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Comorbidity between major depressive disorder and physical diseases: a comprehensive review of epidemiology, mechanisms and management

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Populations with common physical diseases – such as cardiovascular diseases, cancer and neurodegenerative disorders – experience substantially higher rates of major depressive disorder (MDD) than the general population. On the other hand, people living with MDD have a greater risk for many physical diseases. This high level of comorbidity is associated with worse outcomes, reduced adherence to treatment, increased mortality, and greater health care utilization and costs. Comorbidity can also result in a range of clinical challenges, such as a more complicated therapeutic alliance, issues pertaining to adaptive health behaviors, drug-drug interactions and adverse events induced by medications used for physical and mental disorders. Potential explanations for the high prevalence of the above comorbidity involve shared genetic and biological pathways. These latter include inflammation, the gut microbiome, mitochondrial function and energy metabolism, hypothalamic-pituitary-adrenal axis dysregulation, and brain structure and function. Furthermore, MDD and physical diseases have in common several antecedents related to social factors (e.g., socioeconomic status), lifestyle variables (e.g., physical activity, diet, sleep), and stressful live events (e.g., childhood trauma). Pharmacotherapies and psychotherapies are effective treatments for comorbid MDD, and the introduction of lifestyle interventions as well as collaborative care models and digital technologies provide promising strategies for improving management. This paper aims to provide a detailed overview of the epidemiology of the comorbidity of MDD and specific physical diseases, including prevalence and bidirectional risk; of shared biological pathways potentially implicated in the pathogenesis of MDD and common physical diseases; of socio-environmental factors that serve as both shared risk and protective factors; and of management of MDD and physical diseases, including prevention and treatment. We conclude with future directions and emerging research related to optimal care of people with comorbid MDD and physical diseases.

Key words: Depression, physical diseases, comorbidity, cardiovascular diseases, cancer, inflammation, lifestyle factors, childhood trauma, collaborative care, digital technologies

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Major depressive disorder (MDD) is prevalent within the general population, with an approximate global point prevalence of 4.7%[1]. In populations with common physical diseases – such as cardiovascular diseases[2,3], cancer[4] and neurodegenerative disorders[5-8] – this prevalence is much higher, with several meta-analyses reporting MDD rates of up to 41% in selected physical diseases[2-8]. This relationship is often bidirectional, with both observational and some Mendelian randomization studies demonstrating that MDD and physical diseases can be predictors and outcomes of each other[9-14].

There are a range of potential explanations for the high level of comorbidity between MDD and physical diseases[15-18]. Shared genetic and biological pathways suggest that there are numerous pathological mechanisms implicated in both MDD and physical diseases that may increase risk or exacerbate comorbidity[15,16]. Furthermore, there are several shared antecedent social, lifestyle and life event risk factors for MDD and physical diseases[17,18]. In addition, factors precipitated by one disease can increase the risk of another. For example, motivational impairments present in MDD may affect the ability to exercise and maintain a healthy diet, resulting in an increased risk of physical diseases.

The consequences of this high level of comorbidity are far reaching, with evidence supporting worse outcomes[19], reduced adherence to treatment[20], increased mortality[21], and increased health care utilization and costs[22-26]. MDD poses a substantial disease burden, ranking second among leading causes of years lived with disability according to the Global Burden of Disease Study[27]. Using data from the Danish registry and previously published methods[28], more than one third of the total nonfatal burden (34.4%) in people with MDD was due to comorbid physical diseases, such as respiratory diseases (e.g., asthma and chronic obstructive pulmonary disorder), pain-related conditions, cardiovascular diseases, and gastrointestinal disorders.

Comorbidity of MDD and physical diseases also introduces several clinical challenges that are often not apparent within the published literature, in which clinical populations can be highly selected. These include a higher prevalence of other mediating or moderating disorders such as substance abuse and personality dis-

orders, a more complicated therapeutic alliance, issues pertaining to adaptive health behaviors[29], drug-drug interactions and adverse events induced by medications used for physical and mental diseases.

This paper draws on meta-analyses and Mendelian randomization studies, as well as on randomized controlled trials (RCTs) where appropriate, to provide a detailed, up-to-date overview of: a) the epidemiology of the comorbidity of MDD and physical diseases, including prevalence and bidirectional risk; b) shared biological pathways implicated in the pathogenesis of MDD and physical diseases, c) socio-environmental factors that serve as shared risk and protective factors; d) clinical management of MDD and physical diseases, including considerations regarding prevention and treatment; and e) future directions and emerging research related to optimal care of people with comorbid MDD and physical diseases.

While this review focuses on, and primarily refers to, MDD and its relation to physical diseases, it is also informed by evidence concerning closely related constructs, such as elevated depressive symptoms, as well as by studies that investigate depression but have not used formalized DSM-5/ICD-11 diagnoses of MDD. Furthermore, we use the term "physical diseases" throughout to refer to non-psychiatric and non-communicable diseases discussed in the review. We do, however, acknowledge that this is an imperfect definition, as MDD itself can also be considered a physical disease with well-observed physical mechanisms (as discussed in the paper) and clinical manifestations.

EPIDEMIOLOGY OF THE COMORBIDITY OF MAJOR DEPRESSIVE DISORDER AND SPECIFIC PHYSICAL DISEASES

In this section, we provide an overview of the association between MDD and specific physical diseases as emerging from meta-analytic data.

MDD has been identified as a risk factor for several physical diseases (see Figure 1), with much evidence suggesting a bidirectional relationship. We explore this further using results from Mendelian randomization studies, which use genetic variation as a natural experiment to investigate the causal relations between potentially modifiable risk factors and health outcomes[30]. This method is arguably less susceptible to known limitations of observational studies such as confounding or reverse causation[30], thus complementing

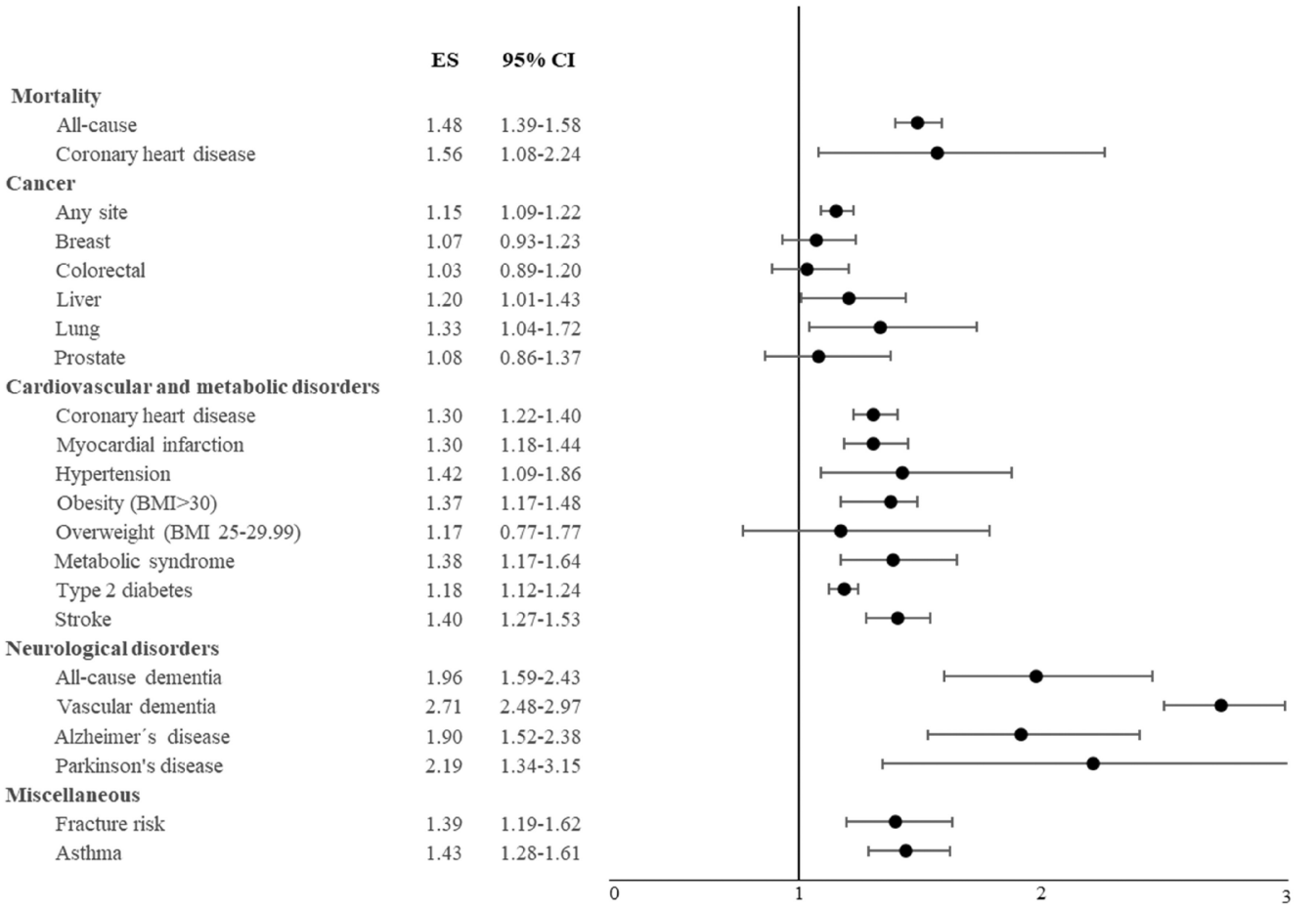

Figure 1 Meta-analytic data on the risk for mortality and physical diseases among individuals with major depressive disorder compared to people without this condition. ES – effect size (risk ratio or odds ratio), BMI – body mass index (see also supplementary information).

