CANADIAN PARTNERSHIP AGAINST CANCER
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Mental Health Commission of Canada
Commission de la santé mentale du Canada

Towards Better Mental and Physical Health: Preventing and Managing Concurrent Mental and Physical Conditions

A Scoping and Rapid Realist Review

Mental Health Commission of Canada
mentalhealthcommission.ca

Acknowledgements

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We wish to thank the members of the Mental Health and Chronic Disease Network for their review and feedback on this document. We also wish to thank the Canadian Partnership Against Cancer for their partnership on the development and promotion of this document.

Keywords: Mental Health, non-communicable disease, comorbidity, multimorbidity, cancer

Ce document est disponible en français

Citation information

Suggested citation: Mental Health Commission of Canada. (2021). *Towards better mental and physical health: Preventing and managing concurrent mental and physical conditions: A scoping and rapid realist review.* Ottawa, Canada: Mental Health Commission of Canada.

ISBN: 978-1-77318-257-5

Legal deposit National Library of Canada

Health Canada Santé Canada

The views represented herein solely represent the views of the Mental Health Commission of Canada. Production of this material is made possible through a financial contribution from Health Canada.

Glossary

Chronic condition self-management:	A self-management program is a structured program applied at the individual or group level that explicitly aims to improve the way individuals self-manage their chronic conditions, optimize their health, and live well. They may be delivered in a number of ways including face-to-face, by telephone or on a computer.[1]
Collaborative care:	Multi-professional approaches, that employ structured management, scheduled follow-up, and enhance inter-professional communication.[2,3,4]
Comorbidity:	Refers to the co-occurrence of at least one mental health problem or illness and at least one physical disease or disorder in the same person, regardless of the chronological order in which they occurred or the causal pathway linking them.[5]
Frailty:	The Canadian Frailty Network defines frailty as a medical condition of reduced function and health in older individuals. It often includes several features such as inactivity, poor nutrition, social isolation or loneliness, and the use of multiple medications.
Mental health problems or illnesses:	Mental health problems or illnesses include a broad range of conditions that affect one's mood, thinking, and/or behaviour. This report includes information about NCDs that are comorbid with depressive and anxiety disorders, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, substance use and addictive disorders (see separate definition), or feeding and eating disorders. In addition, common mental health symptoms that are comorbid with NCDs, such as depression and anxiety, are discussed. These terms are used interchangeably with mental health conditions throughout the report.
Metabolic Syndrome (MetS):	MetS is a health disorder that, if left untreated, increases the risk of many chronic conditions such as type 2 diabetes and cardiovascular disease. MetS is diagnosed when a person has three of the following conditions: high blood pressure, high blood glucose levels, high triglycerides, low HDL-cholesterol, or large waist circumference.[6]
Non-communicable diseases (NCDs):	NCDs, also often referred to as chronic diseases, last for at least 3 months, are not passed between people, and are progressive. Some of conditions, such as Huntington's disease, may be inherited. In this report, the NCDs and related conditions included are arthritis (rheumatoid and osteoarthritis), cancer, cardiovascular disease, chronic respiratory diseases, dementia, diabetes mellitus, epilepsy, frailty, Huntington's disease, inflammatory bowel disorders (ulcerative

	colitis and Crohn's disease), kidney disease, metabolic syndrome, obesity, and Parkinson's disease.
Priority and equity-seeking populations:	These are diverse populations that the Mental Health Commission of Canada (MHCC) seeks to improve mental health services, supports and policies for. They include immigrant, refugee, ethnocultural and racialized (IRER) communities, First Nations, Inuit and Métis, the 2SLGBTQ+ community, people in minority language situations, individuals living in rural or remote communities, those earning low income, and seniors.
Substance misuse and substance use disorders:	Substance misuse is defined as the use of a substance for a purpose not consistent with legal or medical guidelines.[7] The criteria for substance-use disorders are defined in the DSM-5, and may be generally defined as symptom patterns that result from the use of a substance that one continues to take, despite experiencing problems as a result.[8]

Summary

Background

Physical and mental health co-morbidities are common, however, little is known about their prevalence, incidence, associated healthcare-related costs, shared etiology, prevention and management. A better understanding of how to prevent, screen, diagnose, and treat common physical and mental health co-morbidities can lead to the development of improved and sustainable health system approaches for diverse populations.

This report provides a synthesis of current international knowledge about physical and mental health co-morbidities, including information, where available, about how they intersect with sex/gender and how their characteristics may vary across priority and equity-seeking populations such as immigrant, refugee, ethnocultural and racialized (IRER) communities, First Nations, Inuit and Métis, the 2SLGBTQ+ community, and linguistic minorities. The non-communicable diseases (NCDs) discussed in this report include arthritis, cancer, cardiovascular disease, chronic respiratory diseases, dementia, diabetes mellitus, epilepsy, frailty, Huntington's disease, inflammatory bowel disorders, kidney disease, metabolic syndrome, obesity, and Parkinson's disease. The mental health comorbidities discussed with these NCDs include depressive and anxiety disorders, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, substance use and addictive disorders, or feeding and eating disorders. In addition, common mental health symptoms that are comorbid with NCDs, such as depression and anxiety, are discussed. Finally, a rapid realist review that drew upon selected interventions from the literature was conducted to better understand what strategies are considered for different people and the mechanisms to explain why they were effective.

Highlights and Recommendations

Based on the synthesis of more than 800 research documents, a number of conclusions and recommendations arise from this review that are aimed at practitioners, policy-makers, decision-makers, and researchers.

Policies

- All of the physical and mental health comorbidities highlighted have shared biological, psychosocial, and environmental etiological pathways. Policies and preventive programming that target these pathways, particularly psychosocial and environmental targets, are recommended. These should aim to address resource allocation to mental health promotion, screening and monitoring practices, and interventions.
- Policies aimed at life course, population health, and mental health promotion have the potential to prevent or delay the development of physical and mental health conditions. Policy targets should include food environments, healthy eating, food security, physical activity, affordable childcare, affordable housing, social assistance, employment, as well as health and income equity.

Programs, Education, and Services

- Interventions that are comprehensive, integrated, tailored, and based on shared decision-making will help to address the multiple underlying factors contributing to physical and mental health comorbidities. These practices can reduce health system costs by shifting resources towards health promotion and prevention, reducing reliance on acute care, facilitating health care continuum transitions, and fostering health system sustainability.
- As part of integrated health services, stepped-care models show potential to further optimize care for those with physical and mental health comorbidities and reducing health care costs. Stepped care refers to the delivery of care intensity that is matched to the complexity of the health issue. To facilitate the delivery of these approaches, supportive administrative and reimbursement structures are needed that are inclusive of allied health professionals who can work collaboratively with other practitioners to best support the end-user's physical and mental health needs.
- Collaborative care models need to target human capacity and technology to optimize service provision. These approaches need to be inclusive of all health disciplines, including substance use disorder experts.
- Public health campaigns which help to dispel myths and stigma associated with having chronic conditions could minimize potential of mental health impacts. Exemplars of positive messaging and images could include showing individuals with health conditions leading healthy productive lives and working effectively with their health care team.
- While primary care provides the foundation for physical and mental health care services, there is a need to better integrate these approaches with social services to address the multi-faceted complex needs of those with mental and physical health comorbidities. These services need to be accessible to all, particularly groups which face barriers to access such as those residing in rural and remote communities.

Research

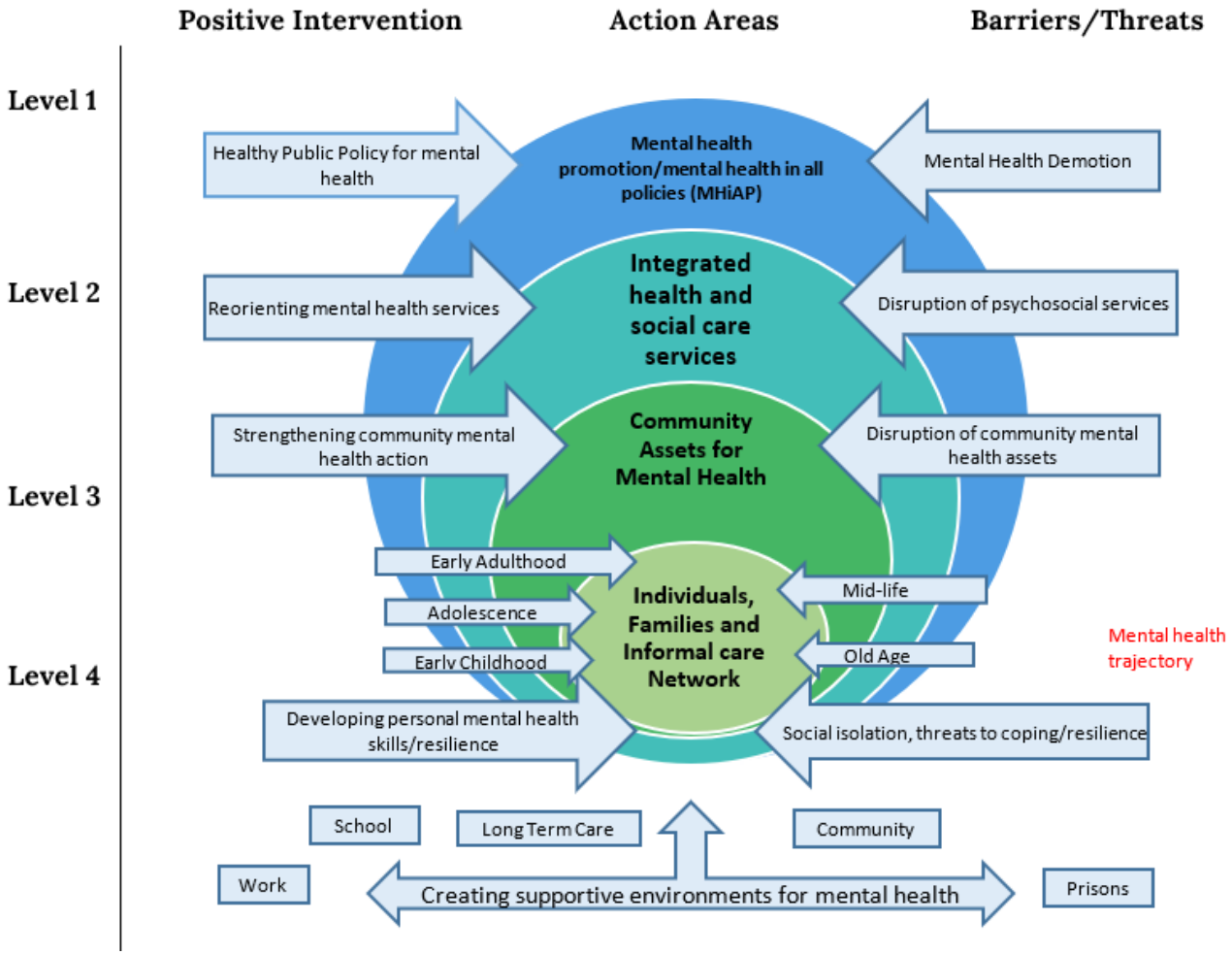
- Health research that can better inform practice, programming, and policy includes ongoing exploration of the determinants of health condition comorbidities, optimal delivery and integration of health and social services, and examining policy alternatives to optimize population mental health interventions, or a co-intervention (pulmonary rehabilitation).
- Future research should include individuals with lived experiences of physical and mental health comorbidities, their families, and carers.

Rapid Realist Findings and Outcomes

Further exploration of the literature using a rapid realist approach was conducted to understand how, for whom, and under what circumstances interventions function in different environments. Using an approach called context-mechanism-outcome (CMO) configuration, the rapid realist synthesis aimed to generate new ideas for programming and policy beyond that which is achieved in reviews providing a summary of aggregated evidence. Further

analysis of key interventions located from the literature search within a socio-ecological framework for mental health promotion (see diagram) lead to four broad guideline recommendations to better direct efforts at the prevention and management of physical and mental health comorbidities. These are highlighted in the following:

A Socio-ecological Model of Mental Health Promotion Interventions



Level 1: Healthy Public Policy for Mental Health: Mental Health Promotion/Mental Health in All Policies (MHiAP)

Individuals living with mental and physical illnesses have the potential to live a flourishing, joyful life. We must also try to promote and strengthen health assets, including structurally (social, economic, cultural) supportive environments, community resilience, and life coping skills.

A Program Theory for Mental Health in All Policies (MHiAP)
A MHiAP strategy → Intersectoral governance for mental health → Changes in policies (usually signaled by some sort of strategic document/plan) → Policy actions (legislative, regulatory, budgetary/investment tools) to promote mental health → Impact on social determinants of mental health → Improved mental health outcomes (e.g. increased well-being, happiness, improved coping and resilience, reduced mental stress, reduced incidence of mental illness, reduced harms from substance misuse, reduced incidence of suicide).

Agenda Setting for a MHiAP Strategy

A 'Health in All Policies' (HiAP) approach to intersectoral collaboration has been gaining ground globally as a policy-level agenda aimed at addressing the wider social determinants of health. Advocates of HiAP highlight the importance of mental health promotion as central to successful HiAP approaches, and as a means to contribute to addressing health equity and inequality;[9, 10] conversely, advocates of mental health promotion have identified HiAP as a key policy framework for advancing mental health and physical health.[11,12]

Based on a review of the literature on HiAP adoption and implementation, we propose five simple rules for successful HiAP initiation:

1) Developing a shared language and fluency around a broader understanding of 'health' to include well-being and happiness, and general welfare;
2) Linking evidence for how HiAP initiatives are able to contribute to sustainable economies and sustainable health systems (both theoretical and empirical);
3) Having an 'entry point' to initiate an HiAP agenda;
4) Developing 'win-win' scenarios, goals and objectives across sectors;[13]
5) Building and fostering long-term collaborative partnerships and engagement with intersectoral stakeholders.

In the Canadian context, not only is mental health well placed to be included in any HiAP policy agenda, it may in fact be the key entry point for raising the awareness and urgency of an HiAP approach at the federal and provincial levels. First, with the help of key policy elites, such as Senators Kirby and Wilson, and with the establishment of the Mental Health Commission of Canada (MHCC), much of the foundational work in boosting awareness has already taken place. In this collective work, Canadian researchers, practitioners, policy-makers and people with lived experience have worked on developing a more inclusive, shared language around mental health, that by its nature tends to be less 'deficit-focused' and more positive and strengths-based.

Level 2: Reorienting Mental Health Services: Integrated Health and Social Services

Beyond the HiAP approach, a key role for public policy is to provide the regulatory, legislative, and financial context for the transformation of health and social services more broadly in society. For Canadians, 'health reform'[14] is an ongoing reality that is complex and multi-faceted, with varying objectives across provinces, and widely differing governance strategies

and outcomes. However, a common recurrent theme is the need to develop *integrated, collaborative systems of health and social care* to address the increasingly complex needs of an aging population, with the concomitant multimorbidity of chronic diseases, both physical and mental, being the driving force of this complexity. While these efforts require many transformational changes at the health and social service/organizational level, there is a strong role for high-level policy in successfully moving towards the ideal system. It is generally acknowledged, based on decades of research evidence,[15] that comprehensive primary health care, as originally outlined in the Alma Ata Declaration,[16] is the overarching framework for efficiently, effectively, and equitably organizing health and social services in order to produce optimum health in populations.

> The **program theory** at this level is: by providing *universal financial coverage, under government control and regulation*, with *equitable distribution of services, comprehensive coverage*, and *with low or no co-payments*, then you attain "*greater first contact access and use, more person-focused care over time, greater range of services available and provided when needed, and coordination of care.*" (Starfield, 2012, p. 20).

Integrating care via simple rules allows relatively autonomous actors to use their contextual knowledge to come up with creative implementation solutions. At the integrated care level, there are some important contextual factors to consider. In order for clients to have a voice in decision-making (e.g., priority physical and social/mental needs), power differentials need to be 'smoothed.' Differential power dynamics impede effective collaborative practice among different service providers,[17] but they also relegate clients to a marginalized role with respect to decisions around their care needs. Physicians are considered the top of the healthcare hierarchy, and this conceptual approach can break the success of any reform program or change initiative.

Level 3: Strengthening Community Mental Health Action: Community Assets for Mental Health

At this systems level, community "assets" for mental health are the chosen foci, as they bring together three important theoretical approaches to mental health: mental health promotion;[18] the two-continuum approach;[19] and, the Canadian Mental Health Association's framework for support approach.[20,21]

> The **program theory** at the community level is: by helping to *co-create, strengthen and sustain community mental health assets*, people can be supported to live happy, joyful, flourishing lives, whether or not they are living with mental or physical illness *and* they can be empowered to help co-produce and shape the mental health services they receive in community through context-appropriate co-produced mental health service planning.

We propose a series of context-mechanism-outcome configurations (CMOCs). Many of the CMOCs are similar to those derived through community-based participatory action

research.[22] Based on our review of literature at the other systems levels, there is evidence that these "collaboration" CMOCs are relevant to each systems levels and our simple rules approach and are outlined as follows.

Context-Mechanism-Outcome (CMO) Configurations to Complement Simple Rules	
Factor	**CMO**
Trust	High trust (context) creates partnership synergy (mechanism) leading to successful outcomes at all systems levels (e.g., mental health services delivery).
Formalization	Formalization through policy (context) creates greater initial trust (mechanism) leading to greater uptake of mental health inclusion, mental health awareness at all systems levels.
Shared Vision	Having a shared vision (context) reduces the potential for conflict (mechanism) leading to improved trust/high trust (outcome) at all systems levels.
Commitment/ Accountability	Evidence of preparedness and accountability (context) results in reduced conflict (mechanism) leading to greater trust (outcome) among partners at each systems level.
Power	Power imbalances among partners (context) creates partner domination (mechanism) leading to reduced trust, blocked mental health services delivery at each systems level.
Faith	High faith (context) creates partnership synergy (mechanism) leading to enhanced mental health services delivery at each systems level.
Authenticity	Authentic collaboration (context) increases faith (mechanism) leading to increased agreement over common goals, such as mental health services delivery (at each systems level).
Leadership	Positive, authentic leaders (context) create more effective integration of different partners/cultures (mechanism) leading to greater trust among partners at each systems level (outcome).
Culture	Cultural closeness or coherence (context) decreases conflict (mechanism) leading to greater trust among partners at each systems level.
Flexibility	Greater flexibility in directives/guidelines (context) increases the likelihood of goal achievement (mechanism) leading to more efficient, effective mental health services delivery (outcome) at each systems level.
Entry Point	Designated entry points (context) provide clarity (mechanism) leading to more confidence (e.g., consistent model for mental health services delivery) (outcome) at every systems level.

Level 4: Developing Personal Health Skills/Resilience: Individuals, Families and Informal Supports

This level examines the personal resources individuals utilize to help them develop resilience, hope, confidence and well-being. There are many resources and interventions that aim at strengthening individual coping skills and resilience to bolster mental health and prevent the worst impacts of mental illness (e.g., self-aid, mutual aid, peer support networks).

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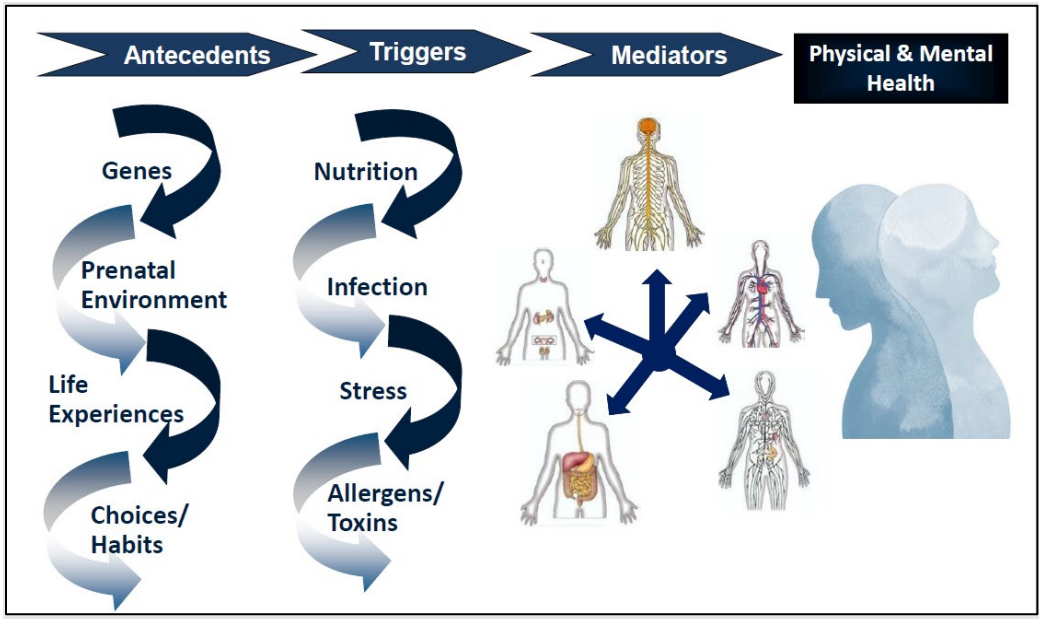
1. Introduction

1.1 Background

Non-communicable diseases (NCDs) and their behavioural and metabolic risks are a leading global cause of mortality and morbidity that contribute to an escalating economic, public health, and societal burden.[23,24,25] NCDs often co-occur with poor mental health as the interplay of biology, illness experience, behavioural risk factors (e.g., poor diet, physical inactivity, substance use) and the determinants of health (e.g., income, housing) can increase the likelihood of someone living with a physical health condition developing mental health symptoms or a co-existing mental health condition or vice versa.[26,27, 28] (Figure 1.1) Mental health conditions, such as major depression, schizophrenia spectrum conditions, psychosis, anxiety disorders, bipolar affective disorders, and eating disorders, are commonly linked with diabetes, cancer, cardiovascular disease, chronic respiratory diseases, arthritis, and inflammatory bowel disorders.[29,30,31,32,33,34,35,36,37,38,39] For example, some studies estimate that the prevalence of depression and anxiety is at least double amongst those being treated for cancer.[40,41]

Figure 1.1: Overview of Shared Etiology Between Physical and Mental Health[42,43,44]



Current knowledge about the shared etiology of physical and mental health comorbidities draws on unifying theories of neurobehaviour. Health is heterogeneous and culminates from many factors that include an interplay of antecedents, such as prenatal environment, life experiences, choices and habits, genetic background; triggers that may include "pro-inflammatory factors" such as exposures to infection, stress, allergens, or toxins. These factors interact with various mediators in different body systems that lead to specific physical and/or mental health outcomes.

Although there are many biological, behavioural, social, and environmental intersections between NCDs and mental health-related conditions (e.g., major depressive disorder, schizophrenia spectrum disorders), several knowledge gaps currently exist related to prevalence and incidence in Canada, healthcare-related cost estimates, shared mechanisms and effective targets for primary prevention, screening, assessment, management, and policy.[45] Better understanding, screening, diagnosis, and treatment of mental health conditions and NCDs can have a positive global impact on formulating integrated approaches and fostering health system sustainability.[30,31]

To better address the prevention or treatment of physical and mental health co-morbidities, an integrated scoping and rapid realist review was conducted to help address knowledge gaps related to their prevalence/incidence, shared etiology, prevention, and management.

1.2 Rationale and Scope

The project objectives of this evidence synthesis were to synthesize and appraise international knowledge about common physical and mental health comorbidities related to:

i. Their prevalence, incidence, and healthcare-related cost estimates across the lifespan and as they intersect with sex/gender and among priority and equity-seeking populations including immigrant, refugee, ethnocultural and racialized (IRER) communities, First Nations, Inuit and Métis, the 2SLGBTQ+ community, and linguistic minorities;
ii. Biological, behavioural, and social pathways that contribute to their shared etiology;
iii. Efficacious models for screening, primary prevention, care, and treatment of comorbidities for priority and equity-seeking populations; and
iv. Gaps and biases in knowledge related to prevalence and incidence, healthcare-related cost estimates, causal pathways, screening, prevention and management of physical and mental health co-morbidities, including priority and equity-seeking populations.

2. Approach

2.1 Questions of Interest

The questions guiding this report include:

1. What is the prevalence, incidence, and healthcare-related cost estimates of common physical and mental health comorbidities? How do these differ by sex/gender and across the lifespan and among priority and equity-seeking populations including immigrant, refugee, ethnocultural and racialized (IRER) communities, First Nations, Inuit and Métis, the 2SLGBTQ+ community, and linguistic minorities?
2. What are biological, behavioural, social, and environmental pathways that contribute to both common physical and mental health co-morbidities?
3. What models for screening, primary prevention, care, and treatment of common physical and mental health co-morbidities work for what populations, in what contexts, and why? What enables or constrains the implementation of screening, primary prevention, care, and treatment of common physical and mental health co-morbidities?

2.2 Approach

2.2.1 Evidence Searches

A comprehensive literature search of standard bibliographic databases that cover a range of health and related disciplines (i.e., MEDLINE, CINAHL, PsycInfo, Sociological Abstracts) and grey literature sources (e.g., theses, dissertations, conference proceedings, digital publications repositories of relevant government, non-profit, and health care provider organizations) was undertaken (see Appendix A for full search strategy). In addition, cited reference checking and consultation with relevant knowledge users was undertaken. All types of literature were considered ranging from systematic reviews with meta-analyses to opinion papers. In topic areas where extensive literature was located, the scope of documents included in this knowledge synthesis focused on highest level evidence sources.

Abstracts located from the academic literature searches were screened by two reviewers. Full text articles of the abstracts which met the criteria were subsequently reviewed by two reviewers. The final set of selected documents were assessed for quality using various standard assessment tools. Data extraction was undertaken using an extraction template developed by the team.

2.2.2 Evidence Synthesis

Scoping Review

For all NCDs, information from the evidence searches was summarized in relation to mental health-related comorbidities. For each comorbidity, evidence was highlighted about prevalence and incidence estimates of the physical and mental health comorbidity, shared etiology, mental health screening of individuals who have the indicated NCD, prevention strategies, as well as management and interventions.

Rapid Realist Review

For literature sources which provided in-depth information about how interventions interact with contexts and mechanisms to influence the effectiveness of strategies aimed at managing symptoms of physical and mental health comorbidities, rapid realist review methods[46] were applied. The rapid realist review was guided by a Mental Health Promotion Framework co-constructed by the project team and in consultation with the MHCC (see Figure 4.1). The framework provided guidance about which interventions work, for whom, how, to what extent and in which contexts. The framework and review focused on applications in health and social services provided at macro, meso, and micro intervention levels (e.g. policy, design, implementation, delivery of services). The review addressed the following questions:

1. What are guiding principles by which interventions can be implemented successfully?
2. What are the mechanisms by which these principles operate? What are the contextual factors influencing the principles?
3. What impact do the interactions between contextual factors and mechanisms have on intervention outcomes?

For the rapid realist review, data was extracted regarding the interventions' strategies, activities and resources, and the context, mechanisms and outcomes directly stipulated in the documents. To aid the project team during the extraction process and to ensure consistency and transparency, specified definitions of important realist concepts (Table 3.1) were used as realist methods are still developing and realist evaluators continue to unpack and operationalise terms like 'context', 'mechanisms', and 'interventions' and how these interrelate.[47]

Table 2: Definitions of Realist Concepts Applied	
Intervention:	interventions' implemented activities, strategies, and resources[47] (e.g., health behaviour module)
Mechanism:	what 'triggers' participants to want to participate, or not, in an intervention. Mechanisms usually pertain to cognitive, emotional, or behavioural responses to intervention resources and strategies (e.g., participant feels enabled from skills development)
Context:	an intervention's background or setting. Context includes the pre-existing organizational structures, the cultural norms, history of the community, the nature and scope of pre-existing networks, and geographic location

	effects[48,49] (e.g., previous experience of organization co-conducting interventions with community partners)
Outcome:	intervention outcomes that can be either intended or unexpected[48] (e.g. macro-level: well integrated services; meso-level: participants' engagement in health and social services; or micro-level: participants' health outcomes)

Using completed extractions, Context-Mechanism-Outcome configurations (CMOs) were constructed to better understand and explain why interventions work, or not, and to generate guiding principles. For this review, the project team only created CMOs if the contexts, mechanisms and outcomes were explicitly correlated in the papers themselves. The CMOs were clustered intervention types to ensure that the guiding principles were supported by mechanisms located across different interventions and contexts. Mechanisms were thematically clustered and from these, guiding principles were developed. Each guiding principle was cross-referenced to mechanisms from different documents to verify they were transferable across different interventions and contexts.

3. Evidence Highlights: Physical and Mental Health Comorbidities

In this section, the results of the scoping review are highlighted by physical health condition (alphabetical). Each section highlights the prevalence, incidence, associated healthcare-related costs, shared etiology, and management interventions to support mental health.

3.1 Mental Health Characteristics by Physical Health Condition

3.1.1 Arthritis

A. OSTEOARTHRITIS (OA)

OA involves the degeneration of cartilage in the joints that leads to joint pain, stiffness and limitations of motion, and can cause significant disability. The hand, knee, and hip are the commonest sites of the body to be affected. OA is prevalent in mid-age to older adults. Women over the age of 50 years are more likely to have the condition.[50]

Prevalence and Incidence of OA with Mental Health Problems or Illnesses

- Based on studies of modest samples, 58-66% of people with OA have some type of mental health concern including depression, anxiety, psychosis, and obsession/compulsion. Results can vary by the affected joint[51]
- Measures of depression among people with OA at the hand, knee, hip, back/neck or other indicated that having multi-site OA (i.e., OA ≥2 sites; OR=1.48, 95% CI 1.07–2.05) and the specific presence of hip (OR=1.72; 95% CI 1.08–2.73) or knee OA (OR=1.43; 95% CI 1.03–1.98) were associated with greater odds of developing depressive symptoms compared to people without OA[52]
- A longitudinal study of 74,393 individuals with mental health conditions reported that affective psychoses, neurotic illnesses or personality disorders, as well as alcohol and drug dependence or abuse were risk factors for OA. Individuals with schizophrenia were not at risk of OA[53]
- A longitudinal study of adults (n = 3,662) aged ≥45 years reported an increased risk of arthritis for those with depressive symptoms (Men: Hazard Ratio (HR)[1] =3.51, 95% CI 2.32–5.29; women: HR=2.03, 95% CI 1.45–2.85) compared to those who did not develop depressive symptoms[54]

[1]Hazard ratio (HR) is a measure of how different factors or an intervention are associated with an outcome of interest over time

Mental Health Screening

- A cost-utility analysis of routine anxiety and depression screening in people with OA suggests routine screening by general practitioners appears to not be cost-effective[55]

> Regular screening for depression in people with OA is recommended by the National Institute for Health and Care Excellence[50]

- A cluster randomized trial conducted in primary care that assessed point-of-care electronic template to prompt routine anxiety and depression screening in people with OA showed no beneficial outcome for self-reported pain reduction or functional outcomes[56]
- It is recognized that screening could identify subthreshold anxiety and depression symptoms which are more common and facilitate dialogue with clinicians to identify unmet needs contributing to distress[57]

Common Pathways

- Pain and inflammation are underlying shared pathways of OA and mental health (Figure 3.1)
- OA and poor mental health may be mediated by abnormal regulation of the hypothalamic–pituitary–adrenal (HPA) axis and inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α)[58]
- Alterations in the autonomic nervous system combined with sleep disturbances can worsen joint pain. This can lead to a vicious cycle with declining mental health by boosting sympathetic nervous system activity.[59] Abnormal HPA axis regulation can amplify centralized pain and lower mood[58]
- Mechanical burden on joints, reactive oxidative stress, and low-grade cartilage cell (chondrocyte) inflammation worsen OA.[60] Altered neurotransmitter transmission followed by pro-inflammatory reactions can increase production of neurotoxic catabolites and impact mental health[61]
- For women, estrogen deficiency after menopause could contribute to the development of OA, depression, and anxiety disorders[62]
- For men, aging-related decline of testosterone levels might cause metabolic imbalance leading to sarcopenic obesity, which in turn can contribute to the risk of OA[63,64] and depression[65]

Management of OA and Mental Health

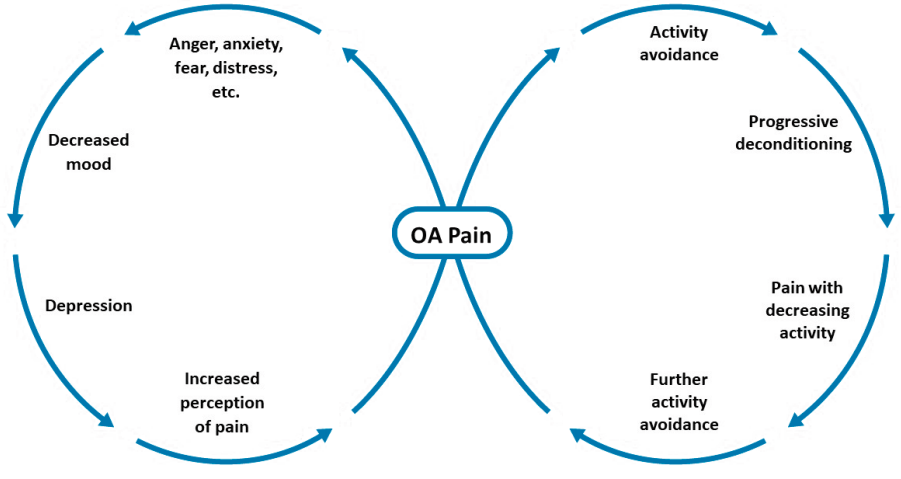
- Mental health, particularly depression, and OA pain appear to be interlinked. Studies which have focused on pain reduction or coping have shown to simultaneously improve both physical and mental health symptoms[66]
- The results of studies about the benefits of exercise interventions and concurrent reductions in mental and physical symptoms are mixed. Further research needs to clarify the importance of exercise programmes in terms of duration, intensity, and frequency[66]

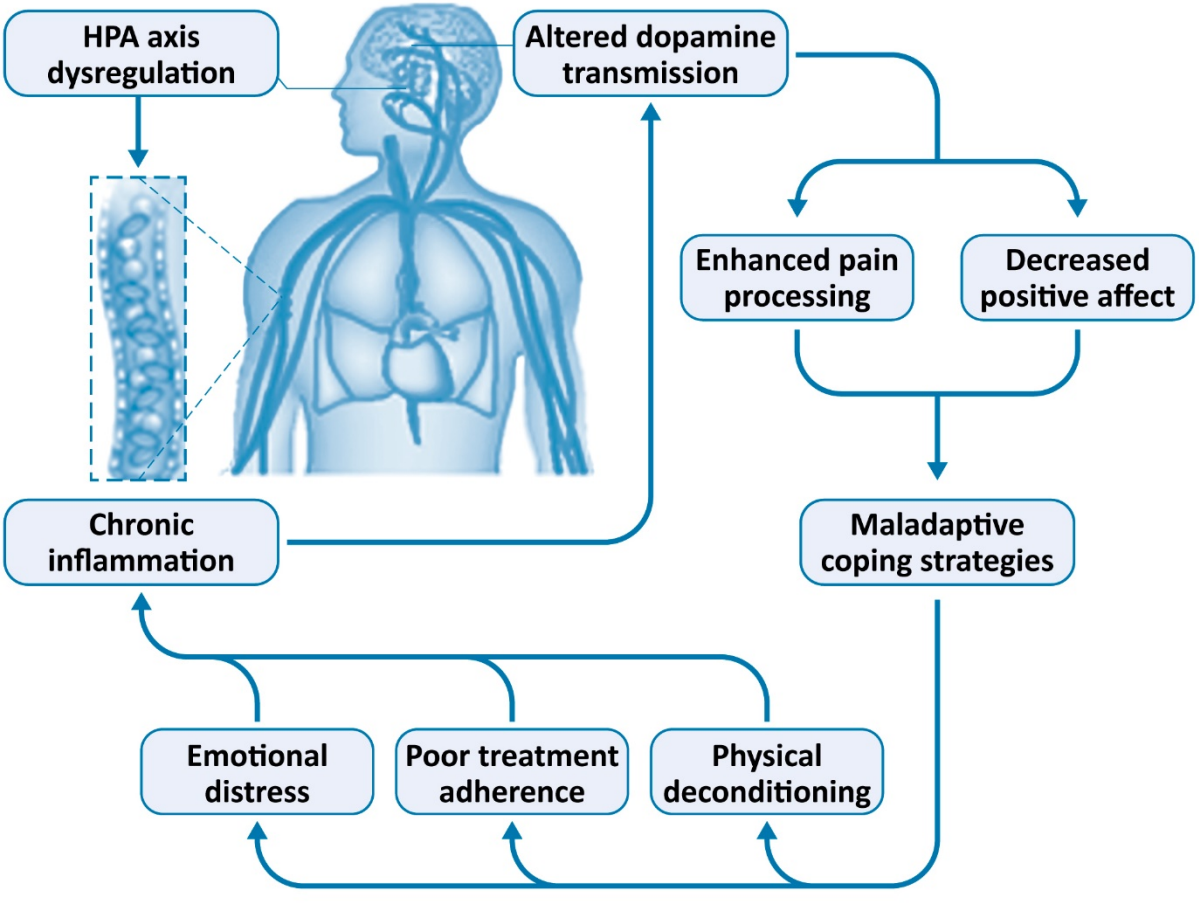
- A review of complementary therapies to treat musculoskeletal conditions and mental health found moderate to good quality evidence for acupuncture and tai chi[67]
- Results of a meta-analysis reported that psychotherapeutic counselling and psychoeducational interventions improve pain and pain coping. Anxiety and depression also improved but were not significant. More rigorous studies are needed[68]

> Interventions provided under a collaborative care model may significantly reduce healthcare costs associated with comorbid depression and anxiety that occurs in individuals with OA[71]

- To optimize psychosocial well-being, strategies such as maintaining function, using positive language to describe the condition, increasing social participation, and maintaining employment are recommended. For example, a person's harmful attitudes towards pain and damage may be reduced through education that addresses negative mistaken language and mistaken beliefs
- Beliefs about the health condition may be formed from external sources of information, such as the media, and prior to diagnosis.[69] Public health campaigns can help to dispel myths about OA more broadly and help to minimize mental health impacts post-diagnosis
- Cognitive behaviour therapy, neuroscience education, and centrally-acting drugs could be alternative treatment modalities for relieving OA-related pain and poor mental health[70]
- Researchers suggest combined intervention approaches for depression and pain, for example, aerobic exercise with psychological support may be effective[66]
- Among individuals with coexisting OA and depression, excess healthcare expenditures associated with depression were mainly due to comorbid anxiety[71]

Figure 3.1: Shared etiology between OA and mental health[72]





OA contributes to inflammation through HPA axis dysregulation, which leads to altered responses to stress, such as muscle tone that is maintained predominantly by impulses from the sympathetic nervous system. Chronic inflammatory states can alter neurotransmission in the brain which can enhance pain processing and dampen positive affective responses. This can manifest as depression, potentially affect disease-relevant behaviour, such as exercise, treatment adherence, and social withdrawal, and lead to further adverse effects on both physical and mental health.

B. RHEUMATOID ARTHRITIS (RA)

RA is a chronic, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken. Damage to the joints causes deformities, bone erosion, and pain. Common symptoms include morning stiffness of the affected joints, weight loss, and joints that are tender, swollen, and warm. The onset of RA is usually between 35-60 years.[73]

Prevalence and Incidence of RA with Mental Health Problems or Illnesses

Depression and Anxiety

- Estimates of depression and anxiety in individuals with RA are reported to range from 10-42%[74]
- Anxiety is reported to occur in 22-31% of those with RA;[75] lifetime prevalence rates of anxiety disorders have been reported at 16%.[76] Anxiety is associated with higher RA disease activity[77]
- A systematic review reported the incidence of anxiety for those with RA to be 1.2 (95% CI OR 1.03–1.39)[78]
- A meta-analysis about depression and RA comorbidity found a prevalence of 17% for major depressive disorder[79]

Bipolar Disorder, Schizophrenia, and Post-Traumatic Stress Disorder

- An analysis of population-based administrative health data from Manitoba, Canada of 10,206 incident cases of RA and 50,960 sex-, age-, and geographically matched controls reported that the incidence rate ratio (IRR) of bipolar disorder was 1.21 (95% CI 1.00–1.47); the incidence of schizophrenia did not differ between groups (IRR 0.96, 95% CI 0.61–1.50)[80]
- Post-traumatic stress disorder (PTSD) may be a risk factor for developing RA in adulthood.[81] Only a few studies, most based on veteran samples, have demonstrated this relationship[81,82]
- Individuals with RA seem to show decreased rates of schizophrenia compared to the general population[83]

Mental Health Problems and Illnesses

- The co-occurrence of RA with psycho-social problems is reported to be 46%[84]
- For community-based adults (<45 years), arthritis is a risk factor for the development of a mental health condition in later life; conversely, having a mental health condition does not reliably predict the later development of arthritis[85]

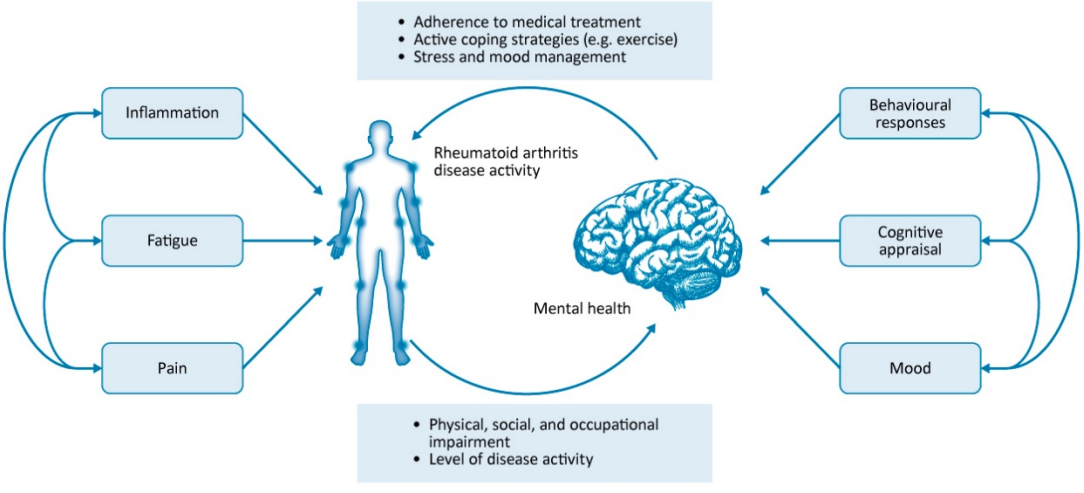
Mental Health Screening

- Clinicians recommend use of the Hospital Anxiety and Depression Scale (HADS) for screening,[86] however its validity and reliability in this population has not been assessed

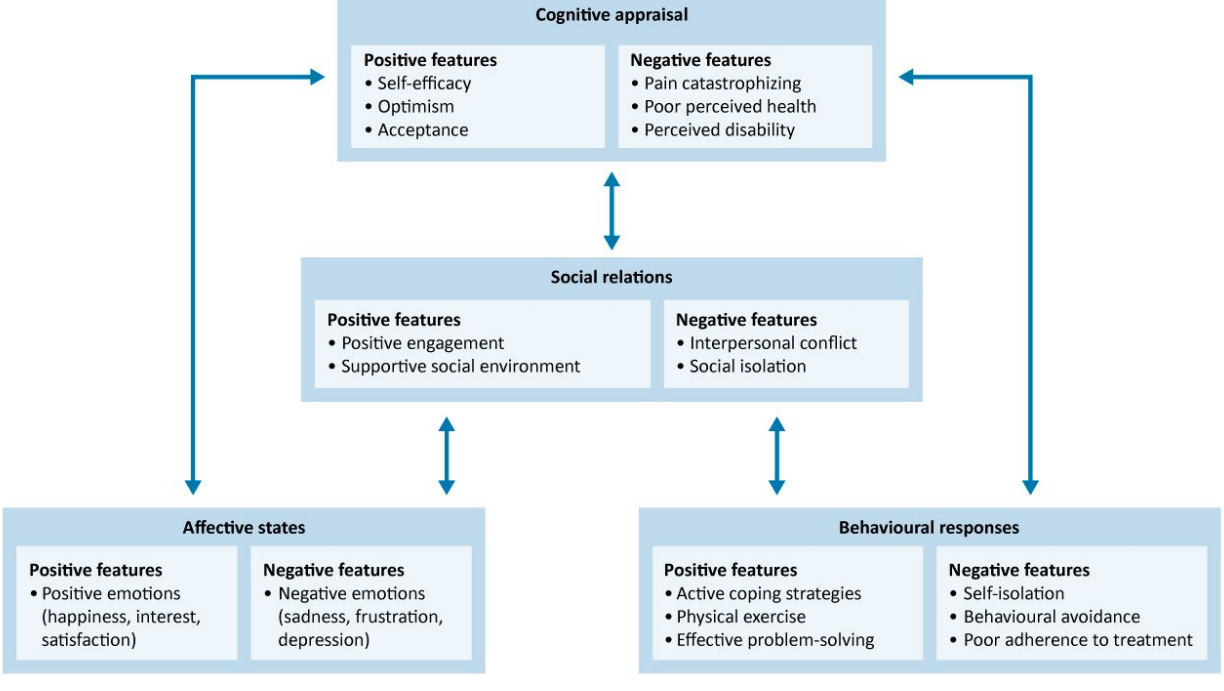
Common Pathways

- Mental health and RA comorbidity interactions include dysregulation of inflammatory responses, difficulties with pain and fatigue, and the development of cognitive and behavioural responses that could exacerbate physical and psychological difficulties (Figure 3.2)[87]
- Social contexts can affect coping strategies, psychological responses, and impair responses to treatment due to disruption of therapeutic alliance and treatment adherence (Figure 3.2)[87]

Figure 3.2: Shared etiology between RA and mental health[87]



Interactions of social and psychological factors



RA manifestations, such as pain, fatigue, and inflammation, act as stressors and influence mental health by influencing changes in one's interpretation or appraisal of disease status, affective states, and coping responses. Cognitive, affective, and behavioural factors interact with one's self-efficacy. The extent to which one uses healthy coping responses impacts their ability to self-manage. How a person responds to their RA psychologically is also dependent on the broader social environment and this relationship is bi-directional. Supportive social environments foster an individual's resilience to declines in physical and psychological function. Conversely, individual level responses, such as self-imposed isolation, can adversely influence their immediate social environments.

