.[608] Collaborative care integrates team-based health, social, and support services. It offers a ready platform for reaching underserved populations, engaging in task sharing of mental health care with non-specialist providers, mitigating the barriers posed by stigma (in that people receive care at home or where they want to receive it), promoting engagement with family caregivers, implementing 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. Crucial to this goal is the use of shared decision making, giving primacy to the individual's perspective. Functional recovery is often as important as is symptomatic recovery and is an important factor in predicting longer term prognosis.[609] Vocational recovery can be achieved with support from practitioners with educational and employment expertise.[610] 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—recognising that family caregivers are often demoralised; require information about depression and its treatment; and play a vital role in providing advice about their family member's background and condition, forming part of a safety net to prevent suicide and encourage 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, might 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). Mental health specialists can be co-located in primary care or in mental health services; the crucial requirement is coordination between these sectors. Collaborative care can be enabled or enhanced in low-resource settings with the engagement of lay counsellors or community health workers.[611] Task sharing with lay community workers aims to confront the scarcity of specialised health and mental health workers and improve access to care and delivery of 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 can be used to assist clinicians to dynamically assess outcomes and initiate modifications in treatment plans accordingly. Measurement-based care includes standardised assessment of depressive symptoms and side-effects and adherence to medication. It typically uses a multistep algorithm in treatment planning to match the level or intensity of care with the needs of individuals and assist with consistent follow-up. Measurement-based care shows a higher promise of patient remission and recovery than does care-as-usual.[539,612]

Collaborative care also allows the integration of specific care for people at risk of death by suicide and

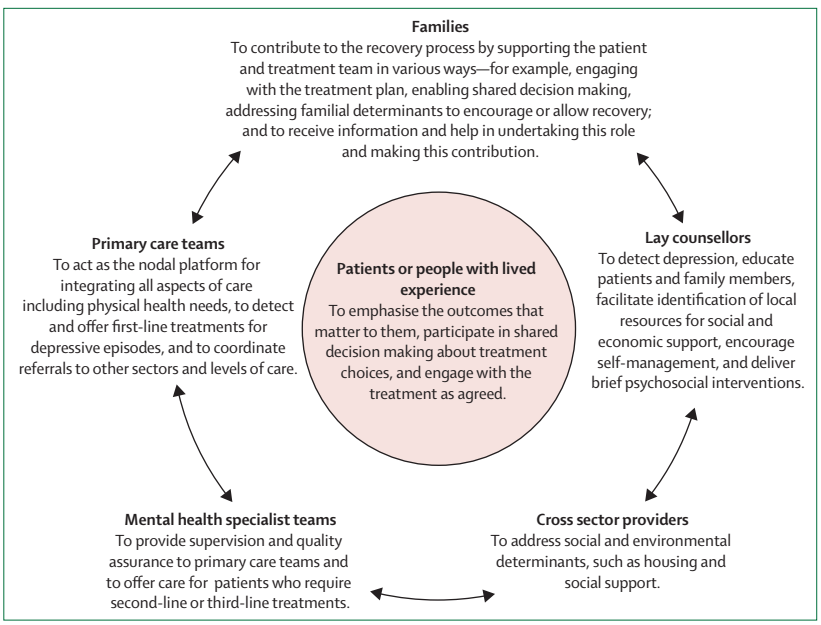


Figure 12: **Collaborative care team**

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,[613] but also has a beneficial effect on self-management of chronic disease.[614] For example, the COINCIDE trial[615,616] 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.[615] Both clinical and cost-effectiveness persisted at 2 years.[616] The INDEPENDENT trial replicated these findings in a low-resource setting: India.[617] The cost-effectiveness of collaborative care for depression in the UK[618] and in India has been demonstrated over the past 15 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.[619]

Personalised care

There are two distinct perspectives to personalised care for depression. The first 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. Outcomes that matter to individuals are not necessarily present in currently available instruments used to capture the construct of depression. For example, domains such as mental pain and overall functioning—despite being highly ranked by people with depression, informal caregivers, and health-care professionals—are not covered by most depression rating scales used in clinical trials.[620] This perspective is synonymous with the concept of so-called person-centred care and central to collaborative care.