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the extensive observational literature in this area.

MDD is also highly prevalent in a range of physical diseases (see Figure 2), with an approximate mean aggregate point prevalence of 25%. While this is higher than the general population[1,31], meta-analyses that have synthesized prevalence estimates often report high heterogeneity (with I^2 typically higher than 90%)[32-34], suggesting that prevalence is highly variable. The influence of factors such as disease stage, severity, setting (e.g., hospital vs. community), tim-

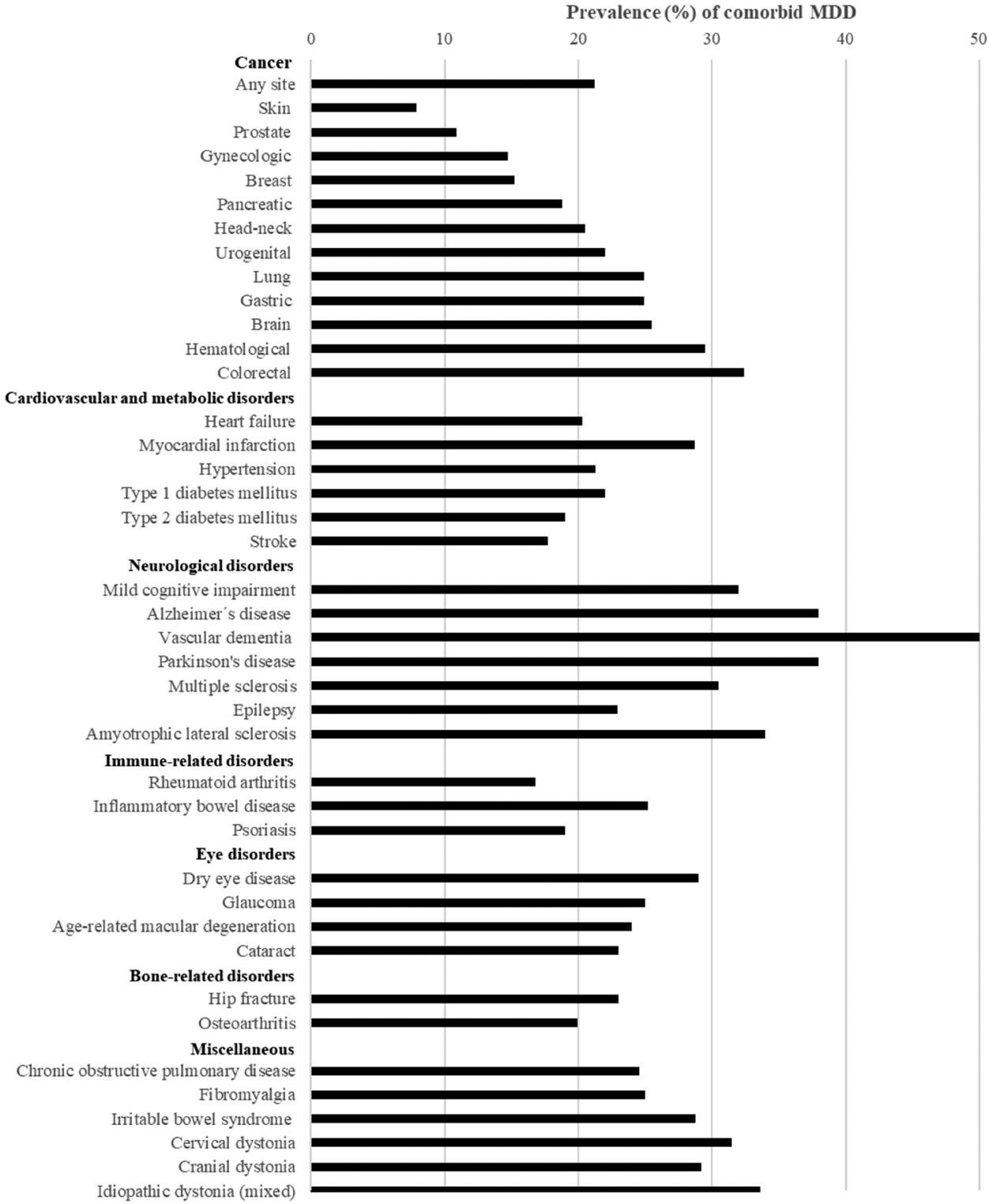

Figure 2 Point prevalence of comorbid major depressive disorder (MDD) in physical diseases, using estimates from published meta-analyses (see also supplementary information).

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ing (e.g., immediate vs. years after disease onset), measurement methods (e.g., self-report, clinical diagnosis, clinician rating), and definition of MDD used (e.g., clinical cut-offs vs. elevated symptoms) in determining these estimates should be considered. Such factors are explored in the following disease-specific sections.

Cardiovascular diseases

The point prevalence of MDD after myocardial infarction is reported to be 28.7%, while it is 17.7% after stroke[33,35]. Prevalence rates of MDD are influenced by the severity of the comorbid disease[36]. For example, in people with heart failure, MDD rates range from 11% in people with less functional impairment (class 1 according to the New York Heart Association) to 42% in those with severe impairment (class 4)[36].

Many guidelines and position statements, such as those of the American Heart Association and the European Society of Cardiology[2,37], consider MDD a potentially modifiable risk factor for cardiovascular diseases. Indeed, several meta-analyses of prospective cohort studies have reported that baseline MDD increases the risk of future cardiovascular events[38-41]. While previous meta-analyses have raised concerns regarding a variety of potential confounders[39], a recent meta-analysis of Danish registry cohorts that accounted for these confounders reported that MDD diagnosis was associated with higher risk of subsequent ischemic heart disease (hazard ratio, HR: 1.63, 95% CI: 1.36-1.95) and stroke (HR: 1.94, 95% CI: 1.63-2.30)[11]. On the other hand, baseline ischemic heart disease (HR: 1.79, 95% CI: 1.43-2.23) and stroke (HR: 2.62, 95% CI: 2.09-3.29) were associated with subsequent MDD, demonstrating a bidirectional relationship[11].

Recent Mendelian randomization studies have indicated that the genetic liability for MDD is associated with an increased risk for coronary artery disease (odds ratio, OR: 1.26, 95% CI: 1.10-1.43)[42], small vessel stroke (OR: 1.33, 95% CI: 1.08-1.65)[43], and myocardial infarction (OR: 1.15, 95% CI: 1.07-1.23)[44], while there is a null association between genetic liability for cardiovascular diseases and subsequent increased MDD risk (see Figure 3)[42-44].

In people with cardiovascular diseases and stroke survivors, MDD is associated with increased health care costs and unplanned rehospitalizations[23,25], an increased risk of atrial fibrillation and chest pain[2], and a significant decrease in quality of life[45,46]. Furthermore, MDD occurring after a cardiovascular event is associated with poorer adherence to treatments and adaptive lifestyle changes[20],