- Reciprocal relations between mood and RA may be due to factors such as reduced medication and physical activity adherence, leading to deconditioning and increased pain. Psychological factors may impact disease activity by altering immune response, increasing pro-inflammatory cytokines (e.g., TNF and IL-6)[2], and lead to inflammation[88, 89]
- For individuals with schizophrenia, rates of RA are lower due to high blood concentrations of IL-1 receptor antagonist, an anti-inflammatory cytokine that may be protective to RA[90]

Management of RA and Mental Health

- Psychological evaluation and care are recommended to be among the therapeutic objectives for those with RA and mental health illnesses or problems[86]
- Broad positive social messaging about RA should be employed to mitigate affective responses post-diagnosis[86]
- The goals of care should aim to engage and motivate the person toward goal-setting, attend to psychological needs of caregivers, generate trust and empathy, negotiate treatment options, and promote self-efficacy[86]
- For individuals not achieving joint remission, it is recommended that increased emphasis be placed on depression and anxiety being considered as part of a treat-to-target[3] strategy.[91] Alternative targets may be considered in the shared decision making between the individual and practitioner[4]
- Support by psychologists and patient associations can foster mental health by offering support and empathy relation[86]

A systematic review concluded that better physical and mental health outcomes for those with RA are likely to result from integrated mental health care provided within routine clinical practice[567]

[2]A proinflammatory or inflammatory cytokine is a signaling molecule secreted from immune and other types of cells that promote inflammation. Examples include interleukin-1 (IL-1), IL-12, and IL-18, and tumor necrosis factor alpha (TNF-α). Excess chronic production of inflammatory cytokines contribute to inflammatory physical and mental health conditions[573]

[3]Treat-to-target (TTT) strategy is a therapeutic approach which specifies that the therapeutic target in RA should be a state of remission, or an alternative goal could be a low disease activity. TTT should be based on shared decision making and aim to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, and normalization of function, and social participation[91]

[4]This is in reference to recommendation #5 and #6 of the "Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force" which indicates that the choice of the measure of disease activity and the target value should be influenced by comorbidities (e.g., depression, anxiety), individual factors, and drug-related risks. Furthermore, disease activity measures must be obtained and documented regularly. This should be done monthly for those with high/moderate disease activity or less frequently (such as every six months) for those in sustained low-disease activity or remission[91]

C. PSORIATIC ARTHRITIS (PSA)

PsA is a chronic inflammatory arthritis, associated with psoriasis. People with PsA may present with musculoskeletal involvement (peripheral arthritis, inflammation at the sites where tendons or ligaments insert into the bone, spine inflammation, skin and nail disease or extra-articular manifestations, e.g. inflammatory bowel disease). PsA is a distinctive disease because it sums up the effect of both arthritis and skin psoriasis.[92]

Prevalence and Incidence of PsA with Mental Health Problems or Illnesses

- Prevalence estimates based on self-report of diagnosis according to International Classification of Disease Codes indicate that one in three people with PsA have at least mild anxiety, while 1 in 5 report at least mild depression. These conditions tend to occur with greater disease activity[93]
- It has been reported that depression and anxiety in individuals with PsA ranges between 9 to 37%[94]
- One study suggested a higher incidence rate of "any suicidality" in people with PsA than the general population.[95] More research is needed about suicide/self-harm and substance misuse

Mental Health Screening

- Screening tools that were reported in the literature as being used in practice include the Hospital Anxiety and Depression Scale (HADS), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9). However, there is a need to validate these tools in populations with inflammatory rheumatic diseases[93]

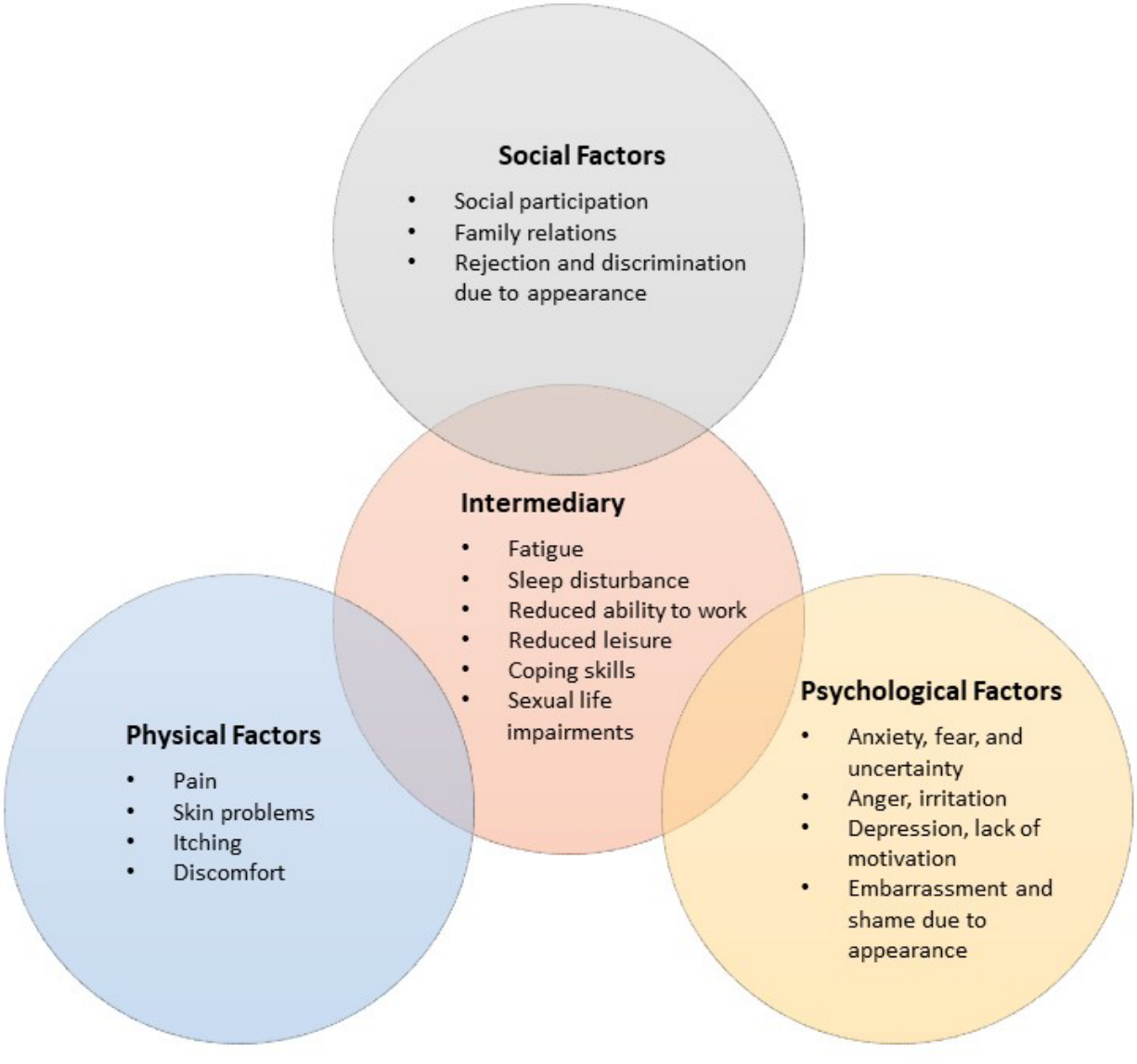
Common Pathways

- Several physical, social, and environmental factors interact and impact the individual with PsA (Figure 3.3)[92]
- Poor mental health is a predictor for developing fibromyalgia for those with PsA. This, in turn, is associated with worse physical health outcomes[96]
- Composite treatment targets, such as the Disease Activity Score 28 (DAS 28) or minimal disease activity[97], include components such as pain and patient global visual analogue scales that may be influenced by comorbid mental health conditions
- Treatment escalation driven by non-inflammatory symptoms may increase adverse events and appears to provide modest improvements in mental health-related areas (e.g., quality of life)[98]
- Inflammation may influence neurocognitive functions;[99] studies have found significantly higher disease activity and pain in those with comorbid anxiety or depression[93]

Management of PsA and Mental Health

- Based on joint guidelines of care, people with psoriasis should be informed about the association of psoriasis and anxiety and depression and asked about signs and symptoms by their health provider[100]
- If positive signs or symptoms of anxiety, depression, or suicidal ideation are indicated, referral should be made to an appropriate health care professional[100]
- Psoriasis-specific therapy is recommended to improve psoriasis-associated anxiety and depression in individuals with psoriasis[100]

Figure 3.3: Shared etiology between PsA and mental health[92]



3.1.2 Cancer

Cancer is a collection of diseases that can start almost anywhere in the body. Cancer develops when the instructions from genes get mixed up, causing our cells to grow and divide out of control or not die when they should. Many cancers form solid tumours. Cancers of the blood (e.g., leukemias) generally do not form solid tumours. Cancerous tumours are malignant, which means they can spread into, or invade, nearby tissues. As these tumours grow, some cancer cells can break off and travel in the body through the blood or the lymph system and form new tumours at other sites.[101,102]

Prevalence and Incidence of Cancer with Mental Health Problems or Illnesses

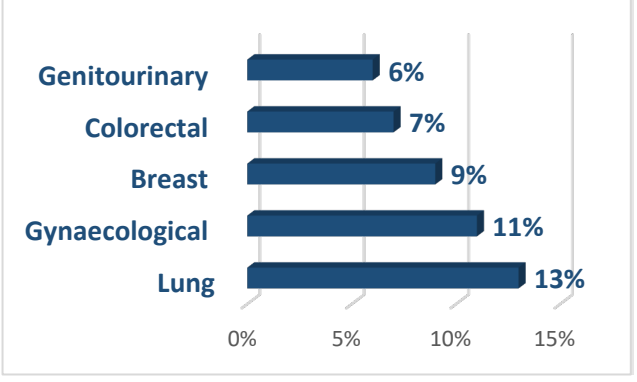
A. DEPRESSION AND ANXIETY

- A meta-analysis of incidence studies indicated a small and positive association between depression and cancer (RR=1.15, 95% CI: 1.09-1.22)[103]
- A systematic review and meta-analysis reported the prevalence of major depression (15%), minor depression (20%), and anxiety (10%) in people treated for cancer was at least double that of general population estimates[40,41]
- Meta-analyses indicate that approximately one-third of persons with cancer in acute care hospitals are affected by common mental health conditions, particularly anxiety and depression[104,40]
- A history of anxiety or trauma[105] and metastatic disease (for some cancers) appear to be stronger predictors of depression[106]
- A systematic review focused on those undergoing chemotherapy reported that lower social support, higher anxiety, higher perceived stress, and lower self-efficacy were consistently associated with depression[107]
- Limitations of incidence estimates include the variability in depression indicators used, lack of account for important confounding factors (e.g., substance use), and omission of relevant factors for specific cancer subtypes (e.g., no account of menopausal status in relation to breast cancer)[103]
- Risk factors identified for depression in cancer include younger age and social deprivation, which is broadly defined as having reduced access to aspects of one's culture and society due to many factors (e.g., poverty, family intervention)[108]
- A systematic review examining depression in cancer survivors indicated a pooled prevalence of 21% for depression and anxiety and these do not differ from the general population[109]
- A Canadian survey of 12,929 adult cancer survivors found that 78% experienced at least one emotional concern one to three years post cancer treatment; 42% experiencing 3 or more[39]

Estimates of Depression or Anxiety by Cancer Subtypes

- Among cancer subtypes, significant overall risks were found for liver (RR = 1.20, 95% CI: 1.01-1.43) and lung cancer (RR = 1.33, 95% CI: 1.04-1.72). For breast, prostate, and colorectal/colon cancer, no significant associations with depression were found[103]
- Estimates of depression vary by cancer type with highest estimates among those which impact the reproductive systems (e.g., 17% for gynecological and genitourinary cancers) (Figure 3.4) [108]
- The highest levels of anxiety are reported in lung, gynecological, and haematological (affect blood, bone marrow and lymph nodes) cancers[41]

Figure 3.4: Prevalence Estimates of Depression by Cancer Subtypes[108]



Genitourinary cancers occur in the male reproductive system and adrenal glands. They include prostate cancer, kidney cancer, bladder cancer, testicular cancer and cancers of the penis; Gynaecological cancers occur in the female reproducitve system and include ovarian, endometrial/uterine, cervical, vulvar and vaginal cancer.

Estimates of Depression or Anxiety by Subpopulations

- The prevalence of depression, using the GADS screening tool, in older African Americans with cancer was reported to be 27%[110]
- For colorectal and lung cancers, female gender is an identified risk factor[108]
- Among Latino and Afro-Caribbean immigrants diagnosed with cancer and living in New York City, the prevalence of depression was reported to be 10%; slightly more Latino immigrants (12%) showed depression symptoms compared to those who were Afro-Caribbean (7%)[111]
- A mediation analysis that compared US Hispanic and non-Hispanic cancer survivors, that included tumour characteristics and treatment factors, reported that most of the ethnic differences of heightened anxiety or depression among Hispanic cancer survivors were explained by younger diagnosis age, lower education level, lower proportions of employment, less likely of being born in the USA, less insurance, and less social support[112]

B. OBSESSIVE-COMPULSIVE DISORDER (OCD)

- A national population retrospective cohort study that examined 22 cancer types among people with OCD found overall cancer rates were not elevated among people with OCD. A slight association was found only within the first year of OCD diagnosis (standardized incidence ratio (SIR)=1.21, 95% CI 1.01-1.43)[113]

C. POST-TRAUMATIC STRESS DISORDER (PTSD)

- A random effects meta-analysis estimated an odds of 1.66 (95% CI 1.09-2.53) for PTSD in cancer survivors compared to controls. The prevalence of PTSD diagnosis in breast cancer was higher than that in colorectal, head and neck, and prostate cancers, but lower than that in brain, gynecological, and hematological cancers[114]
- Factors associated with PTSD include measurement type (clinical interview vs. self-report instrument), type of cancer, type of treatment, geographic region, prior trauma, age, and time since diagnosis[114]

D. SCHIZOPHRENIA

- Mortality risk from cancer diagnosis is reported to be 90% higher in individuals with schizophrenia and 20% higher in patients with prior depression with concurrent cancer diagnosis[115]

E. SUBSTANCE USE

Alcohol Use

- Alcohol use has been reported to contribute to approximately 3.5% of all cancer deaths and approximately 18 years of potential life lost for each alcohol-related cancer death; it is estimated 30% of alcohol-related cancer deaths are attributed to heavy drinking[116]
- The Canadian Population Attributable Risk of Cancer (ComPARe) study indicates that alcohol is attributable to 5.1% of all alcohol-related cancer cases in Canada[117]
- Based on analysis of data from 193,197 individuals, including 16,504 cancer survivors, with age ≥18 years old in the 2012–2017 National Health Interview Survey, the prevalence of heavy drinking was identical for cancer and non-cancer individuals at 5.2%.; for frequent binge drinking, the prevalence was lower in cancer survivors (2.8% vs. 4.9% in non-cancer survivors)[118]
- Compared with cancer survivors with a short cancer history (2–4 years), survivors with a cancer history of 5–9 years were more likely to be current drinkers after adjusting for the selected factors. Cancer status, alcohol-related cancer type, and length of cancer history had no impact on excessive alcohol intake[118]

Drug Use

- Among 169,162 respondents of the National Survey on Drug Use and Health (2015-2018), 5.2% were cancer survivors, with 1.2% and 4.0% reporting having more recent and less recent cancer histories, respectively. Rates of prescription opioid misuse were similar among more recent (3.5%; 95% CI 2.4%-5.2%; OR, 1.27; 95% CI 0.82-1.96; P = .36) and less recent (3.0%; 95% CI 2.4%-3.6%; OR 1.03; 95% CI 0.83-1.28; P = .76) survivors compared with respondents without cancer (4.3%, reference group)[119]
- Among 169 162 respondents of the National Survey on Drug Use and Health from (2015-2018), factors associated with prescription opioid misuse among cancer survivors included younger age (18-34 vs ≥65 years: OR 7.06; 95% CI 3.03-16.41;

P < .001), alcohol use disorder (OR 3.22; 95% CI 1.45-7.14; P = .005), and nonopioid drug use disorder (OR 14.76; 95% CI 7.40-29.44; P < .001)

Tobacco Use

- In 2018, 11.8% of cancer survivors aged 18 and older in the United States were current cigarette smokers[120]
- Compared with non–smoking-related cancer survivors, smoking-related cancer survivors have a higher risk of being cigarette smokers and of continuing smoking (10.63% vs 19.78%)[121]
- Cancer survivors that were younger, had lower education levels, were any marital status other than married or widowed, were uninsured, or survived cervical cancer were more likely to be smokers than other survivors[122]
- National data indicate that between 44% and 48% of cervical cancer survivors are current smokers;[123,124] nearly 3 times as high as the smoking rate of survivors of all cancers combined[123,125]

Various Substances

- In a large study of US veterans with cancer diagnoses (n=482,688), 6.6% had a comorbid substance use disorder diagnosis[126]
- A retrospective longitudinal cohort study of young-old (66-74 years) and old-old (≥ 75 years) men who were fee-for-service Medicare enrollees with advanced prostate cancer reported prevalence of substance use as 12.4% in the young-old and 7.4% in the old-old group[127]
- The young-old men whose substance use were in the 'drug psychoses and related' category had higher inpatient, outpatient, and ER usage as well as mortality (HR=2.2; CI=1.5, 3.1) compared to those without substance use. For the old-old men, the 'drug psychoses and related' category was associated with highest inpatient and outpatient use; and 'Non-dependent use of drugs' was associated with highest ER use, compared to those without substance use[127]

Estimates of Substance Use by Subpopulation

- Three studies show that sexual minority cancer survivors are more likely to be current smokers as compared to heterosexual cancer survivors[128,129,130]
- Compared to heterosexual cancer survivors, sexual minority male cancer survivors consume alcohol more days/week, more drinks/day, and more drinks/30 days[129]
- Of the 602 cancer survivors who participated in the National Health and Nutrition Examination Survey (NHANES) from 2001–2010, sexual minorities were 2.6 times more likely to report a history of illicit drug use (aOR=2.4, 95% CI 1.04, 5.35)[131]

F. SUICIDE

- A retrospective, population-based study of program data collected between 1973-2014 reported that the rate of suicide was 28.58/100,000-person years, and the standardized mortality ratio (SMR) of suicide was 4.44 (95% CI 4.33-4.55)[132]

- Suicide is reported to be more common in men (83%) and in those who are white (92%)[132]
- Cancers of the lung, head and neck, testes, bladder, and Hodgkin lymphoma had the highest SMRs (> 5-10). Compared to others with cancer, elderly, white, unmarried males with localized disease are at highest risk[132]
- A systematic review examining association between suicide ideation and physical illness in older adults found suicidal behaviour was associated with malignant diseases[133]

G. OTHER MENTAL HEALTH ILLNESSES AND PROBLEMS

- Nearly one-third of cancer survivors are diagnosed with mental health conditions[40]
- The most common occurring mental health illnesses among cancer survivors, including those in active treatment and long-term survivors, are major depression, generalized anxiety disorder, adjustment disorder, panic disorder, and post-traumatic stress disorder[134]
- For people with severe mental illnesses and substance use disorders, significantly worse survival after cancer diagnosis is reported. This is independent of cancer stage at diagnosis and other potential confounders[115]

Mental Health Screening

It is recommended screening be done at different stages of cancer (e.g., pre-treatment, periodic follow-ups post-treatment, and survivorship periods)[576]

- Many different screening tools are used such as the Center for Epidemiologic Studies Depression Scale (CES-D) and Hamilton Depression Scale (HAM-D); there is no clear consensus about the use of one specific screening tool
- The challenges in screening tool selection are that symptoms can differ by cancer type and they can overlap with features of the health condition (e.g., fatigue)
- A prospective longitudinal study of adults newly diagnosed with a first occurrence of primary head and neck cancers, indicated that anxiety was a precursor to post-treatment Major Depressive Disorder (MDD). Identification and prophylactic treatment of anxiety upon diagnosis of head and neck cancer may prevent or delay MDD diagnosis[135]

Common Pathways

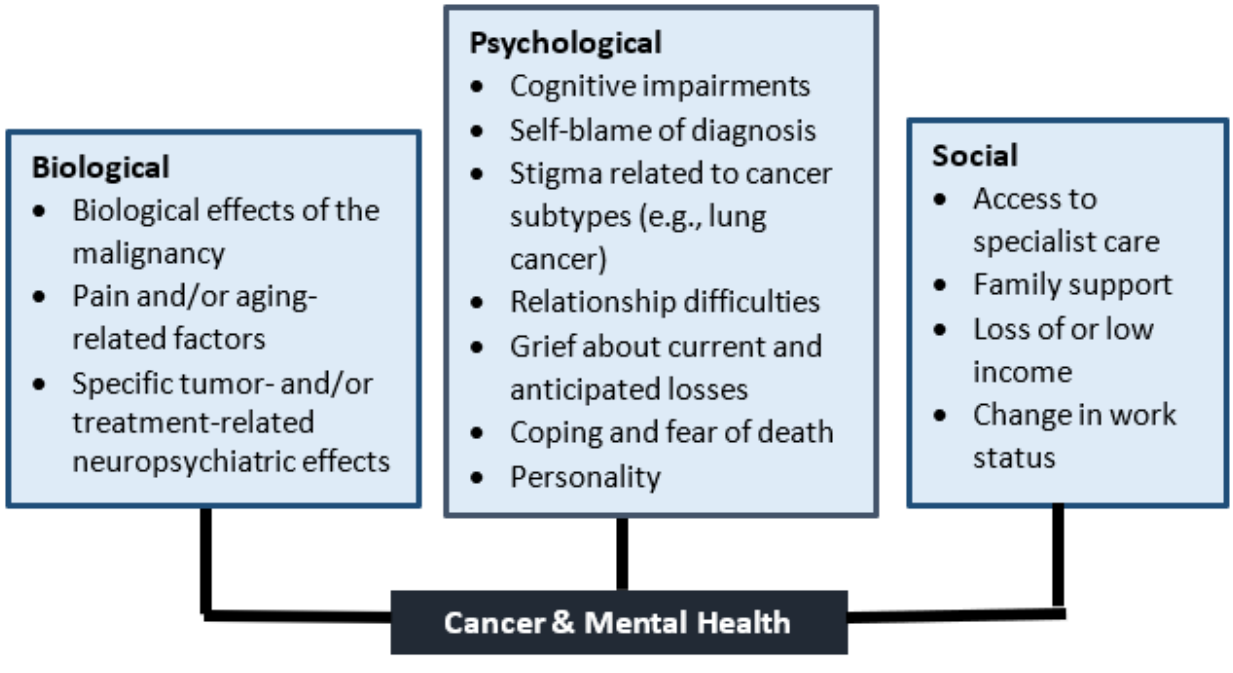
Common Factors Contributing to Mental Health Illnesses or Responses

- Psychological reactions, such as depression and anxiety, tend to occur in response to diagnosis, treatment, relapse, end of life care, or survivorship
- Common shared biological pathways include dysfunctional immune responses, including increased concentrations of inflammatory cytokines such as TNF-α and IL-6
- Psychological, biological, and social factors intersect to impact mental health in those with cancer (Figure 3.5)[136]

Factors Contributing to Mental Health Problems or Illnesses by Cancer Subtypes

- Depression and anxiety may occur secondary to or in response to cancer treatments (Figure 3.6). The most common include tumours of the pancreas (severe cytokine-mediated depression) and lung (depression and anxiety due to endocrine paraneoplastic syndromes[5])
- Among individuals with small cell lung cancer (SCLC), 15% develop the syndrome of inappropriate antidiuretic hormone secretion (SIADH) which can lead to mood changes due to hyponatremia (low sodium concentration in blood)[136]
- Depression secondary to hypercalcemia can be driven by ectopic parathormone-related peptide production in non-small cell lung cancer (NSCLC), myeloma, sarcoma, breast, renal, gynecological, head and neck cancers, and bone metastases[137]
- For individuals diagnosed with lung cancer that are current or former smokers, stigma can lead to negative psychosocial impact[138]

Figure 3.5: Shared etiology between cancer and mental health



[5]Paraneoplastic syndromes occur due to the production of chemical signalling molecules (such as hormones or cytokines) by tumour cells or by an immune response against the tumour.

Figure 3.6: Examples of shared depression and anxiety etiology related to specific tumours and cancer treatments[136]

Cancer Treatments	Tumours
Cancer Surgery • gastrectomy or ileal resection → vitamin B_{12} deficiency • oophorectomy → estrogen depletion • frontal lobe neurosurgery → apathy and/or emotional lability	**Brain** • meningiomas, gliomas, or metastases → frontal &/or temporal lobe changes → apathy, emotional lability, hallucinations, executive function deficits, motor behavioral disturbance • pituitary tumours → altered secretions (e.g., adrenocorticotropic hormone, prolactin)
Radiotherapy • head and neck → hypothyroidism • pelvic → Vitamin B_{12} deficiency • brain → melatonin deficiency & insomnia, thyroid stimulating hormone, growth hormone, &/or gonadotropin deficiency	**Parathyroid** • overproduction of parathyroid hormone → cognitive impairment
Chemotherapy (e.g., mitotic spindle toxins, anti-metabolites) → mood disturbance & instability	**Lung** • bronchus carcinoid tumours → carcinoid syndrome, paraneoplastic endocrine syndrome, &/or pellagra → aggression, cognitive impairment, Cushing's syndrome, irritability • non small cell lung cancer → paraneoplastic endocrine syndrome → hypercalcemia • small cell lung cancer → paraneoplastic Cushing's syndrome or SIADH → Cushing's syndrome, encephalopathy, delirium
Monoclonal antibodies (e.g., checkpoint inhibitors, EGFR inhibitors)	**Pancreas:** interleukin-6 release
Hormone Treatments • corticosteroids → agitation, psychosis, euphoria, mania, suicidal ideation	**Ovary** • onconeural (anti-NMDA receptor) antibody-mediated limbic encephalitis → psychosis

• androgen deprivation → irritability	
	Adrenal • cortical → Cushing's syndrome • phaeochromocytoma → mood swings, psychosis, irritability
	Testicular • paraneoplastic endocrine syndrome → hyperthyroidism • onconeural (anti Ma2) paraneoplastic syndrome → disorientation, hallucinations
	Other Tumour Types Examples: myeloma, breast, renal, gynecological, sarcoma, breast, head, neck → hypercalcemia

Management of Cancer and Mental Health

Cancer and Mental Health Considerations in Management

- Some components of cancer care may contribute to re-traumatization:[139]
  - Pelvic, breast, or rectal examinations may exacerbate pre-existing posttraumatic stress disorder
  - Relapses of a depressive disorder may occur after mastectomy
  - Relapse of manic or depressive episodes in bipolar affective disorder may occur secondary to essential treatment with corticosteroids
- Individuals treated with some chemotherapeutic agents, hormone deprivation treatment, immunotherapies and targeted agents, radiotherapy, and cancer surgery may experience neuropsychiatric effects, such as depression, anxiety, and/or suicidal ideation:[139]
  - About 10% of individuals who receive radiotherapy for head and neck cancer develop clinical hypothyroidism; of these, about 66% may develop depressive symptoms
  - After pelvic irradiation, about 14% of individuals acquire vitamin B_{12} deficiency due to disrupted gut absorption; depression is a common presenting symptom
  - Bilateral oophorectomy in premenopausal women is associated with a long-term increased risk of depressive disorder and of anxiety symptoms
- Addressing underlying factors such as vitamin B_{12} deficiency, hypothyroidism, SIADH, hypercalcemia, and pain can improve mental health[139]

Management Approaches

Mental Health

Medications and Complementary Therapies

- A Cochrane review of anti-depressants for depression in people with cancer reported overall low quality evidence. The authors recommended antidepressants be prescribed on an individual basis; selective serotonin reuptake inhibitors (SSRIs) are suggested to have a positive safety profile[140]
- Complementary therapy use, such as herbs for symptom relief, is common. A systematic review that examined 100 single-herb RCTs that were considered safe for use in cancer treatments found that lavender, passionflower, and saffron produced benefits comparable to standard anxiety and antidepressant medications; 45% of the studies reported fewer adverse effects than conventional medications. Results need to be confirmed with larger RCTs[141]
- A systematic review of music therapy for individuals receiving cancer treatment reported no positive effect on anxiety; several methodological limitations were noted among the trials included[142]
- Results of a systematic review that examined yoga for improving mental health and cancer-related symptoms in women diagnosed with breast cancer indicated moderate-quality evidence for yoga as a supportive intervention for reducing depression and anxiety when compared with psychosocial/educational interventions[143]

Models of Care

- In a meta-analysis that examined collaborative care, pharmacological, and psychological treatments, collaborative care interventions were significantly more effective than usual care and depression reduction was maintained after 12 months[144]
- Results of a systematic review of 9 studies indicated that life review programs benefited individuals with cancer by reducing depression and anxiety, as well as improving self-esteem and quality of life[145]
- Stepped care is a system of delivering and monitoring treatments, such that effective, yet least resource-intensive, treatment is delivered to individuals first. It is recommended that stepped care approaches for mental health interventions in cancer should include the following considerations:[146]
    i. Medication: psychotropic medications should be guided by clinical parameters, particularly interactions with chemotherapies, to identify specific contraindications;
    ii. Psychological therapies: Cognitive-behavioural interventions can help to understand the thoughts, feelings, and behaviours that can cause or maintain symptoms of depression or anxiety (e.g., treatment refusal, avoidance behaviour, excessive reassurance seeking);
    iii. Availability of specialist psychological therapy varies geographically and by expertise. Therapeutic expertise needs include complex illness beliefs, challenging side effects (e.g., psychosexual), physical disfigurement, and end-of-life issues.

- Integrated mental and physical cancer care approaches are also recommended. One reported model of the UK NHS Cancer Strategy includes:[147]
    i. Collaborative screening and treatment;
    ii. Cancer clinical nurse specialist delivery of supervised cognitive-behavioural interventions for depression; and
    iii. Guidance to general practitioners by liaison psychiatrists to optimize the prescribing of antidepressant medication
- In Canada, examples of integrated mental and physical cancer care approaches exist. For example, The Tom Baker Cancer Centre and the Odette Cancer Centre at Sunnybrook Health Sciences Centre.
- Better integration between primary and tertiary cancer care is understood to lead to improved coordination, continuity and quality of care.

Peer, Self-Care, and Education Approaches

- A randomized longitudinal study of 50 women with breast cancer, 21 years+ who were randomly assigned to moderated or peer-led groups found no significant differences in depressive symptoms by group or by extent of group participation[148]
- A clinical trial that compared an intervention where women with breast cancer received training sessions (three 25- to 30-minute sessions) based on the Orem's model,[6] on a weekly basis with the control group that received only routine care, reported significantly different pre- and post-anxiety levels in the intervention group when compared to the control group ($P < 0.001$)[149]
- An RCT compared comprehensive education and care (CEC) program versus basic health education and rehabilitation over 12 months and the effects on anxiety, depression, quality of life, and survival in patients with hepatocellular carcinoma who underwent surgical resection. The CEC group received health education, psychological nursing, caring activity, and telephone condolence. The results showed greater improvements in HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) scores as well as better survival[150]
- A systematic review examining supportive care interventions (psychoeducation, psychoeducation alone, exercise program) for individuals diagnosed with lung cancer reported that psychotherapy plus psychoeducation and exercise significantly improved depressive symptoms. Psychoeducation alone did not yield significant effects[151]

Substance Use

- Quitting smoking prior to cancer treatment may improve survival, as continuing to smoke after a cancer diagnosis is associated with higher risk of cancer recurrence,

[6]Dorothea Orem's Self-Care Model[574] focuses on an individual's "ability to perform self-care, defined as 'the practice of activities that individuals initiate and perform on their own behalf in maintaining life, health, and well-being.'". Orem's self-care deficit theory focuses on scenarios needing the attention of nurses, and ways to help such as acting for and doing for others, guiding others, supporting another, providing an environment promoting personal development in relation to meeting future demands, and teaching another.

second primary cancers, and development and progression of other smoking-related morbidities, such as cardiovascular and respiratory diseases[152]

Multi-level approaches to reduce stigma barriers in the context of lung cancer help to improve quality of care. Examples include patient-focused stigma-reduction interventions to facilitate timely diagnosis and treatment adherence, and training focused on clinician empathy and communication with lung cancer patients[138]

- Cervical cancer survivors should be provided with a survivorship care plan that addresses the dangers of continued tobacco use and the risk of subsequent malignancy that persists throughout the survivor's lifetime[153]

3.1.3 Cardiovascular Disease (CVD)

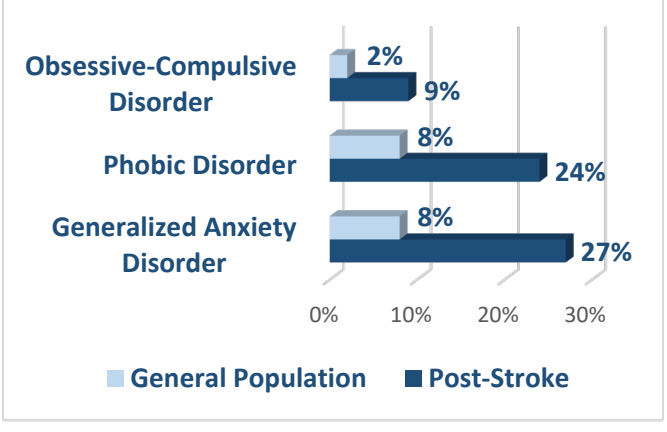
CVD refers to a group of conditions that affect the structure and functions of the heart. These conditions can include hypertension, coronary artery disease (CAD) which can lead to coronary heart disease (CHD) and myocardial infarction (MI), cerebrovascular disease (stroke), peripheral vascular disease, and heart failure (HF).[154]

Prevalence and Incidence of CVD with Mental Health Problems or Illnesses

A. ANXIETY

- A meta-analysis examining anxiety and new onset of CVD combined 37 studies (n = 1,565,699) with follow-up ranges of 1 to 24 years. Anxiety was associated with a 52% increased incidence of CVD (HR = 1.52, 95% CI 1.36–1.71) suggesting it is a causal factor[156]
- There is high prevalence of different types of anxiety after stroke (Figure 3.7) with the biggest difference in estimates between generalized anxiety disorder versus the general population
- Female sex and having depression were significant predictors of anxiety disorder in those with who experienced a stroke[155]

Figure 3.7: Post-Stroke Prevalence Estimates of Different Types of Anxiety-Related Conditions[155]



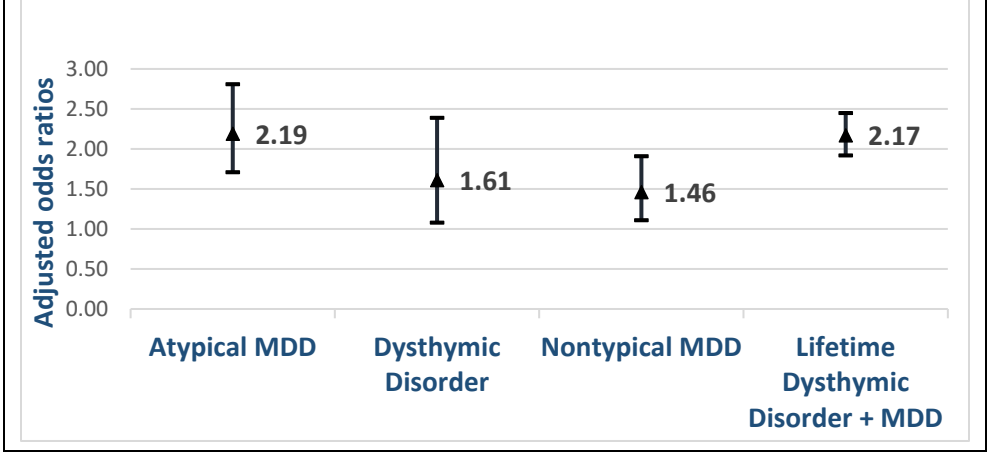
B. DEPRESSION

- Depression can occur with CVD in two forms: precardiac and postcardiac:

- *Precardiac depression* is more common, persistent, and chronic and has been linked to additional risk of reoccurrences of depressive symptoms and relapses. Those with precardiac depression experienced major depression on average 17 years prior to the CVD onset[157]
- *Postcardiac depression* is transient and can remit after the stress of an acute exacerbation subsides[158]

- Prevalence of depression varies by type of heart disease and severity with estimates between 15-20%; at the high end of this range is depression which occurs in relation to CAD, peripheral artery disease, and HF[159]
- Depression has been reported to be more than three times that which occurs in general populations. Higher reports of depression in CVD may be due to changes in quality of life[159]
- Higher prevalence of depression occurs among those who have had a stroke (34%, 95% CI 29%–38%) or myocardial infarction (MI) (24%, 95% CI 20%–28%)[160]
- Prospective data from 28,726 adults reported those with different forms of depression had higher odds of incident CVD than no depression history (Figure 3.8)[161]

Figure 3.8: Odds (95% Confidence Intervals) of Incident CVD and Different Depression-Related Diagnoses[161]



- Based on a systematic review, the prevalence of depression in those with stroke was reported as 29% (95% CI 25–32) and remained stable for 10 years, with a cumulative incidence of 39–52% within 5 years of stroke. Major predictors of depression were disability, depression pre-stroke, cognitive impairment, stroke severity, anxiety, lower quality of life, mortality, and disability[162]
- A meta-analysis with meta-regression reported that depression can occur from 2 days to 7 years after stroke (mean 6.87 months, N=33 in acute, N=43 in rehabilitation and N=69 in the community/outpatients). The point prevalence of depression was 17.7% (95% CI=15.6% to 20.0%). Dysthymia was present in 3.1% (95% CI=2.1% to 5.3%). Any depressive disorder was present in 33.5% (95% CI=30.3% to 36.8%)[163]

- Relative risk of any depressive disorder was reported to be higher following left (dominant) hemisphere stroke, aphasia, and among people with a family history and past history of mood disorders[163]

C. BIPOLAR DISORDER

- In an analysis of two waves of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the 3-year incidence of CVD for bipolar I disorder (n = 1,047), bipolar II disorder (n=392), MDD (n=4,396), and among controls (n=26,266) was 6.30%, 5.74%, 3.98%, and 3.70%, respectively. Adjustments were made for age, sex, race, cigarette smoking, hypertension, obesity, and alcohol and drug use disorders[164]

D. OBSESSIVE-COMPULSIVE DISORDERS

- In a longitudinal analysis of individuals diagnosed with OCD (n=25,415) from a cohort of 12,497,002 individuals, those with OCD had a higher risk of any metabolic or cardiovascular complications compared with the general population (adjusted HR=1.45, 95% CI 1.42-1.49) and their unaffected full siblings (adjusted HR=1.47, 95% CI 1.40-1.54)[165]

E. PATHOLOGICAL GAMBLING

- A prospective study about at-risk/problem/pathological gambling (ARPG) and incident medical conditions among older adults reported that the odds of arteriosclerosis was 2.3 times that of those who identified as having no APRG (p=0.0035) after adjustment for socio-demographic characteristics, psychiatric comorbidity, substance use, and BMI[166]

F. POST-TRAUMATIC STRESS DISORDER

- A cohort study of 6,481 first responders nested within the World Trade Center Health Program in New York City reported, even after controlling for depression, an elevated risk (HR=2.22, 95% 1.30–3.82) for MI and stroke (HR=2.51, 95% CI 1.39–4.57) among those with PTSD. There were no significant differences between men and women[167]

G. SCHIZOPHRENIA

- A study comparing effects of schizophrenia on major adverse cardiac events, length of hospital stay, and prevalence of somatic comorbidities following acute coronary syndrome reported heightened risk for major adverse cardiac events (HR=1.62, 95% CI 1.45–1.81) and stroke (HR= 1.51, 95% CI 1.15–1.99)[168]

H. SUBSTANCE USE

- A study that examined primary heart failure hospitalizations in the 2014 National Inpatient Sample reported that of 989,080 heart failure hospitalizations, 15.5% (n =

152,965) had documented tobacco (n = 119,285, 12.1%) or substance (n = 61,510, 6.2%) use disorder[169]

- After accounting for demographic factors in the above-indicated study, female sex was associated with lower rates of tobacco (OR=0.72; 95% CI 0.70–0.74) and substance (OR=0.37; 95% CI 0.36–0.39) use disorder. Native American race was associated with increased risk of alcohol use disorder (OR=1.67; 95% CI 1.27–2.20); Black race was associated with alcohol (OR=1.09; 95% CI 1.02–1.16) or drug (OR=1.63; 95% CI 1.53–1.74) use disorder. Medicaid insurance or income in the lowest quartile were associated with increased risk of tobacco and substance use disorders[169]

I. SUICIDE IDEATION

- A systematic review examining association between suicide ideation and CVD in older adults found mixed results among 7 studies[133]