The second perspective of personalised care is aligned with precision medicine and aims to identify characteristics of an individual that are associated with the outcome of different treatment options to offer the individual the most effective treatment plan.[190,605,621] Although most treatments of depression have comparable effects at the group level with no differences or only small group differences, individuals with specific genetic, biological, psychosocial, 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 is psychotherapy in individuals with dysthymia and persistent depression,[622] and combined treatments are more effective than either treatment alone in older adults.[515] The efficacy of pharmacological treatments could be improved with increasing knowledge of genotyping,[623] because a high proportion of the response to antidepressants can be attributed to genetic factors.[624] Applying a precision treatment algorithm to data from a trial comparing antidepressant medication with CBT yielded an additional benefit on remission of matching individuals to either of the two treatments on the basis of only five clinically sensible indices (personality disorder, marital status, employment status, number of previous medication trials, and number of precipitants).[625] Despite the promise of these preliminary studies, knowledge of moderators and prognostic factors is not yet sufficient to effectively guide personalised care.[626]

Machine learning techniques using big datasets offer a promising approach to developing personalised treatments of depression and prediction models for treatment outcomes.[601] Another promising area of research is the identification of neuroimaging patterns or biomarkers to predict susceptibility to illness, 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. Previous studies implementing this general approach have identified several putative treatment selection brain biotypes with potential uses for selecting between psychotherapy and medication and for choosing between stimulation-based treatments such as transcranial magnetic stimulation and deep brain stimulation.[333,336] Other research studies continue to search for biological or behavioural surrogates of such brain-based biotypes, with equivalent specificity, but with more potential widespread availability.[516,627]

Digital strategies

The enhancement of treatment and care by leveraging digital technologies is an important new frontier in health care. Digital strategies can extend the reach of other clinical interventions to underserved populations, or increase the period, intensity, or quality of care for those who already have access to interventions. 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,[628] although a previous review concluded that face-to-face CBT had a higher probability of being cost-effective than did iCBT.[629] Unguided iCBT can also have smaller but clinically significant effects.[502] Computer-based iCBT is rapidly being superseded by smartphone application (app)-based iCBT and novel app-based approaches are emerging, such as cognitive-emotional training.[630] However, none of the thousands of apps available has yet obtained regulatory approval. A previous individual participant network meta-analysis was able to distinguish potentially helpful (eg, behavioural activation), less helpful, or potentially harmful (eg, relaxation) iCBT components. The study also showed a decrease in dropout rates when human encouragement to proceed with iCBT was combined with automated encouragement.[631]

Digital technologies also offer new possibilities for screening, diagnosing, assessing, and monitoring people with depression and the way in which mental health-care personnel are trained and monitor their care delivery. Computerised adaptive testing enables more efficient, flexible, and precise administration of individual-reported outcome measures.[632] Digital technologies for workforce training[633] 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 use of telemedicine. This extension has been demonstrated in various contexts during the COVID-19 pandemic wherein digital technology has become a standard delivery platform for mental health care. Shared decision making can be facilitated for individuals who prefer automatic, interactive display of information specific to their own characteristics and needs[634] on interactive web pages or smartphone apps.[635] Several trials are examining the feasibility and effects of such personalised interactive decision aids.[636] There is special interest in support for decisions regarding use of antidepressants in pregnancy.[637]

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"[638] 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.[639] Such phenotyping might lead to support for differential diagnosis[640] and prediction of relapses or recurrences.[641] Systems have been developed that integrate digitally assisted diagnostics, prognostics, decision making, therapeutics, and outcome assessments into an electronic health record system—for example, the Learning Healthcare System—to create a continual cycle of care improvement.[642] 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 uptake and sustained use of digital strategies by the intended users is low.[643] In one large pragmatic trial of unguided iCBT, the median number of completed sessions for two widely used programs was one of eight and one of six.[644] Although the dropout rate from routine treatment, mainly antidepressant pharmacotherapy, might be high (eg, in one claims database analysis, 28% of participants never returned after the initial prescription and 55% dropped out within 3 months),[645] the rate of dropouts is greater for digital therapies than for face-to-face routine treatments.[501]

Second, installing, updating, and troubleshooting digital devices can be complicated for some individuals or health-care professionals. In a previous study, although about half of 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 were currently using an app.[646] Relying on digital interventions can widen inequalities in access to care due to the so-called digital divide. Collaborative care teams should consider the inclusion of so-called digital navigators to help support both patients and clinicians in engaging with the digital world.[647] Third, innovative ways to assess and control the quality of the thousands of mental health apps already on the market, entering the market, and any updates are required. The UK National Health Service has launched an Apps Library homepage listing evaluated applications. Finally, the whole health-care system must be accountable for privacy and ethical concerns.[648,649]

