**Title: Depression in Disabling Medical Conditions – current perspectives**

**Authors:**

Hugo Senra, Ph.D[1,2]; Susan McPherson, Ph.D.[2]

**Affiliation:**

[1] Centre for Research in Neuropsychology and Cognitive and Behavioural Intervention (CINEICC) – University of Coimbra, Portugal;

[2] School of Health and Social Care, University of Essex, United Kingdom;

**Corresponding Author:**

Hugo Senra, Ph.D. Centre for Research in Neuropsychology and Cognitive and Behavioural Intervention (CINEICC) – University of Coimbra, Portugal.

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**Abstract**

Chronic diseases commonly entail disability and are highly comorbid with mental health problems, particularly depression. Prevalence of depression across different disabling conditions affecting adult patients, as well as risk factors for depression in these patient groups are reviewed in the current work, with a particular focus on the literature published in the past 5 years. The prevalence of depression in disabling conditions is higher than in the general population, and is associated with different factors. Examples of disease specific factors include neurological implications of stoke, diabetic related conditions (e.g. amputation), limitations imposed by vision loss caused by age-related eye diseases, fatigue in rheumatoid arthritis, and pain in cancer. Common factors identified across different conditions include pre-morbid depression, history of mental health problems, poor social support, disease-related disability, multi-morbidity, and less adaptive coping strategies. We also reviewed studies suggesting a potential bidirectional relationship between depression and chronic disease, particularly for stroke, cardiovascular disease, diabetes, and potential factors mediating that relationship. Current findings suggested that long-term depression might be associated with an increased risk of subsequent physical health problems, although the nature of that relationship and its underlying mechanisms are still unclear.

**Key Words:**

Depression; Disability; Chronic Diseases.

## Introduction

The World Health Organization estimates over a billion people have some form of disability (1). Disability is commonly associated with factors such as poor health, chronic medical conditions, multiborbidity, ageing, and age-related conditions (1). In adults, disability is generally caused by a primary condition entailing long-term negative implications for functioning. Common examples of this are neurological diseases (e.g. stroke, dementia), metabolic diseases (e.g. diabetes), auto-immune diseases (e.g. rheumatoid arthritis), cancer, and eye diseases (e.g. age-related macular degeneration). Mental health problems are often comorbid with disabling conditions, particularly depression, which tends to be more prevalent in these patient groups than in the general population (2-4). The co-occurrence of mental health problems and disabling conditions has posed a great challenge to clinicians and researchers, as depression itself is a source of disability (5,6), and can entail further implications for physical health (7,8). The World Health Organization ranked depression as the single largest contributor to global disability, having accounted for 7.5% of all years lived with disability in 2015 (9). The chronicity of disabling conditions together with the disabling effect of depression makes these cases even more complex and difficult to treat. To understand the interplay of depression and disabling conditions is paramount to improve care, and to prevent long-term disability among these patient groups.

The current work intends to provide a narrative review of literature addressing depression associated with disabling conditions in adults, with a particular focus on large cohort studies and meta-analyses published since 2015. The main goals of this review are to summarize, provide an update, and discuss: the prevalence of depression in several disabling conditions; the main risk factors for depression across different disabling conditions; and the hypothesis of a bidirectional relationship between depression and disabling conditions. In the first two sections of this review we summarize recent findings on the prevalence of depression across disabling conditions, and the main risk factors for depression in those conditions. In the third section of this review, the literature suggesting depression as a risk factor for developing further chronic disease, and / or a potential bidirectional relationship between both conditions, is examined in more detail, including risk ratios (RR), odds ratios (OR), and hazard ratios (HR) found in those studies.

## Prevalence of depression in disabling conditions

Epidemiological studies and meta-analyses have estimated the prevalence of depression across different disabling conditions in adult patients, as summarised in Table 1. In these

patient groups, prevalence of depression ranges between 12% and 39%, as presented in Table 1. Studies suggest that the prevalence of depression tends to vary slightly according to the way depression was measured, such as diagnostic classification systems (e.g. ICD, DSM), and standardized instruments (e.g. HADS; PHQ-9; CES-D).

*Table 1. Prevalence of Depression across Disabling Medical Conditions in Adults*