J. ESTIMATES OF MENTAL HEALTH COMORBIDITIES BY SUBPOPULATIONS

Depression and Anxiety

- Among women with CHD, prevalence estimates of depression range between 36-40%; higher prevalence occurs both at baseline (hospitalization [36% vs 23%]) and over 24 months (23% vs 20%) when compared to men[170]
- Studies of gender differences regarding anxiety after acute myocardial infarction indicate that women tend to have higher anxiety than men. This appears to be consistent across the western and eastern cultures[171]
- A meta-analysis examining depression in older adults reported that among the pooled sample of 47,625 older people (mean 74, SD ± 7.4 years), over a median follow-up of 8.8 years, participants with depressive symptoms had a comparably higher risk of stroke (HR 1.36, 95% CI 1.18–1.56) and all-cause mortality (HR 1.44, 95% CI 1.35–1.53), but not of MI (HR 1.08, 95% CI 0.91–1.29)[172]
- In a cross-sectional study which compared stroke survivors who were Latino, Black, and white, Those who were Latino were three times the odds of depression (95% CI 1.18–6.35) in compared to those who were white; People who were Black and white had similar odds of depression[173]
- Logistic regression results from analysis of National Survey of American Life (NSAL) data indicated that African American women with MDD were 1.59 times more likely to have CVD compared to those without MDD and these results were similar among those living in and not living in poverty[174]
- A prospective, descriptive-correlational repeated-measures study involving individuals living in rural settings admitted to hospital for ACS suggested that persistent anxious state occurs in individuals up to 8 hours later. The development and testing of protocols for anxiety reduction may be needed[175]

PTSD

- Using data from the Collaborative Psychiatric Epidemiology Surveys (CPES), the National Latino and Asian American Study (NLAAS) and the National Comorbidity

Survey Replication (NCS-R), an increased likelihood of cardiovascular events was reported for those with a diagnosis of PTSD (OR = 2.10, 95% CI 1.32-3.33) when compared to those who had not experienced trauma[176]

- Among subgroups studied in the above-indicated study, the likelihood of having a cardiovascular event in those with PTSD was significant for non-Latino Whites (OR=1.86, 95%CI, 1.08-3.11), Latinos (OR = 1.94 95% CI 1.04-3.62) and non-Latino Blacks (OR=3.73, 95%CI 1.76-7.91, but not for Asian respondents[176]

Mental Health Screening

Mental Health

- Various studies recommend that all people diagnosed with CVD be screened for depression and anxiety, particularly at key periods such as post myocardial infarction or major surgical interventions
- A systematic review of studies about heart failure and coronary artery disease concluded that screening and treating of depression did not improve heart failure management or reduce rates of heart attacks or death[177]
- Although there is currently no direct evidence that screening for depression leads to improved outcomes in cardiovascular populations, depression has been linked with increased morbidity and mortality, poorer risk-factor modification, lower rates of cardiac rehabilitation, and reduced quality of life[157]
- Screening tools to assess cardiac and mental health comorbidity should screen for symptoms, stress, quality of life, risk factors, and protective factors[178]
- Self-report questionnaires used for screening of depression in CVD include the Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI), Hospital Anxiety Depression Scale (HADS), Cardiac Depression Scale (CDS), and the Center for Epidemiologic Studies Depression Scale-10 (CES-D). Many of these have been validated in many different languages. An American Heart Association Science Advisory suggested the PHQ is most useful[179]
- The two-item PHQ for identifying individuals with depression may be used in outpatient settings, and added to questionnaires that are completed at registration[178]
- The CDS measures the range of depressive symptoms in CVD and is reported to have excellent psychometric properties (e.g., high sensitivity and specificity) for the diagnosis of MDD[180]
- The European Guidelines on CVD prevention suggest two core questions that cover mandatory criteria for MDD diagnosis: 'Do you feel down, depressed, or hopeless?' and 'Have you lost interest and pleasure in life?'[181]
- For people thought to have Type D personality,[7] which is characterized by enduring features of depression, it is recommend asking: 'In general, do you often feel

[7]Type D personality is described as one where the person has the tendency to experience increased negative emotions across time and situations and tend not to share these emotions with others, because of fear of rejection or disapproval[575]

anxious, irritable, or depressed?' and 'Do you avoid sharing your thoughts and feelings with other people?"[181]

- For people that have had an acute coronary syndrome, depression screening is recommended while in hospital and rescreening should occur two months after the acute event[182]

Substance Use

- Tobacco[183] and cocaine[184] use are associated with increased readmission risk in heart failure patients
- Screening for tobacco and substance use disorders has historically been deficient in primary care, emergency department, and hospital settings[185]

> Screening for tobacco and substance use disorders is recommended in those hospitalized for heart failure[169]

- A Danish longitudinal record linkage study of consecutive drug use disorder (DUD) treatment admissions (2000 and 2006) reported that of 17,642 patients seeking treatment for DUD, 4.5% had a history of CVD at treatment entry; 1,535 new incident cases of CVD were observed during a mean follow-up time of 7.5 years[186]
- CVD incidence in the above indicated study was associated with intravenous drug use [sub hazard ratio (SHR)=1.41, $p<0.001$], not responding to injection question (SHR=1.23, $p=0.005$), older age (SHR=1.04 per year, $p=0.000$), use of prescription methadone (SHR=1.32, $p<0.001$), use of benzodiazepines (SHR=1.21, $p=0.005$), and being referred to methadone treatment (SHR=1.15, $p=0.022$). The use of amphetamines was negatively associated with CVD risk (SHR=0.75, $p=0.001$)[186]

Common Pathways

Mental Health

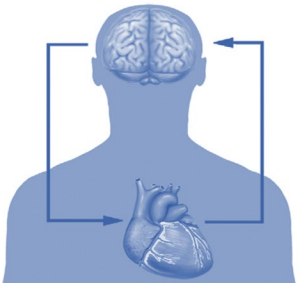
- Biological and behavioural pathways that include insulin resistance and high circulating levels of stress hormones interact in a vicious cycle with health behaviours (Figure 3.9)
- MDD can cause deregulation in the sympathetic nervous system and HPA axis which can lead to effects such as hypertension, left ventricular hypertrophy, coronary vasoconstriction, endothelial dysfunction, platelet activation, and the production of proinflammatory cytokines. Potential consequences include an elevated risk of ventricular arrhythmias and MI[187] (Figure 3.9)
- Inflammatory markers that include C-reactive protein (CRP), and proinflammatory cytokines, such as interleukin 1, 2, 6, and TNF may also be part of the shared etiology[187]
- A large prospective study reported that the presence of a major depressive episode is a risk factor for stroke, especially in those who smoke[188]
- A meta-analysis examining the magnitude of cardiovascular responses (heart rate, diastolic and systolic blood pressure) to sadness and angry rumination (43 studies;

3,348 participants) found association between rumination and cardiovascular reactivity; angry rumination may have larger cardiovascular effects than sadness rumination. Autonomic dysregulation due to long-term rumination may be linked to depression and hostility to CVD[189]

Figure 3.9: Shared etiology between CVD and mental health[190,191,192]

Biological Factors
- Insulin resistance
- Platelet receptor and function; activation
- Coagulation factors (e.g., fibrinogen)
- Pro-inflammatory cytokines
- Endothelial function
- Neurohormonal
- Genetic (e.g., serotonin mechanism)
- Stress and its effects on the autonomic nervous system

Behavioural Factors
- Substance use
- Poor diet
- Inactivity
- Poor adherence to medication and/or rehabilitation programs



Psychosocial Factors
- History of poor mental health
- Personality
- Social isolation
- Bereavement

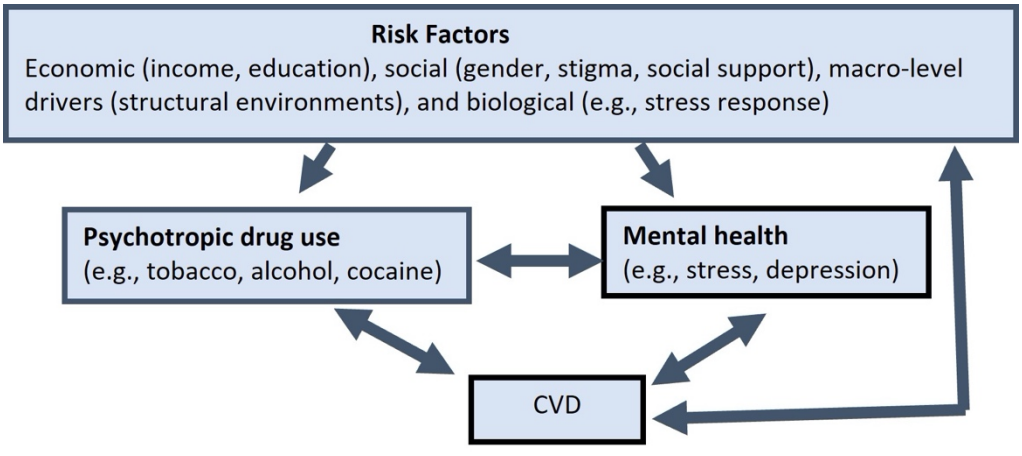
Actual or Perceived Loss(es)
- Health and functional capacity
- Immortality/immobility
- Independence
- Sexual relationships
- Employment and financial security

Substance Use

- A number of mechanisms related to economic, social, macro-level drivers, and biological pathways explain potential inter-relations between substance use and CVD (Figure 3.10)
- Injection use may lead to venous disease,[193] and thrombosis, septicaemia or endocarditis[194]
- Opioid exposure is associated with increased arterial stiffness and vascular age[195] in a dose-dependent fashion[196]
- High doses of methadone may worsen CVD by causing QT interval prolongation[197,198]
- High doses of cocaine and amphetamine are associated with acute vascular events, such as arrhythmias and elevated blood pressure[199,200]
- Benzodiazepines are associated with risk of CVD among patients with depression or anxiety;[201] this association is difficult to disentangle from the severity of mood and anxiety disorders[202]

- Case reports have indicated that cannabis use may be associated with acute myocardial infarction[203]

Figure 3.10: Examples of shared etiology between CVD and substance use



A number of mechanisms related to economic, social, macro-level drivers, and biological pathways explain potential inter-relations among substance use, mental health, and CVD. It is well established that poor mental health and substance use frequently co-occur.[204] Substance use may be a cause or consequence of mental ill health or share a common origin with mental ill health. An alternative explanation is that mental ill health and substance use interact and maintain each other.

Management of CVD and Mental Health

- Lower treatment rates for depression occur among those who have had a stroke (24%, 95% CI 20%–27%) when compared to those who have had an MI (14%, 95% CI 8%–19%).[160] Frequent assessments with needed treatment plan adjustments are recommended

A. CARDIAC REHABILITATION AND EXERCISE

- Cardiac rehabilitation, based on exercise training in a group setting, results in less depression[205]
- For those with CHD, aerobic exercise in a group setting reduces depression to levels similar to antidepressant medication; improved cardiovascular function (VO_2 peak) was also found[206]
- Based on clinical trial data, exercise training reduces depression in people with heart failure, even up to 12 months after the intervention[207]
- An RCT that compared supervised exercise vs home-based exercise vs antidepressant medication (sertraline, 50–200 mg daily) vs a placebo in individuals with CHD risk factors (brachial artery flow-mediated dilation, carotid intima-media thickness, serum lipids, and 10-year atherosclerotic cardiovascular disease (ASCVD)

risk), indicated that compared with the placebo, both exercise groups and sertraline therapy were associated with an improvement in CHD risk factors[208]

B. PSYCHOLOGICAL INTERVENTIONS, INCLUDING COMBINED TREATMENTS

- An RCT that compared internet based CBT with treatment as usual in people with recent MI reported lowered HADS scores over time (mean delta=-5.1, P<.001) but no difference between the study groups at follow-up (beta=-0.47, 95% CI -1.95-1.00). Treatment adherence was low with only 46% of the intervention group completing the introductory module.[209] Internet-based CBT has also been indicated to be unsuitable for moderate-to-severe depression or anxiety[210]
- A meta-analytic review concluded that CBT and problem solving showed some benefit for those with CVD.[211] CBT may also reduce subsequent cardiovascular events[212]
- A 3-group, parallel, RCT where individuals with stroke were randomized within 1 month of hospital admission to problem-solving therapy or non-specific support given by volunteers or treatment as usual indicated, at 6- and 12-month follow-ups, psychological and activity measures favoured problem-solving therapy. The authors concluded that the results suggest it is possible to prevent mood disorder in stroke patients using a psychological intervention[213]
- A study of CBT in reducing depression in this population found CBT in combination with exercise was effective[211]
- In a controlled, randomized study that examined uncertainty management intervention delivered over 10 months to outpatients with COPD, the intervention group showed significant improvement in uncertainty, coping strategy, anxiety, depression, and the mental health domains of quality of life compared to controls[214]

C. PHARMACOLOGICAL TREATMENTS

- Anti-depressant medications are reported to improve depression in individuals with CVD, however, efficacy vs. potential risks need to be considered.[215] For example, tricyclic anti-depressants have been shown to alter cardiac muscle cell activity (e.g., lengthen cardiac muscle cell action potentials)[215]

D. STEPPED-CARE

- Combination therapies appear to reduce depression after acute coronary syndrome (ACS). In a multi-centre RCT of people with some depression 2–6 months after an ACS, a combined therapeutic approach of ‘stepped’ care resulted in significantly less depression after 6 months compared with usual care[216]

E. TARGETED EDUCATION

- A systematic review of heart failure (HF) disease management reported that anxiety and depression were better in programs offering CBT plus an HF disease

management education program when compared to usual care plus an HF education program only; improvement was sustained over time[217]

- A single-blind RCT that involved distributing four text messages/week for 6 months that provided education, motivation and support for diet, physical activity, general cardiac education and smoking, reported lower depression at 6 months compared with the control group. The frequency of mild or greater depressive symptoms at 6 months were significantly lower in the intervention group (6.3% vs 24.6%) and lowered risk (relative risk (RR) 0.26, 95% CI 0.16-0.40)[218]

F. HOME-BASED INTERVENTIONS

- A systematic review and meta-analysis of a small number of RCTs that examined the effects of home-based interventions on anxiety reduction in people with CAD reported that compared with usual care or center-based cardiac rehabilitation, home-based interventions had a small but significant effect in reducing anxiety (effect size: 0.13; 95% CI 0.20-0.06)[219]
- A multi-site RCT examined the effects of home-based robot-assisted rehabilitation coupled with a home exercise program compared with a home exercise program (control) on depression and quality of life in people after stroke and reported significant changes in all but one domain on the Stroke Impact Scale and the CES-Depression Scale for both groups[220]
- An RCT comparing a web-based distance education remote training program for individuals post MI vs standard care found significantly reduced depression and anxiety symptoms in the intervention group. The program covered seven topics including structure of the heart, myocardial infarction, risk factors, and daily life activities such as nutrition and physical activity[221]

G. INTERVENTIONS FOR SUBPOPULATIONS

Gender-Specific

Results of a clinical trial indicated that gender-tailored cardiac rehabilitation programs were more effective at reducing depressive symptoms in women when compared to traditional programs[577]

- Qualitative work examining psychosocial issues affecting underserved individuals' ability to manage CVD that compared textual data by gender reports that:[222]
  - Interventions for women should include peer-led support groups rather than an emphasis on family inclusion in self-management plans and self-management training that focuses on self-efficacy and empowerment as women report greater vulnerability to illness (internal effects of disease) than men
  - Interventions for men may need to include help with anger management, as well as social services support to help them deal with the external effects of CVD, such as financial impacts

Older Adults

- A meta-analysis of selected cardiac rehabilitation programs for CAD and congestive heart failure for older adults (64 years+) offered in their home reported significant reduction in depression. It was concluded that tailored interventions combined with psychosocial interventions are likely to be more effective in decreasing depression in older adults with heart disease than usual care[223]

3.1.4 Dementia

Dementia is a term used to describe loss of memory, language, problem-solving and other thinking abilities that are severe enough to interfere with daily life. Alzheimer's disease (AD) is the most common cause of dementia.[224]

Prevalence and Incidence of Dementia with Mental Health Problems or Illnesses

Depression and Anxiety

- Prevalence estimates of depression and AD/dementia range between 12-42% based on defined diagnostic criteria for both depression and dementia from the American Psychiatric Association[225]
- Prevalence estimates of comorbid depression and dementia are reported to be higher among women (57%, 95% CI 50-64%) versus men (43%, 95% CI 37-50%)[226] and among those receiving home care (34%) versus those in long-term care (18%)[227]
- A systematic review reported that late-life depression was associated with a significant risk of all-cause dementia (1.85, 95% CI 1.67-2.04) and AD (1.65, 95% CI 1.42-1.92)[228]

Psychosis and Schizophrenia

- Psychotic symptoms, defined as the occurrence of delusions or hallucinations, are frequent in AD, and are reported to affect about 40%-60%[229] of people with AD
- It is reported that dementia is twice as common among people living with schizophrenia, compared to those without the illness; the most common type of dementia in people living with schizophrenia differs from Alzheimer's in its clinical features[230]

PTSD

- In a longitudinal study examining medical records, it was reported that PTSD was associated with increased risk of dementia over an average of 8 years of follow-up (Females: HR= 1.59, 95% CI 1.30–1.95; Males: HR= 1.96, 95% CI 1.51–2.55) [231]
- A two-fold risk of dementia has been reported in those with both PTSD and depression (Females: HR= 2.08; 95% CI 1.66–2.59; Males: HR= 2.06; 95% CI 1.47–2.91) compared to those without[231]

Mental Health Screening

- There is no strong consensus about what criteria should be used to diagnose depression in AD as symptoms, such as apathy and anxiety, occur in both conditions
- Screening tools for subtypes of depression, such as dysthymia, need to be validated for use with AD. For example, increased awareness of function deficits is significantly associated with dysthymia but not with major depression, suggesting there are different depressive syndromes[232]
- Most existing depression self-report scales used for older adults (e.g., Beck Depression Inventory-II, CES-D, Zung Self-Rating Depression Scale) do not consider the level of cognitive impairment and visual deficits[233]

Common Pathways

Dementia and Depression

- There may be a common event underlying both the occurrence of major depressive disorder (MDD) and AD. For example, with a diagnosis of MDD the brain may be sensitized to a second event ('hit') that precipitates AD (Figure 3.11)
- Having an MDD may accelerate brain aging, by pathways involving DNA and increased stress hormones, such as cortisol
- Based on studies reported to date, common genetic predisposition for MDD and AD appears unlikely. Genes predicting risk for AD (e.g., variants of ApoE4) are not risk factors for MDD. Other genes, implicated in MDD development (e.g., variants of SLC6A4 gene) are not risks for AD[234]
- There is no strong indication that an environment/gene event occurs during some forms of MDD that predisposes individuals to later AD, though the evidence is limited[234]
- Glucocorticoids have been shown to be altered in some cases of MDD and in AD which may have degenerative actions on the brain regions such as the hippocampus, affect new cell development, and brain plasticity
- Reported risk factors for the development of depression in people with AD include ApoE4 positivity[235] and the use of medications such as beta-blockers, corticosteroids, benzodiazepines, dopamine agonists, stimulants, anticonvulsants, hormone-altering drugs, proton pump inhibitors and H2 blockers, statins or lipid-lowering drugs, and anticholinergics[236]

Dementia and Psychosis

- AD and psychosis are associated with polygenic risk for a set of novel loci and inversely associated with polygenic risk for schizophrenia. Biologic pathways identified by the associations of schizophrenia with AD and psychosis are endosomal trafficking, autophagy, and calcium channel signalling[237]

Dementia, MDD, and PTSD

- There are proposed shared links among MDD, PTSD, and dementia:[238]

i. Increased activation of the HPA axis and increases in cortisol[239,240] impact cognitive ability and lead to later life cognitive impairment.[240] Prolonged exposure to high cortisol levels results in neurodegeneration.[239,240] Increased levels of inflammatory cytokines may also be released and this is seen in both MDD and PTSD and may increase risk of dementia[241,242]

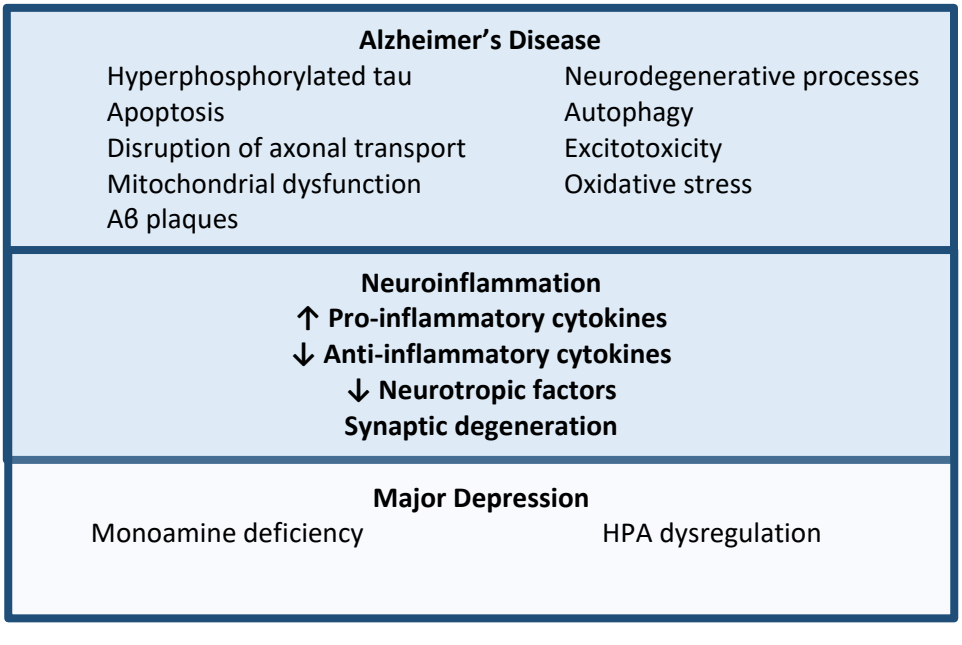
ii. Increase in amyloid beta (Aβ) plaques. The Aβ plaques, a diagnostic feature of AD, are also present in MDD. People with both AD and MDD show an increased rate of Aβ deposition compared to those with AD alone.[242] PTSD may also cause alterations of hormones involved in the production and deposition of Aβ plaques[243]

iii. Cognitive reserve. PTSD and MDD may diminish cognitive reserve, which may increase the risk of or speed up dementia development.[239,244] Factors such as higher SES may be protective against this[245]

iv. Inflammatory neurodegeneration. Related to the above-indicated mechanisms (i to iii). Exposure to stress, acute or prolonged, increases inflammation and can result in neurodegeneration.[246] The inflammatory response involves an increase in pro-inflammatory cytokines, which in turn activate microglia[246] which leads to an increase in the release of inflammasomes that induce inflammation and inhibition of brain-derived neurotrophic factor (BDNF), and result in neurodegeneration.[246] Dementia is characterised by lower levels of BDNF and higher levels of the inflammasome NLRP3, stimulated by increased levels of Aβ plaques.[246] Inflammatory markers may mediate MDD/PTSD and dementia[246]

v. Reduced brain reserve. Shared mechanisms of MDD/PTSD may increase levels of reduction in brain reserve and increase risk of dementia[247]

Figure 3.11: Shared etiology between AD and depression



AD is characterized by Aβ plaques and neurofibrillary tangles which results in neurodegeneration via mechanisms including excitotoxicity and mitochondrial dysfunction. Depression is characterized by monoamine deficiency and HPA-axis dysregulation. Common factors include inflammation and reduction in neurotrophic support.

Management of Dementia and Mental Health

Exercise

- A systematic review found that exercise programmes may significantly improve cognitive functioning and improve the ability of people with dementia to perform daily activities[248]
- A systematic review of 13 RCTs of physical activity interventions in people with dementia reported there is some evidence that physical activity interventions improve physical function in older people with dementia, however, evidence for an effect on depression is limited[249]

Peer Approaches

- In an evaluation conducted by the Mental Health Foundation about peer support groups for people with dementia living in extra care housing, those with early stage dementia who participated in the groups showed improvements in wellbeing, social support, and practical coping strategies[250]

Pharmacological Interventions

- Based on a systematic review that examined the anti-depressants sertraline, sertraline combined with mirtazapine, imipramine, fluoxetine, and clomipramine, seven studies met inclusion criteria and reported no statistically significant difference between these and a placebo[251]
- Few RCTs are available on the efficacy of antidepressants to treat depression in AD, limiting clear conclusions of their potential role
- Current National Institute for Health and Care Excellence (NICE) guidelines for dementia indicate that antidepressants should not be offered to manage mild to moderate depression in people living with mild to moderate dementia, unless they are indicated for a pre-existing severe mental health problem[252]

Psychological Treatments

- Emotion-oriented therapies aim to provide therapy to the emotional needs of people with AD by utilizing approaches such as validation, reminiscence, reality, and simulated-presence therapy. There is insufficient research providing data on their effects on depression[236]
- Brief psychotherapeutic interventions have also been shown to be particularly effective in this population.[253] Behavioural therapies are more commonly applied in

the later stages of dementia, while modified cognitive-behavioural strategies appear to be more successful with those in the earlier stages of cognitive decline[254]

National Institute for Health and Care Excellence (NICE) guidelines suggest psychological treatments for people with mild-to-moderate dementia who have mild-to-moderate depression[568]

- Most CBT programs for persons with dementia involve their caregivers, both as CBT coaches for the care recipient and as treatment partners. The strongest evidence is for short-term CBT and problem-solving therapy[255]
- Based on research that compared social engagement, medication use, and depressive symptoms of older adults, including African Americans, with incident dementia, it was found that size of social network and lower perceived social isolation were associated with lower depression. This suggests depression management at the time of dementia diagnosis should include interventions to increase social engagement[256]

Sensory Therapies

- A RCT that compared the effects of bright light vs low intensity light exposure on depression and agitation in persons with dementia residing in long-term care reported significant improvements in depression (3 measures) and agitation (4 measures) in those exposed to bright light therapy[257]
- Sensory stimulation therapies, such as music therapy, art therapy, pet therapy, aromatherapy, activity therapies, and multisensory approaches (e.g., Snoezelen), have the potential for benefit in depressed patients with cognitive impairment. However, few rigorous studies have been performed, and efficacies are mixed

3.1.5 Diabetes Mellitus (DM)

DM is a metabolic disease that results from impairments of insulin. Type 2 DM (T2DM), which accounts for 90–95% of cases of DM, is thought to be due to insulin resistance. Conversely, type 1 DM is due to absolute insulin deficiency. Apart from genetic disposition, the factors associated with risk of T2DM appear to be diet, inactivity, and excess body weight. T2DM often goes undiagnosed in its early stages because of lack of symptoms. DM, if undetected or poorly controlled, can result in health problems such as diabetic neuropathy, retinopathy, peripheral vascular disease, renal failure, heart disease and stroke.[258]

Prevalence and Incidence of DM with Mental Health Problems or Illnesses

A. ANXIETY AND DEPRESSION

- A systematic review of 248 studies reported 28% (95% CI 27-29%) of individuals with T2DM live with different severity levels of depressive disorders[259]

- Prevalence estimates are higher among females (34%, 95% CI 31-38) compared to males (23%, 95% CI 20-26), those who are younger than 65 compared to older adults (31% vs. 21%), and in those with prediabetes and undiagnosed DM compared to those diagnosed with DM[259]
- Estimates are three-times higher in those with T2DM compared to T1DM; estimates are twice as high in people with T2DM compared with the general population worldwide[259]
- A meta-analysis of longitudinal data reported no increased risk for depressive symptoms in individuals with prediabetes or newly developed diabetes, whereas there was an increased risk for individuals with clinically identified DM[260]
- Based on findings of a cohort study of 30 to 75 year olds, depression with comorbid anxiety may be a subgroup that is at risk of T2DM[261]

B. EATING DISORDERS AND IMPULSE CONTROL DISORDERS

- A systematic review examining eating disorders and DM reported that both binge eating disorder (OR 3.69, 95% CI 1.12-12.12) and bulimia nervosa (OR 3.45 1.92-6.1) were associated with T2DM, while anorexia nervosa was not. Cohort studies showed increased risk of T2DM with bulimia nervosa (RR 1.7, 95% CI 1.2-2.5), and decreased risk with anorexia nervosa (RR 0.71, 95% CI 0.52-0.98). For binge eating disorder the association was not significant[262]
- A series of cross-sectional face-to-face household surveys of community-dwelling adults (n=52,095) in 19 countries assessed associations between 16 DSM-IV mental disorders and type 2 DM. Based on multivariable analysis, associations were found for intermittent explosive disorder (OR 1.6; 95% CI 1.1, 2.1), binge eating disorder (OR 2.6; 95% CI 1.7, 4.0) and bulimia nervosa (OR 2.1; 95% CI 1.3, 3.4)[263]

C. PTSD

- The prevalence of PTSD among Indigenous people in the USA with T2DM is reported as 22%[264]

D. SUBSTANCE USE

- An analysis of electronic health record data on 170,853 unique adults aged ≥18 years reported that prevalent diagnoses among adults with T2DM were substance use disorders (SUD) (17.02%: tobacco 13.25%, alcohol 4.00%, drugs 4.22%). SUD was positively associated with mood, anxiety, personality, somatic, and schizophrenia diagnoses.

E. ESTIMATES OF MENTAL HEALTH COMORBIDITIES BY SUBPOPULATIONS

- The prevalence of depression among individuals with DM living in rural settings is estimated as 17%. Associated factors include lack of sleep and frequent inactivity[265]
- Secondary analysis of a national electronic database that examined PTSD in asylum seekers and the relationship to DM indicated age-adjusted prevalence ratios (APR)

of 1.40 (95% CI 1.12–1.76) in men and 1.22 (95% C, 0.95–1.56) in women compared with individuals without PTSD. Individuals with PTSD had a higher prevalence of T2DM compared with those without PTSD (APR=1.47, 95% CI, 1.15–1.87 in men and APR=1.27, 95% CI, 0.97–1.66 in women). Among the depressed individuals, however, there was no association between PTSD and T2DM (APR=0.87, 95% CI 0.43–1.76 in men and APR=1.00, 95% CI, 0.54–1.83 in women][266]

- A Canadian study that examined a cohort of new anti-diabetic (AD) medication users from administrative claims data identified 114,366 new oral AD users (18 years+) and an overall incidence rate of depression of 10.72/1,000 person years (PYs) for women and 8.27/1,000 PYs for men. The results suggested that among new anti-diabetic medication users, women, individuals of younger age, those with a low SES, and a history of anxiety or depression may need to have their physical and mental health tracked closely[267]

Mental Health Screening

- The BDI and CES-D Scale are popular screening tools (used in ~45% of studies)
- The cultural applicability of screening tools has not been thoroughly assessed. Most studies only include details of the language translation process, few reported reliability data, and most showed moderate-good sensitivity and specificity but a high rate of false positives
- In longitudinal studies, people with both diabetes and depression were found to have a higher risk of developing microvascular and macrovascular complications of diabetes and mortality compared with people without depression;[268] screening may help to reduce or delay these risks
- Screening individuals using home healthcare services for mental health comorbidity with the PHQ-2 (and PHQ-9 if applicable) is required by the Centers for Medicare and Medicaid Services Outcomes and Assessment Information Set (OASIS-C) used to collect baseline information at the start of care and at each time point[269]

Common Pathways

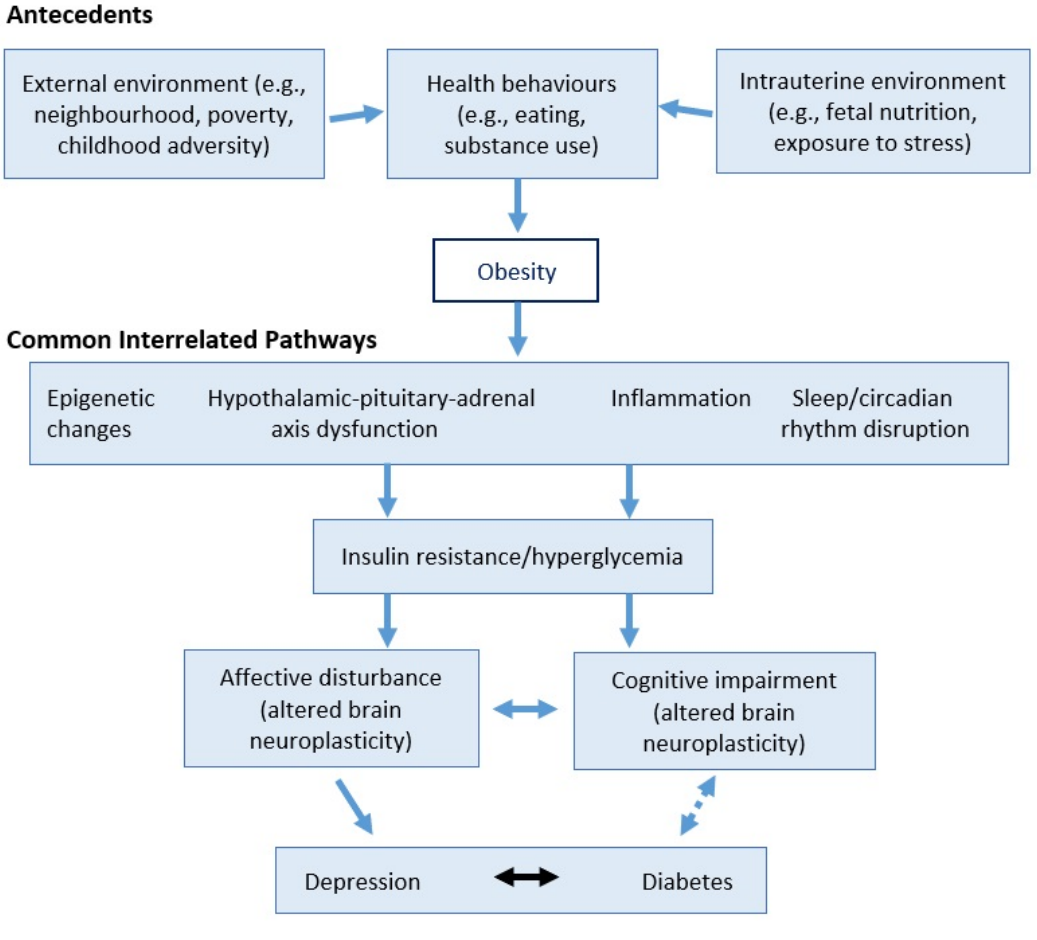
- Various pathways link DM and mental health such as inborn immunity, inflammation, the HPA axis, insulin resistance, and circadian rhythms. A pathway that is often overlooked is in-utero and early childhood experiences, which can be particularly relevant to T2DM and mental health[270]
- The relationships between DM and mental health appear to be bidirectional[271] (Figure 3.12)
- Three inter-related major pathophysiologic pathways are often discussed as common mechanisms for the development of depression in T2DM:

    1. Hyperglycaemia and T2DM
        - The brain is vulnerable to fluctuating plasma glucose levels because neurons do not have an active glucose transporter
        - High intracellular glucose levels can induce oxidative stress and the formation of advanced glycation end products (AGEs). Both processes may lead to neuronal damage and depression[272,273]

- Hyperglycaemia also leads to increased levels of cortisol, a known pathway that is also involved in the development of depression[274]

2. **Small blood vessel (Microvascular) dysfunction**
   - In DM, blood vessel damage in certain brain regions may impact mood regulation[275]
   - A meta-analysis of longitudinal studies identified that brain scans which show small vessel disease are associated with a higher risk of depressive symptoms[276,277]
   - Studies of pathways related to small blood vessel dysfunction and artery stiffening that are involved in the development of cerebrovascular damage are strongly related to diabetes[278,279,280]
3. **Low-grade inflammation, diabetes, and depression**
   - T2DM is accompanied by systemic low-grade inflammation,[281] which is a mechanism that is involved both in the development of its cardiovascular complications and depression[282,283]
   - A meta-analysis reported that treatment resistance to antidepressants is associated with higher low-grade inflammation[284] suggesting that treatment-resistant depression differs from other types of depression

Figure 3.12: Common etiological pathways of DM and mental health[271]



- Risk factors for depression in DM include living alone, poor social support, low SES, persistent poor glycaemic control, insulin therapy in T2DM, lower literacy, rural domicile, marriage and duration of DM of >2 years, and presence of DM-related complications[285]
- Sedentary life without adequate physical activities and lack of self-care are often the factors that precipitate depression in a T2DM patient and vice versa
- Schizophrenia is associated with an at-risk allele for T2DM located in the TCF7L2 gene, suggesting that DM and schizophrenia may share familial risk factors or common genetic predisposition[286]

Management of Diabetes and Mental Health

A. DIGITAL HEALTH APPLICATIONS

- There are many digital health applications available as complementary to care but evidence to support their use is preliminary. Trials of eHealth and mobile technology–based health (mHealth) interventions suggest these are less effective than face-to-face psychotherapeutic treatments[287]

B. PHARMACOLOGICAL INTERVENTIONS

- A Cochrane review reported that antidepressants had a moderate effect on depression severity and improved glycemic control with a mean difference for glycosylated hemoglobin (HbA1c) of 0.4% (95% CI -0.6 to -0.1)[288]

C. PSYCHOLOGICAL INTERVENTIONS

- An RCT of adults with T2DM that compared usual care plus psychotherapy for depression via home telehealth (home monitor that captured clinical measures) and usual care reported significant reductions of HbA1c and healthcare costs (mean $3,781 vs. $4,662; p<0.001) in the intervention group compared with usual care. Depression outcomes were not specifically evaluated[289]

D. MODELS OF CARE

- Holistic, preventive services focusing on healthy diet, physical activity, and healthy weight management to promote both physical and mental health is recommended
- A Cochrane review examining self-management programs for individuals with severe mental health conditions indicated there was insufficient evidence demonstrating efficacy in reducing physical or mental health outcomes[290]
- Although there are mixed effects on glycemic control, interventions that include diabetes self-management education reported benefits for glycemic control[291]
- Depression in T2DM varies among ethnic groups, which suggests the need to address stressors unique to racial/ethnic minorities to improve diabetes-related outcomes[292]
- An RCT comparing pharmacist-led group shared medical appointment visits versus standard care found that the intervention was efficacious in attainment of glycemic

control in people with T2DM and depression without change in depression symptoms[293]

Collaborative care presents good results for treatment of depression and anxiety in diabetes. Delivery of collaborative care, which provided a stepped care intervention with a choice of starting with psychotherapy or pharmacotherapy, to a primary care population, yielded an effect size of -0.29 (95% CI -0.43 to -0.16 [569]

- A pilot trial of an integrated intervention that included behavioural activation and motivational interviewing techniques, co-developed with end-users (Latino immigrants), their family members, and provider stakeholders, had a positive impact on both diabetes and depression-related outcomes[294]
- A pilot trial comparing a basic integrated intervention to an integrated intervention that used patient prioritized planning (incorporated financial, social and emotional needs for primary care patients with T2DM and depression) was reported to be effective in improving HbA1c and depression symptoms (CES-D)[295]
- Collaborative care models should be expanded to also address SUD and related psychiatric comorbidity for people with diabetes[296]

3.1.6 Epilepsy

Epilepsy is a brain disease that is characterized by abnormal electrical activity which can cause seizures or unusual behaviour, sensations and sometimes loss of awareness. It is one of the most common neurological diseases. Mental health issues such as depression and anxiety, make seizures worse and reduce quality of life.[297]

Prevalence and Incidence of Epilepsy with Mental Health Problems or Illnesses

A. ANXIETY

- Prevalence estimates of anxiety disorders were reported as 17% in a small study of individuals with epilepsy (n=96);[298] anxiety symptom estimates are 46%[299]

B. DEPRESSION

- Depression rates appear to increase as one moves from primary to secondary and tertiary care[300]
- Based on a systematic review the overall prevalence of active (current or past-year) depression in people with epilepsy was 23% (95% CI 21%–28.%).[300] A subset of the studies (5/14 total studies) reported that the overall odds of active depression were 2.77 (95% CI 2.09–3.67). For lifetime depression, 4 studies reported overall prevalence of 13% (95% CI 5–33%), and 3 studies reported overall odds of 2.20 (95% CI 1.07–4.51)[300]

C. PTSD

- In a large national longitudinal study, it was reported that individuals with PTSD had an elevated risk of developing epilepsy (HR=3.72, 95% CI 2.27–6.11) after adjustment for demographic data and medical and psychiatric comorbidities[301]
- A study of 120 individuals with difficult-to-treat epilepsies that completed the Posttraumatic Stress Diagnostic Scale as part of an interview indicated that 50 participants identified a seizure that fulfilled the criteria for a traumatic event and 6 fulfilled all PTSD criteria caused by a traumatic seizure (three had PTSD)[302]

D. SUICIDE IDEATION

- A meta-analysis reported the pooled prevalence for suicide ideation in people with epilepsy (24 studies) and suicide attempts (18 studies) was 23.2% (95% CI 18-30%) and 7% (95% CI 3-17) respectively. The pooled rate of death due to suicide (10 studies) was 0.5% (95% CI 0.2-2%)[303]

E. ESTIMATES OF MENTAL HEALTH COMORBIDITIES BY SUBPOPULATIONS

- A study of 38 Spanish-speaking immigrants with epilepsy and 47 US-born persons with epilepsy reported that depression was significantly higher in the immigrant population (21.65±14.6 vs 14.50±10.2; p=.025)[304]

Mental Health Screening

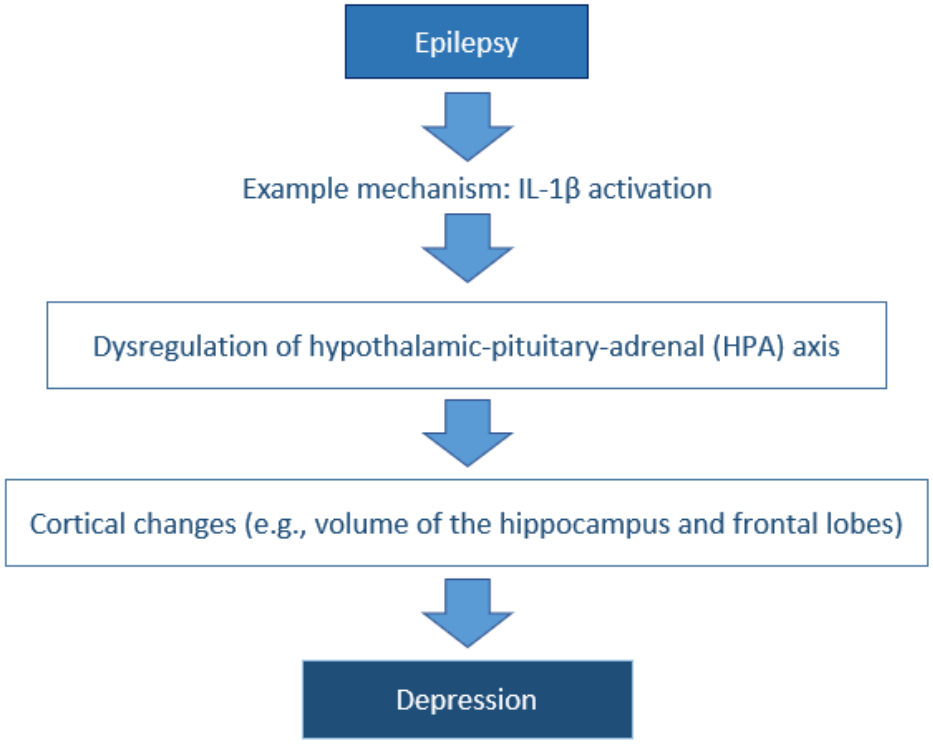
- The Beck Depression Inventory (BDI) I and II have been well-validated as a depression screening tool in epilepsy[305]
- Depression in people with epilepsy is categorized into four types suggesting screening tools and management may need to be adapted:[306]
    i. Peri-ictal: Dysphoric, depressive symptoms or anxiety that precedes the seizure and subsides with the ictus
    ii. Ictal: described in temporal lobe epilepsy, has an incidence of about 10%
    iii. Post-ictal: second most common form, seen with unilateral frontal or temporal foci, and thought to be due to inhibitory mechanisms that result in cessation of seizure activity
    iv. Inter-ictal: the most common form and includes episodes of major depression, dysthymia or affective mood disorder