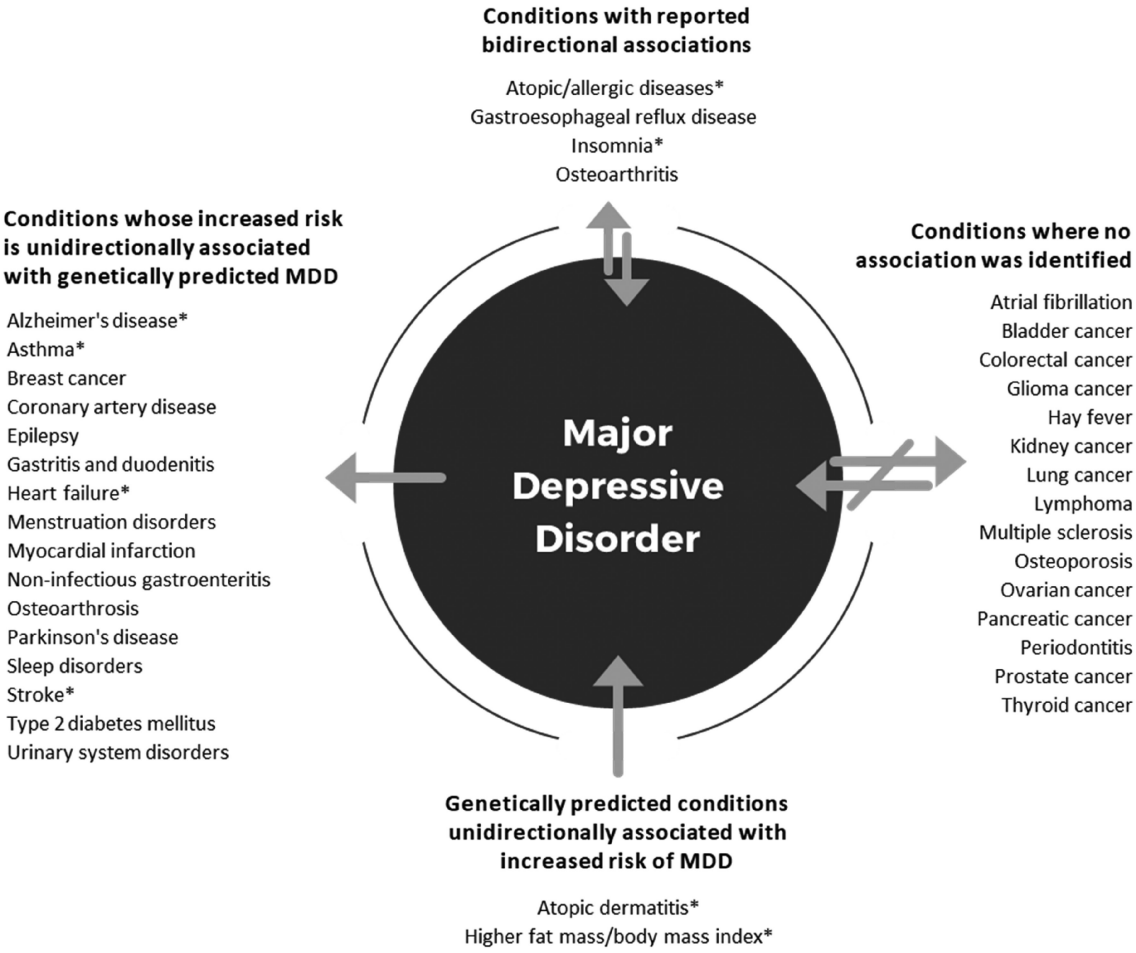

Figure 3 Association between major depressive disorder (MDD) and physical diseases according to Mendelian randomization studies. Asterisks indicate conditions where the evidence is mixed (see also supplementary information).

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including attendance and completion of rehabilitation[47], which improves after resolution of depressive symptoms[48].

Diabetes mellitus

The point prevalence of MDD is high in both type 1 (22%) and type 2 (19%) diabetes mellitus[32]. People with MDD have a higher risk of type 2 diabetes (risk ratio, RR: 1.18, 95% CI: 1.12-1.24)[49] and people with type 2 diabetes have a higher risk of MDD (RR: 1.15, 95% CI: 1.02-1.30)[50]. Previous meta-analyses of prospective cohort studies suggest a bidirectional association between MDD and type 2 diabetes. However, recent Mendelian randomization studies suggest a unidirectional relationship, with genetic liability for MDD associated with increased risk of type 2 diabetes[42,51].

Comorbid MDD in people with type 2 diabetes is associated with poorer adherence to diabetes treatment[52] and self-care activities (e.g., exercise, healthy eating)[53,54], increased health care costs[22,54], reduced glycemic control[55,56], and increased hospital admissions and complications[57-60]. A recent meta-analysis reported that baseline MDD is associated with an increased risk of incident diabetes-related complications (HR: 1.14, 95% CI: 1.07-1.21)[57]. The risk of functional disability is also substantially increased in people with comorbid MDD and diabetes compared to individuals with one disease[58].

Furthermore, comorbid MDD and diabetes may increase the risk of other physical diseases[59]. For example, a prospective study reported that individuals with diabetes and comorbid MDD had an increased risk of dementia (HR: 2.69, 95% CI: 1.77-4.07) compared to individuals with diabetes only[41,59].

Metabolic syndrome

The metabolic syndrome includes insulin resistance, central obesity, impaired glucose tolerance, raised triglycerides, reduced high density lipoprotein (HDL) cholesterol, non-alcoholic fatty liver disease, and hypertension[61]. It is a major risk factor for developing both type 2 diabetes and cardiovascular diseases, as well as for premature mortality[62].

There is a bidirectional association between MDD and the metabolic syndrome. People with MDD are 1.38 (95% CI: 1.17-1.64) times more likely than the general population to develop the metabolic syndrome[63], while people with the metabolic syndrome are 1.49 (95% CI: 1.20-1.87) times more likely to develop MDD[10]. This association exists in both adults and older people[64]. However, a Mendelian randomization study suggests that genetically predicted MDD is positively associated with the risk of the metabolic syndrome, but that genetically predicted metabolic syndrome is not associated with the risk of MDD[65].

Individual components of the metabolic syndrome, such as obesity, may also have a bidirectional association with MDD. Meta-analyses of prospective observational studies report that baseline MDD increases the risk of developing obesity (RR: 1.37, 95% CI: 1.17-1.48), and baseline obesity increases the risk of onset of future MDD (RR: 1.18, 95% CI: 1.04-1.35)[66]. However, several recent Mendelian randomization studies have shown that genetically predicted increased body mass index and fat mass are associated with an increased risk of MDD, while the reverse is not true[67-70].

Emerging studies also suggest that the metabolic profile can influence the association between obesity and MDD, with a recent meta-analysis of cross-sectional studies reporting that metabolically unhealthy obesity was associated with a 30% to 83% increased risk of MDD, whereas obesity with a favorable metabolic profile was not associated with an increase of that risk[71]. Furthermore, one cohort study found that, while the metabolic syndrome overall was not associated with the resolution of MDD symptoms, abnormal circulating triglycerides and cholesterol were associated with a lower likelihood of symptom resolution[72]. This is in keeping with another small case-control study which found an association between low HDL cholesterol and poorer MDD prognosis[73].

Cancer

Large meta-analyses have estimated the point prevalence of MDD in people with cancer to be around 21%[4,74,75]. However, this estimate is highly variable depending on a range of factors related to disease course (e.g., early vs. advanced stages), treatment time point (acute treatment vs. survivorship), and assessment method (self-reported or clinical diagnosis)[4,74,75].

A previous meta-analysis demonstrated that prevalence rates of MDD are generally highest during the acute phases of the disease and during treatment (estimates between 14% and 27%)[4]. Prevalence rates at 2- and 5-year post-treatment generally return to similar estimates as the general population or healthy controls[76,77].

Previous meta-analyses and large cohort studies have also identified that the prevalence of MDD can substantially vary based on cancer type[78-80]. While there is some inconsistency between studies, hematological, gastrointestinal, lung and gynecological cancers are often identified as having a higher MDD prevalence compared to other types of cancer[78-80].

A large number of factors have been associated with a greater risk of MDD in people with cancer[81]. A recent systematic review identified a range of somatic (e.g., advanced cancer stage, comorbidities, pain), sociodemographic (e.g., female gender), social (e.g., low socioeconomic status, impaired social support), and psychiatric (e.g., previous history of MDD) factors that were commonly associated with increased MDD risk. Pre-existing MDD and personality factors such as neuroticism were the most consistently associated[81].

MDD may modestly increase the risk of cancer onset and mortality. A recent meta-analysis reported that MDD and anxiety were associated with a significantly increased risk of cancer incidence (RR: 1.13, 95% CI: 1.06-1.19) and cancer-specific mortality (RR: 1.21, 95% CI: 1.16-1.26)[82]. These estimates are similar to a previous meta-analysis that examined MDD separately from anxiety[83,84].

Mendelian randomization studies suggest that genetically predicted MDD is associated with a slightly increased risk of breast cancer (OR: 1.09, 95% CI: 1.02-1.17), but not of a range of other can-

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cer types[85,86]. Some studies have also reported that MDD may predict lower T-cell cytokine expression and reduce treatment adherence or initiation[87,88], while improvement in depressive symptoms has been associated with increased survival in people with cancer[89].

Neurological diseases

MDD is associated with multiple neurological diseases. Meta-analytic evidence from longitudinal studies indicates that MDD is a meaningful risk factor for future Alzheimer's disease (RR: 1.90, 95% CI: 1.52-2.38)[90], all-cause dementia (RR: 1.96, 95% CI: 1.59-2.43)[90], vascular dementia (RR: 2.71, 95% CI: 2.48-2.97)[90], and Parkinson's disease (RR: 2.20, 95% CI: 1.87-2.58)[91]. Some authors suggest that MDD may be considered a prodrome of these neurological diseases[92].

Mendelian randomization studies provide further support to a unidirectional association for some neurological diseases, but not all. Genetically predicted MDD is a risk factor for Parkinson's disease and epilepsy, while there is no evidence for genetically predicted neurological diseases being a risk factor for MDD[93,94]. Two Mendelian randomization studies provided contrasting results for MDD and Alzheimer's disease[95,96], and two studies found no association between genetically predicted MDD and multiple sclerosis[97,98].

Meta-analyses and reviews indicate an overall high point prevalence of MDD in Parkinson's disease (38%)[34], epilepsy (22.9%)[5], migraine (up to 47.9%)[99], multiple sclerosis (30.5%)[6], mild cognitive impairment (32%)[7], and Alzheimer's disease (41%)[8]. MDD is consistently associated with reduced quality of life across several neurological diseases[100], as well as with increased disability and poorer functioning. For example, MDD is associated with increased seizure frequency in people with epilepsy and excessive daytime sleepiness in Parkinson's disease[101,102].

Furthermore, MDD increases the risk for progression and chronicity[103-105]. For example, the presence of depressive symptoms is associated with faster progression from mild cognitive impairment to Alzheimer's disease[104]. A separate study reported similar results for migraine, where depressive symptoms dose-dependently increased the risk of progression from episodic to chronic disease[105].