| Condition | Study | Type of Study | Number of Studies Reviewed | Sample Size | Prevalence of Depression | Measure of Depression | 95% CI (%) | $I^2$ Heterogeneity |
|---|---|---|---|---|---|---|---|---|
| Stroke | Ayerbe et al., 2013[18] | Meta-analysis | 43 | 20 293 | 29% | DSM; Standardized measures[a] | 25-32 | 93.9% |
| Stroke | Mitchell et al., 2017[10] | Meta-analysis | 108 | 15 573 | 33.5% | ICD or DSM | 30-37 | =80% |
| Spinal Cord Injury | Williams et al., 2015[11] | Meta-analysis | 19 | 35 676 | 22.2% | ICD | 18.7-26.3 | 90.4% |
| Limb Amputation | Mckechnie et al., 2014[19] | Systematic Review | 9 | NA | 35.2%[b] | DSM; ICD; Standardized measures[a] | NA | NA |
| Limb Amputation | Singh et al., 2009[20] | 3-Year Prospective | NA | 68 | 19.1% | HADS | NA | NA |
| Peripheral artery disease[c] | Arya et al., 2018[21] | 11-Year Retrospective | NA | 155 647 | 16% | ICD | NA | NA |
| Coronary Disease[d] | Correa Rodrigues et al., 2020[12] | Meta-analysis | 8 | 596 | 19% | Standardized measures[a] | 13-26 | 92.2% |
| Coronary Disease | Murphy et al.,2020[22] | 12-month Cohort | NA | 911 | 15%-22%[e] | HADS | NA | NA |
| Diabetes | Roy et al, 2012[23] | Systematic Review | 20 | NA | 12% (type 1) 19% (type 2) | Standardized measures[a] Diagnostic Interviews | NA | NA |
| Type 2 Diabetes | Lloyd et al., 2018[24] | Multi-center Observational | NA | 2783 | 17% | PHQ-9 | NA | NA |
| Diabetes | Kahledi et al., 2019[13] | Meta-analysis | 248 | 83 020 812 | 28% | Standardized measures[a] | 27-29 | >98% |
| Rheumatoid Arthritis | Matcham et al., 2013[14] | Meta-analysis | 72 | 13 189 | 16.8%-38.8%[f] | Standardized measures[a] | Variable[f] | 19.8%-90.0% |
| Rheumatoid Arthritis | Fragoulis et al., 2020[25] | 12-month Cohort | NA | 848 | 12.2%[g] | HADS | NA | NA |
| Osteoarthritis | Stubbs et al., 2016[15] | Meta-analysis | 49 | 15 855 | 19.9% | GDS; CES-D | 15.9-24.5 | 96.1% |
| Eye Diseases | Zheng et al., 2017[16] | Meta-Analysis | 28 | 6589 | 25% | Standardized measures[a] | 20-30 | 96.5% |
| Cancer | Krebber et al., 2014[17] | Meta-analysis | 211 | 82 426 | 14%-24%[h] | ICD; DSM; HADS; CES-D | variable[h] | 86%-96% |
| Cancer | Linden et al., 2012[26] | 6-year Cohort | NA | 9394 | 13% and 16.5%[i] | 21-itemPsychosocial Screen for Cancer | NA | NA |
| Cancer | Hartung et al., 2017[27] | Epidemiological multi-centre | NA | 4020 | 24% | PHQ-9 | NA | NA |

DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; HADS: Hospital Anxiety and Depression Scale; PHQ-9: Patient Health Questionnaire; GDS: Geriatric Depression Scale; CES-D: Centre for Epidemiological Studies of Depression; (a) Several standardized measures of depression used across studies, including HADS, PHQ-9, GDS, CES-D. (b) Mean of values reported in 9 studies, ranging between 20.6% and

63%; (c) 40.6% of deaths, and 9% of amputations during the follow-up period; (d) Meta-analysis conducted to examine the prevalence of depression before and after coronary artery bypass graft surgery – in our table we only report prevalence of depression after surgery; (e) Prevalence of depression: 22% in patients while in hospital after admission; 17%, 2-4 months after the event; 15%, 6-12 months after the event; (f) Prevalence of depression varied according to the measure of depression used in studies, being 16.8% (95% CI, 10-24; $I^2$=73,4%) for DSM major depressive disorder; 34% (95% CI, 25-44; $I^2$=90.9%) for HADS (cut-off score of 8); 36% (95% CI, 32-40; $I^2$=83,1%) for CES-D; and 38.8% (95% CI, 34-43; $I^2$=19.8%) for the PHQ-9; (g) Baseline prevalence of depression; (h) Prevalence of depression varied according to the measure of depression used in studies, being 14% (95% CI, 11-16) for ICD / DSM major depressive disorder; 18% (95 CI, 16-20) for HADS; and 24% (95% CI, 21-26) for CES-D; (i) 13% of prevalence of clinical depression and 16.5 % of prevalence of sub-clinical depression. NA: Not applicable or Not-available.

Studies show a tendency for patients with chronic disabling conditions to experience more persistent forms of depression. In stroke patients, depression persists over 10 years after the initial event (18). Among patients who underwent limb amputation the incidence of depression varies in the first 2-3 years following amputation, but increases again after the second year of follow-up (20). In patients with coronary disease, depression is more prevalent in the first months after surgery, but persists at least 1 year after the event (22). Research suggests that depression can persist in several conditions such as cancer (17), rheumatoid arthritis (25), vision impairment (16), diabetes (28), and stroke (29).