Common Pathways

- The relationships between epilepsy and depression are believed to be bidirectional[307]
- Depression may develop through chronic stress exposure and inherent vulnerability.[308] The unpredictability of seizures may induce learned helplessness[309]
- Depression may facilitate the epileptic activity through hyperactivity of the HPA axis and disturbances of glutamate and γ-aminobutyric acid (GABA) neurotransmitters,[307] and cortical changes (Figure 3.13)

- A systematic review examining risk factors for depression in epilepsy living in community found that sociodemographic, disease-related, psychological, treatment-related, and genetic risk factors are consistently associated with depression[300]

Figure 3.13: Example of a common etiological pathway of epilepsy and depression[310]



Chronic epilepsy leads to the dysregulation of the HPA axis[311] via several mechanisms, one of those being activation of IL-1β signalling in the hippocampus[312] resulting in compromised hippocampal serotonergic transmission and behavioural symptoms of depression[312]

Management of Epilepsy and Mental Health

- A systematic review of treatments for individuals with epilepsy and comorbid depression did not provide strong evidence. Oxcarbazepine, venlafaxine, and lamotrigine may improve mood, CBT improves both depression and epilepsy outcomes, and quality of life improves with treatment of depression among those with epilepsy[313]
- A systematic review of self-management interventions for epilepsy indicated limited evidence for the effectiveness of interventions to improve quality of life in people with epilepsy. Two intervention types, the specialist epilepsy nurse and self-management education, have some evidence of benefit. At present it is not possible to advocate any single model of service provision for self-management in epilepsy[314]

3.1.7 Frailty

There are many ways in which frailty is defined. Frailty is a medical condition of reduced function and health in older individuals. It often includes several dimensions or features, such as inactivity, poor nutrition, social isolation or loneliness, and the use of multiple medications.[315]

Prevalence and Incidence of Frailty with Mental Health Conditions

- Reports about the prevalence of frailty and depression are highly variable; reported ranges are 2.5%–21.1% (cross-sectional studies) and 6.5%–25.3% (longitudinal studies at baseline) for frailty and depressive symptomatology[316]
- The high variability is due to differences in the classification and nature of depressive symptomatology and liberal inclusion criteria (e.g., include dementia or stroke)

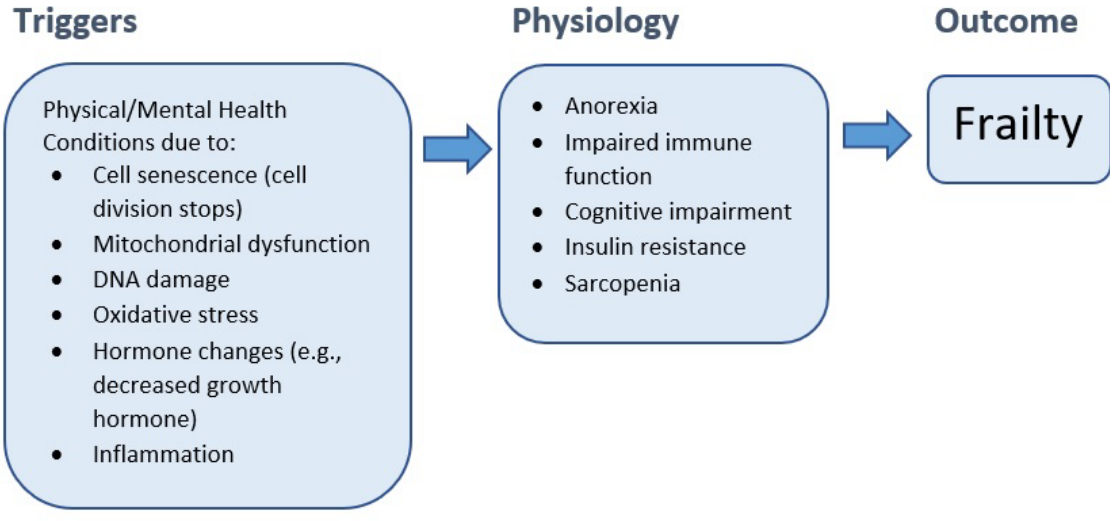
Mental Health Screening

- The frailty phenotype is a topic of debate. Experts agree frailty should include the assessment of mental health.[317] For this report, frailty is defined as a geriatric syndrome distinct from multimorbidity, characterized by increasing vulnerability and decreasing physical reserve due to accumulating multisystem deficits[318]
- Screening of mental health in frailty is complicated as mental health may be considered part of the condition's definition
- Of the screening tools used to assess depression in frailty, the most common are the Geriatric Depression Scale, HADS, Yesavage Depression scale, and the CES-D. None have been specifically evaluated in these populations for reliability and validity

Common Pathways

- Although similar biological mechanisms such as subclinical CVD and inflammation are part of physical and mental health manifestations,[319] it is unlikely that one mechanism is largely responsible for either or both syndromes in all individuals
- Figure 3.14 illustrates the different biological pathways of frailty; many are shared with depression
- Frailty and depression have been associated with higher serum CRP and IL-6 levels. High circulating levels of neutrophil gelatinase–associated lipocalin (NGAL), an acute phase protein, may also be a factor[320]

Figure 3.14: Example of etiological pathways between frailty and depression[321,322,323,324]



Management of Frailty and Mental Health

- When targeting frailty in disability prevention or intervention, identifying subgroups in which the largest effect is likely to result may be the most pragmatic approach in real-world settings with limited resources
- Group and individual sessions with a geriatrician may impact risk of depression with frailty[325,326]
- The task force of the International Conference of Frailty and Sarcopenia Research (ICFSR) recommend the following guidelines for managing frailty: [327]
    i. Address polypharmacy, the management of sarcopenia, the treatable causes of weight loss, and the causes of exhaustion (depression, anaemia, hypotension, hypothyroidism, and vitamin B_{12} deficiency)
    ii. All persons with frailty should receive social support as needed to address unmet needs and encourage adherence to a comprehensive care plan
    iii. Include a multi-component physical activity programme with resistance-based training
    iv. Provide protein/caloric supplementation when weight loss or undernutrition are present
- At this time, there is insufficient evidence to support therapies such as cognitive therapy, problem-solving therapy, vitamin D supplementation, and hormone-based treatment[327]

3.1.8 Huntington's Disease (HD)

HD is a progressive brain disorder that causes uncontrolled movements, emotional problems, and loss of cognition. Adult-onset HD usually appears in a person's thirties or forties. Early signs and symptoms can include irritability, depression, small involuntary movements, poor coordination, and trouble learning new information or making decisions. Affected individuals may have trouble walking, speaking, and swallowing. People with this disorder also experience changes in personality and a decline in thinking and reasoning abilities. Individuals with the adult-onset form usually live about 15 to 20 years after signs and symptoms begin.[328]

Prevalence and Incidence of HD with Mental Health Problems or Illnesses

- Prevalence estimates of mental health-related concerns in HD include ranges between 15-69% for depression, with no significant differences in the estimates between men and women,[329] 28-62% for apathy,[330,331] 13% for irritability and aggression,[331] 1% for psychotic symptoms, and 2-20% for suicidal ideation or attempts[332]
- Reports of depression are most prevalent during stage 2 (~45%), where the individual is functioning at work, but at a lower capacity[333]
- Behavioural symptoms are common during the illness period before manifestation of motor symptoms (prodrome) and can lead to family disruption, social isolation, and withdrawal[334]
- Obsessive/compulsive behaviours are estimated at 13%.[331] Perseveration, or the repetition of a thought, behaviour, or emotion beyond the psychological context, is most common[335]

Mental Health Screening

- Mental health-related comorbidities reported in HD have included depression, irritability, anxiety, apathy, hallucinations, and perseveration[336]
- An assessment of the quality of behavioural rating scales commissioned by The Movement Disorder Society concluded that of 27 behavioural rating scales examined, the Irritability Scale was recommended for irritability; the Beck Depression Inventory-II and the Hospital Anxiety and Depression Scale were recommended for depression[336]
- Challenges associated with mental health screening are the co-occurrence of multiple behavioural symptoms, features of behavioural symptoms in HD, and the need to address stage- and disease-specific features, including cognitive impairment and insight[336]

Common Pathways

- Current evidence supports a model in which biological risk factors interacting with life stresses/events lead to the development of mental ill-health (Figure 3.15)[337]

- Irritability and impulsivity symptoms can be caused by the frustrations of loss of capacities, difficulties in expressing oneself, and related neurological/psychological fatigue
- Anxiety correlates with loss of essential functions, family, social and economic issues, depression, suicide, irritability, quality of life, pain, illness beliefs, and coping[334]

Figure 3.15: Common Etiological Pathways of Huntington's Disease and Mental Health[337]

Management of HD and Mental Health

- Mental health management should be based on the identification of underlying environmental or somatic (e.g., pain, side effects of medications) triggers causing changes in mood or behaviour
- International Guidelines for the Treatment of Huntington's disease suggest mindfulness-based cognitive therapy and Acceptance and Commitment Therapy, personalized cognitive stimulation, establishing routines, a structured programme of activities, and psycho-education for the family regarding diversion strategies to mitigate confrontations[334]
- There has been limited study of the effectiveness and risk/benefits of psychotropic medications. Current recommendations include SSRIs or serotonin noradrenaline reuptake inhibitors (SNRIs), or Mianserin or Mirtazapine in case of sleep disruption. Neuroleptics have been prescribed for symptoms such as agitation[334]
- For depression that is resistant to medications, electroconvulsive therapy (ECT) may be indicated[334]
- Suicide risk should be assessed regularly, including at diagnosis and when the disease starts to impact on daily activities. Individuals with active suicidal ideation and a plan require immediate psychiatric evaluation[334]
- Over the course of HD, symptoms of repetitive thoughts may replace obsessive–compulsive disorder. The distinction between obsessive–compulsive phenomena and perseverations will lend to differential approaches[334]

3.1.9 Inflammatory Bowel Diseases (IBDs)

IBD is a term for two conditions (Crohn's disease and ulcerative colitis) that are characterized by chronic inflammation of the gastrointestinal (GI) tract. Crohn's disease can affect any part of the GI tract (mouth to the anus). Most often it affects the portion of the small intestine before the large intestine/colon. Ulcerative colitis occurs in the large intestine (colon) and the rectum.[338]

Prevalence and Incidence of IBDs with Mental Health Problems or Illnesses

- Prevalence estimates of depression and anxiety within the IBD literature have most commonly been based upon anxiety and/or depression-specific questionnaires, such as the HADS and PHQ9, with reported ranges of 26-42% for depression, 20-28% for presence of at least one anxiety condition, and 11% for depressive disorder[339, 340,341,342]
- Analysis of data from the 2012 Canadian Community Health Survey-Mental Health examined presence of generalized anxiety disorder using the WHO-CIDI lifetime criteria and self-reported IBD. The likelihood of individuals with IBD having anxiety was about twice that of those without IBD (OR=2.18; 95% CI 1.50-3.16) and this was similar among those with Crohn's disease and ulcerative colitis. The factors most closely linked with anxiety were childhood sexual abuse, female gender, and chronic pain[343]
- One survey suggested that 21% currently sought help for mental health issues while 12% reported having at least one psychological condition but not seeking treatment[340]
- The prevalence of mental health issues may be as high as 80% during flare-ups[344]
- Analysis of data from the National Health Insurance Research Database (3,590 people with IBD and 14,360 propensity score-matched individuals without IBD) reported low prevalence of bipolar disorder (BD) (0.72%). Regression modelling results reported heightened odds of BD among those with IBD (OR=2.10, 95% CI 1.30-3.38) compared to the comparison group. Those with ulcerative colitis had slightly higher likelihood (OR=2.23, 95% CI: 1.31-3.82) compared to the comparison group[345]

Mental Health Screening

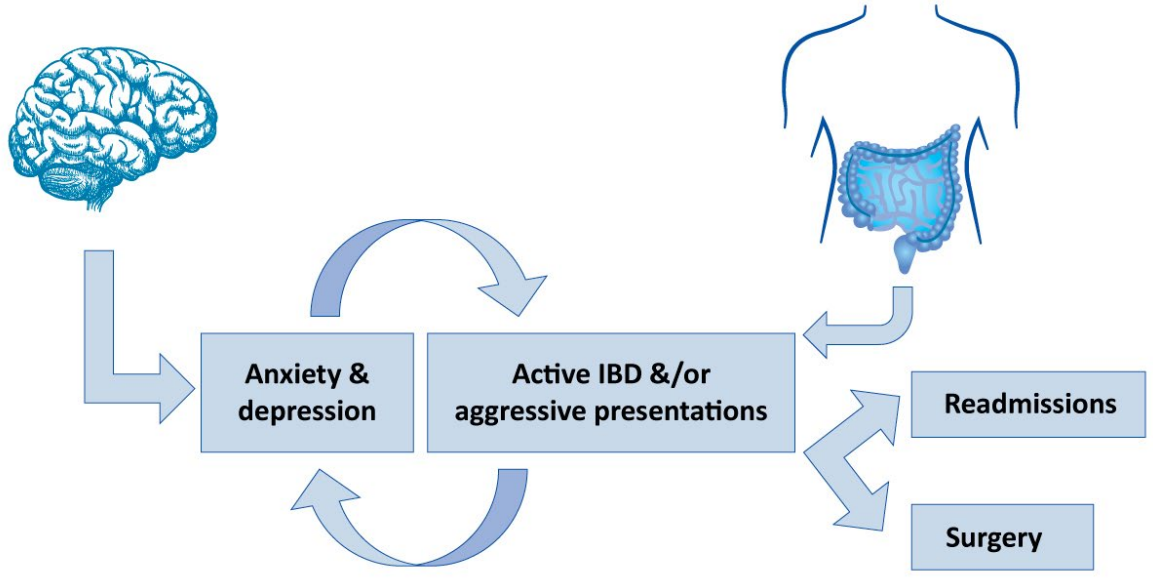
- Anxiety and depression symptoms are commonly identified to be associated with increased IBD activity and reduced quality of life[346]
- Ongoing psychological distress can exacerbate disease activity, and increase the risk of flare-ups and health care costs[339]

Common Pathways

- Anxiety, depression, and relapse appear to be concomitant in a self-perpetuating cycle with devastating effects for IBD patients[347]

- Interactions between the digestive tract, and its microbiome, and the central nervous system are bidirectional and form the gut-brain-microbiota axis (GBA)[348,349] that can influence central neurochemistry and behaviour[350]
- The aggravation of GI symptoms can be attributed to the worsening of co-morbid psychological disorders[33,351]
- Figure 3.16 outlines how the use of anti-depressants can help reduce mental and physical health symptoms

Figure 3.16: Shared links between mental health and IBD[352]



Management of IBD and Mental Health

- Research suggests that the management of IBDs can be improved by reducing stress with support from psychological interventions, which in turn improves health-related quality of life[353]

> The British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults suggest psychological interventions (psychotherapy, patient education and relaxation techniques) for anxiety, pain, and stress levels improve mood[570]

- The availability of psychotherapy is limited for GI conditions due to limited psychological resources available to these populations.[354] Online approaches have been proposed, however, a systematic review of online psychological interventions found limited research and insufficient evidence to demonstrate the effectiveness of online CBT to manage mental and physical outcomes in gastrointestinal diseases[355]
- A Cochrane Review reported no benefit of psychological interventions for adults with IBD[356]
- The evidence for benefits of CBT is mixed[357,358,359]

- Mindfulness as an adjunct to pharmacological therapy may improve psychological symptoms in IBD and facilitate coping with symptoms during a disease flare[360,361,362]
- Gut directed hypnotherapy has an established evidence base for the control of IBS symptoms, however more research is needed to determine if there are mental health benefits in those with IBD[363,364]

3.1.10 Kidney Disease (Chronic) or CKD

CKD refers to the progressive and irreversible loss of kidney function. In early stages, management is based on controlling blood pressure and other risk factors. As the condition progresses, pharmacological treatment and other interventions are intensified to prepare for renal replacement therapy (e.g., surgery, kidney transplantation). These changes have been associated with increased psychological distress.[365]

Prevalence and Incidence of Chronic Kidney Disease with Mental Health Problems or Illnesses

- Diagnosis of major depression in individuals with CKD is challenging as the symptoms of uraemia (increased blood levels of urea) can mimic those of clinical depression[366]
- The overall prevalence estimate of depression is reported at 27%; estimates vary according to disease stage ranging from 27% for those with kidney transplant to 39% for those in the end stages of the disease[367,368]
- Incidence of self-reported depressive symptoms is reported to be higher in individuals with chronic graft failure compared with those with well-functioning grafts or dialysis patients awaiting transplantation
- Results of a nationwide population study of people diagnosed with schizophrenia (n = 27,516), and matched by age and sex controls, indicated higher odds of CKD in those with schizophrenia (adjusted OR = 1.62, 95% CI 1.45–1.82)[369]
- Among those receiving hemodialysis, higher levels of depression are found among those who are younger and of Chinese ethnicity[370]

Mental Health Screening

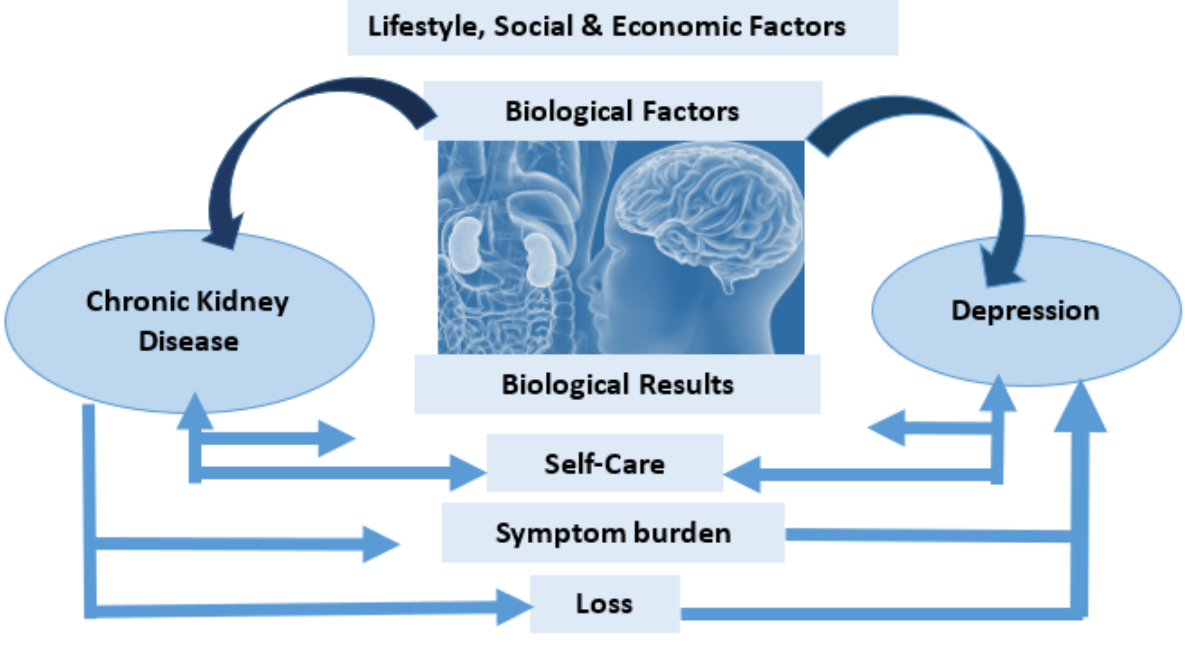
- Some research suggests there is insufficient high-quality data to show that screening for, or treatment of, depression in CKD populations improves clinical symptoms and quality of life[366]
- Other studies support screening programs and suggest screening for depression should take place at key transition points such as at the initial evaluation, dialysis initiation, and regular intervals thereafter[366]

Common Pathways

- Health related, socio-economic, and biological factors contribute to CKD and comorbid mental ill health (Figure 3.17) [337,371]

- The relationships among kidney function tests, self-care factors, and mental health are bidirectional; one-directional pathways are reported between associated symptom burden and loss in relation to depression in CKD[337,371]
- Inflammatory cytokines, deregulation of the HPA axis, disturbance in glucose-insulin homeostasis, and oxidative stress are thought to be involved in the etiology of depression and CKD[371]
- Chronic pain, a frequent symptom in CKD, can induce clinical depression through chronic, stress-mediated activation of the HPA axis
- Psychosocial factors such as changed identity, symptom burden, fear of dialysis, uncertainty of the disease outcome, negative experiences with the healthcare system, lifestyle disruption, financial struggles, changes in self-concept and self-esteem, guilt feelings for the perceived burden on family members, and side effects of medications may contribute to depression[371]
- Donor transplant recipients may mourn the death of the unknown deceased donor and may feel guilty for having their lives saved at the cost of another life. Live donor recipients may struggle with handling their indebtedness to the donors or feel guilty and fear graft failure[371]

Figure 3.17: Common Etiological Pathways of Chronic Kidney Disease and Mental Health[337,371]



Biological Factors	Psychosocial Factors
• Uremic toxins • Chronic inflammation • Disturbance of glucose-insulin homeostasis • HPA axis dysregulation • Chronic pain leading to stress-mediated activation of the HPA axis • Side effects of medications ↓ **Changes in neuro-hormonal activity** ↓ **Somatic symptoms** • Sleep disturbance, pain, fatigue • Reduced appetite • Decreased sexual drive	• Changes in lifestyle, social role, self-concept, and self-esteem • Decreased autonomy and control • Limited capacity for self-expression, productivity, and social involvement • Body image concerns • Low self-esteem • Symptom burden; fear of dialysis, fear of uncertain future, ill health, death and dying; existential questions, meaning of life • Negative experiences with healthcare system • Guilt feelings for the perceived burden on family members • Low perceived social support • Unemployment

Management of Chronic Kidney Disease and Mental Health

A. PHARMACOLOGICAL INTERVENTIONS

- The benefits and harms of anti-depressants need to be weighed. The medications are broken down by the liver and end products may not be removed significantly by the kidneys or through dialysis. Further concerns are increased risk of drug interactions and accumulation of toxic metabolites. The evidence about the effectiveness of antidepressants versus placebo in patients with CKD3-5 and depression is insufficient and well-designed RCTs are needed[366]

B. PSYCHOLOGICAL INTERVENTIONS

- CBT may be beneficial during changes in dialysis regimen[366]

A potential target for management is illness perceptions;[366] a person's cognitive appraisal and understanding of their health condition.[578] These perceptions may include both positive and negative illness beliefs that can influence the ability to cope with the disease and to perceive it as manageable or threatening[579]

- Positive illness perceptions are associated with higher autonomy and self-esteem levels which can support mental health[366]

C. SELF-MANAGEMENT INTERVENTIONS

- An RCT of a nurse-led, in-center breathing training program for individuals on maintenance hemodialysis reported significantly greater improvements in depression (Beck Depression Inventory-II scores) compared to controls[372]
- Chronic disease self-management programming that includes activities such as exercise therapy may foster mental health[366]

3.1.11 Metabolic Syndrome (MetS)

MetS is a health condition that, if left untreated, increases the risk of many chronic conditions such as type 2 diabetes and cardiovascular disease. MetS is diagnosed when a person has three of the following conditions: high blood pressure, high blood glucose levels, high triglycerides, low HDL-cholesterol, or large waist circumference.[6]

Prevalence and Incidence of MetS with Mental Health Problems or Illnesses

- Approximately 40% of those with a serious mental illness meet National Cholesterol Education Panel-Adult Treatment Panel III (NCEP-ATP-III) guidelines for MetS[373,374]
- A meta-analysis reported that the prevalence of MetS is 58% higher in people with mental health conditions than in the general population[375] and the risk was similar in those with schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD)
- A meta-analysis reported that in individuals with BD, using antipsychotic medication contributed to 1.72 times greater risk of MetS compared to those not taking antipsychotic medication[376]
- A meta-analysis reported that individuals with schizophrenia have a significantly higher risk of MetS (OR=2.35);[377] metabolic disturbances increase with illness duration[378] and age.[379] Individuals with schizoaffective disorder have slightly higher rates of MetS compared to those with schizophrenia[380]
- In a cross-sectional study of individuals with verified diagnosis of MDD and MetS, effect modifications were observed by sex and age; younger females (20-49 years) with MDD were more often affected by MetS than younger females without MDD (OR=2.21, 95% CI 1.39-3.50). This association was not observed in older participants (50-82 years)[381]
- Among individuals with alcohol dependence syndrome, the prevalence of MetS was found to be 21% and 10% according to revised National Cholesterol Education Programme Adult Treatment Panel (NCEP ATP-III) criteria and International Diabetes Federation (IDF) criteria, respectively.
- Among individuals with opiate dependence syndrome, the prevalence of MetS was found to be 20% and 5% according to revised NCEP ATP III criteria and IDF criteria, respectively[382]

Mental Health Screening

- Screening for metabolic syndrome in individuals with mental health conditions, particularly those taking anti-psychotic medications, is part of standard care
- Based on a validation study, the HADS is considered to be a reliable screening tool for current major depressive episode and generalized anxiety disorder in middle aged and elderly population with and without MetS. Optimal thresholds of the HADS-Depression subscale for current MDD is ≥9 for individuals with MetS. Optimal threshold of the HADS-Anxiety subscale is ≥9 for current GAD in individuals with and without MetS[383]

Common Pathways

- Antidepressant medications, especially tricyclic antidepressants (TCAs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), change heart-related regulation,[384,385] which contributes to hypertension among medication users[386]
- A meta-analysis of treatment trials that evaluated short-term weight change after antidepressant treatment found that amitriptyline, mirtazapine, and paroxetine were associated with a greater risk of weight gain[387] which can lead to MetS
- Recent studies point to MetS abnormalities in depressed persons with many atypical, neurovegetative symptoms, including hyperphagia, hypersomnia, lack of energy, and leaden paralysis[384,388,389]

There are several shared etiological pathways between mental health and MetS (Figure 3.18) summarized as follows:

A. LIFESTYLE AND MEDICAL CARE

- Health behaviours such as poor quality diet, smoking, and lack of physical activity may be part of the shared etiology of MetS and serious mental illness[390,391]
- Long-term treatment with first and second-generation antipsychotic medication can increase the risk of diabetes, hypertension, and hyperlipidaemia[392]
- The reduced likelihood of people with mental health conditions receiving standard (optimal) levels of medical care likely contributes to an unhealthier metabolic profile[393]

B. CENTRAL AND PERIPHERAL IMMUNE, METABOLIC, AND ENDOCRINE DYSREGULATIONS

- Different groups with mental health conditions share inherent features of deregulated homeostasis systems, including the HPA-axis and inflammatory responses linked to MetS development
- Disturbances of glucocorticoid sensitivity[394] accompanied with hypercortisolemia induces lipolysis, the release of fatty acids, and synthesis of very-low-density lipoprotein (VLDL), resulting in hypertriglyceridemia[395]
- White adipose tissue produces inflammatory cytokines and hormones (e.g., leptin) and contributes to pathogenic immune- and metabolic-related responses in the central nervous system and peripherally

- Inflammatory cytokines can enter the brain and lead to decreased nerve cell development (neurogenesis) in emotion-regulating brain structures.[396] They also reduce synthesis of serotonin and increase synthesis of tryptophan breakdown products (catabolites), which alter neurotransmission and lead to neuronal damage[397]
- Proinflammatory response stimulates the release of lipids in the bloodstream, resulting in a reduction in HDL-C and an increase in triglycerides. The sustained HPA-axis and inflammatory activation may affect insulin sensitivity[397]
- Higher levels of oxidative and nitrosative stress (overproduction of nitric oxide) may be involved in both the development of mental health issues or problems and metabolic dysregulations[398]

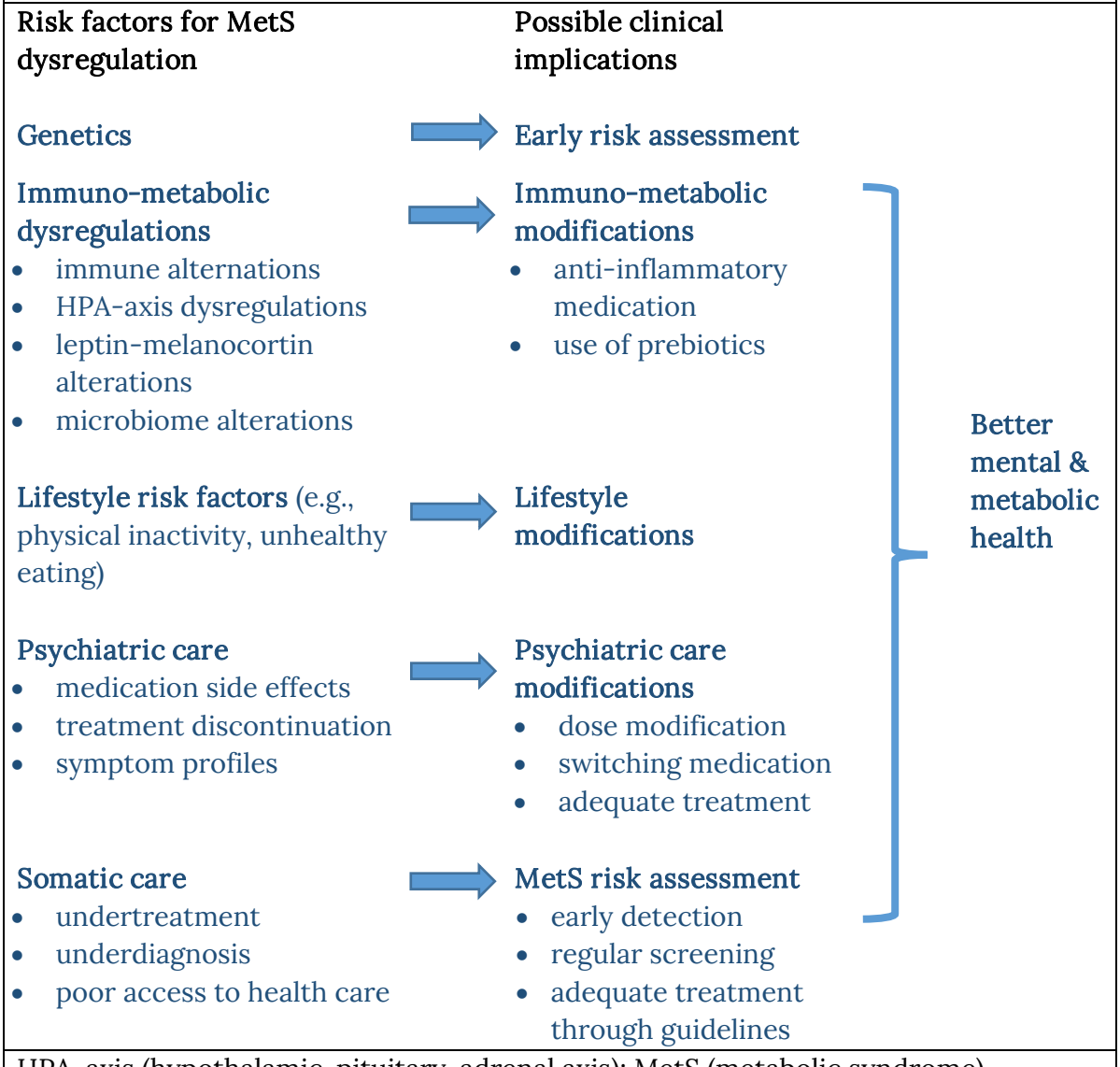
C. SHARED GENETIC VULNERABILITY

- There appears to be pharmacogenetic risk for metabolic syndrome and poor mental health[374,399]
- Certain genes seem to be shared between mood disorders and cardiometabolic conditions,[400] including CACNA1D (encoding calcium voltage-gated channel subunit α1 D), FTO (encoding fat mass and obesity-associated protein), BDNF (encoding brain-derived neurotrophic factor), POMC (encoding proopiomelanocortin), and IGF1 (encoding insulin-like growth factor 1)
- Shared genetic pathways include corticotropin-releasing hormone, axonal guidance, serotonin and dopamine receptors, circadian rhythm, and leptin signaling
- Leptin genes, MTHFR (encoding methylenetetrahydrofolate reductase), and serotonin receptor 2C genes may be involved in the pathogenesis of both MetS and schizophrenia[401]

D. GUT MICROBIOME ALTERATIONS

- Commensal bacteria, which act on the host's immune system to induce protective responses that prevent colonization and invasion by pathogens, are a connecting factor to both metabolic and mental health. The penetration of bacteria across the gut epithelium may modulate a range of proteins involved in brain development and plasticity, resulting in chronic low grade inflammation, which further induces MetS[402]

Figure 3.18: Factors underlying shared etiology of MetS and mental health with clinical implications[395]



HPA-axis (hypothalamic-pituitary-adrenal axis); MetS (metabolic syndrome)

Management of MetS and Mental Health

A. ANTIPSYCHOTIC MEDICATIONS AND METABOLIC MONITORING

- Baseline metabolic screening should be part of standard care for all individuals with a regular prescription of any antipsychotic medication[403]
- Reports of routine metabolic screening practices in high-income countries (USA, UK, Australia, Canada and Spain) have shown that metabolic testing was inconsistent despite widespread dissemination of the guidelines[404, 405]
- A systematic review reported there was some indication of a possible protective effect by antipsychotics in preventing diabetes and high blood cholesterol levels (e.g., hyperlipidaemias). Long-term prospective studies are required for accurate

appraisal of risk for diabetes, hypertension, and hyperlipidaemia in those exposed to antipsychotic polypharmacy[406]

- A study of mental health based primary care of individuals accessing services of a community mental health center that assessed quality indicators related to outpatient medical visits, diabetes HbA1c[8] monitoring, and metabolic monitoring of antipsychotic treatment reported that the program improved metabolic monitoring for individuals taking antipsychotics, but did not impact other quality indicators[407]

B. PHARMACOLOGICAL INTERVENTIONS

- A meta-analysis of 22 studies reported that antidepressants, mainly SSRIs, reduced cytokine levels during treatment,[408] and may be protective against MetS

3.1.12 Obesity

Obesity (BMI > 30) is characterized by excess or abnormal body fat that can impair one's health. Many organizations, including Obesity Canada, the Canadian Medical Association, the American Medical Association, and the World Health Organization, consider obesity to be a chronic disease because it is a lifelong process to manage it.[409]

Prevalence and Incidence of Obesity with Mental Health Problems or Illnesses

A. ANXIETY AND DEPRESSION

- Mental health concerns, particularly depression, are common in obesity (>50% screen positive)
- Studies of patients seeking bariatric surgery report prevalence rates of 21 – 56% for any current Axis I disorder, 22-32% for mood disorders, and 15-24% for anxiety disorders[410]

B. BIPOLAR DISORDER

- A meta-analysis of nine cross-sectional epidemiological studies reported that obesity is associated with an increased prevalence of bipolar disorder (BD) (OR=1.77, 95% CI 1.40-2.23).[411] The rate of obesity in women with BD has been found to be higher than in men with BD[412]

C. EATING DISORDERS

- Studies of patients seeking bariatric surgery report prevalence rates of 3-23% for binge eating disorders (BED)[410]

[8]Glycated hemoglobin refers to the attachment of glucose (a type of sugar) molecules in the blood to hemoglobin molecules. Hemoglobin A1c, or HbA1c is a test that can be done to detect how much glucose has attached to hemoglobin in a given time period and is an indicator of blood glucose control

D. SUBSTANCE USE

- Among candidates for bariatric surgery, the prevalence of being a former or recent tobacco user is 55%; history of a substance use disorder is 13%[413]

E. ESTIMATES OF MENTAL HEALTH COMORBIDITIES BY SUBPOPULATIONS

- In two longitudinal studies of African Americans (17-29 years), 23%–27% showed increasing substance use over time, 18%–27% showed increasing obesity over time, and 9%–11% showed increases in both[126]
- Depression in obesity varies by race and income. Among white women, obesity is positively associated with depressive symptoms across income levels, while obesity was not associated with depression for African American women at any income level. Obesity was only associated with depressive symptoms among middle-income white men (OR=1.44, 95% CI 1.02–2.03) and among high-income African American men (OR=4.65, 95% CI 1.48–14.59)[414]

Mental Health Screening

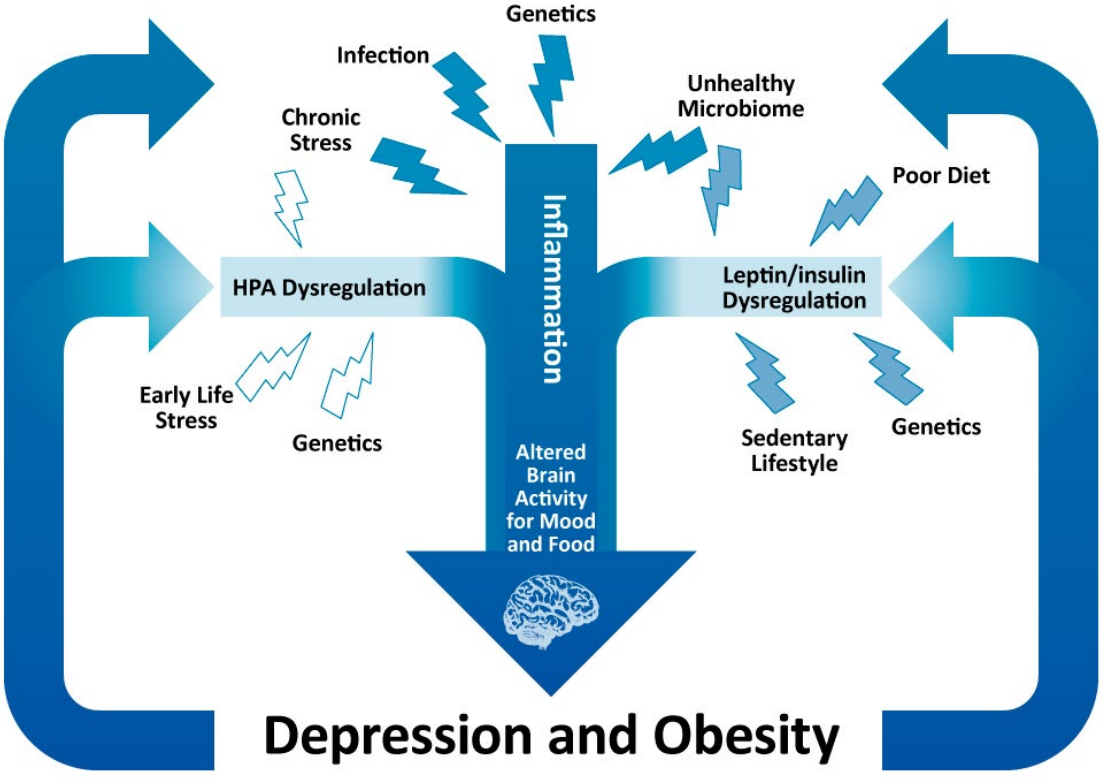
- A typical tool used for mental health screening is the Patient Health Questionnaire-9 or PHQ-9
- Screening is particularly recommended in sarcopenic obesity, defined as the presence of loss of muscle and obesity typically related to aging

Common Pathways

A. DEPRESSION

- Shared biological pathways of depression-obesity include genetics, alterations in systems involved in homeostatic adjustments (HPA axis, immuno-inflammatory activation, neuroendocrine regulators of energy metabolism including leptin and insulin, and microbiome) and brain circuitries integrating homeostatic and mood regulatory responses (Figure 3.19)[415, 416,417]
- Factors that can induce inflammation and depressive symptoms include psychological stress and obesity.[44] Central adiposity in obesity is a source of inflammatory cytokines that can promote neuroinflammation. Metabolic disturbances in obesity can lead to increases in cortisol, leptin, and insulin levels resulting in HPA axis dysregulation and insulin resistance, with subsequent inflammation and worsened depression[418]
- Obesity and the co-morbid chronic conditions associated with it are closely associated with multiple mental health concerns.[419] Factors such as prejudice, stigmatization, and employment discrimination may contribute to both obesity and poor mental health[420]
- A systematic review examining whether obesity and depression relationships are bi-directional reported that the association between overweight and depression was not found to be significant in either direction. The strength of the association is greater for the direction leading from depression to obesity and more pronounced for young and middle-aged women[421]

Figure 3.19: Shared etiology of obesity and depression[415]



B. BIPOLAR DISORDER (BD)

- BD and obesity also share common pathogenic pathways:
  - i. Similar phenotypic expression of the brain reward system is observed in both overeating behaviour and hypomania, which is related to self-stimulating behaviours such as food seeking and hypomanic symptoms[422]
  - ii. Regulatory pathways, especially mediated by serotonin and dopamine, are involved with energy balance and mood modulation[423]
  - iii. Obesity and BD are associated with cognitive dysfunction and body mass index, and depressive and manic episodes are negatively correlated with memory and executive function.[424]
  - iv. The HPA axis may be disrupted by increased leptin released by adipose tissue, which affects normal mood modulation, and leads to extreme and/or rapid mood fluctuations such as depression, mania, or the cycle of both
  - v. Adipose tissue in obese individuals can release increased amounts of inflammatory cytokines, such as IL-6 and TNF-α, leading to HPA axis abnormalities and are linked with BD[425]
  - vi. Mood stabilizing drugs like lithium, valproate, and certain antipsychotics (e.g., olanzapine) are related to increased food intake and weight gain. The obesity-BD link may mutually increase the occurrence of both obesity and BD[411]

C. SCHIZOPHRENIA

- The links between obesity and schizophrenia are also multifactorial and include dietary intake, treatment with second-generation antipsychotics, particularly clozapine and olanzapine, and psychosocial factors such as social isolation, negative discrimination, stigma, and low SES.[426] Factors such as deficits in executive function and memory, residual psychotic symptoms, self-management skills, and substance misuse can be barriers to management of the conditions[427]

Management of Obesity and Mental Health

A. BEHAVIOURAL AND LIFESTYLE INTERVENTIONS

- A meta-analysis that examined psychosocial effects of exercise in individuals with obesity did not show that exercise was better than control conditions for quality of life or depression[428]
- Behavioural interventions that involve treatments that modify behaviour, emotions, and cognition can improve both psychological and physical well-being[419]
- Current work is being done to investigate tools which can engage self-regulation and behaviour change targets to improve mood and weight outcomes that include microbiome-gut-brain and immune pathways in integrated behavioural treatment[429]

B. DIGITAL HEALTH APPLICATIONS

- Mobile health (mHealth), a health practice supported by mobile devices, such as mobile phones, monitoring devices, personal digital assistants (PDAs), and other wireless devices, may have potential in managing obesity and mental health. They can be used in everyday lives (i.e., in real time) and in natural settings (i.e., real world) and may facilitate remote access to health services
- Apps that monitor weight, physical activity, psychological wellness, cognitions, and emotions separately generally show favourable outcomes. No mobile app was found that integrated all of these features to enable simultaneous management of overweight/obesity and depression/anxiety[430]

C. METABOLIC MONITORING

- Current guidelines related to management of overweight and obesity in adults align with risk profiles for CVD[431] and integrate guidelines for cardiometabolic monitoring for those with weight gain related to anti-psychotic use (Figure 3.20)

Figure 3.20: Cardiometabolic monitoring of individuals receiving anti-psychotics as mental health treatment

a) Suggested algorithm for cardiometabolic monitoring of patients treated with antipsychotics.