Osteoporosis

A growing body of evidence shows that MDD is associated with poor bone health[106-109]. A meta-analysis pooling the results of 21 cross-sectional studies involving 1,842 participants with MDD and 17,401 controls found that MDD was associated with lower bone mineral density at the lumbar spine, femur and total hip, with small to medium effect sizes[110].

A separate meta-analysis also reported that MDD was prospectively associated with an increased annual bone loss rate of 0.35% (95% CI: 0.18-0.53), and a 39% increased risk of fracture (RR: 1.39, 95% CI: 1.19-1.62)[106]. Complicating this, the use of selective serotonin reuptake inhibitors (SSRIs) is independently associated with osteoporosis[107].

A recent Mendelian randomization analysis failed to substantiate these findings, reporting that a genetic predisposition towards MDD showed no effect on bone mineral density or fracture risk, concluding that reverse causality or residual confounding may be at play[108]. In support to these latter data, there is some evidence that the prevalence of MDD is increased in those with osteoporosis, with a recent meta-analysis reporting that 23% of older adults with osteoporosis also reported MDD[109]. MDD is also common following fractures, likely due to associated pain and reduced functional status[111].

Mortality

While both MDD and several physical diseases are associated with independent increases in mortality, their coexistence compounds this risk. For example, a prospective analysis using the UK Biobank (N=499,830) reported that both MDD (HR: 1.26, 95% CI: 1.19-1.33) and diabetes mellitus (HR: 1.62, 95% CI: 1.52-1.72) independently increased the risk of mortality; however, the presence of both conditions amplified that risk (HR: 2.16, 95% CI: 1.94-2.42)[112]. Furthermore, a recent umbrella review found that MDD increased all-cause or cardiovascular-related mortality in patients with several physical diseases (i.e., heart failure, coronary heart disease, stroke, cancer, chronic kidney disease, diabetes mellitus)[113]. The associations between MDD and all-cause mortality among populations with cancer, post-acute myocardial infarction, and heart failure showed the strongest level of evidence[113]. There is also evidence that increasing levels of psychological distress can confer greater risk of premature death owing to cardiovascular diseases [114].

Research using Danish registers and the recently introduced life-years lost metric[115] examined the overall reduction in life expectancy associated with MDD, and explored how different types of physical diseases contribute to this premature mortality[21]. Overall, men and women with MDD lost 8.27 (95% CI: 8.10-8.47) and 6.40 (95% CI: 6.25-6.55) years of life respectively, compared to age- and sex-matched controls from the general population. The co-occurrence of a mood disorder such as MDD and substance use disorders (e.g., alcohol use disorder) had a substantial further impact on premature mortality, with an additional ~6 years lost[116]. The contribution of comorbid cardiovascular disease to premature mortality in those with MDD was comparable in men and women (~1 year), while respiratory diseases accounted for further 0.71 and 0.99 years lost in men and in women respectively.

COVID-19 and neuropsychiatric sequalae

A global 27.6% (95% CI: 25.1-30.3) increase in MDD prevalence due to the COVID-19 pandemic has been estimated[117], although this finding remains controversial[118]. The long-term psychiatric and physical disease consequences of the infection or "Long COVID" are currently unclear and an area of emerging research[119,120].

Long COVID has been associated with new onset of a range of physical diseases (e.g., cardiovascular disease, type 2 diabetes)[120].

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There also appears to be an increased risk of MDD as well as other mental disorders[121]. However, this risk may be transient and similar to non-COVID severe respiratory infections[122].

Furthermore, COVID-19 infection has also been implicated in several biological processes relevant to MDD and associated physical diseases, such as immune activation, particularly in those with severe acute infection[120,123]. Neuroimaging studies in people who have recovered from the infection have also identified numerous small brain changes, including structural and functional alterations within the hippocampus[124]. Continued research is required to elucidate the potential neuropsychiatric sequelae of COVID-19 infection.

SHARED RISK FACTORS

Lifestyle and behavioral risk factors

To fully understand the comorbidity between MDD and physical diseases, it is crucial to consider the role of health behaviors. In the general population, there is broad acceptance that adverse health behaviors, such as alcohol consumption, tobacco smoking, or illicit drug use can increase the risk of physical diseases and associated mortality[125,126]. Additionally, there is strong evidence that low physical activity, poor diet, and poor sleeping patterns are key drivers of subsequent physical diseases.

For instance, the World Health Organization's 2020 Physical Activity Guidelines presented moderate-certainty evidence of a curvilinear dose-response relationship between physical activity and risk of all-cause mortality and multiple life-threatening physical diseases, including cardiovascular diseases, diabetes mellitus and even cancers[127]. Similarly, striking data on the impact of eating patterns was provided by the 2016 Global Burden of Disease Study[128], which identified "poor dietary habits" as one of the leading risk factors for mortality worldwide, with almost one fifth of all deaths attributable to it.

While the relationship between sleep and disease is non-linear, there is a strong indication from large-scale studies that sleeping problems are a risk factor for common physical diseases[129], with either too short or too long sleep durations associated with increased mortality risk[130].

These lifestyle factors are also likely to be a central driver of the heightened rates of physical diseases (and associated mortality) observed in MDD, especially when considering the extensive evidence that people with MDD are affected by the same lifestyle and behavioral health risks[131,132]. For instance, systematic reviews have found that people with MDD are significantly more likely to engage in excessive alcohol and tobacco use[131,132], and have a higher total food intake and reduced diet quality[133], higher levels of sedentary behavior[134], and poorer sleep continuity and quality[135], compared to non-depressed people.

Despite the observed trends, the causality of the relationships between health behaviors and MDD is unclear and likely bidirectional. On the one hand, multiple independent meta-analyses of prospective data have shown that physical inactivity, tobacco smoking, excessive alcohol consumption, impaired sleep, and poor diet at baseline are all associated with a subsequently increased risk of developing MDD[136,137]. On the other hand, developing MDD can have a pronounced detrimental impact on an individual's health behaviors, including sleep impairment, low motivation for physical activity, over/under-eating, and a propensity to self-medicate with tobacco, alcohol or substance use[138,139].

MDD is also associated with reduced adherence to treatment for chronic diseases, which may further exacerbate disease outcomes[140]. Furthermore, certain medications used to treat MDD may induce behavioral risks. For instance, the appetite-increasing effects of medications such as mirtazapine and quetiapine may partially account for the increased risk of obesity and cardiometabolic diseases among people treated with these medications[141,142], while the sedative effects of agents such as mirtazapine and tricyclic antidepressants (e.g., amitriptyline, clomipramine)[138] could inhibit individuals from engaging in regular physical activity.

Stressful life events

Life stressors can have negative consequences on both mental and physical health across the lifespan. Research on early life stress – often referred to as childhood adversity or adverse childhood experiences – primarily focuses on experiences of maltreatment (e.g., abuse or neglect) and household dysfunction (e.g., domestic violence or parental mental illness)[143,144]. For instance, accumulating evidence from several meta-analyses of both retrospective and prospective studies suggests that adverse childhood experiences are related to a more than two-fold increase in the risk of developing MDD in adulthood[143,145].

In parallel, a recent meta-review of 16 meta-analyses indicated moderate associations between adverse childhood experiences and respiratory diseases (d=0.44), gastrointestinal diseases (d=0.38), neurological diseases and pain (d=0.34), and cardiovascular diseases (d=0.32), as well as weak associations with cancer (d=0.24), diseases of the musculoskeletal system (d=0.21), and endocrine and metabolic diseases (d=0.17) in adulthood[144].

Adverse childhood experiences are additionally associated with a higher likelihood of experiencing further severe stressful life events later in life (e.g., losing one's job or divorce)[146-149]. Notably, severe stressful life events frequently precede the onset of a first episode of MDD[150]. Furthermore, a meta-analysis of six RCTs[151] suggests that, although severe stressful life events affect the prognosis of individuals seeking treatment for MDD, these effects are largely shared with environmental factors (e.g., social support or employment status) that may be a consequence of the experience of trauma.

Severe stressful life events are also associated with an increased risk of physical diseases, particularly cardiovascular diseases[152]. Adults from the general population who experienced a stressful life event had a 1.1 to 1.6-fold elevated risk of incident coronary heart disease and stroke[152]. Stressful life events can also act as a disease trigger among individuals at risk for cardiovascular diseases, and as a factor aggravating the prognosis of these diseases[152]. A further consideration is that physical diseases and their related symptoms

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(e.g., pain, fatigue), as well as treatment-related factors (e.g., surgery, medication side effects), can be a stressful life event accompanied by feelings of grief, stress, shame, and other negative psychological states that can exacerbate or increase the risk of MDD.

It is important to note that not all individuals who experience life stress develop MDD and/or a physical disease[153,154]. Indeed, a meta-analysis of cross-sectional studies showed that resilience (i.e., the ability to successfully adapt to difficult, challenging or disruptive life events) significantly mediated the association between adverse childhood experiences and symptoms of MDD[155]. Likewise, social connection and belongingness, adaptive lifestyle behaviors, positive parenting, and supportive relationships from carers, friends and within the community are all resilience-promoting factors that may have a protective effect on an individual's risk for MDD following adverse childhood experiences[156,157].