Preventing death by suicide in the context of caring for people with depression

Although people living with depression have a much higher risk of death by suicide than do others in the population, most do not die by suicide or attempt suicide. Clinicians should aim to identify and intervene with those at higher risk. Interventions that are typically 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 (eg, safety planning), and attention to contextual factors such as family discord and the need for social support. These interventions and similar elements of re-engineering practice have been associated with reductions in suicide of up to 29% in clinical populations in the UK,[650] and with even more marked reductions associated with changes in the Henry Ford Health System in the USA.[651] Use of antidepressants has a modest effect in reducing deaths by suicide[652] in adult and older populations with depression. Ecological studies in Europe[653] 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 might be specific to individuals with bipolar depression).[654] Evidence suggests a potential beneficial use of ketamine intravenously for rapid reduction of suicidal ideation;[655,656] however, the long-term effects are still unknown.[657] Some individuals with depression who are at risk of death by suicide might require admission to hospital, but evidence to support suicide watch and the close monitoring prescribed by most guidelines is weak.[658] Such workforce intensive protocols are potentially intrusive and unwelcome, and could be unwarranted given their questionable efficacy.[659]

Despite such evidence gaps, very few cost-effectiveness studies have been published 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 in England to identify individuals at risk of death by suicide linked to moderate or severe depression. Other suicide prevention programmes including screening and intervention in hospital emergency departments have been evaluated and found to be highly cost-effective.[660,661]

Meta-analyses show that clinical judgments about suicide risk are weak predictors of subsequent suicidal behaviours.[662] On the basis of 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 extensively reviewed.[663–665] Composite prediction strength for most such models is in the range considered either acceptable (area under the

curve [AUC] 0·7–0·8) or excellent (AUC 0·8–0·9).[666] However, given the rarity of suicidal behaviours, positive predictive value (prevalence of subsequent suicidal behaviour among patients predicted to be at high risk) is low even among patients predicted to be at high risk, and a substantial proportion of patients who go on to engage in suicidal behaviours are predicted not to be at high risk. This finding has led many critics to argue that suicide prediction tools have no clinical value.[667] This negative evaluation should be balanced against two considerations.[668–670] First, no existing suicide prediction study, to our knowledge, has ever applied the full range of significant predictors found in the literature to a large heterogeneous sample of patients and used best-practice statistical methods to develop a stable prediction model. Second, even though positive predictive value in such an optimal model would still be relatively low, the net benefit would probably be positive given that several suicide prevention interventions are cost-effective even at low positive predictive value.[671,672]

Treating maternal depression

Another important area of care is treating maternal depression. The general principles of treating depression in mothers in the perinatal period 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 fetal exposure to SSRIs remain unclear and given the suggested caution in their use during pregnancy,[673] an individualised collaborative risk-benefit analysis is a sensible option. This analysis considers the consequences of untreated depression as well as the effects of antidepressants on both mother and infant. A national case series of suicides revealed that perinatal deaths of women by suicide were associated with depression that had not been actively treated with medication.[674] Although there are fewer studies on breastfeeding exposure, most SSRIs have been found to pass only minimally into breast milk.[675] 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, in cases of psychosis, when pharmacotherapy is indicated).

A 2020 systematic review assessed effective psychosocial interventions for depression in women experiencing intimate partner violence in low-income and middle-income countries.[676] Strong evidence supports the effectiveness of psychosocial interventions for perinatal depression delivered by non-specialist providers, including those delivered by peers in these contexts.[677]

Remission of depression in a mother has positive effects on her school-aged and adolescent children[565,678] for at least a year afterwards,[679] including the children of mothers treated with medication[678,680] or psychotherapy.[681–684] The positive effects vary with the severity of maternal depression.[685] Coexisting problems such as intimate partner violence need to be addressed for immediate safety for the family and to reduce deleterious effects on children.[686]