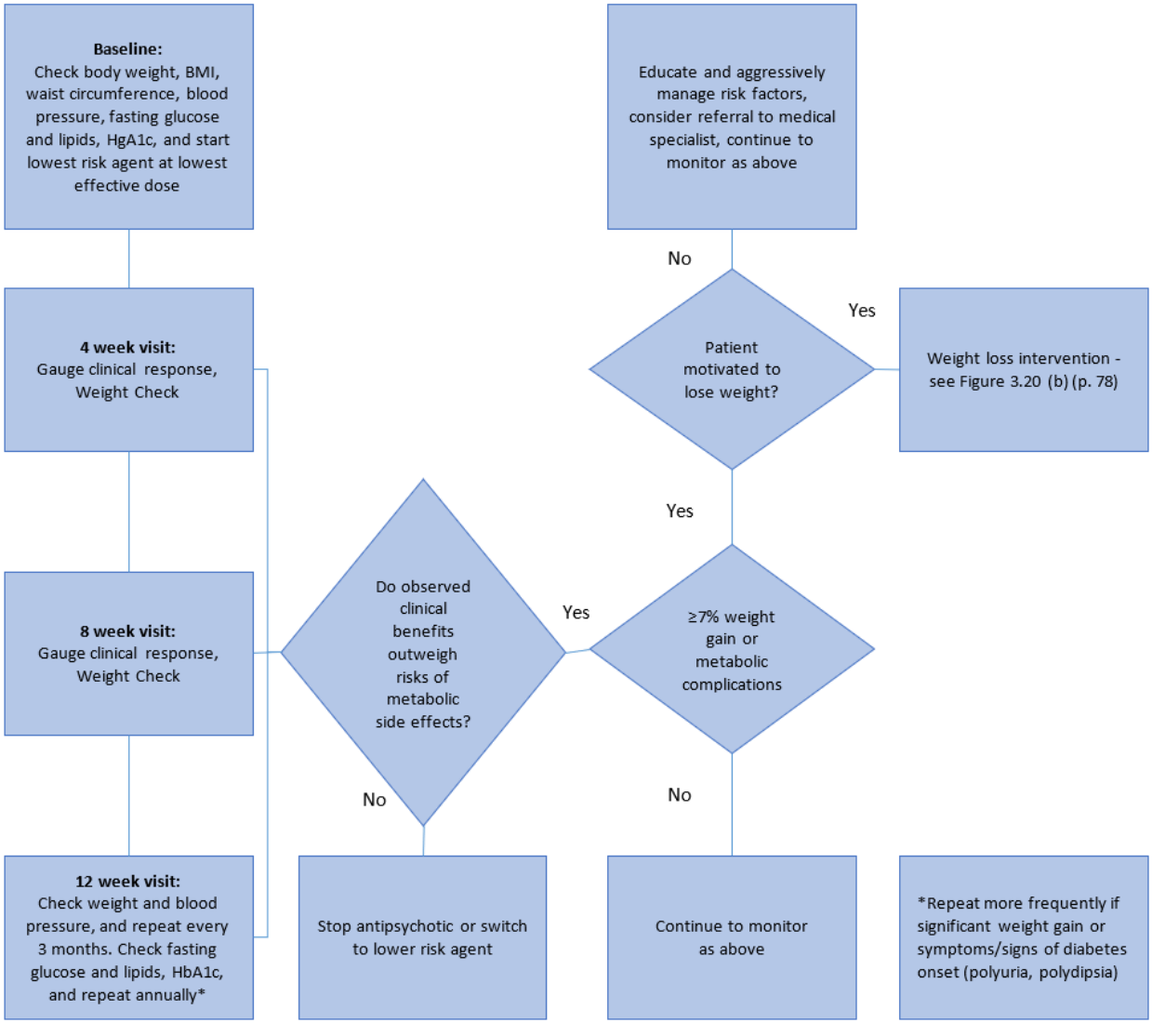
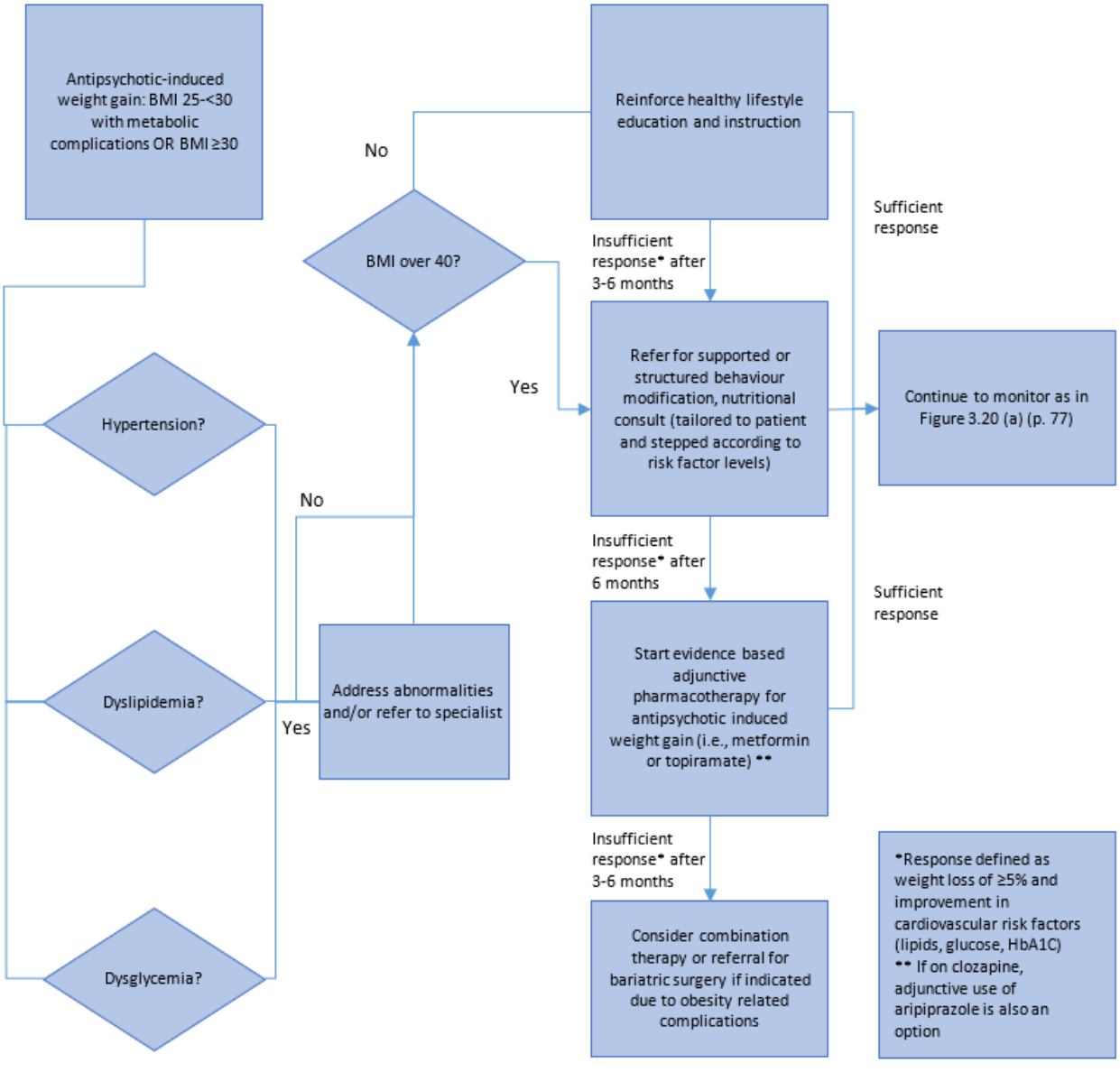


Figure 3.20: Cardiometabolic monitoring of individuals receiving anti-psychotics as mental health treatment

b) Suggested algorithm for managing antipsychotic-related weight gain.



D. PHARMACOLOGICAL AND SURGICAL INTERVENTIONS

- When pharmacological and surgical interventions are combined with psychological supplements via behavioural health interventions, treatment adherence and long-term sustainability are enhanced[419]
- Antipsychotics are currently the only medication that effectively treat psychosis[432] and reduce risk of mortality.[433] Other psychotropic medications, including mood stabilizers and antidepressants, can also lead to weight gain, and adversely affect lipid and glucose metabolism.[434] Healthcare providers need to consider these factors when making treatment choices[435] and implement integrated education,

assessment, and care for those with mental health concerns and at risk for weight gain

E. INTERVENTIONS FOR SUBPOPULATIONS

- Based on limited research about the experiences of lesbian women, overweight and obesity were associated with more public identification as a lesbian, more depressive symptoms, increased heavy drinking, and longer relationship length. These findings suggest health promotion and weight loss intervention programs for lesbians should incorporate psychological, relationship, and alcohol use components to reduce overweight and obesity[436]

3.1.13 Parkinson's Disease (PD)

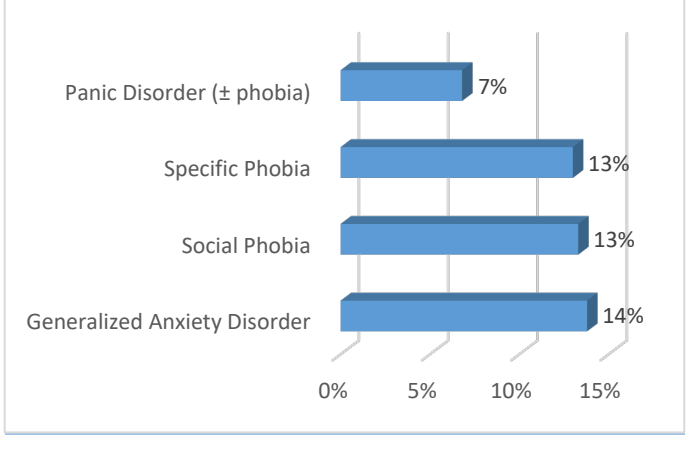
PD is a neurodegenerative disorder that affects mainly dopamine-producing ("dopaminergic") neurons in a specific area of the brain called substantia nigra. The symptoms may include tremor, slowed movement, rigidity of the limbs, as well as gait and balance problems. The symptoms generally develop slowly over years.[437]

Prevalence and Incidence of PD with Mental Health Problems or Illnesses

A. ANXIETY

- A meta-analysis of 45 studies reported an average point prevalence of anxiety disorders in PD of 31%, with non-episodic anxiety being more prevalent than episodic anxiety[438]
- Estimates among subtypes of anxiety-related conditions range from 6.8 to 14%. Of the samples, 31% fulfilled the criteria for current multiple anxiety disorders. Based on anxiety rating scale cut-off scores, clinically significant anxiety symptoms were present in a weighted average of 25.7%. (Figure 3.21)[438]

Figure 3.21: Average Point Prevalence of Anxiety-Related Conditions in PD



B. DEPRESSION

- Depression affects 44%-51.7% of all people with PD[438]
- Depression and PD share overlapping symptoms such as reduced facial expression, problems with sleeping, fatigue, psychomotor retardation, and reduced appetite.

These similar symptoms may contribute to the underdiagnosis of depression in patients with PD[439]

- Risk factors for the development of depression in PD are being female, having family problems, early manifestations of disease, "atypical" parkinsonism, concomitant affective disorders such as anxiety, apathy, sleeplessness, and psychoses,[440] history of depression, concomitant moderate cognitive disorder, and a higher daily dose of levodopa[441]

C. IMPULSE CONTROL DISORDERS

- Prevalence estimates of impulse control disorders in PD have been reported to be 6%. Among this group, most were men (81%), had a mean age-at onset of PD of 48 years and disease duration of 8 years. Punding was the most frequent behavioural problem (57%), 42% exhibited aggressive hypersexuality, 27% compulsive eating, 24% pathologic shopping, and 21% compulsive medication[442]

D. PTSD

- A longitudinal study conducted in Taiwan reported an increased risk of developing PD in people with PTSD (HR=3.46, 95% CI 1.72–6.96) compared with individuals without PTSD[443]

Mental Health Screening

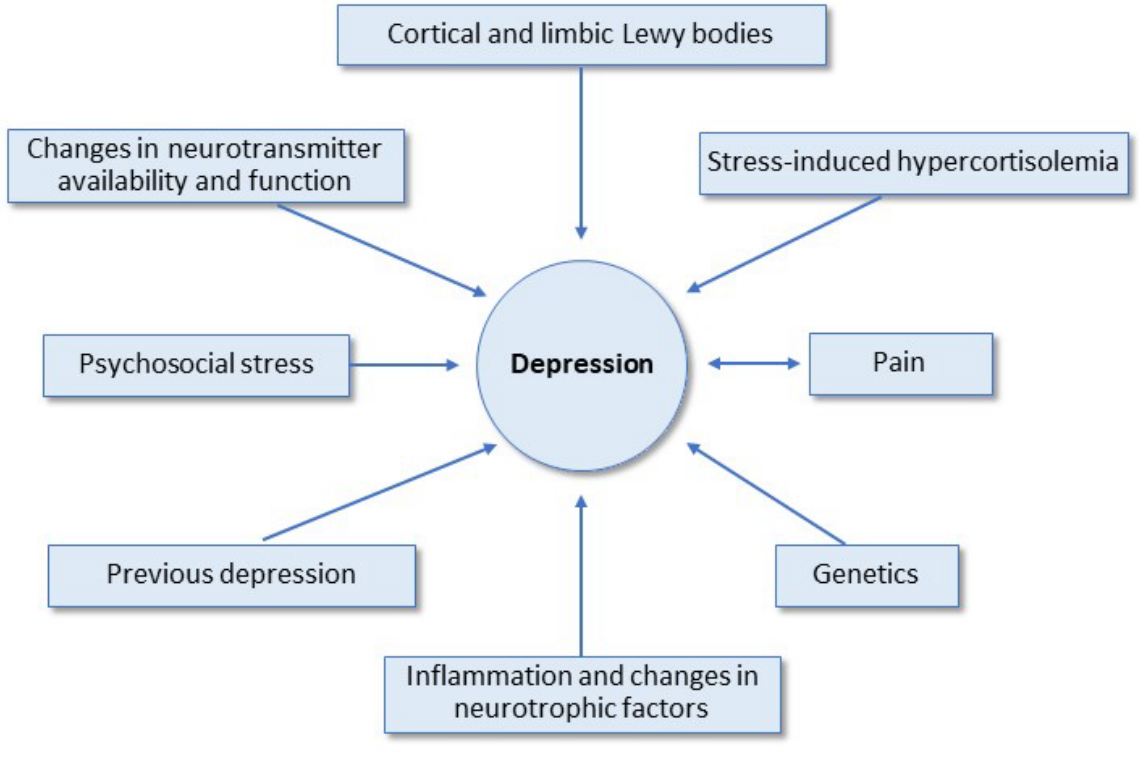
- The Movement Disorder Society recommends that the selection of screening tools needs to be guided by testing aims. The most suitable scales for screening for depression disorders are the Ham-D and BDI scales, the geriatric depression scale, the HADS, and the Montgomery Asberg Depression Rating Scale (MADRS)[441,444]
- Use of the Ham-D and BDI, the Montgomery rating scale, and the Zung self-rating scale are considered more useful for assessment of the severity of the symptoms of depression[441]
- Up to 68% of individuals with Parkinson's are reported to have depression;[445] there appears to be higher prevalence among men (65%) compared to women (35%)[226]
- Some research suggests there are gender effects of depression in PD. For example, partitioning items of the BDI has shown to be useful in identifying that melancholy features prominently in women, while classical factors associated with depression in PD (apathy and loss of libido) features more prominently in men[446]

Common Pathways

- The literature suggests various factors related to PD that can contribute to depression (Figure 3.22)[447]
- A systematic review of imaging studies reported increased neural activity in the prefrontal regions and decreased functional connectivity between the prefrontal-limbic networks in individuals with depression. Both nigrostriatal and extra-nigrostriatal pathways (especially the frontal region and its connecting areas) are dysregulated in mood disorders in PD[448]

- The neurochemical changes in PD involving dopamine, norepinephrine, and 5-hydroxytryptamine are also related to the pathophysiology of depression and anxiety[448]
- Familial susceptibility factors might have a role in shared pathophysiology, as first degree relatives of people with PD show an increased risk of experiencing anxiety and depressive disorders[448]
- Certain genetic markers, DNA sequences with a known physical location on a chromosome, have linked PD with mental health outcomes such as depression. These include glucocerebrosidase (GBA) variants rs76763715, rs421016, rs387906315 and rs80356773[449]
- The link between anxiety and PD is thought to be due to impairments of noradrenaline, serotonin, dopamine, and GABA synthesis[415]

Figure 3.22: Factors Contributing To Depression In Individuals With PD[447]



Management of PD and Mental Health

A. DEEP BRAIN STIMULATION

- An investigation of deep brain stimulation on non-motor symptoms for individuals with moderate to severe PD reported improved depression 6 months post-operatively. Improvements in depression are maintained over time and correlate with improvements in sleep quality and quality of life[450]

B. EXERCISE

- Physical activity can improve clinical status in areas such as function, fatigue, depressive symptoms, sleep disorders, and quality of life.[451] The American College of Sport Medicine activity guidelines can be applied to patients with PD: aerobic exercise, strengthening, and balance training flexion is recommended three times a week for at least 30 minutes[452]
- Mind-body exercises may improve motor function, depressive symptoms, and quality of life, however, more needs to be known about specific factors such as gender, severity of disease, specific drug use, and intervention cycle[453]

C. PHARMACOLOGICAL INTERVENTIONS

- Antiparkinsonian medications might improve mood disorders by alleviating motor manifestations and disability, fostering feelings of disease mastery, or restoring dopaminergic signalling[454]

D. PSYCHOLOGICAL INTERVENTIONS

- Results for CBT and other modes of therapy are promising for acute management of depression and anxiety; longer term effects after treatment have been variable[455]
- Treatment of PD patients with signs of anxiety must be directed primarily to optimizing anti-parkinsonism therapy, with decreases in "off" periods

3.1.14 Respiratory Diseases (Chronic)

Chronic respiratory diseases are chronic diseases of the airways and other parts of the lung. Some of the most common are asthma and chronic obstructive pulmonary disease (COPD). Most of these diseases have a major impact not only on the individual with the disease but also on the family.[456]

Prevalence and Incidence of Chronic Respiratory Diseases with Mental Health Problems or Illnesses

A. ANXIETY

- Anxiety is more frequent (21-28%) among people with COPD compared with the general population or people with other chronic health conditions[457,458]
- Individuals with anxiety tend to have their first hospitalization earlier in the natural course of COPD.[459] It is reported that they tend to more intensely irritated by their shortness of breath, and have higher rates of mortality and readmission after an exacerbation[460]
- Respiratory failure, the number of acute exacerbations in the previous year, and the COPD evaluation test (CAT) score representing symptoms and quality of life of COPD are reported to be strongly related to anxiety in COPD[461,460,462]
- A systematic review and a meta-analysis reported that anxiety increases the risk of hospitalization[463]

- The highest risk of death related to COPD and anxiety tends to occur among females[464]

B. DEPRESSION

- Depression is common with COPD, with a prevalence reported to be between 9-27%[465,466,467,457, 468]
- A systematic review reported a pooled odds ratio of 3.74 (95% CI 2.4-5.9) for depression in those with COPD compared to those who did not have the condition[468]
- Respiratory failure, the number of acute exacerbations in the previous year, and the COPD evaluation test (CAT) score representing symptoms and quality of life of COPD are reported to be strongly related to depression in COPD[461,460,462]
- A systematic review and a meta-analysis reported that depression increases the risk of hospitalization[463]

C. PTSD

- In a longitudinal study of people with PTSD, an increased risk of asthma (hazard ratio (HR)=2.30, 95% CI 1.60–3.30) was reported among those 20-64 years of age[469]

D. PSYCHOSIS

- A regression analysis of 28,002 adults in 16 countries from the WHO World Mental Health (WMH) Surveys that assessed psychotic experiences reported, after adjustment for several comorbid mental health conditions, significant association between asthma and subsequent psychotic experiences (OR=1.6, 95% CI 1.2–2.1)[470]

E. SUICIDE IDEATION AND BEHAVIOUR

- A systematic review examining suicide ideation and physical illness in older adults found suicidal behaviour was associated with COPD[133]

F. ESTIMATES OF MENTAL HEALTH COMORBIDITIES BY SUBPOPULATIONS

- Women are more susceptible to the development of depression and/or anxiety in acute exacerbation of COPD[471]
- Age, body mass index, and duration of illness have been reported to be related to COPD combined with depression and/or anxiety in some studies, but not in others. This may be due to variability across countries and different cultural backgrounds within countries[472]

Mental Health Screening

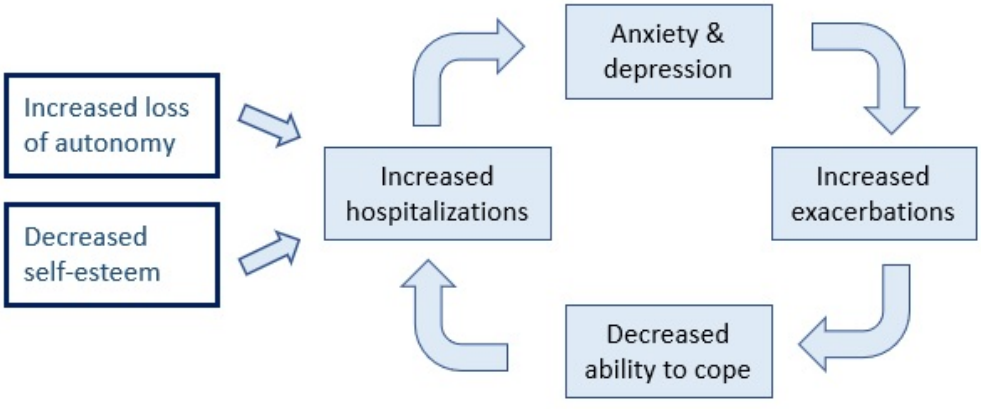
- The literature reports the use of the Ham-A and Ham-D, however, there is no consensus on the evaluation tools and diagnostic criteria of COPD with depression and anxiety

- Increases in maximum respiratory volume per second (VEMS) are correlated with higher anxiety (Ham-A Rating) and depression (Ham-D Rating Scale) scores[473]

Common Pathways

- The pathophysiology of depression and anxiety in chronic respiratory diseases may be explained by multiple risk factors, systemic inflammation, and response to COPD symptoms (Figure 3.23)
- Smoking, COPD, and depression are mutually reinforcing. Depression has a role in the initiation and maintenance of smoking, smoking leads to the development of COPD, and COPD contributes to the development of depression[474]
- COPD is associated with chronic hypoxemia; a known after effect of recurrent nocturnal hypoxemia is depressed mood[475]
- Both depression and COPD have been associated with processes that affect the brain microvasculature. There is evidence for systemic inflammation and elevated biomarkers of oxidative damage[476] (e.g., soluble tumor necrosis factor receptor-1 (sTNFR-1) has strong association with depression in people with COPD)[477]
- A systematic review of stigma-related experiences in non-communicable respiratory disease reported that these experiences were significantly correlated with psychosocial, behavioral, physical, treatment, and work-related domains[478]
- In women, links to depression may involve female sex hormone secretion and reaction to social stress; severe breathing difficulties and subjective feelings about low social function are stronger in women when compared to men[479]
- Common diseases coexisting with COPD, such as heart disease, gastroesophageal reflux disease, and lung cancer, can worsen mental health. The greater the number of comorbidities, the greater the risks of depression and/or anxiety (OR=2.14, 95% CI 1.28–3.60)[472]
- Glucocorticoid inhalation is unlikely to accumulate in the body and lead to poor mental health. However, it is unknown if this is also true for oral or intravenous glucocorticoids. Glucocorticoid receptors in the hippocampus of the brain are activated by excess glucocorticoids in the body, causing degeneration and necrosis of hippocampal neurons, which can induce depression[472]
- The pathogenesis of panic and anxiety in COPD may be related to anxiogenic effects of hyperventilation, misinterpretation of respiratory symptoms, neurobiologic sensitivity to CO_2, lactate, or other signals of suffocation, and the stress of coping with chronic disease[480,474]

Figure 3.23: Simplified shared etiology of COPD and mental health (anxiety)[465]



Management of Chronic Respiratory Diseases and Mental Health

Pharmacological Interventions

- A Cochrane review of pharmacological interventions for depression in COPD reported insufficient evidence about the efficacy or safety of antidepressant use[321]
- The choice of antidepressant depends on the pattern of depression. Late-onset depression or geriatric vascular depression develops after COPD diagnosis and is more refractory to antidepressant treatment. Early-onset depression develops prior to the diagnosis of COPD and is often reflective of a genetic vulnerability to depression[474]
- Medications with the lowest potential to interfere with cytochrome P450 system should be considered; up-regulation of this system can make the lungs more susceptible to oxidant damage[481]
- A Cochrane review of pharmacological interventions for the treatment of anxiety in COPD found insufficient evidence of benefit for any of the medications included[482]

Psychological/Behavioural Interventions

- Behavioural interventions that include Personalized Intervention for Depressed Patients with COPD (PID-C), a treatment mobilizing people to participate in their care, are more effective than usual care. Problem Solving-Adherence intervention integrating problem solving into adherence enhancement procedures found comparable results for depression to PID-C[483]
- An RCT of older adults (67-85 years) hospitalized for COPD with controlled breathing techniques as the intervention reported significantly improved dyspnea, anxiety, and mobility in the intervention group[484]
- A Cochrane review of psychological treatments in COPD reported limited evidence that psychological therapies (CBT-based approach) may be effective for treating COPD-related depression. Depressive symptoms improved more in the intervention groups compared to: 1) no intervention (attention placebo or standard care), 2) educational interventions, and 3) a co-intervention (pulmonary rehabilitation)[485]

Models of Care

- The inter-connectedness of stigma-related experiences to these conditions (e.g., stigma related to smoking, a common cause of respiratory disease, and having a mental health condition) highlights the need for integrated approaches[478]
- Although the measurement and management of symptoms tends to be the primary focus for clinicians, individuals with asthma or COPD are typically more concerned with the overall impact of their condition on their quality of life[486]
- Management of chronic respiratory diseases should aim for individualized care. For example, individuals with COPD tend to prefer treatments that provide symptom relief (e.g., dyspnea), positive physician relations, and improve quality-of-life. Individuals with asthma prefer treatments that increase symptom-free days and may be willing to trade days without symptoms for a reduction in adverse events and greater convenience[487]
- Pulmonary rehabilitation is beneficial for those with comorbidities and has been shown to reduce the severity of depression and cardiovascular risk factors, including blood pressure[488,473]
- Mindfulness-based cognitive therapy may impact affective and sensory perceptions related to difficulty in breathing (dyspnoea), however, more research is needed[489]

The National Institute for Health and Care Excellence (NICE) has guidelines for the use of stepped approaches to psychological and/or pharmacological treatment of depression in people with long-term conditions, including respiratory conditions[572]

3.2 Implications for Health Education, Services, and Policy

In this section various physical health and mental health comorbidities were discussed based on screening, prevalence/incidence estimates, what is currently known about shared etiology, and their management. While there are attributes that are unique to the different physical and mental health comorbidities that were discussed, many commonalties were present as well. These are discussed as means to provide suggestions for practice and policies related to physical and mental health comorbidities.

3.2.1 Health Education

Stigma which can occur with both physical (e.g., obesity, lung cancer, arthritis) and mental health important public health concerns,[490] with negative effects including anxiety,[491] stress,[492] depression,[493] reduced self-esteem/self-efficacy,[494] reduced or delayed care-seeking,[495] and lowered adherence to treatment.[496] Studies also suggest that, as physical health worsens, the risk of experienced discrimination increases.[497] Public health campaigns focused on reducing health condition-related stigma can help educate the public and subsequently minimize burden for those diagnosed with a physical or mental health condition. Coordinated, interdisciplinary, and well-conceptualized efforts across the

health care continuum have the potential to reduce the barrier of stigma and facilitate improvements in care and quality of life.[138]

Successfully addressing stigma, through targeted efforts aimed at intrapersonal, interpersonal (e.g., clinician, family), and society (e.g., social attitudes, policy) levels, is important in reducing the burdens associated with both physical and mental health conditions.

3.2.2 Health Services

The collaborative care model, is recognized as a best practices mechanism to provide for optimal management of physical and mental health comorbidities[2,3,4]

Across all of the physical and mental health comorbidities that have been discussed, the need for more integrated health services were consistently identified. Better integrated health and social services contribute to:[498]

- better screening and management of physical and mental health comorbidities which reduces reliance on higher cost acute care services;
- mitigate morbidity, and prevent premature death;
- ease of transitions across the health care continuum;
- improved health care access, sustainability, and stability; and
- improved community health, including social services and/or education.

Currently, the collaborative care model, broadly defined as multi-professional approaches that employ structured management, scheduled follow-up, and inter-professional communication, is recognized as a best practices mechanism to provide for optimal management of physical and mental health comorbidities.[2,3,4] These approaches, which are particularly relevant for services addressing mental health, addiction, and physical comorbidity, have been challenging to address. Specific evidence-based models and approaches for collaboration across mental health, addiction, and physical health include the Canadian Collaborative Working Group on Shared Mental Health Care, the Chronic Care Model, and the Tiered Model. Common features across these approaches include a focus on a broad continuum of severity, multi-sectoral involvement, multiple levels of collaboration that align with different types of needs and levels of severity; and a distinction between service- and system-level initiatives.[499]

The collaborative model of care may also include stepped care approaches which have been adopted in several international evidence-based clinical guidelines such as those of the National Institute for Health and Clinical Excellence. Stepped-care approaches, which offers end-users interventions of low intensity first (e.g., problem solving, psycho-education) and, where needed, progresses them to more intensive treatment options, has been shown to foster well-being and reduce healthcare costs.[500,501] As noted by system stakeholders and researchers, enhanced efforts for the integration of stepped depression care in primary care are needed. This includes reducing barriers related to effective education programs for practitioners and care managers, reimbursement, as well as

communication and monitoring systems.[502,503] To build appropriate capacity for collaborative health services will require both increases in human resources and enhancements in technology that facilitate sharing information across functional boundaries securely.[499] In particular, the potential for integrated mobile apps that monitor both physical and mental health symptoms may improve efficiencies in care provision.

3.2.3 Health Practice

Models of Care

> Collaborative primary care models that include allied health professionals such as dietitians, occupational therapists, social workers, and substance use disorder specialists integrated with well-established models of mental health services delivery such as peer support, include specialized services for physical health (e.g., diabetes), and encompass alternative mechanisms of delivery such as telehealth will help to address the complex needs of those with physical and mental health comorbidities.

The care of individuals with physical and mental health co-morbidities includes primary health care settings, hospitals, mental health, allied health services, and social services. Primary care is the foundation and is in need of integrating services such as mental health promotion, screening, and treatment,[504] which will promote both physical and mental well-being.[53] Services, such as those aimed at mental health promotion and screening, must align with policy-level directives to create equitable, accessible, and appropriately resourced primary health care.[505] For example, issues such as access to social workers, psychiatrists, psychologists, and substance use disorder experts need to be addressed, particularly for those who face additional barriers to receiving specialty health services due to factors such as cost, living in rural or remote areas, or being newcomers to Canada.[506] The Mental Health Commission of Canada endorses that primary health care must increase the availability and coordination of both community-based mental health services as well as appropriate access to intensive, acute, and highly specialized services, treatments, and supports.[507] In alignment with these priorities, collaborative primary care models that include allied health professionals such as dietitians, occupational therapists, social workers, and substance use disorder specialist integrated with well-established models of mental health services delivery such as peer support, include specialized services for physical health (e.g., diabetes, cardiovascular, respiratory care), and encompass alternative mechanisms of delivery such as telehealth will help to address the complex needs of those with physical and mental health comorbidities. Furthermore, long-term issues of fair compensation for primary care physicians who provide mental health care[508] must be resolved to foster equity of service access for individuals struggling with mental health problems and illnesses.[509] Care that is collaborative, integrated, tailored, and flexible (e.g., home visits, extendedhours, provide online service delivery, group virtual visits) will also better meet the needs of those with physical and mental health comorbidities. As the prevalence of comorbidities in the aging Canadian population rises, it is evident that collaborative care models will be increasingly critical. Strategies that have been identified to facilitate integrated care include: [510,511,512]

- having registries of people with complex needs to track preventative care, disease/illness management, and referrals to secondary and tertiary care
- providing health care system navigation supports
- implementing shared decision-making approaches
- adequately resourcing secondary and tertiary mental health services
- supporting competency development among practitioners to deliver high-quality health care to people with mental health problems and illnesses
- training practitioners in the recovery model, including stigma and discrimination, illness perceptions, trauma-informed care, positive communications, and social support interventions
- evidence-based and clear screening guidelines, pathways to management, and integration with social services

It is also evident that receiving collaborative care as compared to usual care has been found to be beneficial among those with mental health issues and illnesses for improving adherence and functional status.[513] Demonstration projects for providing coordinated care for high-cost and high-need individuals have also proven to be cost-effective. Specifically, the Hamilton Family Health Team model for collaborative care (the HFHT-model) which involves placing various health professionals within existing general practitioners practices to form Family Health Teams that can then offer coordinated mental and somatic health care has shown positive intended effects.[514]

Finally, at the organisation level, efforts to foster relationships between mental health and physical health representative organisations are needed. For example, advocacy work to include people living with physical and mental health problems within reviews of relevant clinical and intervention guidelines would lead to the development of more relevant interventions for mental and physical health care.

Pharmaceutical Interventions

For many of the physical and mental health comorbidities reviewed in this report, high-quality efficacy and safety data on the use of psychiatric medications, such as anti-depressants, in the context of specific physical health conditions were lacking and in need of well-designed RCTs to clarify the balance between benefits and harms. For example, it is questioned if anti-depressants would be beneficial for those with chronic kidney disease and depression, as good kidney function is needed to help eliminate end-products of drug metabolism. Studies with long follow-ups are needed to demonstrate a sustained benefit of pharmacologic treatment and evaluate whether end-points, such as hospitalization and mortality, are affected without too many side-effects. In addition to better data, decision-making tools are needed by practitioners to help determine appropriate pharmacologic treatment pathways for different physical and mental health comorbidities.

Screening and Assessment

> Appropriate screening for mental health problems and illnesses in those with chronic physical conditions needs to be priority. Health care professionals will need to expand their use of standardized screening tools that capture various psychosocial factors in the populations they work with.

A recurring issue among the assessment of physical and mental health comorbidities was the heterogeneity of mental health measures used which contributes to variability in estimates of prevalence and incidence. Issues with mental health screening in those with physical health conditions include a lack of consistent guidelines and implementation, varying symptom profiles, and a lack of clear guidelines for follow-up should someone screen positive. Appropriate screening for mental health problems and illnesses in those with chronic physical conditions needs to be priority. Health care professionals will need to expand their use of standardized screening tools that capture various psychosocial factors in the populations they work with. Tools to assess physical and mental health comorbidity should screen for symptoms, stress, quality of life, risk factors, and protective factors. Brief screening tools such as the two-item PHQ can be easily offered in busy clinic settings as part of questionnaires that used to register clients. If more comprehensive assessment is needed, people can be scheduled for an assessment with standardized instruments validated for their particular circumstances (e.g., condition diagnosis, gender). Finally, more research is needed to identify comprehensive screening tools with sound psychometric properties.

Trauma-Informed Care

While a history of trauma is clearly linked to many health issues, a paucity of literature describing approaches to care of physical and mental health comorbidities lacked discussion about trauma-informed care. Furthermore, it is recognized that exposure to multiple adverse childhood experiences (ACEs) is a major risk factor for the development of many physical and mental health conditions. To sustain improvements in health services requires a shift in focus to include ACE-informed service provision. The Sustainable Development Goals provide a platform to help implement strategies to reduce the life-course effect of ACEs on physical and mental health.[515]

Challenges of Multi-morbidities

While comorbidities were the focus of this report, there were numerous studies located in the searchers that discussed multi-morbidities. In contrast to comorbidity which is a disease-centric concept, multimorbidity implies a patient-centred model of care, which does not prioritize a particular index disease and entails more comprehensive evaluation of individual complexity. This may be an approach to consider in the care of those with comorbidities also. Higher prevalence of multi-morbidity can lead to higher medical care utilization and expenditures which has implications for healthcare delivery reforms that focus on care management. For example, the model known as DIAMOND (Depression Improvement Across Minnesota Offering a New Direction) included both an integrated care component and bundled payments to primary care providers for depression. This model has been found to be effective in reducing depression remissions, and is based on

the IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) intervention that uses a collaborative approach for providing treatment.[516] In summary, the increasing prevalence and incidence of comorbidities and multi-morbidities points to the need for even better integration care models.

Psychological, Lifestyle, and Peer Approaches

Additional health service gaps include clear consensus about the need for evidence-based psychological interventions among the different physical and mental health comorbidities. While CBT is considered a cornerstone of mental health care, the literature does not demonstrate its efficacy across all comorbidity types, such as applications in CVD. This suggests further investigative work is needed to determine its efficacy across on physical health conditions. Similarly, the literature was limited in discussion about lifestyle interventions such as physical activity and diet as adjuncts to the care for comorbid physical and mental health conditions. Finally, while peer support approaches are a recommended model for health care, particularly for those facing mental health problems and illnesses, there was very limited discussion of its potential for the care of those with physical and mental health comorbidities. As noted in the obesity literature, most interventions do not include mental health professionals. Future studies should assess the effects of interventionist professions in addition to primary and secondary outcomes for adults with different lifestyle-related conditions, including obesity.[420]

Contextual Factors: Gender and Equity and Priority Seeking Populations

Multidisciplinary care for equity and priority-seeking populations with physical and mental comorbidities, should focus person-in-environment orientations and their service agencies. For example, helplessness experienced by those with CVD may intertwine with factors such as perceived injustice, discrimination, poor family relationships, and previous trauma. For people with a community or extended-family orientation, interventions that focus on connections with others may be more effective than interventions that focus on improving perceptions of individual control.[178] It is important to recognize contextual factors such as non-traditional families, same-sex partners, and chemical dependency. It is also critical to identify issues that might mask health symptoms, such as fears of prejudice or legal ramifications.

The literature about physical and mental health comorbidities yielded limited research about the effects of race and ethnicity. Race and ethnicity may influence individuals coping with stressors[517] and access to resources and quality health care. Services aimed at physical and mental health comorbidity care of those from diverse backgrounds need to include culturally sensitive practices. For example, minorities and immigrants with CVD may not be accustomed to intensive Western-style exercise programs. Alternatives such as integrative therapy (e.g., tai chi, yoga) and community-oriented approaches (e.g., Aboriginal ceremonies and rituals) may be better adopted by those from diverse backgrounds.

While there was limited research that examined physical and mental health comorbidities among LGBTQ populations, research that compared transgender and non-transgender older adults reported that transgender older adults have significantly worse physical health as measured by the Health-Related Quality of Life Scale and depressive symptomology.[518] It

is recommended that effective interventions for populations such as these will need to consider factors such lifetime victimization, stigma, and distinct social support networks.[519]

Manifestations and outcomes of physical and mental health conditions differ between men and women due to both sex (molecular, cellular, epigenetic mechanisms) and gender (adopted or imposed social norms, behaviours, identities and expectations).[520] In the literature about physical and mental health comorbidities, there was limited reference to sex and gender differences. As identified by others, this raises issues about the development and uptake of sex and gender influences into care guidelines and health practice.[521] For example, there are important knowledge gaps that exist about the different impacts of menopause and andropause in relation to physical and mental health comorbidities.

3.2.4 Health Policy

Policy targets aimed at shaping positive food environments, healthy eating, food security, physical activity, affordable childcare and housing, social assistance, as well as health and income equity[580] have potential to help prevent and manage physical and mental health comorbidities.

Mental health policy has the potential to better shape the prevention and management of physical and mental health comorbidities. However, mental health services are poorly resourced and interventions for those with mental health problems are reported to be inadequate. Pharmacotherapy, particularly antipsychotic medication use, is also the mainstay of therapy programs, but has important cardio-metabolic risk factors. While the implementation of routine metabolic screening and monitoring practices have improved, reports in the literature suggest much more can be done to ensure these are consistently offered.

There is much to be gained from using positive mental health approaches to prevent and manage physical and mental health comorbidities. First is the recognition that 70% of mental health problems in Canadian adults have their onset in childhood and adolescence[522] and these are linked to earlier childhood experiences. Many non-communicable diseases also are linked to earlier life experiences and are shaped during key developmental periods such as emerging adulthood.

3.2.5 Health Research

There is a need to advance knowledge in the screening, prevention, characterization, and management of different physical and mental health comorbidities. Research that addresses knowledge gaps about appropriate tools for mental health screening in different physical health conditions and among equity-seeking and priority populations can help to identify the benefits in relation to anticipated improvements in one's overall health. Measures that can estimate trends in physical and mental comorbidities are also needed. In particular, assessments that can reduce the variability across tools used for assessment and diagnosis will help to accurately monitor trends and develop appropriate interventions.

There is much work that could be done to better understand the shared etiology of mental and physical health comorbidities. For example, a better understanding of genetic underpinnings and the role of the human gut microbiome could lead to targeted interventions and more personalized approaches to care. Better knowledge about integrated care implementation and outcomes are needed, and innovations such as those in nanomedicine, mobile health, and imaging need to be critically evaluated.

While there is evidence that the collaborative care model is effective in improving mental health outcomes, including substance use problems,[523] it remains unclear what components of the model are necessary for success. Future research could aim to investigate what combination of components in the model might be most effective. In addition, investigations aimed at developing data systems that provide reliable and valid mental and physical health services data that can be analysed in an integrated and strategic manner may better inform provision, policy, and future research.

Finally, future research about physical and mental health comorbidities needs to be to co-produced with those who have lived experiences, their families, and carers. Recently, the Canadian Institutes for Health Research introduced initiatives that fosters patient-oriented which aims to focus on patient-identified priorities which are believed to lead to better health outcomes.

4. Which Interventions Work? For Whom? How? In Which Contexts?

Realist synthesis begins with testable program theory of how a program should work in the real world. Evidence, from secondary data from documents, is used to refine and shape the program theory. For this report, an adapted a socio-ecological framework (Figure 4.1) with program theories to explain mental health promotion at different systems levels, beginning with the policy level is used as a frame of reference for the rapid realist synthesis. It is important to note that boundaries are permeable across systems levels. This section of the report is subdivided into categories that correspond with the systems levels of the framework.