Social risk factors

Reducing the burden of disease related to MDD and poor physical health requires the focus to move beyond individual risk and protective factors to consider the social determinants of health, i.e., "the conditions in which people are born, grow, live, work and age"[158]. In this context, risk and protective factors cluster and are interwoven at multiple levels. Some occur at different times, while others persist across the life course[159].

There is clear evidence that both MDD and physical diseases are more common in people from disadvantaged backgrounds[160,161]. Both absolute poverty (i.e., level of income necessary to maintain basic living standards) and relative poverty or deprivation (i.e., level of income necessary to maintain minimum living standards relative to those of a society or country) have independent, adverse impacts on mental and physical health. Indigenous people, those from cultural or linguistic minorities, migrants or refugees, and people with a disability are more likely to experience socioeconomic disadvantage than other individuals in the community[162]. Intergenerational poverty and trauma are also common and confer an additional risk to family members of parents who live in poverty.

Other common social determinants that intersect with the aforementioned variables include gender inequality and restrictive gender norms, which, in many settings, privilege the male or masculine over the female or feminine[163]. Discrimination, marginalization and victimization linked to gender are associated with a greater risk of experiencing poor mental and physical health. This appears to be mediated through exposure to stress-related experiences, but may be also driven by gender-specific disparities in access to education, home ownership, and safety in the home and employment (women and girls), or an over-representation in the criminal justice system and reduced access to health care (men and boys)[164].

Racial, ethnic or sexual minority status is associated with higher rates of health problems, through experiences of discrimination and systemic biases[165]. Structural racism, cultural racism[166] and intergenerational trauma can also impact on mental and physical health. As with gender norms, norms related to race become embedded in later childhood and adolescence, and the effects persist across the life course[167].

The above social determinants exert their impacts on mental and physical health through multiple inter-related mechanisms. Effects on health may be direct (e.g., through restricted access to quality nutrition) or mediated through individual (e.g., security provided by safe housing and/or neighborhoods), relational (e.g., exposure to parental stress in childhood; presence of positive peer relationships in adolescence), psychological (e.g., effects on self-efficacy), or institutional (e.g., neighborhood disadvantage, access to health care) factors[168]. These factors interact in complex ways with other social determinants (e.g., gender inequality, exposure to hazardous work, child labor). For example, low social status because of poverty may be associated with discrimination and other disadvantages (e.g., exposure to violence, social isolation or loneliness), all of which are associated with poor mental and physical health[169-172].

Such processes also have a developmental and transgenerational aspect[161]. The impacts of exposure to adversity may differ according to developmental periods, and health impacts may also vary by type of adversity. Children and adolescents raised in poverty may be less likely to accumulate the "health capital" that contributes to educational attainment, health literacy, a healthy parent-child attachment style, positive peer relationships, the development of social and emotional skills, and the ability to parent later in their own life[173]. As a consequence, early life poverty contributes to intergenerational cycles of poverty and transmission of mental and physical health risks[173]. In contrast, protective factors such as access to resources (e.g., education), consistent relationships (i.e., supportive and stable families), and social and policy factors (e.g., access to affordable health care, social welfare) may assist individuals to overcome the impacts of adversity[174].

SHARED BIOLOGICAL MECHANISMS

Several biological pathways are implicated in the pathogenesis of both MDD and physical diseases (see Figure 4). Here, we first provide a conceptual overview of how these shared pathways contribute to disease outcomes, and then discuss several prominently investigated biological mechanisms. Pathogenesis is unlikely to be driven by any singular pathway alone, but rather by the interaction of multiple pathways affecting both mental and physical health.

Neuroprogression and somatoprogression

The term "neuroprogression" refers to the process of psychiatric disease acceleration and its underlying operative factors, including reduced neurogenesis and increased apoptosis as well as hypothalamic-pituitary-adrenal (HPA) axis dysfunction, immune and oxidative stress, and mitochondrial dysfunction. Its manifestations, such as impaired cognitive function and structural neuroimaging changes, and consequent deteriorating function and declining treatment response, tend to increase with stage[175,176].

The same pathways (e.g., inflammation, oxidative stress, mitochondrial dysfunction) that are involved in neuroprogression of MDD

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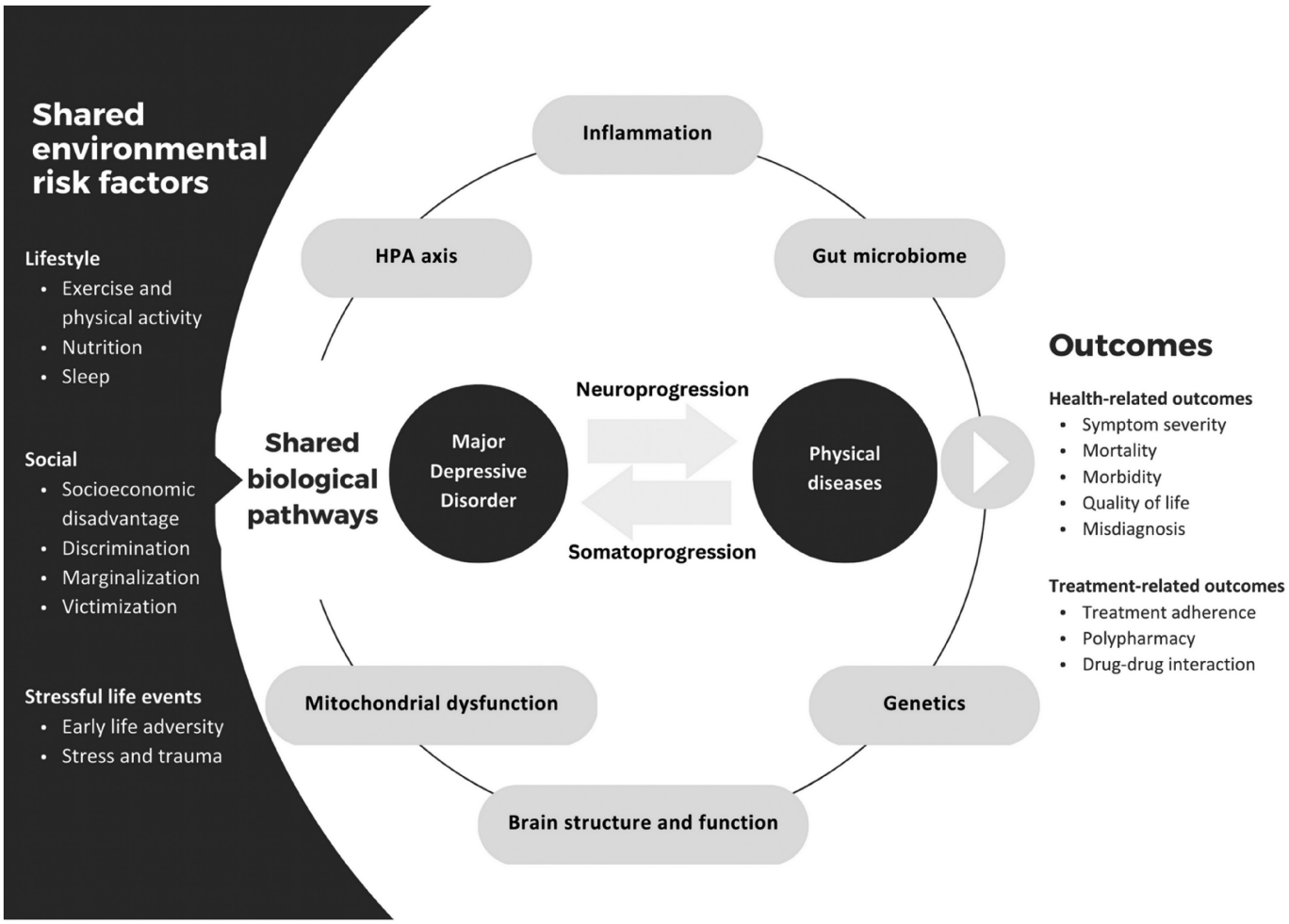

Figure 4 Environmental and biological factors influencing the comorbidity between major depressive disorder and physical diseases. HPA – hypothalamic-pituitary-adrenal.

have a parallel role in the genesis and progression of many physical comorbidities, including cardiovascular diseases and the metabolic syndrome. The term "somatoprogression" refers to these pathways and the accumulation of a physical comorbidity that often occurs in parallel to neuroprogression. This construct overlaps with that of allostatic load, which encompasses biological effects secondary to the aggregate burden of stress and wear and tear on the body[177].

The above two parallel processes provide a theoretical foundation for the comorbidity across MDD and physical diseases. Understanding these processes also provides a mechanistic foundation for the construct of clinical staging[178]. Many of the individual elements of progression – such as inflammation[179], oxidative stress[180], and neurogenesis[181] – are also individually targetable and potentially plastic.

Genetics

Both MDD and several physical diseases have a substantial genetic component. For example, family and twin studies suggest that the genetic contribution to MDD accounts for approximately 37% of the variation in susceptibility[182]. Similar rates are estimated for physical diseases such as coronary artery disease (~43%)[183] and stroke (~38%)[184]. Furthermore, several large meta-analyses of genome-wide association studies (GWAS) have identified genetic loci associated with MDD[185] as well as with many physical diseases, such as obesity[186], type 2 diabetes mellitus[187], and heart disease[188].