Prevalence of depression can vary across different disease sub-types. Type 2 diabetes seems to be associated with higher prevalence rates of depression than type 1 diabetes (23). For eye diseases, depression is more prevalent in patients with ophthalmological conditions leading to vision impairment, such as dry-eye diseases (29%), glaucoma (25%), and age-related macular degeneration (24%) (16). Finally, according to a meta-analysis reviewing 211 studies, the prevalence of depression appeared to be highest in some types of cancer, namely cancer of the digestive tract, the brain, female genitalia and in patients with haematological malignancies (17).

## Risk factors for depression in disabling conditions

*Stroke*

Factors relating to post-stroke depression have been reviewed in a meta-analysis examining 36 studies (30). The highest odds ratios were found for factors such as history of mental health problems, family history of mental health problems, severity of stroke and disability incurred, age (>70) and being female. Social support appears to have a protective effect against depression. Another meta-analysis (10) highlighted risks for post-stroke depression such as disability, aphasia, and lesions affecting the left hemisphere. An updated review (31) found these same factors to be associated with post-stroke depression with the

addition of large and multiple strokes and strokes affecting brain areas such as anterior/frontal, and basal ganglia.

*Spinal Cord Injury*

A systematic review of 24 studies identified psychosocial correlates of depression following spinal injury (32). Protective factors in relation to depression include life satisfaction, disability acceptance, environmental supports, and community participation. Experiences of persisting pain after spinal cord injury were also associated with the co-occurrence of depression (d = -2.49), in a meta-analysis examining 19 studies (N = 2934) (33). Finally, two recent observational studies highlighted the relationship between poor social support and depression in this patient group (34,35).

*Limb Amputation*

Among patients who underwent limb amputation, depression has been associated with factors such as severity of injury (number of amputations), and disability, according to a systematic review of 9 studies (19). Other factors identified in cohort studies include multi-morbidity (20), moderate and low cognitive function (36), poor physical fitness (36), low stress resilience (36), and pre-surgery depression (37). A 12-month cohort study drew attention to the moderation effect that perceived social support might have between functioning and depression (38).

*Cardiovascular Diseases*

A recent 12-month cohort study investigated potential predictors of depression among 911 patients with coronary heart disease after a cardiac event (22). The main predictors of early and late depression include financial strain, poor self-rated health, history of depression, low socioeconomic status, age under 55 and smoking. A recent meta-analysis also highlighted the importance of history of pre-surgery depression as a predictor of post-cardiac event depression (12). A 3-year cohort study carried out with 3013 patients with acute coronary syndrome suggested a longitudinal relationship between low social support and symptoms of depression (39).

*Diabetes*

The co-occurrence of depression and diabetes has been widely studied, with depression itself likewise being identified as a risk factor for developing diabetes (24,40). A

study carried out in 14 countries with 2783 type 2 diabetic patients (41) identified potential risk factors for depression such as being female, lower level of education, poor physical activity, high level of diabetes distress, and history of major depressive disorder. A 10-year cohort study conducted in Canada highlighted being female, history of traumatic events, and having any chronic disease or heart disease as risk factors for depression associated with diabetes (42). Another 11-year cohort study examining risk factors for depression in type 2 diabetic patients (N = 50 590) suggests that depression is strongly associated with severity of disease progression, regardless of other potential covariates such as demographic status, comorbidities, or medication compliance (43). A multicentre European study carried out in 12 countries with type 2 diabetic patients also found that being female and less physically active significantly increases the risk of having major depressive disorder (44). Finally, a cohort study with 3240 patients suggested that being female and younger are risk factors for clinical depression associated with diabetes (45).

*Rheumatoid Arthritis*

A 12-month study examining factors associated with depression in rheumatoid arthritis patients highlighted factors such as baseline depression and anxiety, disease activity (reversible manifestations of rheumatoid arthritis), greater disability levels, and C-reactive protein levels suggesting a possible relationship between inflammation and depression (25). In an observational study conducted with 317 rheumatoid arthritis patients with chronic pain, factors such as low relatedness (defined as the sense or feeling of being genuinely connected to other people), less activity engagement, higher levels of anxiety, and being older were noted as significant predictors of depression in a hierarchical multiple regression model (46). A prospective multicentre study with 1004 rheumatoid arthritis patients (47) found a range of characteristics independently associated with depressive symptomatology: age <60 years, higher impact of disease (e.g. pain, functional disability, fatigue, sleep, physical well-being, emotional well-being, coping), and presence of chronic pain. Poor social support was independently associated with depression in a cross sectional study (48). Finally, comorbid hyperthyroidism was also identified as a risk factor for depression, according to a retrospective cohort study with 3657 rheumatoid arthritis patients (49).