4.1 Level 1: Healthy Public Policy for Mental Health: Mental Health Promotion/Mental Health in All Policies (MHiAP)

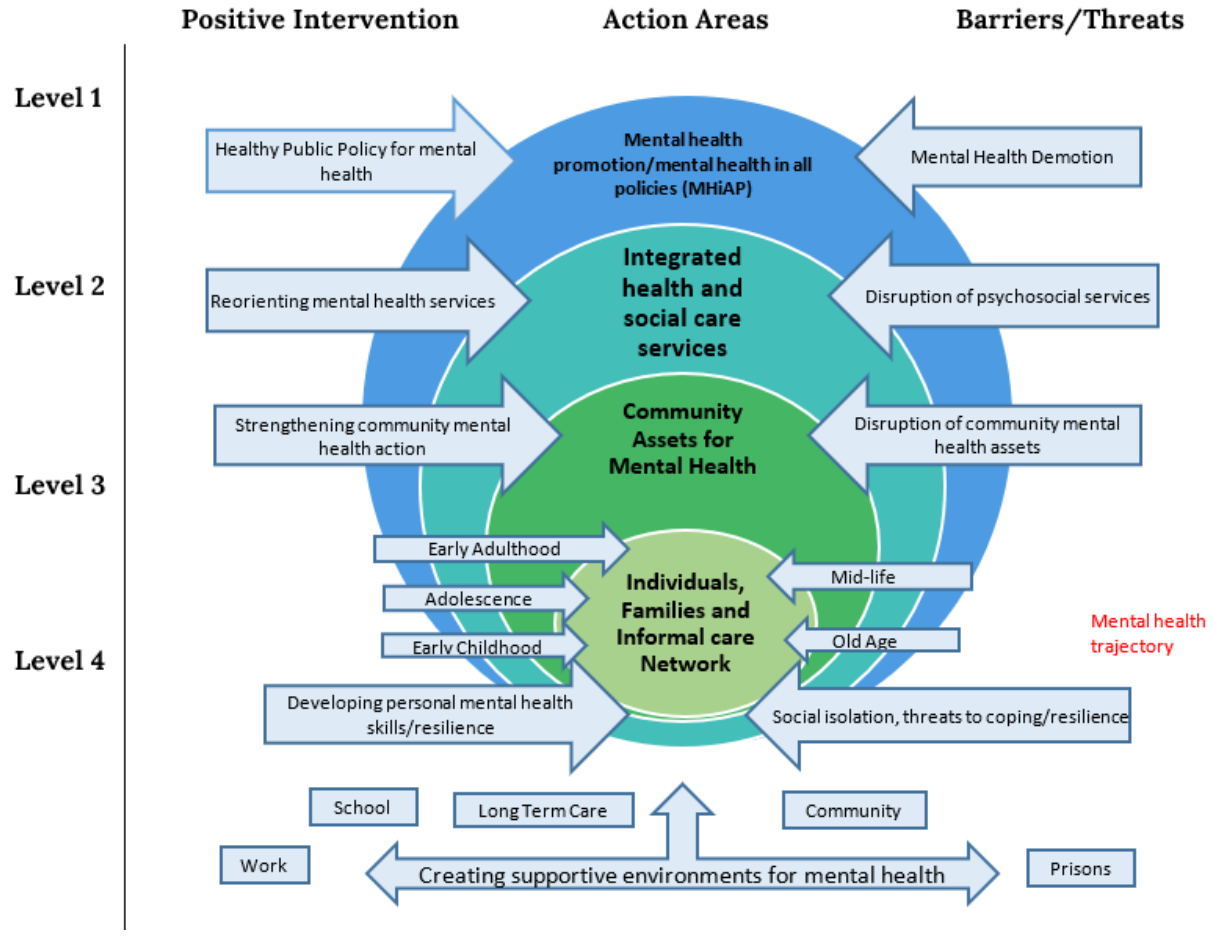
In the first, outer ecological layer of the model, we will discuss an overarching policy strategy for promoting mental health, both for people living with chronic conditions, and at risk for, or living with, mental health stress and illness, *and* for people living with serious mental illnesses and at risk for, or living with chronic physical diseases. However, in line with our health promotion emphasis, and our adoption of the dual continuum model of mental health, we include the latter two populations as part of a general population mental health promotion strategy, that focuses not just on people who are ill, or at risk of getting ill (mentally or physically), but also on promoting general mental health flourishing in the wider population. This approach recognizes that even people living with mental and physical illnesses have the potential to live a flourishing, joyful life, and that while we must try to prevent and manage illness, we must also try to promote and strengthen health assets, including structurally (social, economic and cultural) supportive environments, community resilience and life coping skills. Below is our program theory for how MHiAP is meant to work:

A Program Theory for Mental Health in All Policies (MHiAP)
A MHiAP strategy → Intersectoral governance for mental health → Changes in policies (usually signaled by some sort of strategic document/plan) → policy actions (legislative, regulatory, budgetary/investment tools) to promote mental health → Impact on social determinants of mental health → Improved mental health outcomes (e.g. increased well-being, happiness, improved coping and resilience, reduced mental stress, reduced incidence of mental illness, reduced harms from substance misuse, reduced incidence of suicide).

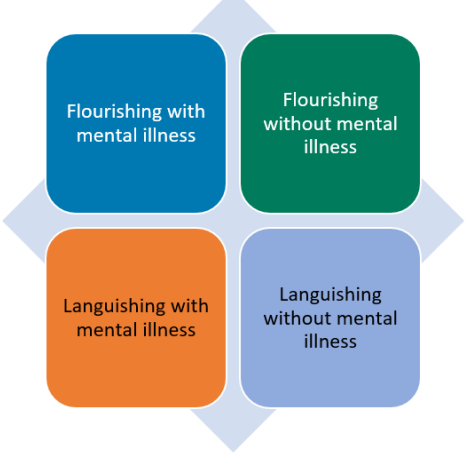
Below, is an outline of what we know about how HiAP is adopted as a policy agenda, is implemented as an intersectoral governance strategy, and sustained as an institutionalized

process that leads to better outcomes, in terms of what types of combinations of contexts-mechanisms-outcomes lead from one part of the theory to the other.

Figure 4.1: A Socio-ecological model of mental health promotion interventions + the Dual Continuum Model of Mental Health



The Dual Continuum of Mental Health



Agenda Setting for a MHiAP Strategy

A 'Health in All Policies' approach to intersectoral collaboration has been gaining ground globally as a policy-level agenda aimed at addressing the wider social determinants of health. Advocates of HiAP highlight the importance of mental health promotion as central to successful HiAP approaches, and as a means to contribute to addressing health equity and inequality.[9, 10] Conversely, advocates of mental health promotion have identified HiAP as a key policy framework for advancing mental health and physical health.[11,12] Evidence discussing the implementation of HiAP is currently limited, as much of the explicit policy initiatives have been initiated only recently; however, there is a growing field of work that tracks well with a realist approach[524,525] and can contribute to identifying C-M-O-Cs that will inform conditions where HiAP approaches will make substantive positive contributions to societal well being.[526,10] Of note are Shankardass et al. (2018),[527] who adopt a realist/systems approach to HiAP and identify four key sub-systems relevant to successful HiAP initiation, implementation and sustainability (Executive (leadership); Intersectoral (across sectors); Intrasectoral (within sectors); and, Extra-governmental). Within these sub-systems there are several components that the authors argue are mechanistically related to successes/failures in HiAP adoption/uptake, implementation and sustainability. In the Canadian context, we can identify in the Executive sub-system, led by policy elites, the lack of an explicit policy agenda for implementing HiAP, either at the federal level or in most provinces (with the exception of Quebec and Newfoundland).[528,529,10] This is an ongoing reality recognized almost a decade ago (Greaves & Bialystok, 2011). Some advocates of HiAP have recognized the deficit in the health promotion and population health fields of a theoretically reflective understanding of the policy development process in relation to work on the social determinants of health,[530] and so have began to integrate a more sophisticated understanding of the latter in their HiAP work.[531,526] Following Exworthy (2008),[530] many have adopted a policy 'streams' (problem, policy, political) process approach based on the work of Kingdon (2011),[532] which is premised on the idea that 'policy windows' are opened when these three streams are coordinated, which can come about partly by chance, and partly through the strategic action of policy networks and policy entrepreneurs.

Recent research shows there is emerging interest in Canadian policy networks in pushing forward an HiAP agenda, with strong leadership from the Quebec government and the National Collaborating Centre on Healthy Public Policy.[533] While mental health has been on the HiAP agenda in most of the key background documents,[11] it suffers from a lack of parity in focus in relation to physical health conditions within the broader field of health promotion, as it does in relation to the health care system's prioritization of physical health. This may lead to some pessimism regarding the prospects of a Mental HiAP agenda, as it requires overcoming the burdens of reversing disproportionate awareness, attention and resources to both health care over health promotion, and physical health promotion over mental health promotion, as well as the other issues associated with HiAP implementation.[526,10]

Based on a review of the emerging literature on HiAP adoption and implementation, we propose five simple rules for successful HiAP initiation: 1) Developing a shared language and fluency around a broader understanding of 'health' to include well-being and happiness, and general welfare; 2) Linking evidence for how HiAP initiatives are able to

contribute to sustainable economies and sustainable health systems (both theoretical and empirical); 3) Having an 'entry point' to initiate an HiAP agenda; 4) Developing 'win-win' scenarios, goals, and objectives across sectors;[13] and 5) Building and fostering long-term collaborative partnerships and engagement with intersectoral stakeholders. See Figure 4.2.

Figure 4.2: Five Simple Rules at the Policy Level

The notion of simple rules comes from complexity science, and the study of complex systems, such as health care systems.[534,534,535,536,17] Given the unpredictability, diversity and variability of complex systems, prescriptive rules do not provide the flexibility needed to adapt to changing conditions. Simple rules are guidelines for successful systems adaptability. Based on our realist review of evidence, we propose that these five simple rules can act as linkages across systems levels. They are particularly critical, at the policy level, to influence change in language and in partnerships and engagement at other systems levels--setting the stage.

While the simple rules approach is sometimes accused of avoiding 'big bang' solutions,[537] and encouraging incrementalism, this would be an inaccurate characterization of the complex systems approach. In fact, the Canada Health Act itself can be read partly as both a 'big bang' solution *and* an example of using broad principles of action to guide or steer divergent policy implementation processes in the provinces. Despite the perennial concerns in Canada about threat to the principles of Medicare, what is more remarkable, is that despite the autonomous powers of the provinces in health system development, there

has been so much relative stability and coherence around the central principles, and this is reflected strongly in Canadians' deeply valuing those principles, making any major reversal in direction toward a less universal, less public system politically unviable.[538] Evidence shows that rather than reversing direction, Canadians overwhelmingly support the expansion of the principles of Canada's universal public health system to cover things like prescription medication for all.[539] This latter example shows how, given the right policy window, a long term policy issue network, with a well-framed communications strategy, can quickly galvanize public opinion to support a fairly major policy change. As the Final Report of the Advisory Council on the Implementation of National Pharmacare demonstrates, this combination of broad policy frameworks, with specific sets of universal principles and a more complex, time-staggered, jurisdiction-variant mode of implementation, is a model of policy change that works, even (or especially) in highly complex constitutional federations like Canada.[540] It is important that, particularly at the federal level, policy-makers continue to build on the success of the Canada Health Act, and develop policy coalitions around expanding coverage that is universal, comprehensive, accessible, portable and public, to a wider set of services for the 21st Century.

In the Canadian context, not only is mental health well placed to be included in any HiAP policy agenda, it may in fact be the key entry point for raising the awareness and urgency of a HiAP approach at the federal and provincial levels. First, with the help of key policy elites, such as Senators Kirby and Wilson, and with the establishment of the MHCC, much of the foundational work in boosting awareness has already taken place. In this collective work, Canadian researchers, practitioners, policy-makers and people with lived experience have worked on developing a more inclusive, shared language around mental health, that by its nature tends to be less 'deficit-focused' and more positive and strengths-based (which relates to simple rule 5 above).

The dual or 'two'-continuum model, depicted at the base of Figure 4.1, is taken from transformative ideas in the MHCC document, Changing Directions, Changing Lives: The Mental Health Strategy for Canada.[507] The model is based on conversations with mental health policy-makers who recognized that new, strategic directions for Canadian mental health policy will only happen with shifts in public perceptions of mental health-mental illness. These policy-makers also acknowledged how language is one critical determinant in how we think about and how we describe mental health-mental illness. The two-continuum model is a "road map" for mental health transformation in Canada.[19] The model proposes that to some degree, every individual is somewhere on a continuum of mental health and illness. This holistic approach recognizes that at any point in an individual's life, mental health needs may shift, as is true of our physical needs. The purpose of this model is to decrease stigmatization and to promote awareness that "at the core we're all the same" (p. 465). Even the language of 'flourishing' points toward a rhetorical broadening of focus and is likely to overcome some of the tendency of advocates from the health sector to slide back into an exclusively epidemiological focus on patterns of disease, which disregards health as a resource for everyday life. Second, the MHCC and others have done very important work establishing the evidence base for investments in mental health promotion (which relates to simple rule 2 above). Finally, existing cross-government, intersectoral work in mental health in Canada (e.g. The 'Tripartite Agreement' on improving mental health and wellness services between the First Nations Health Council, the Government of

Canada and the Province of BC; the Public Health Agency of Canada's Mental Health Promotion Innovation Fund) can be used as a platform for demonstrating how win-win scenarios can be developed and implemented (which relates to simple rule 4 above). In this respect, mental health should be considered foundational to a HiAP approach, just as a HiAP approach should be considered foundational in furthering the promotion of mental health as a critical resource for everyday life.

In lieu of a full blown, explicit HiAP initiative, governments continue to pursue a variety of mainly issue-focused intersectoral collaboration strategies, which have an ongoing direct impact, and indirectly, provide a context for any future more comprehensive approach, coordinated across all health-relevant policy development, implementation and evaluation. However, it is clear from the literature that an explicit HiAP approach has several advantages over ad hoc intersectoral collaborations. First, it embeds formal governance mechanisms with clear terms of reference to develop and sustain intersectoral policy-making for health across governments. This encourages accountability through regular reporting processes, and can lead to establishing frameworks for implementation and evaluation of HiAP initiatives. Second, it provides an opportunity for government to coalesce and concentrate skills and capacities for intersectoral collaboration (e.g., Canada has many experienced professionals and policy practitioners with intersectoral collaboration experience, yet they tend to be dispersed in various parts of the policy system), and to encourage training in the implementation and evaluation of HiAP. Finally, formal HiAP governance mechanisms and skilled practitioners of intersectoral collaboration can act as much needed supports and facilitators of ongoing, issues-based initiatives. The latter can also serve as advocates and conduits to higher-level policy forums, such as Cabinet-level meetings, and Deputy ministerial committees, where executive leadership is enacted and major social investment strategies are decided upon.

4.2 Level 2: Reorienting Mental Health Services: Integrated Health and Social Services

Beyond the HiAP approach, which tends to focus on 'upstream' population health and the social determinants, a key role for public policy is to provide the regulatory, legislative and financial context for the transformation of health and social services more broadly in society. For Canadians, 'health reform'[14] is an ongoing reality, that is complex and multi-faceted, with varying objectives across provinces, and widely differing governance strategies and outcomes. However, a common recurrent theme is the need to develop *integrated, collaborative systems of health and social care* to address the increasingly complex needs of an ageing population, with the concomitant multimorbidity of chronic diseases, both physical and mental being the driving force of this complexity. While these efforts require many transformational changes at the health and social service/organizational level, which will be addressed in the following section, there is a strong role for high-level policy in successfully moving towards the ideal system. It is generally acknowledged, based on decades of research evidence,[15] that comprehensive primary health care, as originally outlined in the Alma Ata Declaration,[16] is the overarching framework for efficiently, effectively, and equitably organizing health and social services in order to produce optimum health in populations.

The **program theory** at this level is: by providing *universal financial coverage*, *under government control and regulation*, with *equitable distribution of services*, *comprehensive coverage*, and *with low or no co-payments*, then you attain "*greater first contact access and use*, *more person-focused care over time*, *greater range of services available and provided when needed*, *and coordination of care.*" (Starfield, 2012, p. 20).

Canadian provincial governments, constitutionally designated to provide health, education and most other social services to Canadians, have operated since 1966 under the *Medical Care Act*, and since 1984 under the *Canada Health Act* (CHA), which offers financial incentives to provinces to provide universally accessible, comprehensive and equitable health insurance coverage to their populations, although limited mainly to physician and hospital-based services. In relation to mental health services in particular, the protection provided by the CHA has serious gaps, leaving "a lack of universal coverage for psychological counseling, prescription drugs, home care and other community supports".[541] Along with other initiatives to expand Canada's commitment to providing universal coverage of health services, such as the 'Pharmacare for All' movement,[540] the Federal Government should use its legislative, regulatory and fiscal muscle to provide leadership on expanding Canadians' access to psychological services, improved home care through publicly funded, relational care-based assisted living and long term care arrangements, and community-based extended health and social supports, that go beyond the narrow, physician-determined concept of 'medical necessity'. In Figure 4.1, we have depicted lifespan mental health needs (and the contexts where you find these needs) as the foundational level of the socio-ecological framework.

At the provincial level, a commitment to supporting collaborative, integrated health and social care systems, means dedicated financing, legislative and regulatory changes. There are multiple models of practice available to help implement such changes, such as: continuing community care, collaborative care models (CCMs), the primary care behavioral health (PCBH) model;[542] patient-centred medical homes, community health centres, community mental health teams, multispecialty community providers, Local Integrated Health Networks (LHINS), primary care networks, and many others. There are also multiple ways of remunerating physicians and other health and social service providers in order to procure their services, including improving existing fee-for-service agreements, capitation formulas, salaried contracts, and pay-for-performance. There seems to be no 'silver bullet' in terms of specific interventions that will 'solve' the integration problem. However, a combination of the CCM and the PCBH models might provide an optimal combination to address a wide range of mental health issues at the primary care level.[543]

Nevertheless, at the policy level, there does seem to be some generic lessons based on the underlying principles of health system reform, that have started to be synthesized over the past two decades of work in health system change and implementation science in integrated care systems.[544,545,546,547,14] The first common finding is that while 'integration' sounds like a simple plea, it is not. Many authors have noted the ambiguity and complexity inherent in the call for 'integrated care'.[548,549,547] Kodner breaks down the complexity into five dimensions (foci, type, level, breadth and degree), each with several sub-dimensions.

Nevertheless, despite the ambiguous nature of this "imprecise hodgepodge" and the fact that "not only is it a difficult concept to understand, but also one that in the final analysis is enormously challenging to implement and manage" (p.12-13),[546] we see consistent advocacy, from even the more skeptical researchers, for its pursuit by policy-makers in order to address the increasingly complex care needs of their citizens. Part of the reason for this seeming paradox (ambiguity and contradictory empirical support, yet consistent advocacy and commitment), is that most experts in this amorphous field recognize that 'integrated care' signifies an entry point at this systems level for transformation--from thinking about (predominantly) physical health needs to physical-mental health needs. The simple rules from Figure 2 may apply at this level as well. The right integrated care model has the capacity to provide a shared language and opportunities for greater collaboration and generation of win-win integrated care (mental-physical) scenarios (rather than a set of prescriptive interventions/directives).

One influential Canadian framework for integrated care, notable for its continuing/community care perspective was developed by Hollander and Prince after extensive consultations with experts and policy/decision-makers across Canada (2008).[545] What makes this framework interesting is that it is one of the few integrated care frameworks that starts from the non-medical community level of care, and then asks what collaborations need to be made to primary care and hospital-based systems. Most other frameworks[544,546,550] start from the opposite perspective, starting with existing systems of primary care, and expanding them out to include integration with broader community and social services. In this framework, 'client-centred' care contrasts with provider-driven objectives. This framework is based on commitment to a comprehensive range of services (psychosocial, physical care) with sufficient and sustainable funding, based on what clients need--first and foremost (pp. 48-49).[545] We believe this integrated care framework can work if it is backed with real funding commitments and specific investments in administrative functions and information technology supports to facilitate transformational change processes.

Integrating care via simple rules allows relatively autonomous actors to use their contextual knowledge to come up with creative implementation solutions. At the integrated care level, there are some important contextual factors to consider. In order for clients to have a voice in decision-making (e.g., priority physical and social/mental needs), power differentials need to be 'smoothed.' Differential power dynamics impede effective collaborative practice among different service providers,[17] but they also relegate clients to a marginalized role with respect to decisions around their care needs. Physicians are considered the top of the healthcare hierarchy, and this conceptual approach can break the success of any reform program or change initiative.

Canadian policy researchers have understood for a long time that physicians play a central role in the health system, and that the history of the Canadian health system's evolution has certain path-dependent features that make negotiations with physician associations often difficult and protracted.[551,552,537] As Best et al.[17] noted 'physician engagement' in transformational change processes is still a foundational principle for any successful health system transformation, even though it is important to emphasize that this has less to do with their intrinsic relative value in an integrated system of care (a key indicator of a

transformed system would be an equitable rebalancing of the value assigned to the many different professions and service workers that form part of an ideal multidisciplinary care team), and more to do with their strategic institutionalized positioning within the health care system. Sociologists of health have developed very influential theories of medical professional power,[553,554,555] and have debated the relative dominance and autonomy of physicians in health systems across the world, under changing political and economic conditions. In Canada, physician autonomy still characterizes the relationship of physicians to the healthcare system as a whole, and furthermore, that this sustained autonomy is often a factor in the difficulty of major system transformation.[14]

Rather than a confrontational approach, tackling the instrumental self-interest of physicians in terms of their financial and work autonomy, governments have tended to try various efforts to enrol them as collaborators, based on the shared values of Quadruple Aim. Quadruple Aim is often used as a means to rally physicians and other healthcare providers around universal quality improvement healthcare goals of enhanced population health, enhanced patient experiences, enhanced cost effectiveness and enhanced service provider experiences (i.e., joy at work).[556] Quality councils in Canadian provinces and territories promote physician engagement in Quadruple Aim initiatives, including leadership development, knowledge development and communications strategies. Education and financial incentives for integrated care development may be generating some power shifts.[557,558]

4.3 Level 3: Strengthening Community Mental Health Action: Community Assets for Mental Health

At this systems level, community "assets" for mental health are the chosen foci, as they bring together three important theoretical approaches to mental health: mental health promotion;[18] the two-continuum approach;[19] and, the Canadian Mental Health Association's framework for support approach.[20,21] Morgan & Ziglio[559] define health assets as: '*as any factor (or resource) which enhances the ability of individuals, groups, communities, populations, social systems and/or institutions to maintain health and wellbeing and to help to reduce health inequalities*'. This approach, founded on the salutogenic[560] understanding of health and well-being has been demonstrated as theoretically compatible with a mental health promotion approach, as well as with the two-continuum model and the framework for support. It has also underpinned a relationship with positive psychology,[561] where it is seen as the umbrella concept that encapsulates a variety of key aspects and dimensions of positive psychological development, including coping, sense of coherence, flourishing, well-being, and many others (Figure 4.3).[562]

Figure 4.3: Salutogenic Understanding of Health and Well-Being

Van Bortel et al.,[563] in a recent review of the salutogenic approaches application globally, identify community health assets as including, among other things: "family and relationships or supportive networks, intergenerational solidarity, community cohesion, religious tolerance and harmony" (2019, p. 2). Building on these connections, we can derive a tentative program theory as below:

> The **program theory** at the community level is: by helping to *co-create*, *strengthen and sustain community mental health assets*, people can be supported to live happy, joyful, flourishing lives, whether or not they are living with mental or physical illness *and* they can be empowered to help co-produce and shape the mental health services they receive in community through context-appropriate co-produced mental health service planning

As Trainor et al.[21] argue, this means shifting from a 'service paradigm' to a 'community process paradigm', where not only is it recognized that community and personal resources are critical for mental health promotion and recovery, but that the whole system needs to shift to a person-centred approach that develops services from the perspective of the person-in-community, rather than from the perspective of the service professionals and administrators exclusively. This is a key way that this program theory connects to the *integrated health and social services level*. It is clear from the literature on integrated care, that a major failing of implementation is often related to the failure to make this paradigm shift that is recommended by Framework for Support model. As a recent review of integrated care makes very clear, there are real tensions between a political economy of health care/organizational perspective that is aimed mainly at integrating care to deal with cost pressures within the overall health and social care system, and that of a truly person-

centred care approach. The authors conclude: “Recognizing rather than resolving these tensions would mean accepting that relationship-based care offering time and space for patients to be seen and heard is likely to be a necessary (if not sufficient) condition that can contribute to the achievement of integrated patient care. Moreover, provision of this care needs to be understood as not necessarily aligning with organizational or system objectives of reduced cost.” (p. 480).[547]

Another tension that has been identified in relation to the assets-based approach, is that it’s reliance on concepts of community cohesion and social capital can lead, if not reflexively and critically implemented, to the marginalization of stigmatized members of the community and thereby increase health inequity (Wakefield & Poland, 2016),[564] particularly if the social capital resources are mainly of the ‘bonding’ type which can reinforce exclusivity and homogeneity, as opposed to ‘bridging’ and ‘linking’ social capital that operates to strengthen ties between heterogeneous groups within the community and make linkages between marginalized groups and people in positions of power that can ally with them.[565] Part of the reason for emphasizing multi-level approaches, is that leaving too much responsibility for producing mental health and well-being to the community and individuals, without paying attention to the wider socio-economic context (influenced profoundly by macro-level public policy), means that community assets can be overwhelmed and even deteriorated by too much stress on their resources and capacities for resistance to a policy context that far from being supportive of mental health promotion, can often actively undermine it.

In a Canadian community-based participatory action research realist evaluation,[22] collaboration across a community depended on power-sharing and co-governance. It took time for partners to establish trust in each other’s commitment to power equity. In a recent realist synthesis on inter-organizational collaborations,[566] inter-organizational collaboration is defined as a “negotiation between people from different organisations with a commitment to working together to secure improvements which could not have been achieved by acting alone (Dickinson and Glasby 2010). This realist synthesis proposes a series of context-mechanism-outcome configurations (CMOCs). Many of the CMOCs are similar to those derived through community-based participatory action research.[22] Table 4.1 contains our adaptations of inter-organizational CMOCs. Based on our review of literature at the other systems levels, there is evidence that these “collaboration” CMOCs are relevant to each systems levels and our simple rules approach.

4.4 Level 4: Developing Personal Health Skills/Resilience: Individuals, Families and Informal Supports

This level looks mainly at the personal resources individuals utilize to help them develop resilience, hope, confidence and well-being. Below we see the model the Framework for Support developed for what they call the Personal Resource Base, which again is very compatible with a mental health promotion, a two-continuum model, and the assets-based approach. Although the authors of the Framework have developed their models for people living with mental illness, this approach clearly applies to the general population other than perhaps the ‘practical understanding of the illness’ dimension, and certainly to those living

with chronic physical conditions that might not yet have developed a mental illness. There are many resources and interventions that aim at strengthening individual coping skills and resilience to bolster mental health and prevent the worst impacts of mental illness (e.g., self-aid, mutual aid, via peer support networks).

Figure 4.4: The Personal Resource Base[21]

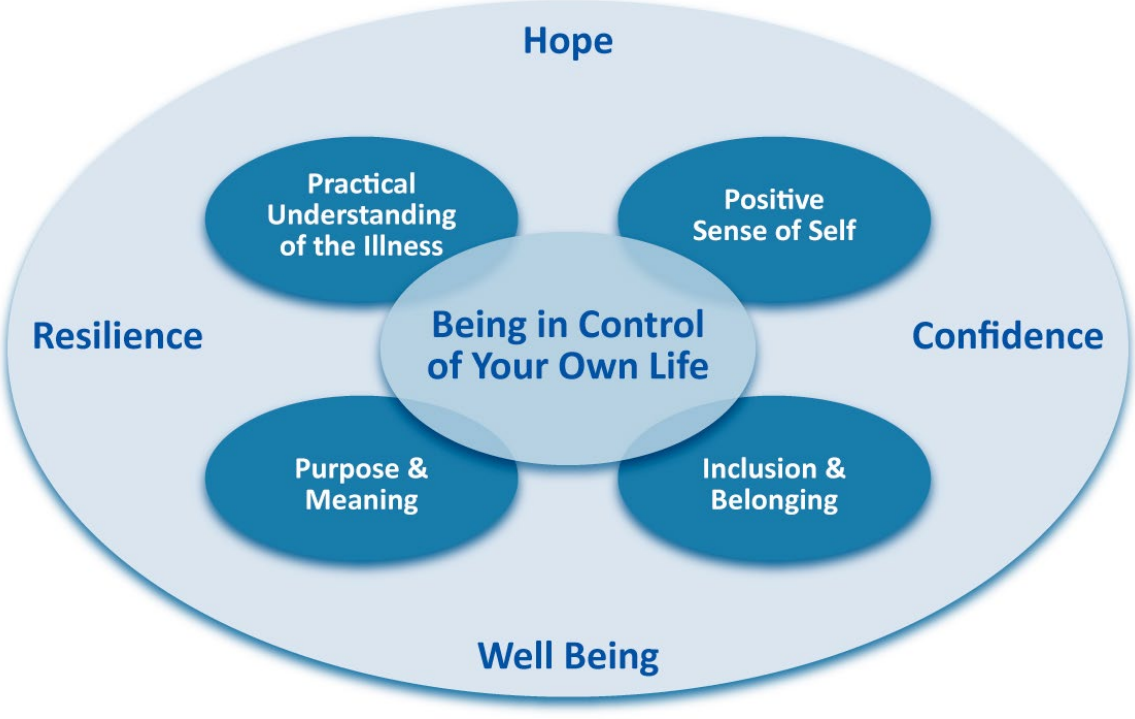


Table 4.1. Context-Mechanism-Outcome (CMO) Configurations to Complement Simple Rules	
Trust	Trust develops over time as partners at different systems levels earn trust through respectful, reliable interactions. **CMO**: High trust (context) creates partnership synergy (mechanism) leading to successful outcomes at all systems levels (e.g., mental health services delivery).
Formalization	Policy, especially at the highest level (national government) is an important context for successful outcomes at all systems levels. **CMO:** Formalization through policy (context) creates greater initial trust (mechanism) leading to greater uptake of mental health inclusion, mental health awareness at all systems levels.
Shared Vision	Shared vision, values and goals help bind diverse stakeholders at different systems levels. **CMO:** Having a shared vision (context) reduces the potential for conflict (mechanism) leading to improved trust/high trust (outcome) at all systems levels.
Commitment/ Accountability	Commitment and accountability are evidenced by partner investment. Is there evidence of preparation to act and to be accountable for actions taken? This is a litmus test for partners at each systems level. **CMO:** Evidence of preparedness and accountability (context) results in reduced conflict (mechanism) leading to greater trust (outcome) among partners at each systems level.
Power	Power differentials are a significant threat to collaboration at every systems level. **CMO**: Power imbalances among partners (context) creates partner domination (mechanism) leading to reduced trust, blocked mental health services delivery at each systems level.
Faith	Faith is belief and confidence in others-an important ingredient/context at every systems level. **CMO:** High faith (context) creates partnership synergy (mechanism) leading to enhanced mental health services delivery at each systems level.
Authenticity	Authenticity or genuineness is an important leadership component. It is also a necessary component of partner collaboration at any systems level. **CMO**: Authentic collaboration of partners (context) increases faith among partners (mechanism) leading to increased agreement over common goals, such as mental health services delivery (at each systems level).

Leadership	There need to be effective leaders at each systems level. Effective leaders are authentic/genuine and they use positive psychology approaches to move others towards collaboration--at every systems level. **CMO:** Positive, authentic leaders (context) create more effective integration of different partners/cultures (mechanism) leading to greater trust among partners at each systems level (outcome).
Culture	Culture is an amalgamation of values, beliefs, attitudes--all influencing what we say and do at any systems level-national to individual. **CMO**: Cultural closeness or coherence (context) decreases conflict (mechanism) leading to greater trust among partners at each systems level.
Flexibility	In complex systems, there is a lot of unpredictability. At each systems level, there needs to be flexibility with respect to directives, guidelines, actions-so that partners can adapt within their own contexts. **CMO**: Greater flexibility in directives/guidelines (context) increases the likelihood of goal achievement (mechanism) leading to more efficient, effective mental health services delivery (outcome) at each systems level.
Entry Point	Within complex systems, there needs to be a designated entry point as a frame of reference for partners. **CMO**: Designated entry points (context) provide clarity (mechanism) leading to more confidence (e.g., consistent model for mental health services delivery) (outcome) at every systems level.

5. Highlights and Recommendations

The intent of this report was to synthesize knowledge about common physical and mental health comorbidities related to their prevalence, incidence, and healthcare-related cost estimates across the lifespan and among priority and equity-seeking populations. In addition, the aim was to conduct a rapid realist review to help determine interventions that may work in different contexts and for different people.

A number of conclusions and recommendations arise from this review.

5.1 Health Education, Practice, Programming, and Policy

- All of the physical and mental health comorbidities highlighted in this report have shared biological, psychosocial, and environmental etiological pathways. Policies and preventive programming that are aimed at these pathways, particularly at psychosocial and environmental targets, are recommended. These should include addressing resource allocation to mental health promotion, screening and monitoring practices, and interventions
- Policies aimed at life course, population health, and mental health promotion have the potential to prevent or delay the development of physical and mental health conditions. Exemplars of policy targets include food environments, healthy eating, food security, physical activity, affordable childcare, affordable housing, social assistance, employment, as well as health and income equity
- Comprehensive, integrated, and tailored management programming that include shared decision-making will help to address the multiple underlying factors contributing to physical and mental health comorbidities. At a broader level, these practices can reduce health system costs
- As part of integrated health programs and practices, stepped-care models show potential to further optimize care for those with physical and mental health comorbidities. To facilitate the delivery of these approaches, supportive administrative and reimbursement structures will be needed that are inclusive of allied health professionals who can work collaboratively with other practitioners to support the end-user's physical and mental health needs
- Public health campaigns, which help to dispel myths and stigma associated with having chronic conditions, could minimize potential of mental health impacts that occur around the time of diagnosis. Exemplars of positive messaging could include showing individuals with health conditions leading healthy productive lives and working effectively with their health care team
- Better integration of primary care with social services is needed to address the multi-faceted complex needs of those with mental and physical health comorbidities. These services need to be accessible, particularly to groups that face barriers to access such as those residing in rural and remote communities. Established effective models of care applied to mental health such as peer support approaches may help to further support the needs of individuals with physical and mental health comorbidities

- Collaborative care models need to include all health disciplines including allied health professionals and substance use disorder specialists
- Health research should continue that informs practice, programming, and policy and include ongoing exploration of the determinants of health condition comorbidities, optimal delivery and integration of health and social services, and exploring policy alternatives to optimize population mental health should continue

5.2 Physical and Mental Health Comorbidities

Arthritis

a. Osteoarthritis (OA)

- Case finding for depression in people with OA has been recommended by the National Institute for Health and Care Excellence[50]
- To optimize psychosocial well-being, models of care should incorporate strategies aimed at maintaining function, using positive language to describe the condition, increasing social participation, and maintaining employment
- Multi-modal interventions that include cognitive behaviour therapy, neuroscience education, centrally-acting drugs, and exercise could improve both OA-related pain and mental health[70,66]

b. Rheumatoid Arthritis (RA)

- Psychological evaluation and care are recommended to be among the therapeutic objectives.[86] Clinicians recommend use of the Hospital Anxiety and Depression Scale (HADS) for screening,[86] however its validity and reliability in this population has not been assessed
- Better physical and mental health outcomes for those with RA are likely to result from integrated mental health care provided within routine clinical practice[567]
- The goals of care should aim to engage and motivate the person toward goal-setting, attend to psychological needs of caregivers, generate trust and empathy, negotiate treatment options, and promote self-efficacy[86]

c. Psoriatic Arthritis (PsA)

- Screening tools used include the HADS, General Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9); however, validation studies are needed[93]
- Treatment escalation driven by non-inflammatory symptoms may increase adverse events and appears to provide modest improvements in mental health-related areas (e.g., quality of life)[98]
- Joint guidelines of care recommend people with psoriasis should be informed about the association of psoriasis and anxiety and depression and asked about signs and symptoms[100]
- Psoriasis-specific therapy is recommended as a measure to improve psoriasis-associated anxiety and depression in individuals with psoriasis[100]

Cancer

- Screening is recommended at different stages of cancer (e.g., pre-treatment, periodic follow-ups post-treatment, and survivorship periods)
- Important considerations in cancer care are risk of potential re-traumatization of PTSD when individuals undergo pelvic, breast, or rectal examinations. Relapses of a depressive disorder may occur after mastectomy, and relapses of manic or depressive episodes in bipolar affective disorder may occur due to essential treatment with corticosteroids
- Addressing underlying secondary or disease-related causes can promote mental health. Examples included treating symptoms such as hypothyroidism that arise from radiotherapy with head and neck cancer and vitamin B_{12} deficiency after pelvic irradiation
- Use of antidepressants should be determined on an individual basis; SSRI are suggested to have a positive safety profile[140]
- Collaborative care appears to be more effective than pharmacological and psychological interventions for depression reduction[144]
- While some complementary therapies such as lavender, passionflower, and saffron may produce benefits comparable to standard anxiety and antidepressant medications. These results need to be confirmed with larger RCTs.[141]
- Life review programs may help reduce depression and anxiety[145]
- Stepped care approaches for mental health interventions in cancer are recommended and should include the following considerations:[146]
    i. Psychotropic medications should be guided by clinical parameters, particularly interactions with chemotherapies, to identify specific contraindications;
    ii. Psychological therapies such as CBT can help in understanding the thoughts, feelings, and behaviours that can cause or maintain symptoms of depression or anxiety (e.g., treatment refusal, avoidance behaviour, or excess reassurance seeking);
    iii. Providing availability of specialist psychological therapy with appropriate expertise. Therapeutic expertise needs include complex illness beliefs, challenging side effects (e.g., psychosexual), physical disfigurement, and end-of-life issues.
- Integrated mental and physical cancer care approaches are also recommended. One reported model of the UK NHS Cancer Strategy includes:[147]
    i. Collaborative screening and treatment;
    ii. Cancer clinical nurse specialist delivery of supervised CBT interventions for depression, and
    iii. Guidance to GPs by liaison psychiatrists to optimise the prescribing of antidepressant medication.
- In Canada, examples of integrated mental and physical cancer care approaches exist.
- Better integration between primary and tertiary cancer care is understood to lead to improved coordination, continuity and quality of care.

- There is some preliminary evidence that comprehensive education and care (CEC) programs are more effective than basic health education and rehabilitation to improve anxiety and depression in those with hepatocellular carcinoma who underwent surgical resection[150]
- Psychotherapy combined with psychoeducation and exercise appears to be more effective in improving depressive symptoms when compared to psychoeducation alone[151]

Cardiovascular Disease (CVD)

- Various studies recommend that all people diagnosed with CVD be screened for depression, particularly at key periods such as post myocardial infarction or major surgical interventions
- For people that have had an acute coronary syndrome, depression screening is recommended while in hospital and rescreening should occur two months after the acute event.[182] Individuals with chronic heart failure also have a high frequency of depression and should be screened at least annually
- Longer-term face-to-face CBT has shown benefit for improving depression.[210] Internet-based CBT has limited evidence and has been indicated to be unsuitable for moderate-to-severe depression or anxiety.[210] Furthermore, treatment adherence may be low.[209]
- Cardiac rehabilitation programs for CAD and congestive heart failure for older adults (64 years+) offered in their home is effective for reducing depression. Tailored interventions combined with psychosocial interventions are likely to be more effective in decreasing depression in older adults with heart disease compared to usual care[223]
- For those with CHD, aerobic exercise in a group setting improves depression and cardiovascular function[206]
- CBT in combination with exercise may help improve depression symptoms[211] and reduce subsequent cardiovascular events[212]
- Anti-depressant medications are reported to improve depression in individuals with CVD, however, efficacy needs to be balance with potential risks.[215] For example, tricyclic anti-depressants have been shown to lengthen cardiac myocyte action potentials[215]
- Combination therapies appear to reduce depression after ACS. Combined therapeutic approaches of stepped care have been reported to be effective in improving depression symptoms[216]
- Anxiety and depression may be more effectively improved in programs offering CBT plus an HF education program[217]
- Compared with usual care or center-based cardiac rehabilitation, home-based interventions may have heightened benefit in reducing anxiety[219]
- Home-based robot-assisted rehabilitation coupled with a home exercise program helps to improve depression, quality of life, and condition impact in people who have had a stroke[220]

- Individuals living in rural settings admitted to hospital for ACS may be prone to heightened anxiety. The development and testing of protocols for anxiety reduction in rural settings may be needed[175]
- Problem-solving therapy may help prevent mood disorder diagnosis in individuals who have had a stroke[213]

Dementia

- Primary prevention strategies that target shared metabolic pathways, such as those contributing to CVD, may prevent depression in AD
- NICE guidelines suggest psychological treatments for people with mild-to-moderate dementia who have mild-to-moderate depression. Antidepressants are indicated for those a pre-existing severe mental health problem[568]
- Several brief psychotherapeutic interventions have been shown to be effective in this population.[253] Behavioural therapies are more commonly applied in the later stages of dementia, while modified cognitive-behavioural strategies appear to be more successful with those in the earlier stages of cognitive decline[254]
- CBT programs for persons with dementia should involve their caregivers, both as CBT coaches for the care recipient and as treatment partners[255]
- Based on social support research findings, depression management at the time of dementia diagnosis should include interventions to increase social engagement[256]
- Physical activity interventions can improve physical function in older people with dementia, however, evidence for an effect on depression is limited[249]
- Bright light therapy may help to reduce depression and agitation in persons with dementia residing in long-term care facilities[257]

Diabetes Mellitus (DM)

- Mental health screening is recommended at least annually
- The initiation of new anti-diabetic medication may be a time of heightened vulnerability to depression. Clinicians should be aware that women, patients starting an AD at a young age, those with a low SES, and a history of anxiety or dementia may need to have their physical and mental health tracked closely[267]
- Targeting the three well established inter-related major pathophysiologic pathways between DM and mental health may optimize both physical and mental health. The pathways include hyperglycaemia, microvascular dysfunction, and inflammation
- Holistic, preventive services focusing on healthy diet, physical activity, healthy weight management, to promote both physical and mental health is recommended
- Antidepressants may both moderate depression severity and improved glycemic control
- Collaborative care with stepped care approaches that include choice of psychotherapy and pharmacotherapy presents good results for treatment of depression and anxiety in diabetes[569]
- Examining indicators of low-grade inflammation as a prognostic tool for choosing the treatment modalities in individuals with both depression and T2DM may have beneficial effects for cardiovascular risk mitigation and management

- Interventions such as diabetes self-management education and pharmacist-led group shared medical appointment visits may improve glycemic control[291,293]
- Depression in T2DM varies among ethnic groups, which suggest the need to address stressors unique to racial/ethnic minorities to improve diabetes-related outcomes[292]
- Integrated interventions co-developed with end-users, their family members, and provider stakeholders may positively impact on both diabetes and depression-related outcomes, particularly among specific ethnic groups[294]
- Integrated interventions that use patient prioritized planning (incorporated financial, social and emotional needs for primary care patients with T2DM and depression) may improve HbA1c and depression symptoms[295]
- Usual care plus psychotherapy for depression via home telehealth (home monitor that captures clinical measures) may improve glycemic control and generate significant healthcare cost savings [289]

Epilepsy

- The BDI-I and BDI-II have been well-validated as a depression screening tool in epilepsy[305]
- Clinicians need to consider that there are various subtypes of depression in people with epilepsy in order to best screen and manage symptoms[306]
- Individuals with PTSD may be at elevated risk of developing epilepsy
- Among intervention options oxcarbazepine, venlafaxine, and lamotrigine may improve mood and CBT may improve both depression and epilepsy outcomes.[313] Specialist epilepsy nursing and self-management education, have some evidence of benefit. At present it is not possible to advocate any single model of service provision for self-management in epilepsy[314]

Frailty

- Screening of mental health in frailty is recommended but complicated as mental health may be considered part of the condition's definition
- The task force of the International Conference of Frailty and Sarcopenia Research (ICFSR) recommend the following guidelines for managing frailty: [327]
    - Address polypharmacy, the management of sarcopenia, the treatable causes of weight loss, and the causes of exhaustion (depression, anaemia, hypotension, hypothyroidism, and vitamin B_{12} deficiency)
    - All persons with frailty should receive social support as needed to address unmet needs and encourage adherence to a comprehensive care plan
    - Include a multi-component physical activity programme with resistance-based training
    - Provide protein/caloric supplementation when weight loss or undernutrition are present
- At this time, there is insufficient evidence to support therapies such as cognitive therapy, problem-solving therapy, vitamin D supplementation, and hormone-based treatment[327]

Huntington's Disease (HD)