Caring for children and adolescents with depression

Several general principles are key to successfully engaging children and adolescents in care. These principles include providing psychoeducation that is appropriate for the developmental stage and implementing person-centred 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.[687] These measures encourage the essential integration of multiple perspectives.[688] The evidence-base for providing collaborative care for depression is growing, including team-based and measurement-guided care, in addition to youth-driven, family-centred approaches.[689] In one randomised 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[690] than did the usual care group—this model also appeared to be cost-effective.[691] A meta-analysis[692] of routine specialist mental health care suggested 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 young people, all factors to foster a more open and empowering relationship between the young people and the practitioners. Evidence for the effectiveness of psychological therapies for depression in adolescents is strong,[693] and evidence is emerging for the use of modular, transdiagnostic psychological treatments (rather than disorder-specific treatments).[694] Beyond clinical approaches, attention has been directed to more rigorous assessment of a variety of self-delivered and community approaches.[695] Children and adolescents spend an important proportion of their time in school settings in which assessment and interventions can take place.[696]

Caring for older adults with depression

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 (eg, bereavement, social role transitions, social isolation and loneliness, and depletion of social and economic resources), exposure to polypharmacy, and risk for death by suicide. Collaborative care involves the delivery of evidence-informed, late-life depression treatment and suicide prevention through coordinated health, including mental

health, services, and social services, offered within primary care. This mode of care is preferred by many to specialty mental health, because of less stigma and greater access, trust, and affordability. Pioneering studies, such as IMPACT[697] and PROSPECT,[578] have identified core components of collaborative care: (1) virtual or actual co-location of mental health expertise within primary care settings; (2) multidisciplinary teams; (3) measurement-based care; (4) engagement of family care-givers; and (5) evidence-informed provision of acute and continuation treatment modalities to achieve remission and to maintain recovery and wellness. As found increasingly in other collaborative care models, especially in low-resource settings, these programmes included community health workers and lay counsellors to facilitate outreach and task sharing, in the service of both treatment and prevention of depression.[471]

Treatment of depression in forced migrants, refugees, and other populations affected by humanitarian crises

More than 235 million people are living in settings of humanitarian crises.[698] The Inter-Agency Standing Committee, which includes UN institutions and a range of humanitarian response organisations, 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.[699] 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 emphasise the roles of psychoeducation, stress management, and strengthening social support, in addition to providing information on evidence-supported psychosocial interventions and prescription of antidepressant medication.

Most evidence on psychosocial interventions focuses on treatments that have been adapted from specialist-delivered interventions in high-resource settings (eg, Trauma-Focused-CBT). New psychological interventions have been developed that are specifically intended for delivery by non-specialists to populations affected by humanitarian crises (eg, Problem Management Plus).[700] Self-help plus is also a new intervention developed for administration to large groups in humanitarian settings; it requires limited involvement of facilitators and is built around audio recordings for guided learning of basic psychological skills for people with mild to moderate psychosocial distress.[701] An umbrella review identifies moderate evidence for the benefit of psychosocial interventions for reducing depressive symptoms in adults (but not to date for children) with depression in humanitarian settings, although the strength of association with symptom reduction is weak for any specific treatment, such as CBT or interpersonal psychotherapy.[419,702]

Section 6: recommendations

This Commission has synthesised 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. This Commission is, for the most part, a narrative review scripted by a team of scholars and practitioners who were chosen to reflect their individual and complementary leadership of this range of disciplines. We as the authors believe that the science points to a number of specific key messages and actionable recommendations.

We present recommendations for action by four primary stakeholders: the general community and people 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 (figure 13).

The community and people 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, age 41 years (Tokyo, 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.[703] 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, effect on daily functioning, and long-term health consequences. Moreover, historical and cross-cultural evidence shows that the condition has been described since ancient times and in diverse civilisations and, although the experience of depression can take many forms, the core illness experience is very similar across cultures. Importantly, depression can affect anyone, and is never the person's fault or a sign of psychological weakness. Although depression can affect a person at any point in their lives, it is most likely to have its onset in young adulthood. Many people will experience just one episode, others will have repeated episodes, and a few might experience persistent distress for long periods of time.