*Eye Diseases*

An 11-year longitudinal study conducted with more than 1 million subjects, 5846 of whom were visually impaired, examined the risk of depression associated with vision

impairment (50). The presence of vision impairment was significantly associated with clinical depression in comparison with the control group (non-visually impaired). Age (>60 years) and being female were also identified as potential risk factors for depression among people with vision impairment. In a cross-sectional study conducted with 990 patients with low vision, factors such as age (older), ethnicity (non-white), poor self-reported health, and poor visual function were independently associated with depressive symptoms (51). A 5-year longitudinal study with 7584 participants found a significant association over time between self-reported vision impairment and symptoms of depression (52). However, in studies where vision impairment / visual acuity was measured, and not self-reported (e.g. logMAR), a direct relationship was not found between visual acuity and depression (53-55). An observational study conducted with 300 patients with wet Age-Related Macular Degeneration suggested that depression might occur in patients who are not yet visually impaired, and therefore are not yet experiencing any kind of disability (55). It was proposed that patients' distress may be associated with anticipatory anxiety of going blind in the future due to disease progression. Finally, there is growing evidence that poor perceived social support might increase the risk for depression in patients with vision impairment (56,57).

*Cancer*

Risk factors for depression among cancer patients have been identified in studies examining different types of cancer. A 24 month longitudinal study with 264 women diagnosed with breast or gynaecologic cancer suggested that patients with high neuroticism scores are more likely to have depressive symptomatology (58). In a 9-year retrospective population-based study conducted with 2625 colorectal cancer survivors, a longer time since diagnosis was associated with fewer depressive symptoms over time, whereas age (older), being male, low education level, and comorbid conditions were associated with higher prevalence of depression (59). A 24-month prospective cohort study of 261 treated uveal melanoma survivors showed that worry about recurrent disease, symptoms (e.g. ocular irritation), and functional problems could be a risk factor for depression over time (60). A systematic review examined 39 studies addressing prospective predictors of longer-term distress after cancer (several types of cancer) (61). The review highlighted baseline levels of distress and neuroticism as risk factors that consistently predicted long-term distress (including depression). According to a systematic review of longitudinal studies on psychological adjustment to breast cancer (62), initial levels of anxiety and depression, fatigue, neuroticism, less adaptive coping (e.g. avoidance, cancer-related rumination), and

poor social support predict late depression symptoms. A 12 month longitudinal study of 219 newly diagnosed head and neck cancer patients identified baseline major depressive or anxiety disorder, stressful life events in the previous year, and neuroticism as the main predictors of depression over time (63). In a sample of 230 Chinese patients diagnosed with oral cancer, positive coping strategies such as hope and optimism were identified as protective factors for depression, whereas perceived stress and stigma, particularly in the dimension of social isolation, were associated with greater risk for depression (64). In a recent systematic review, symptoms of depression at an earlier time point were significantly associated with depression at a later time point, in head and neck cancer patients (65). In the same review, other sociodemographic and clinical factors (e.g. age, gender, tumour location, pain, fatigue, body image, number of events, coping, etc) were not significantly associated with the course of depression. A 12 month cohort study with 309 cancer patients (several types of cancer) showed that after adjusting for covariates such as treatment group, baseline depression, and time point, pain experienced by patients was an important predictor of depression, whereas newly diagnosed or stable cancer, being female, lower physical co-morbidity and higher socioeconomic status were associated with better depression outcomes (66). Finally, a meta-analysis reviewing 41 studies suggested that optimism and adaptive coping (e.g. seeking social support) were key protective factors for depression among women with breast cancer (67).

*Multimorbidity*

Having multiple chronic conditions (multimorbidity) has been identified as an important risk factor for the occurrence of depression. An 8-year cohort study with 3397 subjects showed that the transition to having a diagnosis of multiple chronic conditions considerably increases the incidence of depressive symptoms, after controlling for age, gender, income, race, and a lifetime diagnosis of depression (68).

**Is there a bidirectional relationship between depression and disabling conditions?**

A possible bidirectional relationship between depression and physical illness was hypothesised when it was found that long-term depression could be a key risk factor for developing further chronic disease (69,70), it being already known that chronic diseases lead to an increase in depressive symptoms (71). A longitudinal study carried out in England with 2472 adults aged 50 years and older examined the potential predictive effect of depressive symptoms on the incidence of chronic disease (70). Results showed that for each 1 point

increase in depressive symptoms measured by the Centre of Epidemiological Studies for Depression (CES-D) there was a 5% increase in the incidence of chronic illness up to 10 years later (IRR 1.05). Chronic disease predicted by depression included coronary heart disease (OR 1.08; 95% CI 1.02–1.15), other cardiac illnesses (OR 1.10; 95% CI 1.04–1.17), lung disease (OR 1.13; 95% CI 1.07–1.20), arthritis (OR 1.09, 95% CI 1.04–1.13), and osteoporosis (OR 1.12; 95% CI 1.06–1.18). Diabetes, high blood glucose, stroke, cancer and Parkinson's disease were not significantly predicted by baseline depressive symptoms. Below we summarise recent literature examining a potential reciprocal relationship between depression and chronic disease in stroke, cardiovascular diseases, diabetes, rheumatoid arthritis, eye diseases, and cancer.