There are several shared genetic factors between MDD and physical diseases. For example, in a large UK study, significant genetic correlations were identified between MDD and body mass index, coronary artery disease, and type 2 diabetes mellitus[189]. The significant genetic overlap between MDD and cardiometabolic conditions, in particular coronary artery disease and obesity, has been confirmed in other studies[190]. In contrast, a large study by the Brainstorm Consortium reported little genetic overlap between common neurological diseases (such as Alzheimer's disease, epilepsy, multiple sclerosis, and Parkinson's disease) and psychiatric diseases including MDD[191].

A recent systematic review identified 24 pleiotropic genes that are shared between mood disorders and cardiometabolic condi-

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tions[192]. Shared genetic pathways were detected between type 2 diabetes mellitus, cardiovascular disease, obesity and MDD, relating to axonal guidance (e.g., glycogen synthase kinase-3 beta, insulin-like growth factor-1), corticotropin releasing hormone, and 5′adenosine monophosphate-activated protein kinase signaling[192].

Hypothalamic-pituitary-adrenal axis

Stress is a major precipitating factor for the onset and progression of psychiatric disorders, including MDD. HPA axis dysregulation has been implicated in the onset, symptom profile, severity, chronicity, treatment response, and treatment resistance in MDD[193-196]. A large meta-analysis reported that individuals with MDD tend to display elevated cortisol (d=0.33, 95% CI: 0.21-0.45) and adrenocorticotropic hormone (ACTH) (d=0.27, 95% CI: 0.00-0.54) levels[195].

HPA axis dysregulation in MDD becomes more pervasive with age. For example, basal cortisol is elevated during all phases of the diurnal cycle in older adults with MDD (g=0.88, 95% CI: 0.60-1.15) [197]. This is noteworthy, as late-life MDD is associated with immune dysregulation and high rates of comorbid physical diseases[197] and consequent polypharmacy.

Mechanistically, the signal transduction of glucocorticoids is involved in an array of behavioral, cardiovascular, cognitive, immunological, metabolic and reproductive processes[198,199]. According to longitudinal data from a large cohort study[200], increased levels of hair cortisol were predictive of MDD somatic symptoms. Furthermore, the results of a meta-analysis[195] support the notion that HPA axis hyperactivity is a link between MDD and comorbid physical diseases, such as diabetes mellitus, dementia, coronary heart disease, and osteoporosis. This link seems to be particularly pronounced in people who present with melancholic or psychotic features[195]. It is, however, worth noting that there are several other pathways involved in the stress response that may be relevant to the comorbidity between MDD and some physical diseases, including the renin-angiotensin system[201].

Unfortunately, despite the apparently common co-occurrence of HPA axis dysregulation, MDD and comorbid physical diseases, few clinical studies have specifically investigated their interplay. Exclusion criteria have been often applied to people with both MDD and a comorbid physical disease in clinical trials.

There is some indication that sex-specific differences in HPA axis dysregulation exist in humans. However, the relevant evidence is somewhat contradictory (possibly due to variability in menstrual cycle stage, health, age, or stress modality)[202]. This area is still largely under-researched.

Inflammation

It is generally appreciated that MDD is associated with inflammation[203], at least in a proportion of individuals (~30-50%)[204]. In large meta-analyses, MDD has been related to the up- or down-regulation of acute-phase reactants[205], cytokines[206] and chemokines[207]. Low-grade inflammation – as indexed by a concentration of C-reactive protein (CRP) higher than 3 mg/L – is more likely in individuals with depression than in matched controls, occurring in around a quarter of the former according to a large meta-analysis (OR: 1.46, 95% CI: 1.22-1.75)[205].

Chronic low-grade inflammation is also a feature of a variety of physical diseases (e.g., cardiovascular, metabolic and respiratory diseases; cancer, osteoporosis, arthritis) as well as of other serious mental disorders[208-211]. In both atherosclerotic conditions and depressive episodes, a pro-inflammatory state can be induced by hypercortisolemia, reduced paraoxonase-1 levels, as well as reduced HDL and elevated low-density lipoprotein (LDL) cholesterol, leading to endothelial injury and the downstream release of interleukin-6 (IL-6), CRP, tumor necrosis factor-alpha (TNFα), and soluble endothelial adhesion molecules[211]. Activated immune cells release IL-1β, stimulating the production of interferon gamma and TNFα, which are commonly elevated in MDD, cardiovascular diseases, metabolic diseases such as diabetes mellitus, and autoimmune conditions such as rheumatoid arthritis[212].

Data-driven GWAS analysis supports the association between MDD and immune disorder liability. A recent study (N=500,199) found that MDD was positively correlated with Crohn's disease, ulcerative colitis, hyperthyroidism and asthma (Z-scores: 0.09-0.19, $q<0.05$)[213]. The most robust association was observed for asthma (OR: 1.25, 95% CI: 1.13-1.37)[213]. IL-4 is a major cytokine involved in asthma, and is associated with a T helper (Th)-2 cell response[212]. In MDD, the induction of M1 macrophage cells may lead to IL-4 production via the compensatory immune-regulatory system (CIRS) Th-2 response[212]. Another point of possible overlap is in elevation of highly pro-inflammatory Th-17 cells, which are implicated in autoimmune disorders[212]. Emerging evidence supports a role for Th-17 cells in the genesis and progression of MDD[214,215]. This suggests that there may be a subgroup of MDD people with a "lymphoid immunophenotype" (adaptive immune response), contrasting with the innate-immune response myeloid immunophenotype[204].

Mitochondrial function and energy metabolism

Mitochondrial function is widely recognized as a factor in the pathophysiology of several psychiatric disorders, including MDD[216], and a variety of physical conditions, such as metabolic diseases[217], cardiovascular diseases[218], and neurodegenerative disorders[219].

Mitochondria are dynamic organelles that generate adenosine triphosphate (ATP) and are involved in calcium homeostasis, as well as playing key roles in the redox state of the cell and apoptosis. For example, mitochondrial dynamics substantially affect cardiomyocyte health, with multiple rodent studies showing that alterations to processes such as fusion and fission can lead to cardiomyopathy, hypertension, atherosclerosis and heart failure[220]. ATP production is also impaired in people with MDD compared with healthy controls[221,222]. Preclinical models of MDD suppress mitochondrial function[223]. In humans, there is evidence of reduced mitochondrial respiration[221] and neuroimaging evidence of decreased energy generation[224] in MDD.

Oxidative stress occurs when there is an excess of reactive oxy-

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gen species, which are predominantly produced by mitochondria during the process of respiration, and especially when respiration is inefficient. While reactive oxygen species are required by cells and play a role in processes such as cell signaling, a sustained excess of these species can cause damage to DNA and various cellular structures[225]. There is a wealth of evidence that oxidative stress is associated with both MDD[227] and several physical conditions, such as insulin resistance[217] and cardiovascular diseases[218,227].

Mitophagy is the selective degradation of dysfunctional/damaged mitochondria, and is a crucial process for optimal cellular function and in the adaptation to cellular stress. Adequate mitophagy is not only required for optimal ATP production, but also to reduce oxidative stress, and impairments to mitophagy have been associated with both MDD and physical diseases such as cardiovascular diseases[228,229] and neurodegenerative disorders[230]. For example, insufficient mitophagy has been shown to have a role in the development of atherosclerosis, which is partly mitigated by inflammatory processes, and could contribute to cardiomyopathy, heart failure, and myocardial infarction[231].

Gut microbiome

The gut microbiome, increasingly implicated in MDD and other psychiatric disorders[232], as well as in several physical diseases, may potentially underpin their interactions. The microbiome affects the gut-brain axis through several of the aforementioned shared mechanisms, i.e. regulating physiological homeostasis via the autonomic nervous system and the HPA axis, and signaling within and between the enteric and central nervous systems via neuromodulatory metabolites and immunomodulatory responses[233].

There is overlap in the relevant mechanistic pathways across MDD and physical diseases. Prime amongst these is the physical maintenance of the tight-junction integrity of the intestinal epithelium, which contains immune signaling pathways and is mediated by the microbiome and its metabolites[234]. Disruptions to the gut epithelial cell wall and transfer of microorganism-associated molecular patterns, such as lipopolysaccharides (LPS), cause an immune cascade through the activation of toll-like receptors (TLRs) and inflammatory responses, with flow-on effects to blood-brain barrier function and neuroinflammation[235,236]. In addition to a compelling body of pre-clinical evidence[237], plasma biomarkers of increased gut permeability, including LPS and zonulin, have been found in greater abundance in people with depressive disorders compared to healthy controls[238].

Evidence of bacterial translocation from the gastrointestinal tract to systemic circulation has been observed within several organs and tissues and is considered contributory to a range of physical diseases. For example, atherosclerotic plaques have microbial communities resembling the gut and oral microbiomes. The resulting immune activation may contribute to the pathophysiology of plaques in the context of cardiovascular disease[239]. In the metabolic syndrome, systemic LPS activates a TLR4-mediated inflammatory response and alters insulin signaling within white adipose tissue[240]. Increased osteoclastic activity and reduced bone mineral density have been observed following increased intestinal permeability in the context of osteoporosis[241]. Evidence of serum and plasma IgG against periodontal bacteria in human and animal studies of Alzheimer's disease has also supported the systemic and neurological relevance of the oral microbiome[242].