Reducing the burden of depression requires united action from diverse stakeholders

The general community, including people with lived experience of depression	Health-care practitioners
1) Seek help early to increase 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 people with depression will recover with the right support and treatment. 4) Ensure that treatment is informed by evidence-based practice, is focused on priorities with decisions made collaboratively, and engages (if possible and appropriate) family, friends, community, and peer supporters. 5) Find partners or groups to help sustain education about the illness and practice self-care to get well and stay well, sharing experiences 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, speak up against discrimination, and advocate for social changes that support mental health and reduce the risks of depression.	1) Learn about depression: about the variations in its origins, presentation, and course, and about the lived experience of depression. 2) Proactively 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) Personalise the 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, developmental history, life circumstances, 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, the rights of people to receive care with dignity and choice, the needs of families (if appropriate), and the obligation to reduce stigma associated with depression.
Researchers and research funders	**Decision makers**
1) Understand the multi-factorial causation and nature of the condition across the life course and urgently develop 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 policy makers, 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 programme 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 optimise prevention, care, and recovery.	1) Respond to the experience of people with depression and to the science, recognising that depression has profound effects on people's health, social relationships, and economic and educational opportunities; and affects people everywhere, but is more likely to affect those living in poverty and adversity from historical or contemporary losses, injustices, and inequities. 2) Secure investment across society in prevention and health promotion, targeting determinants of health across the life course during childhood, 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, practice, social, and implementation science.

Figure 13: **Recommendations of the *Lancet*–World Psychiatric Association Commission on depression**

Just as for other health concerns, individuals should seek help for depression—and do so early, because the longer the illness lingers, the more difficult challenges they face and the chances of recovery are diminished. A wide range of interventions that can promote recovery are available, 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 specialised therapies for those who continue to experience the illness despite trying these options. Most people who seek and find health care 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 most people with depression, but no one intervention is right for everyone and multiple trials of different interventions might be needed to find what works best for each individual. Recovery is a journey: if people do not recover after the first treatment trial, persisting with alternatives will incrementally but continuously increase chances of recovery.[704] Mental health professionals often work with primary care providers to support the aim of recovery in people with depression. They also provide direct care to a substantial proportion of people who do not receive interventions in primary care or do not recover with those interventions. A relatively small number of people might need brief periods of care in hospital and other treatments.

The role of the person with depression in the recovery process is central; using information from reliable sources and seeking help early to find the most effective strategy to help with recovery. The individual with depression should be an active partner in the decision-making process, ensuring that priorities and needs are being addressed. Needs and priorities can 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 ideas, concerns, and expectations in a holistic manner is the hallmark of good quality primary care, which is why primary care is the ideal first setting for those seeking help. If the individual with depression and a health-care provider decide together that psychotherapy or medication is likely to be helpful, then it is relevant to engage with the agreed treatment for it will be most effective when used as advised (eg, the number of sessions of therapy), in the correct manner (eg, practicing skills taught in sessions at home), and for the recommended length of time (eg, often up to a year for antidepressant medication). Upon recovery, to prevent relapse, individuals should remember the importance of incorporating the skills learned in everyday life, engaging family and friends and other community resources to provide support through difficult times, and monitoring sensitivity to the signals that might indicate relapse.

An individual's 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. A person's lived experience makes them knowledgeable in understanding this condition and the pathways to recovery. Individuals might wish to play a role in sharing their experience in their community, becoming involved with civil society groups as a peer support worker or advocate, and mobilising the community to demand that policy makers invest in depression prevention and care (in particular, the interventions that have been scientifically proven to work). The voices of people with depression who have recovered are crucial to affect policy change, to ensure that others in the community are able to access care.

Health-care practitioners

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

Depression should receive the same attention as would other common conditions, such as diabetes and hypertension, and practitioners should familiarise themselves with its diverse origins, presentations, and course. Depression usually occurs in a developmental, social, environmental, or economic context, and very often can develop alongside chronic medical conditions (such as diabetes) and can worsen the outcomes of these conditions. It can also co-occur with other mental health conditions (such as harmful drinking). Depression can profoundly affect the health of others in the family, most notably the child of a parent with depression. Depression can be brought to remission in most cases with evidence-based and persistent treatment, but might require many trials of different treatments until a regimen is found that works. However, upon recovery, practitioners should remain aware that depression might be recurrent in some people.

Although the varying presentations of depression often mean that its so-called hallmark features, such as sadness or loss of interest, might not be obvious in many people, detecting depression and offering help as early as possible is important. Proactive detection strategies can be used, such as asking questions about mood and ability to engage with and find pleasure in daily life. Adolescents and young people whose clinical presentation might be changeable and mixed and who might be more reticent to share their inner experiences should not be overlooked. The admission of such symptoms should trigger a full inquiry to assess the range of other symptoms and their severity and duration. Simple screening tools such as the Patient Health Questionnaire-9 can be useful to fully assess symptoms. Bereavement is one life event which requires thoughtful inquiry to distinguish the normative response associated with grief from depression. Additionally, 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 practitioners should personalise their 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. Although no definitive individual characteristics can yet 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 can contribute in several ways, 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 that support women who are experiencing domestic violence, and with spiritual providers in certain contexts, enhances the chances of recovery. Practitioners who work in isolation can benefit from identifying others who could work alongside them to build a team.