- Mental health-related comorbidities reported in HD have included depression, irritability, anxiety, apathy, hallucinations, psychosis, suicide ideation and attempts, obsessive/compulsive disorders, and perseveration[336]
- The Irritability Scale of the Beck Depression Inventory-II, and the Hospital Anxiety and Depression Scale for depression are recommended screening tools[336]
- Mental health management should be based on the identification of underlying environmental or somatic (e.g., pain, side effects of medications) triggers causing changes in mood or behaviour
- International Guidelines for the Treatment of Huntington Disease suggest mindfulness-based cognitive therapy and Acceptance and Commitment Therapy, personalized cognitive stimulation, establishing routines, a structured programme of activities, and psycho-education for the family regarding diversion strategies to mitigate confrontations[334]
- For depression that is resistant to medications, electroconvulsive therapy (ECT) may be suggested under the guidance of a psychiatrist[334]
- Suicide risk should be assessed regularly, including at diagnosis and when the disease starts to impact on daily activities. Individuals with active suicidal ideation and a plan require immediate psychiatric evaluation[334]

Inflammatory Bowel Diseases (IBDs)

- Reducing stress with support from psychological interventions improves health-related quality of life[353]
- There is insufficient evidence to recommend online psychological interventions. The research literature about benefits of CBT is mixed[357,358,359]
- The British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults suggest psychological intervention (psychotherapy, patient education and relaxation techniques) for anxiety, pain, and stress levels to improve mood[570]
- Mindfulness as an adjunct to pharmacological therapy may improve psychological symptoms in IBD and facilitate coping with symptoms during a disease flare-up[360,361,362]
- Gut directed hypnotherapy has an established evidence base for the control of IBS symptoms, however more research is needed to determine if there are mental health benefits[363,364]

Kidney Disease (Chronic) or CKD

- Some studies support mental health screening programs and suggest screening for depression should take place at key transition points such as at the initial evaluation, dialysis initiation, and regular intervals thereafter[366]
- The benefits vs harms of anti-depressant medications need to be considered. The medications are broken down by the liver and end products may not be removed

sufficiently by the kidneys or through dialysis. Further concerns are increased risk of drug interactions and accumulation of toxic metabolites[366]
- Chronic disease self-management programming that includes activities such as exercise therapy may foster mental health.[366] CBT may be beneficial during changes in dialysis regimen[366]
- Nurse-led, in-center breathing training programs for individuals on maintenance hemodialysis may improve depression[372]

Metabolic Syndrome (MetS)

- Screening and monitoring of MetS in individuals with mental health conditions, particularly those taking anti-psychotic medications, is part of standard care
- The HADS is a reliable screening tool for current major depressive episode and generalized anxiety disorder in middle aged and elderly populations with and without MetS.
- A systematic review reported there was some indication of a possible protective effect of drug combinations including aripiprazole for diabetes and hyperlipidaemias. Long-term prospective studies are required for accurate appraisal of diabetes risk, hypertension, and hyperlipidaemia in those exposed to antipsychotic medication polypharmacy[406]
- SSRIs have been shown to reduce cytokine levels[408] and may be protective against MetS
- Mental health based primary care of individuals accessing services of a community mental health center may improve diabetes HbA1c monitoring and metabolic monitoring of anti-psychotic medication treatment[407]

Obesity

- A typical tool used for mental health screening is the Patient Health Questionnaire-9 or PHQ-9
- Screening is particularly recommended in sarcopenic obesity, defined as being the presence of loss of muscle and obesity typically related to aging
- Current guidelines related to management of overweight and obesity in adults align with risk profiles for CVD[431] and integrates guidelines for cardiometabolic monitoring for those with weight gain related to anti-psychotic medication use
- Mobile health (mHealth), health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices may have potential in managing obesity and mental health but further research is needed
- Interventions for obesity should involve mental health professionals.[420] Behavioural interventions, that involve treatments that are taken to modify behaviour, emotions, and cognition to improve psychological and physical well-being are integral[419]
- Research has indicated that when pharmacological and surgical interventions are combined with psychological supplements via behavioural health interventions, treatment adherence and long-term sustainability are enhanced[419]

- Psychotropic medications that treat psychosis and mood stabilization may contribute to weight gain and adversely affect lipid and glucose metabolism.[434] Healthcare providers need to consider these factors when making treatment choices[435] and implement integrated education, assessment, and care for those with mental health concerns and at risk for weight gain
- Health promotion and weight loss intervention programs for lesbians should incorporate psychological, relationship, and alcohol use components to reduce overweight and obesity[436]

Parkinson's Disease (PD)

- The most suitable scales for screening for depression disorders are the Ham-D and BDI scales, the geriatric depression scale, the HADS, and the Montgomery Asberg Depression Rating Scale (MADRS)[441,444]
- Physical activity can improve the clinical status in areas such as function, fatigue, depressive symptoms, sleep disorders, and quality of life.[451] The American College of Sport Medicine activity guidelines can be applied to patients with PD: aerobic exercise, strengthening, and balance training flexion is recommended three times a week for at least 30 minutes[452]
- Mind-body exercises may improve motor function, depressive symptoms, and quality of life, however, more needs to be known about specific factors such as gender, severity of disease, specific drug use, and intervention cycle[453]
- Early identification of mental health symptoms and appropriate multidisciplinary management of depression may improve the quality of life of people with PD[571]
- Antiparkinsonian medications might improve mood disorders by alleviating motor manifestations and disability, fostering feelings of disease mastery, or restoring dopaminergic signalling.[454]
- CBT is promising for acute management of depression and anxiety[455]
- Unilateral subthalamic nucleus deep brain stimulation on non-motor symptoms for individuals with moderate to severe PD may also improve depression, sleep quality, and quality of life[450]

Respiratory Diseases (Chronic)

- The literature reports the use of the Ham-A and Ham-D, however, there is no consensus on the evaluation tools and diagnostic criteria of COPD with depression and anxiety
- The inter-connectedness of stigma-related experiences to these conditions highlight the need for integrated approaches[478]
- Management of chronic respiratory diseases should aim for individualized care. For example, individuals with COPD tend to prefer treatments that provide symptom relief (e.g., dyspnea), positive physician relations, and improve quality-of-life. Individuals with asthma prefer treatments that increase symptom-free days and may be willing to trade days without symptoms for a reduction in adverse events and greater convenience[487]

- Pulmonary rehabilitation is beneficial for those with comorbidities and has been shown to reduce the severity of depression and cardiovascular risk factors, including blood pressure[488,473]
- The National Institute for Health and Care Excellence (NICE) has guidelines for the use of stepped approaches to psychological and/or pharmacological treatment of depression in people with long-term conditions, including respiratory conditions[572]
- Personalized behaviour and problem solving-adherence interventions provide similar improvements in depression[483]
- Older adults (67-85 years) hospitalized for COPD who are offered controlled breathing technique interventions reported significantly improved dyspnea, reduced anxiety, and better mobility[484]
- For individuals with COPD, depression symptoms were shown to be more improved among those receiving psychological therapies (CBT-based approach) compared to standard care, educational interventions, or a co-intervention (pulmonary rehabilitation)[485]

5.3 Mental Health Promotion

Based on an adapted a socio-ecological framework (Figure 4.1) that draws upon program theories to explain mental health promotion at different systems levels, four broad guidelines for mental health promotion to help prevent and manage physical and mental health comorbidities are recommended.

Level 1: Healthy Public Policy for Mental Health: Mental Health Promotion/Mental Health in All Policies (MHiAP)

People living with mental and physical illnesses have the potential to live a flourishing, joyful life. We must also try to promote and strengthen health assets, including structurally (social, economic and cultural) supportive environments, community resilience and life coping skills.

A Program Theory for Mental Health in All Policies
A MHiAP strategy → Intersectoral governance for mental health → Changes in policies (usually signaled by some sort of strategic document/plan) → policy actions (legislative, regulatory, budgetary/investment tools) to promote mental health → Impact on social determinants of mental health → Improved mental health outcomes (e.g. increased well-being, happiness, improved coping and resilience, reduced mental stress, reduced incidence of mental illness, reduced harms from substance misuse, reduced incidence of suicide).

Agenda Setting for a MHiAP Strategy

A 'Health in All Policies' approach to intersectoral collaboration has been gaining ground globally as a policy-level agenda aimed at addressing the wider social determinants of health. Advocates of HiAP highlight the importance of mental health promotion as central

to successful HiAP approaches, and as a means to contribute to addressing health equity and inequality;[9, 10] conversely, advocates of mental health promotion have identified HiAP as a key policy framework for advancing mental health and physical health.[11,12]

Based on a review of the literature on HiAP adoption and implementation, we propose five simple rules for successful HiAP initiation: 1) Developing a shared language and fluency around a broader understanding of 'health' to include well-being and happiness, and general welfare; 2) Linking evidence for how HiAP initiatives are able to contribute to sustainable economies and sustainable health systems (both theoretical and empirical); 3) Having an 'entry point' to initiate an HiAP agenda; 4) Developing 'win-win' scenarios, goals and objectives across sectors;[13] 5) Building and fostering long-term collaborative partnerships and engagement with intersectoral stakeholders.

In the Canadian context, not only is mental health well placed to be included in any HiAP policy agenda, it may in fact be the key entry point for raising the awareness and urgency of a HiAP approach at the federal and provincial levels. First, with the help of key policy elites, such as Senators Kirby and Wilson, and with the establishment of the MHCC, much of the foundational work in boosting awareness has already taken place. In this collective work, Canadian researchers, practitioners, policy-makers and people with lived experience have worked on developing a more inclusive, shared language around mental health, that by its nature tends to be less 'deficit-focused' and more positive and strengths-based.

Level 2: Reorienting Mental Health Services: Integrated Health and Social Services

Beyond the HiAP approach, a key role for public policy is to provide the regulatory, legislative and financial context for the transformation of health and social services more broadly in society. For Canadians, 'health reform'[14] is an ongoing reality, that is complex and multi-faceted, with varying objectives across provinces, and widely differing governance strategies and outcomes. However, a common recurrent theme is the need to develop *integrated, collaborative systems of health and social care* to address the increasingly complex needs of an ageing population, with the concomitant multimorbidity of chronic diseases, both physical and mental being the driving force of this complexity. While these efforts require many transformational changes at the health and social service/organizational level, there is a strong role for high-level policy in successfully moving towards the ideal system. It is generally acknowledged, based on decades of research evidence,[15] that comprehensive primary health care, as originally outlined in the Alma Ata Declaration,[16] is the overarching framework for efficiently, effectively, and equitably organizing health and social services in order to produce optimum health in populations.

> The **program theory** at this level is: by providing *universal financial coverage, under government control and regulation*, with *equitable distribution of services, comprehensive coverage*, and *with low or no co-payments*, then you attain "*greater first contact access and use, more person-focused care over time, greater range of services available and provided when needed, and coordination of care.*" (Starfield, 2012, p. 20).

Integrating care via simple rules allows relatively autonomous actors to use their contextual knowledge to come up with creative implementation solutions. At the integrated care level, there are some important contextual factors to consider. In order for clients to have a voice in decision-making (e.g., priority physical and social/mental needs), power differentials need to be 'smoothed.' Differential power dynamics impede effective collaborative practice among different service providers,[17] but they also relegate clients to a marginalized role with respect to decisions around their care needs. Physicians are considered the top of the healthcare hierarchy, and this conceptual approach can break the success of any reform program or change initiative.

Level 3: Strengthening Community Mental Health Action: Community Assets for Mental Health

At this systems level, community "assets" for mental health are the chosen foci, as they bring together three important theoretical approaches to mental health: mental health promotion;[18] the two-continuum approach;[19] and, the Canadian Mental Health Association's framework for support approach.[20,21]

The **program theory** at the community level is: by helping to *co-create, strengthen and sustain community mental health assets*, people can be supported to live happy, joyful, flourishing lives, whether or not they are living with mental or physical illness *and* they can be empowered to help co-produce and shape the mental health services they receive in community through context-appropriate co-produced mental health service planning.

We propose a series of context-mechanism-outcome configurations (CMOCs). Many of the CMOCs are similar to those derived through community-based participatory action research.[22] Based on our review of literature at the other systems levels, there is evidence that these "collaboration" CMOCs are relevant to each systems levels and our simple rules approach and are outlined as follows.

Context-Mechanism-Outcome (CMO) Configurations to Complement Simple Rules	
Factor	**CMO**
Trust	High trust (context) creates partnership synergy (mechanism) leading to successful outcomes at all systems levels (e.g., mental health services delivery).
Formalization	Formalization through policy (context) creates greater initial trust (mechanism) leading to greater uptake of mental health inclusion, mental health awareness at all systems levels.
Shared Vision	Having a shared vision (context) reduces the potential for conflict (mechanism) leading to improved trust/high trust (outcome) at all systems levels.

Commitment/ Accountability	Evidence of preparedness and accountability (context) results in reduced conflict (mechanism) leading to greater trust (outcome) among partners at each systems level.
Power	Power imbalances among partners (context) creates partner domination (mechanism) leading to reduced trust, blocked mental health services delivery at each systems level.
Faith	High faith (context) creates partnership synergy (mechanism)leading to enhanced mental health services delivery at each systems level.
Authenticity	Authentic collaboration (context) increases faith (mechanism) leading to increased agreement over common goals, such as mental health services delivery (at each systems level).
Leadership	Positive, authentic leaders (context) create more effective integration of different partners/cultures (mechanism) leading to greater trust among partners at each systems level (outcome).
Culture	Cultural closeness or coherence (context) decreases conflict (mechanism) leading to greater trust among partners at each systems level.
Flexibility	Greater flexibility in directives/guidelines (context) increases the likelihood of goal achievement (mechanism) leading to more efficient, effective mental health services delivery (outcome) at each systems level.
Entry Point	Designated entry points (context) provide clarity (mechanism) leading to more confidence (e.g., consistent model for mental health services delivery) (outcome) at every systems level.

Level 4: Developing Personal Health Skills/Resilience: Individuals, Families and Informal Supports

This level looks mainly at the personal resources individuals utilize to help them develop resilience, hope, confidence and well-being. There are many resources and interventions that aim at strengthening individual coping skills and resilience to bolster mental health and prevent the worst impacts of mental illness (e.g., self-aid, mutual aid, peer support networks).

6. Citations

1. S. L. Mills E Vanden. International roundtable on the self-management support of chronic conditions – Workshop reportrt in the Care of Chronic Conditions. In development, The Chronic Conditions Self-Management Support (CCSMS) Framework and Community of Practice Project Team: Vancouver, Canada. p. 1-21. *Chronic Dis Inj Can*. 2011;31(4):176-179.
2. Neville C. Collaborative care approaches for people with severe mental illness. *Clin Nurse Spec*. 2015;29(3):143-144. doi:10.1097/NUR.0000000000000127
3. Gillies D, Buykx P, Parker AG, Hetrick SE. Consultation liaison in primary care for people with mental disorders. *Cochrane database Syst Rev*. 2015;2015(9):CD007193. doi:10.1002/14651858.CD007193.pub2
4. Coventry PA, Hudson JL, Kontopantelis E, et al. Characteristics of effective collaborative care for treatment of depression: a systematic review and meta-regression of 74 randomised controlled trials. *PLoS One*. 2014;9(9):e108114. doi:10.1371/journal.pone.0108114
5. Goodall, S, Druss, BG, Walker E. *Mental Disorders and Medical Comorbidity*.; 2011. https://www.rwjf.org/en/library/research/2011/02/mental-disorders-and-medical-comorbidity.html.
6. Metabolic Syndrome Canada. About Metabolic Syndrome. https://www.metabolicsyndromecanada.ca/about-metabolic-syndrome.
7. Organization WH. Management of substance abuse. https://www.who.int/substance_abuse/terminology/abuse/en/. Published 2020.
8. Association AP. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. Washington, DC; 2013.
9. Kienzler H. Mental health in all policies in contexts of war and conflict. *Lancet Public Heal*. 2019;4(11):e547-e548. doi:10.1016/S2468-2667(19)30208-7
10. Tonelli M, Tang K-C, Forest P-G. Canada needs a "Health in All Policies" action plan now. *C Can Med Assoc J = J l'Association medicale Can*. 2020;192(3):E61-E67. doi:10.1503/cmaj.190517
11. Jenkins, R. & Minoletti A. Promoting mental health: a crucial component of all public policy. In: Leppo, K., Ollila, E., Pena, S., Wismar, M., & Cook S, ed. *Health in All Policies. Seizing Opportunities, Implementing Policies.* Helsinki: Ministry of Social Affairs and Health; 2013.
12. Petek A, Novak M, Barry MM. Interdisciplinary research framework for multisectoral mental health policy development. *Int J Ment Health Promot*. 2017;19(3):119-133. doi:10.1080/14623730.2017.1326398
13. Molnar A, Renahy E, O'Campo P, Muntaner C, Freiler A, Shankardass K. Using win-win strategies to implement health in all policies: a cross-case analysis.. *PLoS One*. 2016;11(2):e0147003. doi:10.1371/journal.pone.0147003
14. Usher S, Denis J-L, Préval J, et al. Learning from health system reform trajectories in seven Canadian provinces. *Health Econ Policy Law*. August 2020:1-17. doi:10.1017/S1744133120000225
15. Starfield B. Primary care: an increasingly important contributor to effectiveness, equity, and efficiency of health services. SESPAS report 2012. *Gac Sanit*. 2012;26 Suppl 1:20-26. doi:10.1016/j.gaceta.2011.10.009
16. Organization WH. *Declaration of Alma-Ata, 1978*. Geneva https://www.who.int/publications/almaata_declaration_en.pdf?ua=1.
17. Best A, Greenhalgh T, Lewis S, Saul JE, Carroll S, Bitz J. Large-System Transformation in Health Care: A Realist Review. *Milbank Q*. 2012;90(3):421-456. doi:10.1111/j.1468-0009.2012.00670.x
18. Barry, M.M., Clarke, A.M., Petersen, I., Jenkins R. *Implementing Mental Health Promotion*. Springer International Publishing; 2019.
19. Mulvale G, Bartram M. No More "Us" and "Them": Integrating Recovery and Well-Being into a Conceptual Model for Mental Health Policy. *Can J Community Ment Heal*. 2015;34(4):31-67.

doi:10.7870/cjcmh-2015-010
20. J Trainor, E Pomeroy, B Pape KC. Building a framework for support: Developing a sector-based policy model for people with serious mental illness. *Can Ment Health*. 1992;40:25-29.
21. Trainor, J., Pomeroy, E., Pape B. A *Framework for Support: 3rd Edition*. Toronto: Canadian Mental Health Association; 2004.
22. Jagosh J, Bush PL, Salsberg J, et al. A realist evaluation of community-based participatory research: partnership synergy, trust building and related ripple effects. *BMC Public Health*. 2015;15:725. doi:10.1186/s12889-015-1949-1
23. Brochmann N, Flachs EM, Christensen AI, et al. Anxiety and depression in patients with Philadelphia-negative myeloproliferative neoplasms: a nationwide population-based survey in Denmark. *Clin Epidemiol*. 2019;11:23-33. doi:http://dx.doi.org/10.2147/CLEP.S162688
24. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)*. 2016;387(10026):1377-1396. doi:10.1016/S0140-6736(16)30054-X
25. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)*. 2016;388(10053):1459-1544. doi:10.1016/S0140-6736(16)31012-1
26. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, Feigl AB, Gaziano T, Mowafi M, Pandya A, Prettner K, Rosenberg L, Seligman B, Stein AZ WC. *The Global Economic Burden of Noncommunicable Diseases*. Geneva; 2011. www3.weforum.org/docs/WEF_Harvard_HE_GlobalEconomicBurdenNonCommunicableDiseases_2011.pdf.
27. Cox J, Hamelin A, Mclinden T, et al. Food Insecurity in HIV-Hepatitis C Virus Co-infected Individuals in Canada: The Importance of Co-morbidities. *AIDS Behav*. 2017;21(3):792-802. doi:http://dx.doi.org/10.1007/s10461-016-1326-9
28. Organization WH. *Global Health Risks Mortality and Burden of Disease Attributable to Selected Major Risk*.; 2009. https://apps.who.int/iris/bitstream/handle/10665/44203/9789241563871_eng.pdf?sequence=1&isAllowed=y.
29. Fiest KM, Hitchon CA, Bernstein CN, et al. Systematic Review and Meta-analysis of Interventions for Depression and Anxiety in Persons With Rheumatoid Arthritis. *J Clin Rheumatol Pract reports Rheum Musculoskelet Dis*. 2017;23(8):425-434. doi:10.1097/RHU.0000000000000489
30. Organization WH. *Integrating the Prevention, Treatment and Care of MH Conditions and Other Noncommunicable Diseases within Health Systems. WHO European High-Level Conference on Non-Communicable Diseases*. Copenhagen; 2019. www.euro.who.int/__data/assets/pdf_file/0004/397786/Mental-Health-Conditions-ENG.pdf.
31. Cohen A. *Addressing Comorbidity between Mental Disorders and Major Noncommunicable Diseases Background Technical Report to Support Implementation of the WHO European Mental Health Action Plan 2013–2020 and the WHO European Action Plan for the Prevention* A. http://www.euro.who.int/__data/assets/pdf_file/0009/342297/Comorbidity-report_E-web.pdf.
32. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia*. 2010;53(12):2480-2486. doi:10.1007/s00125-010-1874-x
33. Mikocka-Walus A, Knowles SR, Keefer L, Graff L. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflamm Bowel Dis*. 2016;22(3):752-762. doi:https://dx.doi.org/10.1097/MIB.0000000000000620
34. Yilmaz Kafali H, Atik Altinok Y, Ozbaran B, et al. Exploring emotional dysregulation

characteristics and comorbid psychiatric disorders in type 1 diabetic children with disordered eating behavior risk. *J Psychosom Res*. 2020;131:109960. doi:10.1016/j.jpsychores.2020.109960
35. Doi M, Fukahori H, Oyama Y, Morita K. Factors associated with depressive symptoms in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A prospective cohort study. *Nurs Open*. 2018;5(4):583-592. doi:http://dx.doi.org/10.1002/nop2.171
36. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord*. 2012;142 Suppl:S8-21. doi:10.1016/S0165-0327(12)70004-6
37. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. *JAMA*. 2011;306(11):1241-1249. doi:10.1001/jama.2011.1282
38. Keyes KM, Susser E. The expanding scope of psychiatric epidemiology in the 21st century. *Soc Psychiatry Psychiatr Epidemiol*. 2014;49(10):1521-1524. doi:10.1007/s00127-014-0938-5
39. Fitch M, Zomer S, Lockwood G, et al. Experiences of adult cancer survivors in transitions. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. 2019;27(8):2977-2986. doi:10.1007/s00520-018-4605-3
40. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011;12(2):160-174. doi:10.1016/S1470-2045(11)70002-X
41. Smith HR. Depression in cancer patients: Pathogenesis, implications and treatment (Review). *Oncol Lett*. 2015;9(4):1509-1514. doi:10.3892/ol.2015.2944
42. Grigoleit J-S, Kullmann JS, Wolf OT, et al. Dose-dependent effects of endotoxin on neurobehavioral functions in humans. *PLoS One*. 2011;6(12):e28330. doi:10.1371/journal.pone.0028330
43. Goldstein BI, Kemp DE, Soczynska JK, McIntyre RS. Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J Clin Psychiatry*. 2009;70(8):1078-1090. doi:10.4088/JCP.08r04505
44. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med*. 2013;11:200. doi:10.1186/1741-7015-11-200
45. Tully PJ. Anxiety and Incident Cardiovascular Disease: Is the Jury Still Out? *Am J Cardiol*. 2017;120(3). doi:http://dx.doi.org/10.1016/j.amjcard.2016.06.027
46. Pawson R, Greenhalgh T, Harvey G, Walshe K. Realist review - A new method of systematic review designed for complex policy interventions. *J Heal Serv Res Policy*. 2005;10(SUPPL. 1):21-34. doi:10.1258/1355819054308530
47. Lacouture A, Breton E, Guichard A, Ridde V. The concept of mechanism from a realist approach: a scoping review to facilitate its operationalization in public health program evaluation. *Implement Sci*. 2015;10:153. doi:10.1186/s13012-015-0345-7
48. Jagosh J, Pluye P, Macaulay AC, et al. Assessing the outcomes of participatory research: protocol for identifying, selecting, appraising and synthesizing the literature for realist review. *Implement Sci*. 2011;6:24. doi:10.1186/1748-5908-6-24
49. Macfarlane F, Greenhalgh T, Humphrey C, Hughes J, Butler C, Pawson R. A new workforce in the making? A case study of strategic human resource management in a whole-system change effort in healthcare. *J Health Organ Manag*. 2011;25(1):55-72. doi:10.1108/14777261111116824
50. (UK) NCGC. *Osteoarthritis: Care and Management in Adults*. London; 2014. https://www.ncbi.nlm.nih.gov/books/NBK248069/.
51. Nazarinasab M, Motamedfar A, Moqadam AE. Investigating mental health in patients with osteoarthritis and its relationship with some clinical and demographic factors. *Reumatologia*. 2017;55(4):183-188. doi:10.5114/reum.2017.69778
52. Veronese N, Stubbs B, Solmi M, ... TS-A and, 2017 undefined. Association between lower limb osteoarthritis and incidence of depressive symptoms: data from the osteoarthritis initiative. *academic.oup.com*. https://academic.oup.com/ageing/article-abstract/46/3/470/2654234.

Accessed May 5, 2020.
53. Huang S-W, Wang W-T, Lin L-F, Liao C-D, Liou T-H, Lin H-W. Association between psychiatric disorders and osteoarthritis: a nationwide longitudinal population-based study. *Medicine (Baltimore)*. 2016;95(26):e4016. doi:https://dx.doi.org/10.1097/MD.0000000000004016
54. Vennu V, Misra H, Misra A. Depressive symptoms and the risk of arthritis: A survival analysis using data from the osteoarthritis initiative. *Indian J Psychiatry*. 2019;61(5):444-450. doi:http://dx.doi.org/10.4103/psychiatry.IndianJPsychiatry_241_18
55. Kigozi J, Jowett S, Nicholl BI, et al. Cost-Utility Analysis of Routine Anxiety and Depression Screening in Patients Consulting for Osteoarthritis: Results From a Clinical, Randomized Controlled Trial. *Arthritis Care Res (Hoboken)*. 2018;70(12):1787-1794. doi:10.1002/acr.23568
56. Mallen CD, Nicholl BI, Lewis M, et al. The effects of implementing a point-of-care electronic template to prompt routine anxiety and depression screening in patients consulting for osteoarthritis (the Primary Care Osteoarthritis Trial): A cluster randomised trial in primary care. *PLoS Med*. 2017;14(4). doi:http://dx.doi.org/10.1371/journal.pmed.1002273
57. Mitchell AJ. Screening for cancer-related distress: when is implementation successful and when is it unsuccessful? *Acta Oncol*. 2013;52(2):216-224. doi:10.3109/0284186X.2012.745949
58. Eller-Smith OC, Nicol AL, Christianson JA. Potential Mechanisms Underlying Centralized Pain and Emerging Therapeutic Interventions. *Front Cell Neurosci*. 2018;12:35. doi:10.3389/fncel.2018.00035
59. Schlereth T, Birklein F. The sympathetic nervous system and pain. *Neuromolecular Med*. 2008;10(3):141-147. doi:10.1007/s12017-007-8018-6
60. Park H-M, Kwon Y-J, Kim H-S, Lee Y-J. Relationship between Sleep Duration and Osteoarthritis in Middle-Aged and Older Women: A Nationwide Population-Based Study. *J Clin Med*. 2019;8(3):356. doi:10.3390/jcm8030356
61. Maes M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. *Neuro Endocrinol Lett*. 2008;29(3):287-291.
62. Sowers MR, McConnell D, Jannausch M, Buyuktur AG, Hochberg M, Jamadar DA. Estradiol and its metabolites and their association with knee osteoarthritis. *Arthritis Rheum*. 2006;54(8):2481-2487. doi:10.1002/art.22005
63. Saad F, Röhrig G, von Haehling S, Traish A. Testosterone Deficiency and Testosterone Treatment in Older Men. *Gerontology*. 2017;63(2):144-156. doi:10.1159/000452499
64. Jin WS, Choi EJ, Lee SY, Bae EJ, Lee T-H, Park J. Relationships among Obesity, Sarcopenia, and Osteoarthritis in the Elderly. *J Obes Metab Syndr*. 2017;26(1):36-44. doi:10.7570/jomes.2017.26.1.36
65. Ford AH, Yeap BB, Flicker L, et al. Prospective longitudinal study of testosterone and incident depression in older men: The Health In Men Study. *Psychoneuroendocrinology*. 2016;64:57-65. doi:10.1016/j.psyneuen.2015.11.012
66. Yohannes AM, Caton S. Management of depression in older people with osteoarthritis: A systematic review. *Aging Ment Health*. 2010;14(6):637-651. doi:https://dx.doi.org/10.1080/13607860903483094
67. Lorenc A, Feder G, MacPherson H, Little P, Mercer SW, Sharp D. Scoping review of systematic reviews of complementary medicine for musculoskeletal and mental health conditions. *BMJ Open*. 2018;8(10):e020222-e020222. doi:10.1136/bmjopen-2017-020222
68. Zhang L, Fu T, Zhang Q, et al. Effects of psychological interventions for patients with osteoarthritis: a systematic review and meta-analysis. *Psychol Health Med*. 2018;23(1):1-17. doi:10.1080/13548506.2017.1282160
69. Leventhal H, Phillips LA, Burns E. The Common-Sense Model of Self-Regulation (CSM): a dynamic framework for understanding illness self-management. *J Behav Med*. 2016;39(6):935-946. doi:10.1007/s10865-016-9782-2
70. Lluch Girbés E, Nijs J, Torres-Cueco R, López Cubas C. Pain treatment for patients with

osteoarthritis and central sensitization. *Phys Ther*. 2013;93(6):842-851. doi:10.2522/ptj.20120253
71. Agarwal P, Sambamoorthi U. Healthcare expenditures associated with depression among individuals with osteoarthritis: Post-regression linear decomposition approach. *J Gen Intern Med*. 2015;30(12):1803-1811. doi:10.1007/s11606-015-3393-4
72. Cooper RG, Booker CK, Spanswick CC. What is pain management, and what is its relevance to the rheumatologist? *Rheumatology (Oxford)*. 2003;42(10):1133-1137. doi:10.1093/rheumatology/keg313
73. Bullock J, Rizvi SAA, Saleh AM, et al. Rheumatoid Arthritis: A Brief Overview of the Treatment. *Med Princ Pract*. 2018;27(6):501-507. doi:10.1159/000493390
74. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2013;52(12):2136-2148. doi:10.1093/rheumatology/ket169
75. Anyfanti P, Gavriilaki E, Pyrpasopoulou A, et al. Depression, anxiety, and quality of life in a large cohort of patients with rheumatic diseases: common, yet undertreated. *Clin Rheumatol*. 2016;35(3):733-739. doi:http://dx.doi.org/10.1007/s10067-014-2677-0
76. Lok EYC, Mok CC, Cheng CW, Cheung EFC. Prevalence and determinants of psychiatric disorders in patients with rheumatoid arthritis. *Psychosomatics*. 2010;51(4):338-338.e8. doi:10.1176/appi.psy.51.4.338
77. Machin AR, Babatunde O, Haththotuwa R, et al. The association between anxiety and disease activity and quality of life in rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol*. 2020;39(5):1471-1482. doi:10.1007/s10067-019-04900-y
78. Qiu X-J, Zhang X-L, Cai L-S, et al. Rheumatoid arthritis and risk of anxiety: a meta-analysis of cohort studies. *Clin Rheumatol*. 2019;38(8):2053-2061. doi:10.1007/s10067-019-04502-8
79. Zhao S, Thong D, Miller N, et al. The prevalence of depression in axial spondyloarthritis and its association with disease activity: a systematic review and meta-analysis. *Arthritis Res Ther*. 2018;20. doi:http://dx.doi.org/10.1186/s13075-018-1644-6
80. Marrie RA, Hitchon CA, Walld R, et al. Increased Burden of Psychiatric Disorders in Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)*. 2018;70(7):970-978. doi:10.1002/acr.23539
81. Boscarino JA, Forsberg CW, Goldberg J. A twin study of the association between PTSD symptoms and rheumatoid arthritis. *Psychosom Med*. 2010;72(5):481-486. doi:https://dx.doi.org/10.1097/PSY.0b013e3181d9a80c
82. Mikuls TR, Padala PR, Sayles HR, et al. Prospective study of posttraumatic stress disorder and disease activity outcomes in US veterans with rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2013;65(2):227-234. doi:10.1002/acr.21778
83. Euesden J, Breen G, Farmer A, McGuffin P, Lewis CM. The relationship between schizophrenia and rheumatoid arthritis revisited: genetic and epidemiological analyses. *Am J Med Genet Part B, Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet*. 2015;168B(2):81-88. doi:10.1002/ajmg.b.32282
84. Gåfvels C, Hägerström M, Nordmark B, Wändell PE. Psychosocial problems among newly diagnosed rheumatoid arthritis patients. *Clin Rheumatol*. 2012;31(3):521-529. doi:10.1007/s10067-011-1894-z
85. van 't Land H, Verdurmen J, Ten Have M, van Dorsselaer S, Beekman A, de Graaf R. The association between arthritis and psychiatric disorders; results from a longitudinal population-based study. *J Psychosom Res*. 2010;68(2):187-193. doi:10.1016/j.jpsychores.2009.05.011
86. Leon L, Redondo M, Fernández-Nebro A, et al. Expert recommendations on the psychological needs of patients with rheumatoid arthritis. *Rheumatol Int*. 2018;38(12):2167-2182. doi:10.1007/s00296-018-4057-6
87. Sturgeon JA, Finan PH, Zautra AJ. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat Rev Rheumatol*. 2016;12(9):532-542. doi:10.1038/nrrheum.2016.112

88. Rathbun AM, Reed GW, Harrold LR. The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: a systematic review. *Rheumatology (Oxford)*. 2013;52(10):1785-1794. doi:10.1093/rheumatology/kes356
89. Liu Y, Ho RC-M, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-α) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. *J Affect Disord*. 2012;139(3):230-239. doi:10.1016/j.jad.2011.08.003
90. Dinarello CA. The many worlds of reducing interleukin-1. *Arthritis Rheum*. 2005;52(7):1960-1967. doi:10.1002/art.21107
91. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis*. 2016;75(1):3-15. doi:10.1136/annrheumdis-2015-207524
92. Gudu T, Gossec L. Quality of life in psoriatic arthritis. *Expert Rev Clin Immunol*. 2018;14(5):405-417. doi:10.1080/1744666X.2018.1468252
93. Zhao SS, Miller N, Harrison N, Duffield SJ, Dey M, Goodson NJ. Systematic review of mental health comorbidities in psoriatic arthritis. *Clin Rheumatol*. 2020;39(1):217-225. doi:10.1007/s10067-019-04734-8
94. McDonough E, Ayearst R, Eder L, et al. Depression and anxiety in psoriatic disease: prevalence and associated factors. *J Rheumatol*. 2014;41(5):887-896. doi:10.3899/jrheum.130797
95. Wu JJ, Penfold RB, Primatesta P, et al. The risk of depression, suicidal ideation and suicide attempt in patients with psoriasis, psoriatic arthritis or ankylosing spondylitis. *J Eur Acad Dermatol Venereol*. 2017;31(7):1168-1175. doi:10.1111/jdv.14175
96. Duffield SJ, Miller N, Zhao S, Goodson NJ. Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2018;57(8):1453-1460. doi:10.1093/rheumatology/key112
97. Gossec L, McGonagle D, Korotaeva T, et al. Minimal Disease Activity as a Treatment Target in Psoriatic Arthritis: A Review of the Literature. *J Rheumatol*. 2018;45(1):6-13. doi:10.3899/jrheum.170449
98. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. *Lancet (London, England)*. 2015;386(10012):2489-2498. doi:10.1016/S0140-6736(15)00347-5
99. Chimenti MS, Caso F, Alivernini S, et al. Amplifying the concept of psoriatic arthritis: The role of autoimmunity in systemic psoriatic disease. *Autoimmun Rev*. 2019;18(6):565-575. doi:10.1016/j.autrev.2018.11.007
100. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol*. 2019;80(4):1073-1113. doi:10.1016/j.jaad.2018.11.058
101. Society CC. Cancer information / Cancer 101 / What is cancer? https://www.cancer.ca/en/cancer-information/cancer-101/what-is-cancer/?region=bc. Published 2020.
102. Institute NC. What Is Cancer? https://www.cancer.gov/about-cancer/understanding/what-is-cancer.
103. Jia Y, Li F, Liu YF, Zhao JP, Leng MM, Chen L. Depression and cancer risk: a systematic review and meta-analysis. *Public Health*. 2017;149:138-148. doi:10.1016/j.puhe.2017.04.026
104. Singer S, Das-Munshi J, Brähler E. Prevalence of mental health conditions in cancer patients in acute care--a meta-analysis. *Ann Oncol Off J Eur Soc Med Oncol*. 2010;21(5):925-930. doi:10.1093/annonc/mdp515
105. Die Trill M. Anxiety and sleep disorders in cancer patients. *EJC Suppl EJC Off J EORTC, Eur Organ Res Treat Cancer . [et al]*. 2013;11(2):216-224. doi:10.1016/j.ejcsup.2013.07.009
106. Vodermaier A, Linden W, MacKenzie R, Greig D, Marshall C. Disease stage predicts post-diagnosis anxiety and depression only in some types of cancer. *Br J Cancer*. 2011;105(12):1814-

1817. doi:10.1038/bjc.2011.503
107. Wen S, Xiao H, Yang Y. The risk factors for depression in cancer patients undergoing chemotherapy: a systematic review. *Support care cancer Off J Multinatl Assoc Support Care Cancer*. 2019;27(1):57-67. doi:10.1007/s00520-018-4466-9
108. Walker J, Hansen CH, Martin P, et al. Prevalence, associations, and adequacy of treatment of major depression in patients with cancer: a cross-sectional analysis of routinely collected clinical data. *The lancet Psychiatry*. 2014;1(5):343-350. doi:10.1016/S2215-0366(14)70313-X
109. Brandenbarg D, Maass SWMC, Geerse OP, et al. A systematic review on the prevalence of symptoms of depression, anxiety and distress in long-term cancer survivors: Implications for primary care. *Eur J Cancer Care (Engl)*. 2019;28(3):1-14. doi:10.1111/ecc.13086
110. Agarwal M, Hamilton JB, Moore CE, Crandell JL. Predictors of depression among older African American cancer patients. *Cancer Nurs*. 2010;33(2):156-163. doi:https://dx.doi.org/10.1097/NCC.0b013e3181bdef76
111. Costas R, Gany F. Depressive symptoms in a sample of Afro-Caribbean and Latino immigrant cancer patients: a comparative analysis. *Support Care Cancer*. 2013;21(9):2461-2468. doi:10.1007/s00520-013-1813-8
112. Yu Q, Medeiros KL, Wu X, Jensen RE. Nonlinear Predictive Models for Multiple Mediation Analysis: With an Application to Explore Ethnic Disparities in Anxiety and Depression Among Cancer Survivors. *Psychometrika*. 2018;83(4):991-1006. doi:http://dx.doi.org/10.1007/s11336-018-9612-2
113. Shen C-C, Hu L-Y, Hu Y-W, et al. The Risk of Cancer in Patients With Obsessive-Compulsive Disorder: A Nationwide Population-Based Retrospective Cohort Study. *Medicine (Baltimore)*. 2016;95(9):e2989. doi:https://dx.doi.org/10.1097/MD.0000000000002989
114. Swartzman S, Booth JN, Munro A, Sani F. Posttraumatic stress disorder after cancer diagnosis in adults: A meta-analysis. *Depress Anxiety*. 2017;34(4):327-339. doi:10.1002/da.22542
115. Chang C-K, Hayes RD, Broadbent MTM, et al. A cohort study on mental disorders, stage of cancer at diagnosis and subsequent survival. *BMJ Open*. 2014;4(1):e004295. doi:10.1136/bmjopen-2013-004295
116. Nelson DE, Jarman DW, Rehm J, et al. Alcohol-attributable cancer deaths and years of potential life lost in the United States. *Am J Public Health*. 2013;103(4):641-648. doi:10.2105/AJPH.2012.301199
117. Canadian Cancer Society. *ComPARe. Risk Factors – Attributable Cancer Case(s) Due to Smoking Tobacco in Canada for All Ages, 2015.*; 2015. https://data.prevent.cancer.ca/current/risk-factors.
118. Lin H-Y, Fisher P, Harris D, Tseng T-S. Alcohol intake patterns for cancer and non-cancer individuals: a population study. *Transl Cancer Res*. 2019;8(Suppl 4):S334-S345. doi:10.21037/tcr.2019.06.31
119. Jairam V, Yang DX, Verma V, Yu JB, Park HS. National Patterns in Prescription Opioid Use and Misuse Among Cancer Survivors in the United States. *JAMA Netw open*. 2020;3(8):e2013605. doi:10.1001/jamanetworkopen.2020.13605
120. National Cancer Institute. *Cancer Trends Progress Report: Cancer Survivors and Smoking.*; 2020. https://progressreport.cancer.gov/after/smoking.
121. Gritz ER, Talluri R, Fokom Domgue J, Tami-Maury I, Shete S. Smoking Behaviors in Survivors of Smoking-Related and Non–Smoking-Related Cancers. *JAMA Netw Open*. 2020;3(7):e209072-e209072. doi:10.1001/jamanetworkopen.2020.9072
122. Swoboda CM, Walker DM, Huerta TR. Likelihood of Smoking Among Cancer Survivors: An Updated Health Information National Trends Survey Analysis. *Nicotine Tob Res Off J Soc Res Nicotine Tob*. 2019;21(12):1636-1643. doi:10.1093/ntr/ntz007
123. Mayer DK, Carlson J. Smoking patterns in cancer survivors. *Nicotine Tob Res*. 2011;13(1):34-40. doi:10.1093/ntr/ntq199
124. Tseng T-S, Lin H-Y, Martin MY, Chen T, Partridge EE. Disparities in smoking and cessation status among cancer survivors and non-cancer individuals: a population-based study from