Microbial metabolites – most notably, short-chain fatty acids, trimethylamine N-oxide and bile acids – have cell-specific effects on the central nervous system as well as on peripheral organs involved in MDD comorbidities[233]. The strength of evidence for microbial causation varies across conditions, being relatively stronger in the metabolic syndrome. For example, germ-free mice are resistant to the obesogenic effects of high-fat diets[243], whilst wild type and germ-free mice experience metabolic alterations from microbiota-modulating antibiotic and fecal microbiota transplant interventions[244-247]. However, this link is less established in osteoporosis and cancers outside of colorectal cancer[241,248]. Larger longitudinal cohort and intervention studies are required to translate pre-clinical observations across all diseases.

Brain structure and function

Severe emotional distress can directly or indirectly (e.g., through functional reorganization of associated neural networks) affect neural substrates that are key in modulating depressive symptoms[249], including hippocampus, amygdala, hypothalamus, insula, striatum, and medial and orbitofrontal as well as anterior cingulate cortices[250-252]. Physical diseases (e.g., stroke, brain tumors, multiple sclerosis, Alzheimer's disease and Parkinson's disease), as well as lesions or neurodegeneration induced by such diseases, can similarly affect these neural substrates via disease-specific pathology or indirectly via elevated emotional distress (e.g., at time of diagnosis and adjustment).

Common neural circuitries can also emerge from shared underlying biological mechanisms. These constitute either common underlying mechanisms influencing the liability to both MDD and physical diseases, or mediating mechanisms in causal relationships between MDD and physical diseases. Autonomic, immunoinflammatory and neuroendocrine dysregulations influence the brain's homeostatic, cognitive, reward and emotional circuitries[253]. The insula, the hypothalamus (particularly the paraventricular nucleus) and the anterior cingulate cortex play a critical role in monitoring the body's homeostatic state. Deficiencies in immunological, glucocorticoid and metabolic (e.g., leptin, insulin) signaling affect the activity of these interoceptive regions and their connectivity with core emotional, cognitive and motivational brain regions[254].

Alterations in interoceptive regions are associated with "sickness behavior", characterized by lack of energy, weakness, hyperalgesia, loss of appetite and insomnia, commonly associated with both MDD and physical diseases such as cancer[255,256], as well as symptoms of increased appetite, energy balance disturbances and hypersomnia, which are shared between atypical MDD and metabolic diseases including obesity, the metabolic syndrome and diabetes mellitus[15,257]. Deficiencies in endocrine and immunological signaling via interoceptive pathways can also lead to interrup-

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tions in dopamine signaling in the brain's reward and motivation circuitries[258], most notably in the orbitofrontal and ventromedial prefrontal cortex, ventral tegmental area and ventral striatum[259,260]. An extensive literature implicates shared alterations in the reward circuitry in MDD, neurodegenerative disorders, and obesity[261-263].

The interoceptive network receives afferent projections from the vagus nerve via the nucleus tractus solitarius and the thalamus[264], thereby receiving information from respiratory, cardiac and gastric sources. A frontal-vagal brain network – including the medulla of brainstem, hypothalamus, amygdala, insula, as well as dorsolateral prefrontal, anterior cingulate and orbitofrontal cortex – has been proposed to link cardiovascular diseases, metabolic diseases and MDD, because of its influence on the cardiovascular system, mood, appetite and sleep[265].

Finally, hippocampal atrophy is shared across MDD and many physical diseases. Impairment of hippocampal neurogenesis, neuroplasticity and dendritic remodeling is critically linked to several physical conditions[266-268]. On the other hand, lower hippocampal volume is one of the most consistently reported structural brain abnormalities in MDD[250,269]. The hippocampus is part of the brain's default mode network. Grey matter and functional connectivity of this network are commonly affected in MDD and neurological diseases[270,271].

CLINICAL MANAGEMENT

Diagnosis of comorbid MDD and physical diseases

Diagnosing comorbid MDD in people with physical diseases can be challenging, as several depressive symptoms overlap with symptoms of these diseases (e.g., fatigue, aching, sleep disturbances, appetite and weight changes), thus showing poorer sensitivity and specificity in this context. Furthermore, grief and distress due to physical diseases are frequent, particularly in severe disease states (e.g., terminal cancer), and can result in clinical difficulties to distinguish between adjustment reactions or "appropriate sadness" and MDD[272]. For example, a study reported that only half of individuals with MDD and diabetes mellitus were recognized as having depression during standard care and, out of those correctly identified, few received adequate treatment[273].

Similar complexities are present for the appropriate diagnosis of physical diseases in people with MDD. This has been termed "diagnostic overshadowing", describing the tendency for clinicians to misattribute physical symptoms (e.g., pain) to a person's mental disorder rather to a potential comorbid physical disease[274].

Prevention of comorbid MDD

Interventions aimed to prevent MDD have been explored in people with at-risk physical diseases. A Cochrane review[275] found very low-certainty evidence from ten RCTs supporting the use of antidepressant medications in the prevention of MDD. Similar results have been reported by systematic reviews of trials exploring antidepressant medications as a means for preventing MDD related to administration of interferon alpha. However, due to the limited evidence base, tolerability and acceptability of preventive antidepressant use has not been rigorously assessed. Further research is required to ensure that the benefits of prophylactic interventions outweigh potential medical (e.g., side effects) and financial considerations.

Preventive psychotherapy interventions have been similarly understudied. The previously cited Cochrane review[275] identified only one trial (N=193), which examined problem-solving therapy in age-related macular degeneration, and found lower odds for developing MDD compared with treatment-as-usual (OR: 0.43, 95% CI: 0.20-0.95). A recent meta-analysis of RCTs of psychotherapy – mostly cognitive-behavioral therapy (CBT) – as a preventive intervention for MDD found positive results, including for a sub-sample of people with physical diseases (n=11; RR: 0.71)[276]. A systematic review of five RCTs evaluating the effectiveness of psychotherapy in preventing MDD in adults with cancer found that it was superior to usual care (standardized mean difference, SMD: –0.23). In a cohort of people with breast cancer, findings were similarly favorable (SMD: –0.32)[277].

However, a large RCT in people with cardiovascular disease and/or diabetes showed that there was no significant effect of a CBT-based preventive program. Four risk factors predicted MDD at follow-up: baseline anxiety and MDD symptoms, stressful life events, and the presence of three or more chronic diseases[278]. It may be that preventive programs will be more effective if targeted at high-risk cohorts such as those with high subclinical depressive symptoms (indicated prevention) or other MDD risk factors (selective prevention).

In summary, proactive treatment to prevent MDD in at-risk individuals with physical diseases may be a viable approach, but large high-quality RCTs are needed.

Treatment of comorbid MDD

Among individuals with MDD and a physical disease, systematic reviews of RCTs have shown that antidepressants, compared to placebo, show effect sizes similar to or even larger (i.e., SMDs higher than 0.50)[279-286] than those for MDD without physical comorbidity, where SMDs range between 0.17 and 0.49[287]. Such effect sizes have been reported for MDD comorbid with cardiovascular diseases (e.g., coronary artery disease[281], ischemic heart disease[282], myocardial infaction[288]), neurological diseases (e.g., multiple sclerosis[279], Parkinson's disease[289], stroke[290,291]), diabetes mellitus[292], cancer[286,293], rheumatoid arthritis[280] and human immunodeficiency virus (HIV) infection[294]. Whether these larger effect sizes are due to differing biological processes, smaller placebo effects, or other reasons such as small-study inflation, needs further study. Indeed, most meta-analyses were based on a few small RCTs.

In other diseases – such as epilepsy, inflammatory bowel disease, traumatic brain injury, asthma and chronic obstructive pulmonary disease – few or no RCTs of antidepressant treatment for comorbid MDD have been conducted[295-301], resulting in a sparse evidence base

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for treatment recommendations.

Many studies have demonstrated that psychotherapies[302] – including CBT[303-305], mindfulness-based interventions[306-308], compassion-focused therapies[309,310] and problem-solving therapy[311] – effectively treat MDD in people with diseases such as cancer[307,308], diabetes mellitus[312,313], cardiovascular diseases[314-318], HIV infection[319], psoriasis[320], multiple sclerosis[279,321,322], inflammatory bowel disease[305], chronic obstructive pulmonary disease[323-325], and kidney failure[326-328].

Regardless of intervention type, effect sizes are generally low to moderate[309], and many individual studies are at risk of bias[309], have low sample sizes, and use heterogenous research designs[310]. Findings concerning cardiovascular diseases are more robust, particularly in people with heart failure. An umbrella review concluded that there is sound evidence that psychotherapy can treat MDD in people with ischemic heart disease, based on the findings of four systematic reviews[318]. Similarly, in a scoping review of nine psychotherapy trials, seven showed significant reductions in MDD symptoms, although two did not maintain benefit at longer-term follow-up[314].

Psychotherapy can also be delivered online or via telephone to people with physical diseases, with comparable outcomes to face-to-face delivery[303,304,322,329], particularly if clinician-guided[303]. These modalities have also been shown to be acceptable to individuals[330,331], which is particularly important for those who may have mobility or accessibility difficulties[322].