*Stroke*

In 2012, a meta-analysis reviewing 17 prospective studies drew attention to the predictive effect that depression could have on subsequent risk of stroke (RR 1.34; 95% CI 1.17–1.54) (72). Since then, evidence is growing that persistent or long-term depression encompasses high risk for further stroke. In longitudinal research carried out with a nationally representative cohort of US adults aged 50 years and older, interviewed between 1998 and 2010, people with stable high depressive symptoms had more than double the risk of suffering a stroke in the subsequent 2 years (adjusted HR 2.14; 95% CI 1.69-2.71), compared with people with stable low or no depressive symptoms (29). A 2-year population based cohort study conducted with 4319 subjects aged 65 and older confirmed that persistent and high depressive symptoms are associated with elevated adjusted hazard of all-cause stroke (adjusted HR 1.65; 95% CI 1.06–2.56) (73). A prospective cohort study adopting a more comprehensive operationalization of depressive symptoms to capture the dynamic nature of depression over time showed that intra-individual variability in depressive symptoms (measured by CES-D) is a predictor of incident stroke (standardized HR 1.11; 95% CI 1.00-1.22), independent of other factors such as average CES-D, sociodemographics, cardiovascular risks, cognition, and daily functioning (74). Post-stroke depression might also increase the chances of a recurrent stroke (RR 1.48; 95% CI 1.22-1.79), according to a recent meta-analysis (75). In a recent study examining 10 population-based cohorts comprising 93076 individuals, a bidirectional relationship was found between stroke and depression (76). Stroke predicted further depression (HR 2.62; 95% CI 2.09–3.29), with a median time of 3.2 years between stroke diagnosis and subsequent depression. Depression was associated with higher risk for stroke (HR 1.94; 95% CI 1.63–2.30), with a median time of 4.4 years between

the diagnosis of depression and subsequent stroke. There is still limited evidence concerning which factors underpin the bidirectional relationship between depression and stroke (76-78). The available literature points out potential factors such as immunological dysregulation (79), hypertension and diabetes (80), poor health behaviours (81), and long-term antidepressant medication use (82).

*Cardiovascular Disease*

A large-scale meta-analysis assessing the prevalence and incidence of cardiovascular disease among patients with severe mental illness showed a significant longitudinal association between major depressive disorder and coronary heart disease (HR 1.72; 95% CI 1.48-2.00) (83). Another meta-analysis of prospective cohort studies suggested that depression was associated with a further risk of myocardial infarction (HR 1.31; 95% CI 1.09–1.57), and coronary death (RR 1.36; 95% CI 1.14–1.63) (84). A recent multicentre, population-based cohort study conducted in several low, medium and high-income countries confirmed a predictive relationship between depression and subsequent cardiovascular disease (HR 1.14; 95% CI 1.05-1.24) (85). In a population-based cohort study conducted with 93 076 individuals (76), ischaemic heart disease significantly predicted subsequent depression (HR 1.70; 95% CI 1.37–2.12), with a reverse significant association (HR 1.79; 95% CI 1.43–2.23). Median times of 4.7 and 5.9 years were found between the diagnosis of ischaemic heart disease and depression, and between the diagnosis of depression and subsequent ischaemic heart disease respectively. Factors underpinning the relationship between heart disease and depression are still unclear. The available literature suggests that behavioural and lifestyle factors (obesity, alcohol intake, smoking), hypertension, disturbance of the hypothalamic–pituitary–adrenal axis, and increased platelet activation and endothelial dysfunction might play an important role in the link between cardiovascular disease and depression (86). A Mendelian randomization study using summary-level data from meta-analyses of genome-wide association studies raised the possibility of a genetic liability to major depressive disorder being associated with coronary artery disease (OR 1.16; 95% CI 1.05-1.29) and with type 2 diabetes (OR 1.26; 95% CI 1.10-1.43) (87). However, in a large population-based cohort study with 367 703 participants conducted in the UK using Mendelian randomization, the disease genetic risk associated with coronary heart disease was not significantly associated with depression (88). Factors significantly associated with depression included genetically-predicted triglycerides (OR 1.18; 95% CI 1.09-1.27), interleukin-6 (OR 1.35; 95% CI 1.12-1.62), and C-reactive protein (OR 1.18; 95% CI 1.07- 1.29).