We emphasise the importance of collaborative care, which is 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 a refractory or complex presentation of depression

Diagnosis-driven and evidence-informed treatment, and individual person-centred case formulation are complementary and synergistic rather than antithetical. People living with depression benefit from shared or supported decision making with clinicians that is informed by the best available scientific evidence and by an empathic understanding of the specific risk and protective factors relevant for a given individual.[705] Available treatment guidelines need to be complemented 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 identified, initiated on evidence-based treatments, and have completed the treatment and recovered.

Remaining persistent and hopeful in pursuing multiple sequential treatments when one treatment has not resulted in patient recovery, and providing encouragement and support to people with depression is important. Finally, all practitioners must respect and champion the rights of individuals with depression to receive good quality care with dignity, as for any other medical condition, and take responsibility for ensuring that the treatment setting is free from stigma towards people experiencing depression. Practitioners should also consider how their 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 emphasise 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 or stressors across the lifespan. The complex and heterogeneous nature of the condition poses challenges for researchers because 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"[706] and should involve a common set of research methods and metrics applied in diverse populations, in the spirit of data-sharing and capacity building. To achieve this goal, support will be needed for large-scale multi-disciplinary consortiums in diverse contexts with long-term funding to conduct coordinated research on common research questions.

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.[555,599] Moreover, a range of approaches exist beyond these biomedical treatments—ranging from exercise, meditation, and yoga[707] to community support—that await further investigation for their utility as preventive, ameliorative, and adjunctive measures. Social and economic policy changes need to be evaluated and monitored for their expected and unexpected effects on the social determinants of depression and its risk factors, and on depression prevalence.[414]

Translation of discoveries into practice in the domains of prevention and therapeutics face formidable barriers limiting the demand for care and access to quality care, and the implementation of practice and policy changes. Although these barriers are present globally, far greater challenges are encountered in low-resourced communities and countries, and evidence does not necessarily generalise to specific regional contexts. Designing and evaluating innovative strategies to address these barriers is essential to achieve higher levels of effective coverage of

evidence-based interventions. The flourishing of so-called frugal innovations in global mental health, such as the use of task sharing of brief psychological therapies, is one example of delivery science showing how some of these barriers can be addressed.

Finally, we strongly recommend the engagement of people 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 makers and policy makers

There is arguably no other health condition which is as common, as burdensome, as global, or as treatable as depression that has attracted such little policy attention and so few resources. Despite the science showing that depression causes profound, enduring suffering and premature mortality, and 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 most people affected by the condition do not seek help. Much of the inaction stems from myths about the condition, such as it is not a real health condition distinguishable from everyday misery, it is a concern only of affluent people or contexts, it requires very expensive treatment programmes, or that prevention and treatments do not work.

These myths also prevail among 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 might be a perceived tension between the concept of scaling up depression care that requires a degree of standardisation of so-called packages of care and the personal formulation approach which we advocate in this Commission. These tensions can be navigated by distinguishing specific, evidence-based guidelines (standardised 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.

Nowadays, sufficient evidence shows the effectiveness of collaborative care models for delivering interventions across the diverse range of presentations of depression. Key members of the team are non-specialist providers, such as community health workers and peer support workers, who can deliver a substantial proportion of front-line care. Use of 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. The collaborative care model is also consistent with the staged approach to depression care, enabling many people 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. The concept of collaborative care consists of 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, policy makers should ensure that only evidence-based interventions are scaled up and those which have historically been neglected (such as psychological therapies) should be given particular attention. Some high-income countries have introduced programmes providing improved access to psychological therapies[708] for people with depression and anxiety symptoms detected in primary care, showing that such programmes are feasible, but need further evaluation in terms of cost-effectiveness.