Effect of MDD treatments on physical disease outcomes

In addition to improving depressive symptoms, antidepressant medication may have positive effects on physical disease outcomes. For example, a recent umbrella review found that SSRIs may improve fasting glucose/HbA1c and pain[332], and may reduce hospitalization rates in coronary artery disease[281]. Among individuals with diabetes mellitus, antidepressant treatment is reported by RCTs to improve glycemic control[292], and is associated with lower mortality[333] and a lower risk for myocardial infarction[334]. Furthermore, antidepressants improve motor function and disability after stroke[290], and motor symptoms in Parkinson's disease[289].

There is also tentative evidence that psychotherapies may improve physical health-related quality of life and fasting glucose/HbA1C[332], and have a positive impact on physical outcomes in people with ischemic heart disease[318]. However, results are limited by the low quality of trials, and recent advances in medical care may have outweighed previously demonstrated benefits of psychotherapy[318]. A systematic review found that the effect of psychotherapy on disease activity in people with inflammatory bowel disease was not clear[305].

A systematic review focusing on people with rheumatic conditions reported that CBT led to reduction of pain severity in four of seven studies, and to significant reduction of fatigue in one of four studies[329]. Psychotherapy may also lead to increased engagement in lifestyle behaviors that positively influence physical health[327,335]. For example, CBT has been found to improve medication adherence in people undergoing dialysis[327]. However, it is not yet known whether these changes translate into improved physical outcomes [327].

Effect of physical disease treatments on MDD outcomes

Medications such as non-steroidal anti-inflammatory drugs (NSAIDs), statins, angiotensin-converting enzyme (ACE) inhibitors, drugs acting on the renin-angiotensin system, and cytokine inhibitors may yield additional positive effects when added to an antidepressant[179,336-339], reducing depressive symptoms among individuals with a physical disease[338,339]. As a prominent example, a recent meta-analysis found that anti-inflammatory drugs improved depressive symptoms with a SMD of 0.64 (95% CI: 0.40-0.88) when used as add-on to antidepressants in MDD, and of 0.41 (95% CI: 0.22-0.60) when used as monotherapy among people with a physical disease[338]. Furthermore, anti-inflammatory add-on to antidepressants in MDD improved response and remission rates[338].

The most frequently studied anti-inflammatory drugs are NSAIDs, cytokine inhibitors and statins. Several of these drugs (e.g., statins) target physical diseases that are disproportionally common in people with MDD (e.g., cardiovascular diseases and diabetes mellitus)[340]. The antidepressant effects of these drugs provide further support to the previously discussed shared biological mechanisms of MDD and physical diseases (e.g., inflammation, HPA axis activation, and mitochondrial dysfunction)[341].

On the other hand, many commonly used treatments for physical diseases can induce depressive symptoms as a side effect[342]. A well-known example is interferon or IL-2 treatment, in which up to 80% of individuals develop depressive symptoms, often dominated by somatic/neurovegetative manifestations within the first weeks, and 25% develop a major depressive episode within 48 weeks[343]. The proposed mechanism is pro-inflammatory and immune-activating[344], with administration of pro-inflammatory cytokines representing one of the most robust human models of MDD[345].

Adverse events and clinical considerations of management

Among individuals with physical diseases, it is important to balance the potential antidepressant effects of pharmacotherapy with possible side effects. The adverse event profile of any antidepressant must be tailored to the symptomatic and risk profile of the comorbid physical disease and the specific individual. Potential adverse events include weight gain and the related risk of developing or exacerbating diabetes mellitus (particularly relevant to tricyclic antidepressants and mirtazapine)[346]; cardiac toxicity and QTc prolongation (highest risk with tricyclic antidepressants and lowest with sertraline)[347,348]; impact on bone metabolism, increasing the risk for osteoporosis and fractures (especially with SSRIs)[349]; and bleeding, which is further increased when combining multiple classes of medications (e.g., SSRIs and NSAIDs[350]). Furthermore, clinicians need to consider potential drug-drug interactions, which are divided

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into pharmacodynamic (more frequent with older antidepressants) and pharmacokinetic (e.g., affecting hepatic metabolism, with antidepressants often being dependent on cytochrome P450 metabolism)[351].

Overall, the antidepressant treatment of MDD that is comorbid with a physical disease will benefit from interdisciplinary care (e.g., frequent discussions with the clinician responsible for the treatment of the physical disease), consideration of patient-related factors (e.g., age, pain, polypharmacy, and previous antidepressant trials all affect choice of antidepressant drug), and ongoing management. Finally, psychotherapy trials have not systematically assessed adverse events or contraindications[352-354]. Therefore, psychotherapy intervention trials in individuals with physical diseases have thus far reported very few adverse events, but clinical monitoring is indicated[310,324].

FUTURE DIRECTIONS AND CONCLUSIONS

This paper reviews the substantial evidence base documenting that MDD is highly prevalent in populations with a range of common physical diseases, and vice versa. This high level of comorbidity translates into poorer economic and treatment outcomes.

A range of mechanisms have been implicated in both MDD and comorbid physical diseases, suggesting shared pathophysiology. We have discussed prominent pathways, such as inflammation, the gut microbiome, mitochondrial function, brain structure and function, and the HPA axis. Additional pathways requiring further investigation are endothelial and autonomic dysfunction, leptin and insulin signaling, and biological aging[2,15].

Shared mechanisms provide opportunities for treatment that may benefit both MDD and comorbid physical diseases, but may also inform the investigation of potential off-label interventions and drug-repurposing strategies. For example, statin therapy, commonly prescribed for cardiovascular diseases, is being trialed for MDD[355,356]. Metformin (a medication typically prescribed for type 2 diabetes mellitus) and candesartan (an angiotensin II receptor blocker) are also being trialed for depression[357].

Similarly, there are a range of lifestyle, physiological, social and genetic risk factors that are shared by MDD and physical diseases[358]. Interventions that address these factors may improve both psychiatric and physical outcomes. An example is the developing evidence base to support the use of lifestyle approaches to mental health care. Clinical guidelines[359] increasingly suggest that lifestyle interventions should be a major component of MDD management. Of the lifestyle domains reviewed in one of these guidelines[360], the strongest recommendations when treating MDD were for exercise, relaxation, and work-directed, sleep and mindfulness-based interventions. There was further evidence to support dietary and green space interventions, but fewer data from RCTs to support interventions targeting smoking, loneliness or social support.

Further to the need for additional intervention and prevention strategies is the need for new models addressing challenges to accessible care and integrating psychiatric and physical considerations[361]. Having MDD, as well as subthreshold depressive symptoms, that are comorbid with a physical health condition amplifies barriers to accessing and engaging in potentially helpful treatments and self-management strategies[16]. Treatment needs are often multiplied, diverse and chronic, placing strain on health services and families, especially in low- and middle-income countries, cultural and linguistic minorities, and First Nations people, and those in rural areas with scarce resources[362]. Innovative strategies to overcome these barriers, incorporating integrated care for physical health conditions (particularly cardiometabolic diseases) in MDD, are required [363].

One example is the collaborative care model, usually involving a physician and at least one other health professional (and sometimes peer or carer supports) who communicate with each other and the individual with MDD in a structured and planned way, to optimize treatment and care[16,61]. Contact and follow-up appointments are organized by a central coordinator (e.g., a case manager) who promotes self-management strategies (e.g., symptom and treatment monitoring and management, goal setting, problem solving, healthy lifestyle habits, and stress management)[364]. There can also be emphasis on enhancing patient-centered decision making, and consideration of patients' broader recovery goals[16,365]. Including lived experience input may also strengthen and support the broader aims of person-centered management.

Collaborative care interventions have shown positive effects for people with depressive symptoms and coronary heart disease[366], breast cancer[367], and diabetes mellitus[292,364]. Such interventions appear to be equally effective in delivering MDD care for people with and without physical diseases[368]. Their effect on physical health, however, varies depending on the specific condition[292,369]. Implementing collaborative care interventions also requires careful consideration of leadership and delivery resources, costs for ongoing care, and cultural context[370].

A further potential way to extend the reach and scope of effective treatment and care is provided by digital technologies. eHealth and mHealth interventions range from multicomponent intensive psychosocial programs to briefer specific self-management interventions (e.g., targeting exercise)[16,371-373]. They can be adapted to suit context and resource capabilities, although the majority of RCTs are being conducted in high-income countries[372].

A meta-analysis of RCTs of digital interventions reported a significant moderate effect on depressive outcomes (g=–0.37, 95% CI: –0.60 to –0.14)[371]. Key predictors of significant effects were a two-way "clinician-patient communication loop", coupled with progress monitoring and adjustment of treatment as well as self-management strategies over time[362,371]. Successful interventions ranged from those delivered via phone to more complex ones delivered via web platforms, highlighting the adaptability of digital approaches[371]. At this stage, however, the number of trials on each comorbid physical disease varies, and results are inconsistent[371,372]. More attention also needs to be paid to the scalability and validation of digital interventions and how they can be better integrated into health services[362,372].

In summary, there is now a substantial body of evidence documenting a shared biological and environmental pathogenesis between MDD and several physical diseases. Further efforts are

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required to develop prevention and intervention strategies that target these shared pathways. These include investigation of therapeutics that target overlapping biological mechanisms (e.g., statins, metformin, interventions on gut microbiome) and the integration of strategies that address risk factors such as lifestyle behavior (e.g., exercise, diet). Furthermore, research and implementation efforts are now required to accelerate the development and translation of transdiagnostic, interdisciplinary models of care that consider both psychiatric and somatic presentations.

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