*Diabetes*

In 2008, a multi-ethnic cohort study conducted in the US (N=6814) suggested a potential bidirectional relationship between elevated depressive symptoms and type 2 diabetes (89). A relative hazard of 1.21 (95% CI 0,87-1.67) was found for risk of type 2 diabetes in patients with elevated depressive symptoms compared with patients with low/normal depressive symptoms. Type 2 diabetes was associated with high odds of developing further elevated depressive symptoms (OR 1.52; 95% CI 1.09-2.12). According to a recent meta-analysis reviewing 22 longitudinal studies (90), diabetic patients with depression have increased risk of developing complications, such as macrovascular (HR 1.38; 95% CI 1.30–1.47) and microvascular (HR 1.33; 95% CI 1.25–1.41) complications. Additionally, it was found that diabetes complications might also entail increased risk for incidence of depressive disorder (HR 1.14; 95% CI 1.07–1.21). A cohort study with 3742 type 1 diabetes patients showed that depression was associated with a 2.5 times risk of further severe hyperglycemic events (HR 2.47; 95% CI 2.00-3.05) and 89% increased risk of severe hypoglycemic events (HR 1.89; 95% CI 1.61-2.22) (91). Factors underpinning the relationship between diabetes and depression remain unclear. A recent meta-analysis reviewed 16 genetically informative studies on comorbid depression and type 2 diabetes and highlighted the absence of evidence of a bi-directional phenotypic causation between depression and diabetes. Neither was there evidence that the co-occurrence of both conditions is driven from any shared genetic liability (92). Finally, a longitudinal study suggested that unhealthy behaviours (e.g. low exercise frequency) might explain incidence of depressive symptoms in type 2 diabetes patients (93).

*Rheumatoid Arthritis*

The literature suggesting a bidirectional relationship between depression and rheumatoid arthritis is still limited. According to a large population-based cohort study conducted in Taiwan, individuals with depression had 65% higher risk of developing rheumatoid arthritis compared with those without depression (adjusted HR 1.65; 95% CI 1.41–1.77) (94). A 2-year longitudinal study conducted in the UK with 520 patients with early rheumatoid arthritis found an association between poor mental health (including major depressive disorder) and worse disease outcomes, including higher levels of disability (coefficient = − 0.01, $p = .006$), lower improvements in disease activity (coefficient = −0.02, $p < .001$), and pain (coefficient = −0.33, $p < .001$) which had a bidirectional relationship with mental health (95). Finally, in an 11-year longitudinal study carried out in Korea, the adjusted

hazard ratio for rheumatoid arthritis among patients with depression was not significantly higher than in healthy controls (96).

*Eye Diseases*

Preliminary evidence has been found for a potential bidirectional relationship between vision loss and depression. A study with 7584 US patients aged 65 and older found a longitudinal association between baseline clinical depression and further self-reported visual impairment (HR 1.37; 95% CI 1.08-1.75), over a period of 5-years (52). The same study also found an association between baseline self-reported visual impairment and later depression (HR 1.33; 95% CI 1.15-1.55).

*Cancer*

Following a previous meta-analysis suggesting that depressive symptoms could be a risk factor for cancer incidence (97,98), a 17-year longitudinal study carried out in the UK with 10 308 adults (aged 33-55), examined associations between depressive symptom history and cancer incidence (99). Having history of chronic depressive symptoms was not found to be a significant risk factor for subsequent cancer (HR 1.03; 95% CI 0.71–1.49), for a 17.4 years follow-up. However, in the first 9 years of follow-up, new onset depressive symptoms were associated with an increased risk of cancer incidence (HR 1.89; 95% CI 1.23–2.90). Such risk of cancer was not found significant in later years (HR 0.84; 95% CI 0.52–1.35). In a recent study conducted in the UK with 19,966 patients with different types of cancer (breast, colorectal, gynaecological, lung and prostate), worse cancer survival was found in patients with greater levels of depression (measured by HADS) ($p < .0001$ in all patient groups) (100). Hazard ratios ranged from 1.81 (95% CI 1.48-2.22) to 4.30 (95% CI 2.63-7.06) for different types of cancer, when comparing patients with HADS depression scores of 0 and 10. A 12-month follow-up study with 1790 lung cancer patients in the US found a predictive association between depression symptoms and survival rates (101). For early stage disease patients, baseline symptoms of depression (HR 1.61; 95%CI 1.26-2.04), and follow-up symptoms of depression (HR 1.71; 95% CI 1.27-2.31) were associated with increased mortality. However, in another study running a secondary analysis from trials of depression treatment in cancer patients (N=642), reduction in severity of comorbid major depression was not significantly associated with longer survival in cancer patients (several types of cancer) (102).