Challenges in scaling up this delivery model include: the difficulties of building a community-based mental health workforce, because the orthodox models of training (typically expert-led workshops) and quality assurance (expert-led supervision) are not sustainable; and the difficulties of enabling seamless coordination of care across the platforms of delivery. Digital platforms offer a unique and 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 telepsychiatry, will enable a high proportion of providers to be trained and greatly increase the reach of experts; their relevance has greatly increased because of the pandemic. However, 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-term and long-term. Another threat to scaling up collaborative care models 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, if such models are adequately resourced to ensure that each worker has access to training and referral at an expert level, and if quality improvement strategies are implemented. Certain signals suggest 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 neglect is in part because most interventions are outside of 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

How depression relates to the Sustainable Development Goal	The Sustainable Development Goal	Actions to prevent or treat depression that contribute to achieving the Sustainable Development Goal
Depression impairs work performance and increases the risk of becoming unemployed, inadequately employed, or inactive, and increases susceptibility 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 the individual's likelihood to find and keep a job, reducing disability associated with comorbid medical conditions, decreasing isolation and morbidity among family caregivers, decreasing health-care costs, and increasing resilience when people are 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 people to take a more active hand in self-care (including provision and intake of adequate nutrition), and enabling parents to create a nurturing environment for the healthy growth and development of children.
Depression is the single most burdensome mental health condition. It 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 a 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; depression during childhood or adolescence has a negative effect on educational performance and outcome; depression reduces the access of adults to technical, vocational, and tertiary education and reduces their chances for successful completion of these courses.	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 women and girls, 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 women and girls: reducing self-harm, increasing self-efficacy and the power to act, and reducing exposure to interpersonal violence.
Depression negatively affects 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.
Marginalised and disadvantaged communities are more clinically vulnerable to depression, and income inequality is associated with a 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 or 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 of depression.	Take urgent action to combat climate change and its impacts. 	Strengthening resilience and adaptive capacity to climate change and 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 of 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 people 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.

Figure 14: **Depression and the Sustainable Development Goals**

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.

Whole-of-government actions are required, well beyond the traditional health sector, to successfully realise 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. However, 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 of the state sector (eg, in workplaces) might also be hard to incentivise. Even when preventive strategies or treatments appear cost-effective, economic and other structural barriers might prevent implementation. Thus, budgetary allocations for preventive strategies need to be earmarked from the relevant ministries concerned with these diverse sectors. Investing in depression prevention and care represents excellent value for money, not least due to the contribution it can make to the attainment of several of the Sustainable Development Goals (figure 14).

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 that affects the people and communities in low-income countries to a greater extent than those in high-income countries. 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, the refugee crisis, and the climate emergency. Nevertheless, development assistance has almost entirely neglected mental health even though these countries require substantial external financial support to adequately resource their mental health-care systems. The time has come for 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 not sufficiently equipped to deal with the burden of depression, not only because of the long-standing under-resourcing of mental health-care systems and the paucity of skilled providers, but also because of the rigid silos that typically separates mental health expertise and mental health care from primary health care and community support sectors, and 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 on how such interventions can be integrated with wider health and social systems and implemented even in the least-resourced contexts. The evidence creates an opportunity for united action to transform mental health-care systems globally. The evidence also calls for a whole-of-society approach to the prevention of depression, which can be expected to result in benefits similar to those from prevention programmes in other fields of medicine, such as heart disease and cancer. Investing in actions to reduce the burden of depression enables individuals to regain and maintain their health and 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. We cannot think of a more important set of investments, now more than ever before.

Contributors

HH, VP, CK, and CB drafted and revised the Commission. MB, PC, TAF, RCK, BAK, MM, PM, CFR, and MMW led the drafting of specific sections of the Commission. DC, LMH, CWH, MK, SX, MT, RU, LV, and MW contributed text to sections of the Commission, and all reviewed and revised the paper for intellectual content. HH, VP, CK, CB, PC, TAF, RCK, MM, CFR, CD, BAK, HSM, and BWJHP also contributed specific non-text items. All authors accept responsibility to submit for publication.

Declaration of interests

HH reports her role as President of the World Psychiatric Association during the period of preparing and submitting the Commission for publication, and support from an 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 National Institute of Mental Health (NIMH) and the Wellcome Trust. CK is a researcher from *Conselho Nacional de Desenvolvimento Científico e Tecnológico*, Brazil, and a UK Academy of Medical Sciences Newton Advanced Fellow. MB reports grants from the 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 of 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 the Wellcome Trust and personal fees from the University of Melbourne and the World Psychiatric Association, during the conduct of the study. PC reports support for unrelated grants from the European Commission and ZonMw, and receives royalties for books and for occasional workshops and invited addresses. TAF reports grants and personal fees from

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