*Other Medical Conditions (COVID-19)*

Intriguingly, the hypothesis of a reciprocal association between depression and chronic disease has led researchers to investigate the same kind of relationship in other non-chronic conditions, such as the recent case of COVID-19 (103). A recent retrospective large-cohort study suggested a bidirectional association between COVID-19 and mental health problems (including depression) (103). History of mental health problems in the previous year was independently associated with higher risk for COVID-19 (RR 1.65; 95% CI 1.59-1.71), and the diagnosis of COVID-19 was associated with higher incidence of mental health problems in the following 14-90 days, in patients with no history of mental health problems, including depression (HR 2.1; 95% CI 1.8-2.5).

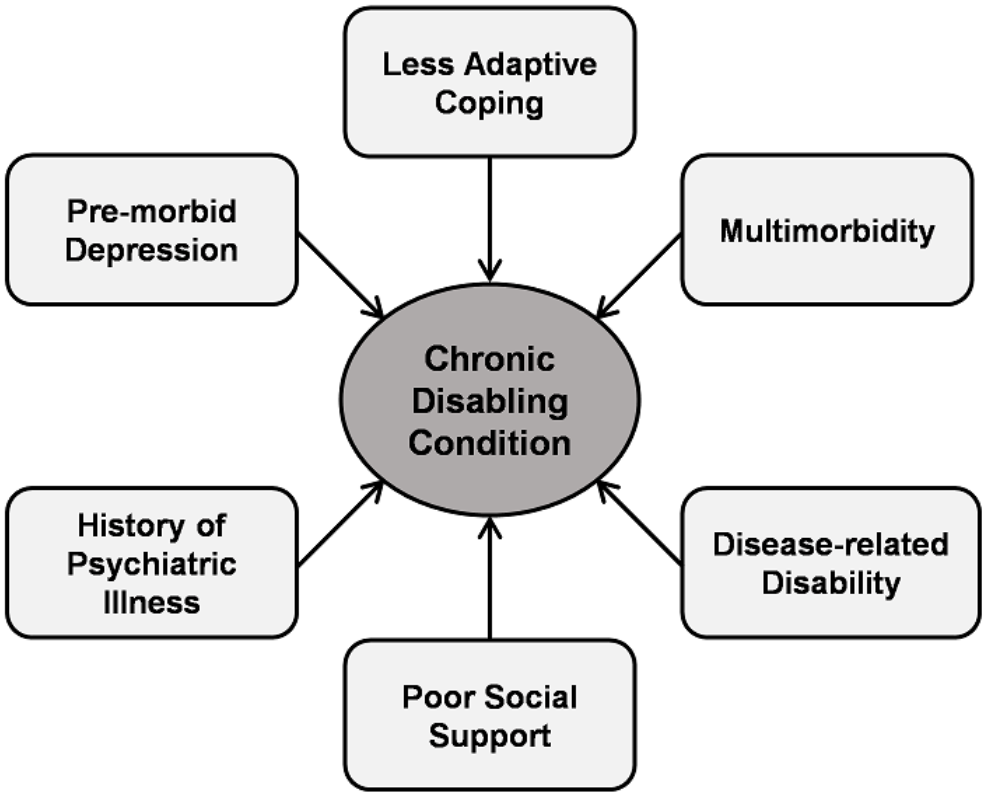
## Conclusions

Recent research has emphasised the potential burden encompassed by comorbid depression in patients with chronic disabling conditions. Evidence is growing on the topic and studies have shown that depression is multifactorial across disabling conditions. Recent studies have allowed us to identify some predictors of depression which are common across different disabling conditions, as illustrated in Figure 1. One of them, pre-morbid depression, has intrigued researchers, raising the hypothesis of a bidirectional relationship between depression and chronic disease. In fact, recent studies have illustrated this relationship, finding depression significantly associated with subsequent chronic disease, with growing evidence for conditions such as stroke, cardiovascular diseases, and diabetes. There is still paucity of evidence on which factors mediate a potential bidirectional association between depression and chronic diseases. The available literature suggests factors such as life-style (e.g. obesity, alcohol intake, lack of physical activity) (81,93), comorbidities (e.g. hypertension) (68,80), and immunologic factors (79). Recently, it has also been proposed that immunologic dysregulation involving increased levels of circulating pro-inflammatory cytokines (e.g. interleukin-6, Tumour Necrosis Factor-alpha) can be associated with symptoms of major depressive disorder (104-106). Future studies will clarify the nature of this relationship, which is particularly suggestive since cancer, diabetes and cardiovascular disease are chronic inflammatory diseases. Another hypothesis raised was the possible association between long-term anti-depressant use and poor health outcomes (82,107-109). Persistent depression is the most common form of depression that has been associated with further risk for chronic diseases (29,74,76,89,90), which would explain why previous research associated depression with a deterioration of disease prognosis over time (75,76,90,91), and

reduce life expectancy by 5 to 10 years (110). Finally, the hypothesis previously raised of a possible shared genetic liability between depression and some chronic conditions (77,87,92) is controversial, and recently contested in a study providing evidence that none of the most studied depression candidate genes were associated with depression phenotypes (111).

In conclusion, it is established that depression is a common problem among people with long-term disabling medical conditions and can entail additional disability and other complications leading to a deterioration in general health. Long-term depression might be associated with an increased risk of subsequent physical health problems, although the nature of that relationship and its underlying mechanisms remain unclear. Further evidence on this topic will be paramount to inform clinical practice, particularly for mental health and primary care settings. Meanwhile, patients presenting with long-term depression would benefit from regular physical health checks, and psychosocial and psychotherapeutic programmes promoting social support and a healthier lifestyle.

*Figure 1. Common Risk Factors for Depression across Disabling Medical Conditions*



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| Condition | Study | Type of Study | Number of Studies Reviewed | Sample Size | Prevalence of Depression | Measure |
|---|---|---|---|---|---|---|
| Stroke | Ayerbe et al., 2013[18] | Meta-analysis | 43 | 20 293 | 29% | DSM; S mea |
| Stroke | Mitchell et al., 2017[10] | Meta-analysis | 108 | 15 573 | 33.5% | ICD |
| Spinal Cord Injury | Williams et al., 2015[11] | Meta-analysis | 19 | 35 676 | 22.2% | |
| Limb Amputation | Mckechnie et al., 2014[19] | Systematic Review | 9 | NA | 35.2%[b] | DS Standardiz |
| Limb Amputation | Singh et al., 2009[20] | 3-Year Prospective | NA | 68 | 19.1% | H |
| Peripheral artery disease[c] | Arya et al., 2018[21] | 11-Year Retrospective | NA | 155 647 | 16% | |
| Coronary Disease[d] | Correa Rodrigues et al., 2020[12] | Meta-analysis | 8 | 596 | 19% | Standardiz |
| Coronary Disease | Murphy et al.,2020[22] | 12-month Cohort | NA | 911 | 15%-22%[e] | H |
| Diabetes | Roy et al, 2012[23] | Systematic Review | 20 | NA | 12% (type 1) 19% (type 2) | Standardiz Diagnos |
| Type 2 Diabetes | Lloyd et al., 2018[24] | Multi-center Observational | NA | 2783 | 17% | P |
| Diabetes | Kahledi et al., 2019[13] | Meta-analysis | 248 | 83 020 812 | 28% | Standardiz |
| Rheumatoid Arthritis | Matcham et al., 2013[14] | Meta-analysis | 72 | 13 189 | 16.8%-38.8%[f] | Standardiz |
| Rheumatoid Arthritis | Fragoulis et al., 2020[25] | 12-month Cohort | NA | 848 | 12.2% [g] | H |
| Osteoarthritis | Stubbs et al., 2016[15] | Meta-analysis | 49 | 15 855 | 19.9% | GDS |
| Eye Diseases | Zheng et al., 2017[16] | Meta-Analysis | 28 | 6589 | 25% | Standardiz |
| Cancer | Krebber et al., 2014[17] | Meta-analysis | 211 | 82 426 | 14%-24%[h] | ICD; D C |
| Cancer | Linden et al., 2012[26] | 6-year Cohort | NA | 9394 | 13% and 16.5%[i] | 21-item Screen |
| Cancer | Hartung et al., 2017[27] | Epidemiological multi-centre | NA | 4020 | 24% | P |

DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; HADS: Hospital Anxiety and Depression Scale; PHQ-9: Patient Health Questionnaire; GDS: Geriatric Depression Scale; CES-D: Centre for Epidemiological Studies of Depression; (a) Several standardized measures of depression used across studies, including HADS, PHQ-9, GDS, CES-D. (b) Mean of values reported in 9 studies, ranging between 20.6% and 63%; (c) 40.6% of deaths, and 9% of amputations during the follow-up period; (d) Meta-analysis conducted to examine the prevalence of depression before and after coronary artery bypass graft surgery – in our table we only report prevalence of depression after surgery; (e) Prevalence of depression: 22% in patients while in hospital after admission; 17%, 2-4 months after the event; 15%, 6-12 months after the event; (f) Prevalence of depression varied according to the measure of depression used in studies, being 16.8% (95% CI, 10-24; $I^2$=73,4%) for DSM major depressive disorder; 34% (95% CI, 25-44; $I^2$=90.9%) for HADS (cut-off score of 8); 36% (95% CI, 32-40; $I^2$=83,1%) for CES-D; and 38.8% (95% CI, 34-43; $I^2$=19.8%) for the PHQ-9; (g) Baseline prevalence of depression; (h) Prevalence of depression varied according to the measure of depression used in studies, being 14% (95% CI, 11-16) for ICD / DSM major depressive disorder; 18% (95 CI, 16-20) for HADS; and 24% (95% CI, 21-26) for CES-D; (i) 13% of prevalence of clinical depression and 16.5 % of prevalence of sub-clinical depression.

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