National Health and Nutrition Examination Survey. *J Cancer Surviv*. 2010;4(4):313-321. doi:10.1007/s11764-010-0127-9
125. Underwood JM, Townsend JS, Stewart SL, et al. Surveillance of demographic characteristics and health behaviors among adult cancer survivors--Behavioral Risk Factor Surveillance System, United States, 2009. *Morb Mortal Wkly report Surveill Summ (Washington, DC 2002)*. 2012;61(1):1-23.
126. Ho P, Rosenheck R. Substance use disorder among current cancer patients: Rates and correlates nationally in the Department of Veterans Affairs. *Psychosom J Consult Liaison Psychiatry*. 2018;59(3):267-276. doi:10.1016/j.psym.2018.01.003
127. Jayadevappa R, Chhatre S. Association between age, substance use, and outcomes in Medicare enrollees with prostate cancer. *J Geriatr Oncol*. 2016;7(6):444-452. doi:10.1016/j.jgo.2016.06.007
128. Boehmer U, Miao X, Ozonoff A. Cancer survivorship and sexual orientation. *Cancer*. 2011;117(16):3796-3804. doi:10.1002/cncr.25950
129. Kamen C, Palesh O, Gerry AA, et al. Disparities in Health Risk Behavior and Psychological Distress Among Gay Versus Heterosexual Male Cancer Survivors. *LGBT Heal*. 2014;1(2):86-92. doi:10.1089/lgbt.2013.0022
130. Boehmer U, Miao X, Ozonoff A. Health behaviors of cancer survivors of different sexual orientations. *Cancer Causes Control*. 2012;23(9):1489-1496. doi:10.1007/s10552-012-0023-x
131. Jabson JM, Farmer GW, Bowen DJ. Health Behaviors and Self-Reported Health Among Cancer Survivors by Sexual Orientation. *LGBT Heal*. 2015;2(1):41-47. doi:10.1089/lgbt.2014.0038
132. Zaorsky NG, Zhang Y, Tuanquin L, Bluethmann SM, Park HS, Chinchilli VM. Suicide among cancer patients. *Nat Commun*. 2019;10(1):207. doi:10.1038/s41467-018-08170-1
133. Fässberg MM, Cheung G, Canetto SS, et al. A systematic review of physical illness, functional disability, and suicidal behaviour among older adults. *Aging Ment Health*. 2016;20(2):166-194. doi:10.1080/13607863.2015.1083945
134. Fox JP, Philip EJ, Gross CP, Desai RA, Killelea B, Desai MM. Associations Between Mental Health and Surgical Outcomes Among Women Undergoing Mastectomy for Cancer. *Breast J*. 2013;19(3):276-284. doi:10.1111/tbj.12096
135. Henry M, Rosberger Z, Ianovski LE, et al. A screening algorithm for early detection of major depressive disorder in head and neck cancer patients post-treatment: Longitudinal study. *Psychooncology*. 2018;27(6):1622-1628. doi:10.1002/pon.4705
136. Darnell R PJ. *Paraneoplastic Syndromes*. Oxford University Press; 2011.
137. Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. *BMJ Br Med J*. 2018;361. doi:http://dx.doi.org/10.1136/bmj.k1415
138. Hamann HA, Ver Hoeve ES, Carter-Harris L, Studts JL, Ostroff JS. Multilevel Opportunities to Address Lung Cancer Stigma across the Cancer Control Continuum. *J Thorac Oncol*. 2018;13(8):1062-1075. doi:10.1016/j.jtho.2018.05.014
139. Wick W, Hertenstein A, Platten M. Neurological sequelae of cancer immunotherapies and targeted therapies. *Lancet Oncol*. 2016;17(12):e529-e541. doi:10.1016/S1470-2045(16)30571-X
140. Ostuzzi G, Matcham F, Dauchy S, Barbui C, Hotopf M. Antidepressants for the treatment of depression in people with cancer. *Cochrane database Syst Rev*. 2018;4:CD011006. doi:https://dx.doi.org/10.1002/14651858.CD011006.pub3
141. Yeung KS, Hernandez M, Mao JJ, Haviland I, Gubili J. Herbal medicine for depression and anxiety: A systematic review with assessment of potential psycho-oncologic relevance. *Phyther Res*. 2018;32(5):865-891. doi:10.1002/ptr.6033
142. Nightingale CL, Rodriguez C, Carnaby G. The impact of music interventions on anxiety for adult cancer patients: a meta-analysis and systematic review. *Integr Cancer Ther*. 2013;12(5):393-403. doi:https://dx.doi.org/10.1177/1534735413485817
143. Cramer H, Lauche R, Klose P, Lange S, Langhorst J, Dobos GJ. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. *Cochrane database Syst Rev*. 2017;1(1):CD010802-CD010802.

doi:10.1002/14651858.CD010802.pub2
144. Li M, Kennedy EB, Byrne N, et al. Systematic review and meta-analysis of collaborative care interventions for depression in patients with cancer. *Psychooncology*. 2017;26(5):573-587. doi:10.1002/pon.4286
145. Zhang X, Xiao H, Chen Y. Effects of life review on mental health and well-being among cancer patients: A systematic review. *Int J Nurs Stud*. 2017;74:138-148. doi:10.1016/j.ijnurstu.2017.06.012
146. Krebber A-MH, Leemans CR, de Bree R, et al. Stepped care targeting psychological distress in head and neck and lung cancer patients: a randomized clinical trial. *BMC Cancer*. 2012;12:173. doi:10.1186/1471-2407-12-173
147. Sharpe M, Walker J, Holm Hansen C, et al. Integrated collaborative care for comorbid major depression in patients with cancer (SMaRT Oncology-2): a multicentre randomised controlled effectiveness trial. *Lancet (London, England)*. 2014;384(9948):1099-1108. doi:10.1016/S0140-6736(14)61231-9
148. Klemm P. Effects of online support group format (moderated vs peer-led) on depressive symptoms and extent of participation in women with breast cancer. *Comput Inform Nurs*. 2012;30(1):9-18. doi:https://dx.doi.org/10.1097/NCN.0b013e3182343efa
149. Tasbandi MJDFKSMTM. Effect of Orem's Self-Care Model Training Program on Anxiety of Women with Breast Cancer: A Clinical Trial Study. *Medical-Surgical Nurs J*. 2018;7(2):1-6.
150. Wang J, Yan C, Fu A. A randomized clinical trial of comprehensive education and care program compared to basic care for reducing anxiety and depression and improving quality of life and survival in patients with hepatocellular carcinoma who underwent surgery. *Medicine (Baltimore)*. 2019;98(44):e17552. doi:https://dx.doi.org/10.1097/MD.0000000000017552
151. Hsieh C-C, Hsiao F-H. The effects of supportive care interventions on depressive symptoms among patients with lung cancer: A metaanalysis of randomized controlled studies. *Palliat Support Care*. 2017;15(6):710-723. doi:http://dx.doi.org/10.1017/S1478951517000335
152. (USDHHS). UD of H and HS. *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General Atlanta, GA.*; 2014.
153. Underwood JM, Rim SH, Fairley TL, Tai E, Stewart SL. Cervical cancer survivors at increased risk of subsequent tobacco-related malignancies, United States 1992-2008. *Cancer Causes Control*. 2012;23(7):1009-1016. doi:10.1007/s10552-012-9957-2
154. Organization WH. About cardiovascular diseases. https://www.who.int/cardiovascular_diseases/about_cvd/en/.
155. Cumming TB, Blomstrand C, Skoog I, Linden T. The high prevalence of anxiety disorders after stroke. *Am J Geriatr Psychiatry*. 2016;24(2):154-160. doi:10.1016/j.jagp.2015.06.003
156. Batelaan NM, Seldenrijk A, Bot M, van Balkom AJLM, Penninx BWJH. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *Br J Psychiatry*. 2016;208(3):223-231. doi:10.1192/bjp.bp.114.156554
157. O'Neil A, Williams ED, Stevenson CE, Oldenburg B, Sanderson K. Co-morbid depression is associated with poor work outcomes in persons with cardiovascular disease (CVD): a large, nationally representative survey in the Australian population. *BMC Public Health*. 2012;12:47. doi:10.1186/1471-2458-12-47
158. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*. 2002;105(9):1049-1053. doi:10.1161/hc0902.104707
159. Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW. Screening and Management of Depression in Patients With Cardiovascular Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;73(14):1827-1845. doi:10.1016/j.jacc.2019.01.041
160. Ladwig S, Zhou Z, Xu Y, et al. Comparison of Treatment Rates of Depression After Stroke Versus Myocardial Infarction: A Systematic Review and Meta-Analysis of Observational Data. *Psychosom Med*. 2018;80(8).

https://journals.lww.com/psychosomaticmedicine/Fulltext/2018/10000/Comparison_of_Treatment_Rates_of_Depression_After.9.aspx.
161. Case SM, Sawhney M, Stewart JC. Atypical depression and double depression predict new-onset cardiovascular disease in US adults. *Depress Anxiety*. 2018;35(1):10-17. doi:10.1002/da.22666
162. Ayerbe L, Ayis S, Wolfe CDA, Rudd AG. Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. *Br J Psychiatry*. 2013;202(1):14-21. doi:10.1192/bjp.bp.111.107664
163. Mitchell AJ, Sheth B, Gill J, et al. Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. *Gen Hosp Psychiatry*. 2017;47:48-60. doi:10.1016/j.genhosppsych.2017.04.001
164. Goldstein BI, Schaffer A, Wang S, Blanco C. Excessive and premature new-onset cardiovascular disease among adults with bipolar disorder in the US NESARC cohort. *J Clin Psychiatry*. 2015;76(2):163-169. doi:10.4088/JCP.14m09300
165. Isomura K, Brander G, Chang Z, et al. Metabolic and cardiovascular complications in obsessive-compulsive disorder: A total population, sibling comparison study with long-term follow-up. *Biol Psychiatry*. 2018;84(5):324-331. doi:10.1016/j.biopsych.2017.12.003
166. Pilver CE, Potenza MN. Increased incidence of cardiovascular conditions among older adults with pathological gambling features in a prospective study. *J Addict Med*. 2013;7(6):387-393. doi:https://dx.doi.org/10.1097/ADM.0b013e31829e9b36
167. Remch M, Laskaris Z, Flory J, Mora-McLaughlin C, Morabia A. Post-Traumatic Stress Disorder and Cardiovascular Diseases: A Cohort Study of Men and Women Involved in Cleaning the Debris of the World Trade Center Complex. *Circ Cardiovasc Qual Outcomes*. 2018;11(7):e004572. doi:https://dx.doi.org/10.1161/CIRCOUTCOMES.117.004572
168. Attar R, Valentin JB, Freeman P, Andell P, Aagaard J, Jensen SE. The effect of schizophrenia on major adverse cardiac events, length of hospital stay, and prevalence of somatic comorbidities following acute coronary syndrome. *Eur Hear Journal Qual Care Clin Outcomes*. 2019;5(2):121-126. doi:http://dx.doi.org/10.1093/ehjqcco/qcy055
169. Snow SC, Fonarow GC, Ladapo JA, Washington DL, Hoggatt KJ, Ziaeian B. National Rate of Tobacco and Substance Use Disorders Among Hospitalized Heart Failure Patients. *Am J Med*. 2019;132(4):478-488.e4. doi:10.1016/j.amjmed.2018.11.038
170. Buckland SA, Pozehl B, Yates B. Depressive Symptoms in Women With Coronary Heart Disease: A Systematic Review of the Longitudinal Literature. *J Cardiovasc Nurs*. 2019;34(1):52-59. doi:https://dx.doi.org/10.1097/JCN.0000000000000533
171. AbuRuz ME, Masa'Deh R. Gender differences in anxiety and complications early after acute myocardial infarction. *J Cardiovasc Nurs*. 2017;32(6):538-543. doi:10.1097/JCN.0000000000000375
172. Eurelings LSM, van Dalen JW, Riet G ter, Charante EPM van, Edo R, van Gool WA. Apathy and depressive symptoms in older people and incident myocardial infarction, stroke, and mortality: a systematic review and meta-analysis of individual participant data. *Clin Epidemiol*. 2018;10:363-379. doi:http://dx.doi.org/10.2147/CLEP.S150915
173. Fei K, Benn EKT, Negron R, Arniella G, Tuhrim S, Horowitz CR. Prevalence of Depression Among Stroke Survivors: Racial-Ethnic Differences. *Stroke*. 2016;47(2):512-515. doi:https://dx.doi.org/10.1161/STROKEAHA.115.010292
174. Copeland VC, Newhill CE, Foster LJJ, et al. Major depressive disorder and cardiovascular disease in African-American women. *J Soc Serv Res*. 2017;43(5):624-634. doi:10.1080/01488376.2017.1370682
175. O'Keefe-McCarthy S, McGillion M, Clarke SP, McFetridge-Durdle J. Pain and anxiety in rural acute coronary syndrome patients awaiting diagnostic cardiac catheterization. *J Cardiovasc Nurs*. 2015;30(6):546-557. doi:10.1097/JCN.0000000000000203
176. Vidal C, Polo R, Alvarez K, et al. Co-Occurrence of Posttraumatic Stress Disorder and Cardiovascular Disease Among Ethnic/Racial Groups in the United States. *Psychosom Med*.

2018;80(7):680-688. doi:https://dx.doi.org/10.1097/PSY.0000000000000601
177. Ontario HQ. Screening and management of depression for adults with chronic diseases: an evidence-based analysis. *Ont Health Technol Assess Ser*. 2013;13(8):1-45. https://pubmed.ncbi.nlm.nih.gov/24133570.
178. Ai AL, Rollman BL, Berger CS. Comorbid mental health symptoms and heart diseases: can health care and mental health care professionals collaboratively improve the assessment and management? *Health Soc Work*. 2010;35(1):27-38. doi:10.1093/hsw/35.1.27
179. Lichtman JH, Bigger JTJ, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council o. *Circulation*. 2008;118(17):1768-1775. doi:10.1161/CIRCULATIONAHA.108.190769
180. Shi WY, Stewart AG, Hare DL. Major depression in cardiac patients is accurately assessed using the cardiac depression scale. *Psychother Psychosom*. 2010;79(6):391-392. doi:10.1159/000320897
181. Perk J, De Backer G, Gohlke H, et al. [European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)]. *Turk Kardiyol Dern Ars*. 2012;40 Suppl 3:1-76.
182. Hare DL, Toukhsati SR, Johansson P, Jaarsma T. Depression and cardiovascular disease: a clinical review. *Eur Heart J*. 2014;35(21):1365-1372. doi:10.1093/eurheartj/eht462
183. Kociol RD, Greiner MA, Hammill BG, et al. Long-term outcomes of medicare beneficiaries with worsening renal function during hospitalization for heart failure. *Am J Cardiol*. 2010;105(12):1786-1793. doi:10.1016/j.amjcard.2010.01.361
184. Amarasingham R, Moore BJ, Tabak YP, et al. An automated model to identify heart failure patients at risk for 30-day readmission or death using electronic medical record data. *Med Care*. 2010;48(11):981-988. doi:10.1097/MLR.0b013e3181ef60d9
185. Pilowsky DJ, Wu L-T. Screening for alcohol and drug use disorders among adults in primary care: a review. *Subst Abuse Rehabil*. 2012;3(1):25-34. doi:10.2147/SAR.S30057
186. Thylstrup B, Clausen T, Hesse M. Cardiovascular disease among people with drug use disorders. *Int J Public Health*. 2015;60(6):659-668. doi:10.1007/s00038-015-0698-3
187. Dhar AK, Barton DA. Depression and the Link with Cardiovascular Disease. *Front psychiatry*. 2016;7:33. doi:10.3389/fpsyt.2016.00033
188. Sun J, Ma H, Yu C, et al. Association of Major Depressive Episodes With Stroke Risk in a Prospective Study of 0.5 Million Chinese Adults. *Stroke*. 2016;47(9):2203-2208. doi:https://dx.doi.org/10.1161/STROKEAHA.116.013512
189. Busch LY, Pössel P, Valentine JC. Meta-analyses of cardiovascular reactivity to rumination: A possible mechanism linking depression and hostility to cardiovascular disease. *Psychol Bull*. 2017;143(12):1378-1394. doi:10.1037/bul0000119
190. Brouwers C, Mommersteeg PMC, Nyklíček I, et al. Positive affect dimensions and their association with inflammatory biomarkers in patients with chronic heart failure. *Biol Psychol*. 2013;92(2):220-226. doi:10.1016/j.biopsycho.2012.10.002
191. de Jonge P, Rosmalen JGM, Kema IP, et al. Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: a critical review of the literature. *Neurosci Biobehav Rev*. 2010;35(1):84-90. doi:10.1016/j.neubiorev.2009.11.025
192. de Jonge P, Roest AM. Depression and cardiovascular disease: the end of simple models. *Br J Psychiatry*. 2012;201(5):337-338. doi:10.1192/bjp.bp.112.110502
193. Pieper B, Kirsner RS, Templin TN, Birk TJ. Injection drug use: an understudied cause of venous disease. *Arch Dermatol*. 2007;143(10):1305-1309. doi:10.1001/archderm.143.10.1305
194. Salmon AM, Dwyer R, Jauncey M, van Beek I, Topp L, Maher L. Injecting-related injury and disease among clients of a supervised injecting facility. *Drug Alcohol Depend*. 2009;101(1-2):132-136. doi:10.1016/j.drugalcdep.2008.12.002
195. Reece AS, Hulse GK. Impact of lifetime opioid exposure on arterial stiffness and vascular age: cross-sectional and longitudinal studies in men and women. *BMJ Open*. 2014;4(6):e004521.

doi:10.1136/bmjopen-2013-004521
196. Reece AS, Hulse GK. Lifetime opiate exposure as an independent and interactive cardiovascular risk factor in males: a cross-sectional clinical study. *Vasc Health Risk Manag*. 2013;9:551-561. doi:10.2147/VHRM.S48030
197. Kao D, Bucher Bartelson B, Khatri V, et al. Trends in reporting methadone-associated cardiac arrhythmia, 1997-2011: an analysis of registry data. *Ann Intern Med*. 2013;158(10):735-740. doi:10.7326/0003-4819-158-10-201305210-00008
198. Roy AK, McCarthy C, Kiernan G, et al. Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. *Addiction*. 2012;107(6):1132-1139. doi:10.1111/j.1360-0443.2011.03767.x
199. De Giorgi A, Fabbian F, Pala M, et al. Cocaine and acute vascular diseases. *Curr Drug Abuse Rev*. 2012;5(2):129-134. doi:10.2174/1874473711205020129
200. Figueredo VM. Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart. *Am J Med*. 2011;124(6):480-488. doi:10.1016/j.amjmed.2010.11.031
201. Seldenrijk A, Vogelzangs N, Batelaan NM, Wieman I, van Schaik DJF, Penninx BJWH. Depression, anxiety and 6-year risk of cardiovascular disease. *J Psychosom Res*. 2015;78(2):123-129. doi:10.1016/j.jpsychores.2014.10.007
202. Jaussent I, Ancelin M-L, Berr C, et al. Hypnotics and mortality in an elderly general population: a 12-year prospective study. *BMC Med*. 2013;11:212. doi:10.1186/1741-7015-11-212
203. Desbois AC, Cacoub P. Cannabis-associated arterial disease. *Ann Vasc Surg*. 2013;27(7):996-1005. doi:10.1016/j.avsg.2013.01.002
204. Abuse CC on S. *Substance Abuse in Canada: Concurrent Disorders*. Ottawa; 2009.
205. West RR, Jones DA, Henderson AH. Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction. *Heart*. 2012;98(8):637-644. doi:10.1136/heartjnl-2011-300302
206. Blumenthal JA, Sherwood A, Babyak MA, et al. Exercise and pharmacological treatment of depressive symptoms in patients with coronary heart disease: results from the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study. *J Am Coll Cardiol*. 2012;60(12):1053-1063. doi:10.1016/j.jacc.2012.04.040
207. Blumenthal JA, Babyak MA, O'Connor C, et al. Effects of exercise training on depressive symptoms in patients with chronic heart failure: the HF-ACTION randomized trial. *JAMA*. 2012;308(5):465-474. doi:10.1001/jama.2012.8720
208. Sherwood A, Blumenthal JA, Smith PJ, Watkins LL, Hoffman BM, Hinderliter AL. Effects of exercise and sertraline on measures of coronary heart disease risk in patients with major depression: Results from the SMILE-II randomized clinical trial. *Psychosom Med*. 2016;78(5):602-609. doi:10.1097/PSY.0000000000000301
209. Norlund F, Wallin E, Gustaf Olsson EM, et al. Internet-based cognitive behavioral therapy for symptoms of depression and anxiety among patients with a recent myocardial infarction: The U-CARE heart randomized controlled trial. *J Med Internet Res*. 2018;20(3). https://ezproxy.kpu.ca:2443/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=psyh&AN=2018-29258-001&login.asp&site=ehost-live&scope=site.
210. Reavell J, Hopkinson M, Clarkesmith D, Lane DA. Effectiveness of cognitive behavioral therapy for depression and anxiety in patients with cardiovascular disease: A systematic review and meta-analysis. *Psychosom Med*. 2018;80(8):742-753. doi:10.1097/PSY.0000000000000626
211. Dickens C, Cherrington A, Adeyemi I, et al. Characteristics of psychological interventions that improve depression in people with coronary heart disease: a systematic review and meta-regression. *Psychosom Med*. 2013;75(2):211-221. doi:10.1097/PSY.0b013e31827ac009
212. Gulliksson M, Burell G, Vessby B, Lundin L, Toss H, Svärdsudd K. Randomized controlled trial of cognitive behavioral therapy vs standard treatment to prevent recurrent cardiovascular events in patients with coronary heart disease: Secondary Prevention in Uppsala Primary

Health Care project (SUPRIM). *Arch Intern Med*. 2011;171(2):134-140. doi:10.1001/archinternmed.2010.510
213. Hill K, House A, Knapp P, Wardhaugh C, Bamford J, Vail A. Prevention of mood disorder after stroke: a randomised controlled trial of problem solving therapy versus volunteer support. *BMC Neurol*. 2019;19(1):128. doi:10.1186/s12883-019-1349-8
214. Jiang X, He G. Effects of an uncertainty management intervention on uncertainty, anxiety, depression, and quality of life of chronic obstructive pulmonary disease outpatients. *Res Nurs Health*. 2012;35(4):409-418. doi:https://dx.doi.org/10.1002/nur.21483
215. Brodrick JE, Mathys ML. Antidepressant exposure and risk of dementia in older adults with major depressive disorder. *J Am Geriatr Soc*. 2016;64(12):2517-2521. doi:10.1111/jgs.14378
216. Davidson KW, Bigger JT, Burg MM, et al. Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial. *JAMA Intern Med*. 2013;173(11):997-1004. doi:10.1001/jamainternmed.2013.915
217. Kalogirou F, Forsyth F, Kyriakou M, Mantle R, Deaton C. Heart failure disease management: a systematic review of effectiveness in heart failure with preserved ejection fraction. *ESC Hear Fail*. 2020;7(1):194-212. doi:10.1002/ehf2.12559
218. Islam SMS, Chow CK, Redfern J, et al. Effect of text messaging on depression in patients with coronary heart disease: a substudy analysis from the TEXT ME randomised controlled trial. *BMJ Open*. 2019;9(2). doi:http://dx.doi.org/10.1136/bmjopen-2018-022637
219. McClure T, Haykowsky MJ, Schopflocher D, Hsu ZY, Clark AM. Home-based secondary prevention programs for patients with coronary artery disease: a meta-analysis of effects on anxiety. *J Cardiopulm Rehabil Prev*. 2013;33(2):59-67. doi:https://dx.doi.org/10.1097/HCR.0b013e3182828f71
220. Linder SM, Rosenfeldt AB, Bay RC, Sahu K, Wolf SL, Alberts JL. Improving quality of life and depression after stroke through telerehabilitation. *Am J Occup Ther*. 2015;69(2):1-9. doi:10.5014/ajot.2015.014498
221. Kokcu PhD OD, Kaya PhD H. The Effect of Web-Based Training on Anxiety and Depression Levels in Myocardial Infarction Patients. *Int J Caring Sci*. 2019;12(3):1372-1379. https://ezproxy.kpu.ca:2443/login?url=https://search.proquest.com/docview/2363845106?accountid=35875.
222. Mead H, Andres E, Katch H, Siegel B, Regenstein M. Gender differences in psychosocial issues affecting low-income, underserved patients' ability to manage cardiovascular disease. *Women's Heal issues Off Publ Jacobs Inst Women's Heal*. 2010;20(5):308-315. doi:10.1016/j.whi.2010.05.006
223. Gellis ZD, Kang-Yi C. Meta-analysis of the effect of cardiac rehabilitation interventions on depression outcomes in adults 64 years of age and older. *Am J Cardiol*. 2012;110(9):1219-1224. doi:https://dx.doi.org/10.1016/j.amjcard.2012.06.021
224. Association A. What is dementia? https://www.alz.org/alzheimers-dementia/what-is-dementia.
225. Kuring JK, Mathias JL, Ward L. Prevalence of Depression, Anxiety and PTSD in People with Dementia: a Systematic Review and Meta-Analysis. *Neuropsychol Rev*. 2018;28(4):393. doi:http://dx.doi.org/10.1007/s11065-018-9396-2
226. Bulloch AGM, Fiest KM, Williams JVA, et al. Depression—A common disorder across a broad spectrum of neurological conditions: A cross-sectional nationally representative survey. *Gen Hosp Psychiatry*. 2015;37(6):507-512. doi:10.1016/j.genhosppsych.2015.06.007
227. Giebel C, Sutcliffe C, Verbeek H, et al. Depressive symptomatology and associated factors in dementia in Europe: home care versus long-term care. *Int Psychogeriatrics*. 2016;28(4):621-630. doi:http://dx.doi.org/10.1017/S1041610215002100
228. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry*. 2013;202(5):329-335.

doi:10.1192/bjp.bp.112.118307
229. Demichele-sweet MAA, Weamer EA, Klei L, et al. Genetic risk for schizophrenia and psychosis in Alzheimer disease. *Mol Psychiatry*. 2018;23(4):963-972. doi:http://dx.doi.org/10.1038/mp.2017.81
230. Kørner A, Lopez AG, Lauritzen L, Andersen PK, Kessing LV. Late and very-late first-contact schizophrenia and the risk of dementia--a nationwide register based study. *Int J Geriatr Psychiatry*. 2009;24(1):61-67. doi:10.1002/gps.2075
231. Flatt JD, Gilsanz P, Quesenberry CPJ, Albers KB, Whitmer RA. Post-traumatic stress disorder and risk of dementia among members of a health care delivery system. *Alzheimer's Dement J Alzheimer's Assoc*. 2018;14(1):28-34. doi:10.1016/j.jalz.2017.04.014
232. Novais F, Starkstein S. Phenomenology of Depression in Alzheimer's Disease. *J Alzheimers Dis*. 2015;47(4):845-855. doi:10.3233/JAD-148004
233. Burke AD, Goldfarb D, Bollam P, Khokher S. Diagnosing and Treating Depression in Patients with Alzheimer's Disease. *Neurol Ther*. August 2019:1-26. doi:http://dx.doi.org/10.1007/s40120-019-00148-5
234. Ng A, Tam WW, Zhang MW, et al. IL-1β, IL-6, TNF- α and CRP in Elderly Patients with Depression or Alzheimer's disease: Systematic Review and Meta-Analysis. *Sci Rep*. 2018;8(1). doi:10.1038/s41598-018-30487-6
235. Qiu WQ, Zhu H, Dean M, et al. Amyloid-associated depression and ApoE4 allele: Longitudinal follow-up for the development of Alzheimer's disease. *Int J Geriatr Psychiatry*. 2016;31(3):316-322. doi:10.1002/gps.4339
236. Burke Danielle Goldfarb Padmaja Bollam Sehar Khokher AD, Burke AD, Bollam ÁP, Goldfarb D, Khokher Wellspan Philhaven S, Gretna M. Diagnosing and Treating Depression in Patients with Alzheimer's Disease. doi:10.6084/m9.figshare.8982449
237. DeMichele-Sweet MAA, Weamer EA, Klei L, et al. Genetic risk for schizophrenia and psychosis in Alzheimer disease. *Mol Psychiatry*. 2018;23(4):963-972. doi:10.1038/mp.2017.81
238. Rafferty LA, Cawkill PE, Stevelink SAM, Greenberg K, Greenberg N. Dementia, post-traumatic stress disorder and major depressive disorder: a review of the mental health risk factors for dementia in the military veteran population. *Psychol Med*. 2018;48(9):1400-1409. doi:http://dx.doi.org/10.1017/S0033291717001386
239. Qureshi SU, Kimbrell T, Pyne JM, et al. Greater prevalence and incidence of dementia in older veterans with posttraumatic stress disorder. *J Am Geriatr Soc*. 2010;58(9):1627-1633. doi:10.1111/j.1532-5415.2010.02977.x
240. Meziab O, Kirby KA, Williams B, Yaffe K, Byers AL, Barnes DE. Prisoner of war status, posttraumatic stress disorder, and dementia in older veterans. *Alzheimers Dement*. 2014;10(3 Suppl):S236-41. doi:10.1016/j.jalz.2014.04.004
241. Yaffe K, Hoang TD, Byers AL, Barnes DE, Friedl KE. Lifestyle and health-related risk factors and risk of cognitive aging among older veterans. *Alzheimers Dement*. 2014;10(3 Suppl):S111-21. doi:10.1016/j.jalz.2014.04.010
242. Byers AL, Yaffe K. Depression and dementias among military veterans. *Alzheimers Dement*. 2014;10(3 Suppl):S166-73. doi:10.1016/j.jalz.2014.04.007
243. Sibener L, Zaganjor I, Snyder HM, Bain LJ, Egge R, Carrillo MC. Alzheimer's Disease prevalence, costs, and prevention for military personnel and veterans. *Alzheimers Dement*. 2014;10(3 Suppl):S105-10. doi:10.1016/j.jalz.2014.04.011
244. Veitch DP, Friedl KE, Weiner MW. Military risk factors for cognitive decline, dementia and Alzheimer's disease. *Curr Alzheimer Res*. 2013;10(9):907-930. doi:10.2174/15672050113109990142
245. DENT OF, JORM AF, TENNANT C, et al. Association between depression and cognitive impairment in aged male war veterans. *Aging Ment Health*. 1998;2(4):306-312. doi:10.1080/13607869856551
246. Boorman E, Romano GF, Russell A MV and PC. Are Mood and Anxiety Disorders Inflammatory Diseases? *Psychiatr Ann*. 45:240–248.

247. Butters MA, Young JB, Lopez O, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci*. 2008;10(3):345-357. https://pubmed.ncbi.nlm.nih.gov/18979948.
248. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane database Syst Rev*. 2015;(4):CD006489. doi:https://dx.doi.org/10.1002/14651858.CD006489.pub4
249. Potter R, Ellard D, Rees K, Thorogood M. A systematic review of the effects of physical activity on physical functioning, quality of life and depression in older people with dementia. *Int J Geriatr Psychiatry*. 2011;26(10):1000-1011. doi:https://dx.doi.org/10.1002/gps.2641
250. Chakkalackal, L., Kalathil J. *Evaluation Report: Peer Support Groups to Facilitate Self-Help Coping Strategies for People with Dementia in Extra Care Housing*. London:; 2014. www.jcpmh.info/wp-content/%0Auploads/10keymsgs-olderpeople.pdf.
251. Orgeta V, Tabet N, Nilforooshan R, Howard R. Efficacy of Antidepressants for Depression in Alzheimer's Disease: Systematic Review and Meta-Analysis. *J Alzheimer's Dis*. 2017;58(3):725-733. doi:10.3233/JAD-161247
252. NICE. *Dementia: Assessment, Management and Support for People Living with Dementia and Their Carers NICE Guideline [NG97].*; 2018. https://www.nice.org.uk/guidance/ng97/chapter/Recommendations.
253. Orgeta V, Qazi A, Spector A, Orrell M. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment: systematic review and meta-analysis. *Br J Psychiatry*. 2015;207(4):293-298. doi:10.1192/bjp.bp.114.148130
254. Gellis ZD, McClive-Reed KP, Brown E. Treatments for Depression in Older Persons with Dementia. *Ann long-term care Off J Am Med Dir Assoc*. 2009;17(2):29-36.
255. Kiosses DN, Leon AC, Areán PA. Psychosocial interventions for late-life major depression: evidence-based treatments, predictors of treatment outcomes, and moderators of treatment effects. *Psychiatr Clin North Am*. 2011;34(2):377-401, viii. doi:10.1016/j.psc.2011.03.001
256. Rodrigues J, Capuano AW, Barnes LL, Bennett DA, Shah RC. Effect of antidepressant medication use and social engagement on the level of depressive symptoms in community-dwelling, older African Americans and Whites with dementia. *J Aging Health*. 2019;31(7):1278-1296. doi:10.1177/0898264318772983
257. Onega LL, Pierce TW, Epperly L. Effect of bright light exposure on depression and agitation in older adults with dementia. *Issues Ment Health Nurs*. 2016;37(9):660-667. doi:10.1080/01612840.2016.1183736
258. Organization WH. Diabetes Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/diabetes. Published 2020.
259. Khaledi M, Haghighatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. *Acta Diabetol*. 2019;56(6):631-650. doi:10.1007/s00592-019-01295-9
260. Tong A, Wang X, Li F, Xu F, Li Q, Zhang F. Risk of depressive symptoms associated with impaired glucose metabolism, newly diagnosed diabetes, and previously diagnosed diabetes: a meta-analysis of prospective cohort studies. *Acta Diabetol*. 2016;53(4):589-598. doi:http://dx.doi.org/10.1007/s00592-016-0845-1
261. Deschênes SS, Burns RJ, Schmitz N. Comorbid depressive and anxiety symptoms and the risk of type 2 diabetes: Findings from the Lifelines Cohort Study. *J Affect Disord*. 2018;238:24-31. doi:10.1016/j.jad.2018.05.029
262. Nieto-Martínez R, González-Rivas JP, Medina-Inojosa JR, Florez H. Are Eating Disorders Risk Factors for Type 2 Diabetes? A Systematic Review and Meta-analysis. *Curr Diab Rep*. 2017;17(12):138. doi:10.1007/s11892-017-0949-1
263. de Jonge P, Alonso J, Stein DJ, et al. Associations between DSM-IV mental disorders and diabetes mellitus: a role for impulse control disorders and depression. *Diabetologia*. 2014;57(4):699-709. doi:10.1007/s00125-013-3157-9

264. Aronson BD, Palombi LC, Walls ML. Rates and consequences of posttraumatic distress among American Indian adults with type 2 diabetes. *J Behav Med*. 2016;39(4):694-703. doi:10.1007/s10865-016-9733-y
265. Lee C-M, Chang C-F, Pan M-Y, Hsu T-H, Chen M-Y. Depression and Its Associated Factors Among Rural Diabetic Residents. *J Nurs Res*. 2017;25(1):31-40. doi:https://dx.doi.org/10.1097/jnr.0000000000000143
266. Agyemang C, Goosen S, … KA-TEJ, 2012 undefined. Relationship between post-traumatic stress disorder and diabetes among 105 180 asylum seekers in the Netherlands. *academic.oup.com*. https://academic.oup.com/eurpub/article-abstract/22/5/658/498282. Accessed May 5, 2020.
267. Lunghi C, Moisan J, Gregoire J-P, Guenette L. Incidence of Depression and Associated Factors in Patients With Type 2 Diabetes in Quebec, Canada: A Population-Based Cohort Study. *Medicine (Baltimore)*. 2016;95(21):e3514. doi:https://dx.doi.org/10.1097/MD.0000000000003514
268. van Dooren FEP, Nefs G, Schram MT, Verhey FRJ, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One*. 2013;8(3):e57058. doi:10.1371/journal.pone.0057058
269. Acee AM. Diabetes, depression, and OASIS-C: a guide for home healthcare clinicians. *Home Healthc Nurse*. 2014;32(6):362-371. doi:https://dx.doi.org/10.1097/NHH.0000000000000091
270. McEniry M. Early-life conditions and older adult health in low- and middle-income countries: a review. *J Dev Orig Health Dis*. 2013;4(1):10-29. doi:10.1017/S2040174412000499
271. Bădescu S V, Tătaru C, Kobylinska L, et al. The association between Diabetes mellitus and Depression. *J Med Life*. 2016;9(2):120-125. https://pubmed.ncbi.nlm.nih.gov/27453739.
272. Chen G, Xu R, Wang Y, et al. Genetic disruption of soluble epoxide hydrolase is protective against streptozotocin-induced diabetic nephropathy. *Am J Physiol Endocrinol Metab*. 2012;303(5):E563-75. doi:10.1152/ajpendo.00591.2011
273. van Dooren FEP, Pouwer F, Schalkwijk CG, et al. Advanced Glycation End Product (AGE) Accumulation in the Skin is Associated with Depression: The Maastricht Study. *Depress Anxiety*. 2017;34(1):59-67. doi:10.1002/da.22527
274. Moulton CD, Pickup JC, Ismail K. The link between depression and diabetes: the search for shared mechanisms. *lancet Diabetes Endocrinol*. 2015;3(6):461-471. doi:10.1016/S2213-8587(15)00134-5
275. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry*. 2013;18(9):963-974. doi:10.1038/mp.2013.20
276. van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT. Association of Microvascular Dysfunction With Late-Life Depression: A Systematic Review and Meta-analysis. *JAMA psychiatry*. 2017;74(7):729-739. doi:10.1001/jamapsychiatry.2017.0984
277. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA. Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2018;90:164-173. doi:10.1016/j.neubiorev.2018.04.003
278. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838. doi:10.1016/S1474-4422(13)70124-8
279. Mitchell GF, van Buchem MA, Sigurdsson S, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain*. 2011;134(Pt 11):3398-3407. doi:10.1093/brain/awr253
280. Muris DMJ, Houben AJHM, Schram MT, Stehouwer CDA. Microvascular dysfunction is associated with a higher incidence of type 2 diabetes mellitus: a systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol*. 2012;32(12):3082-3094. doi:10.1161/ATVBAHA.112.300291
281. Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic

review and meta-analysis. *Diabetes Care*. 2013;36(1):166-175. doi:10.2337/dc12-0702
282. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186. doi:10.1097/PSY.0b013e3181907c1b
283. Pasco JA, Nicholson GC, Williams LJ, et al. Association of high-sensitivity C-reactive protein with de novo major depression. *Br J Psychiatry*. 2010;197(5):372-377. doi:10.1192/bjp.bp.109.076430
284. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: A meta-analysis. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2015;25(10):1532-1543. doi:10.1016/j.euroneuro.2015.06.007
285. Chireh B, Li M, D'Arcy C. Diabetes increases the risk of depression: A systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. *Prev Med reports*. 2019;14:100822. doi:10.1016/j.pmedr.2019.100822
286. Hansen T, Ingason A, Djurovic S, et al. At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia. *Biol Psychiatry*. 2011;70(1):59-63. doi:10.1016/j.biopsych.2011.01.031
287. Piette JD, Richardson C, Himle J, et al. A randomized trial of telephonic counseling plus walking for depressed diabetes patients. *Med Care*. 2011;49(7):641-648. doi:https://dx.doi.org/10.1097/MLR.0b013e318215d0c9
288. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. *Cochrane database Syst Rev*. 2012;12:CD008381. doi:https://dx.doi.org/10.1002/14651858.CD008381.pub2
289. Egede LE, Walker RJ, Payne EH, Knapp RG, Acierno R, Frueh BC. Effect of psychotherapy for depression via home telehealth on glycemic control in adults with type 2 diabetes: Subgroup analysis of a randomized clinical trial. *J Telemed Telecare*. 2018;24(9):596-602. doi:10.1177/1357633X17730419
290. McBain H, Mulligan K, Haddad M, Flood C, Jones J, Simpson A. Self management interventions for type 2 diabetes in adult people with severe mental illness. *Cochrane database Syst Rev*. 2016;4:CD011361. doi:https://dx.doi.org/10.1002/14651858.CD011361.pub2
291. Hermanns N, Caputo S, Dzida G, Khunti K, Meneghini LF, Snoek F. Screening, evaluation and management of depression in people with diabetes in primary care. *Prim Care Diabetes*. 2013;7(1):1-10. doi:10.1016/j.pcd.2012.11.002
292. LeBron AMW, Valerio MA, Kieffer E, et al. Everyday Discrimination, Diabetes-Related Distress, and Depressive Symptoms Among African Americans and Latinos with Diabetes. *J Immigr Minor Heal*. 2014;16(6):1208-1216. doi:10.1007/s10903-013-9843-3
293. Taveira TH, Dooley AG, Cohen LB, Khatana SAM, Wu W-C. Pharmacist-led group medical appointments for the management of type 2 diabetes with comorbid depression in older adults. *Ann Pharmacother*. 2011;45(11):1346-1355. doi:https://dx.doi.org/10.1345/aph.1Q212
294. Kaltman S, Serrano A, Talisman N, et al. Type 2 diabetes and depression: A pilot trial of an integrated self-management intervention for latino immigrants. *Diabetes Educ*. 2016;42(1):87-95. doi:10.1177/0145721715617536
295. de Vries McClintock HF, Boyle KB, Rooney K, Bogner HR. Diabetes and depression care: A randomized controlled pilot trial. *Am J Health Behav*. 2016;40(4):503-513. doi:10.5993/AJHB.40.4.12
296. Huang Y, Wei X, Wu T, Chen R, Guo A. Collaborative care for patients with depression and diabetes mellitus: a systematic review and meta-analysis. *BMC Psychiatry*. 2013;13:260. doi:https://dx.doi.org/10.1186/1471-244X-13-260
297. Organization WH. *Epilepsy: A Public Health Imperative.*; 2019. https://www.who.int/mental_health/neurology/epilepsy/report_2019/en/.
298. Wiglusz MS, Landowski J, Cubała WJ. Prevalence of anxiety disorders in epilepsy. *Epilepsy Behav*. 2018;79:1-3. doi:10.1016/j.yebeh.2017.11.025
299. Munger Clary HM, Snively BM, Hamberger MJ. Anxiety is common and independently associated with clinical features of epilepsy. *Epilepsy Behav*. 2018;85:64-71. doi:10.1016/j.yebeh.2018.05.024

300. Lacey CJ, Salzberg MR, D'Souza WJ. Risk factors for depression in community-treated epilepsy: systematic review. *Epilepsy Behav*. 2015;43:1-7. doi:10.1016/j.yebeh.2014.11.023
301. Chen Y-H, Wei H-T, Bai Y-M, et al. Risk of Epilepsy in Individuals With Posttraumatic Stress Disorder: A Nationwide Longitudinal Study. *Psychosom Med*. 2017;79(6):664-669. doi:https://dx.doi.org/10.1097/PSY.0000000000000463
302. Labudda K, Illies D, Bien CG, Neuner F. Postepileptic seizure PTSD: A very rare psychiatric condition in patients with epilepsy. *Epilepsy Behav*. 2018;78:219-225. doi:10.1016/j.yebeh.2017.08.043
303. Abraham N, Buvanaswari P, Rathakrishnan R, et al. A Meta-Analysis of the Rates of Suicide Ideation, Attempts and Deaths in People with Epilepsy. *Int J Environ Res Public Health*. 2019;16(8). doi:10.3390/ijerph16081451
304. Myers L, Lancman M, Vazquez-Casals G, Bonafina M, Perrine K, Sabri J. Depression and quality of life in Spanish-speaking immigrant persons with epilepsy compared with those in English-speaking US-born persons with epilepsy. *Epilepsy Behav*. 2015;51:146-151. doi:10.1016/j.yebeh.2015.07.024
305. de Oliveira GN, Lessa JMK, Gonçalves AP, Portela EJ, Sander JW, Teixeira AL. Screening for depression in people with epilepsy: comparative study among neurological disorders depression inventory for epilepsy (NDDI-E), hospital anxiety and depression scale depression subscale (HADS-D), and Beck depression inventory (BDI). *Epilepsy Behav*. 2014;34:50-54. doi:10.1016/j.yebeh.2014.03.003
306. Mehndiratta P, Sajatovic M. Treatments for patients with comorbid epilepsy and depression: a systematic literature review. *Epilepsy Behav*. 2013;28(1):36-40. doi:10.1016/j.yebeh.2013.03.029
307. Kanner AM. Depression and epilepsy: A bidirectional relation? *Epilepsia*. 2011;52 Suppl 1:21-27. doi:10.1111/j.1528-1167.2010.02907.x
308. Hoppe C, Elger CE. Depression in epilepsy: a critical review from a clinical perspective. *Nat Rev Neurol*. 2011;7(8):462-472. doi:10.1038/nrneurol.2011.104
309. McLaughlin DP, Pachana NA, McFarland K. The impact of depression, seizure variables and locus of control on health related quality of life in a community dwelling sample of older adults. *Seizure*. 2010;19(4):232-236. doi:10.1016/j.seizure.2010.02.008
310. Sankar R MA. Neurobiology of Depression as a Comorbidity of Epilepsy, 4th Edition. In: Bethesd, (MD: National Center for Biotechnology Information (US); 2012.
311. Mazarati AM, Shin D, Kwon YS, et al. Elevated plasma corticosterone level and depressive behavior in experimental temporal lobe epilepsy. *Neurobiol Dis*. 2009;34(3):457-461. doi:10.1016/j.nbd.2009.02.018
312. Mazarati AM, Pineda E, Shin D, Tio D, Taylor AN, Sankar R. Comorbidity between epilepsy and depression: role of hippocampal interleukin-1beta. *Neurobiol Dis*. 2010;37(2):461-467. doi:10.1016/j.nbd.2009.11.001
313. Maguire MJ, Weston J, Singh J, Marson AG. Antidepressants for people with epilepsy and depression. *Cochrane database Syst Rev*. 2014;(12):CD010682. doi:https://dx.doi.org/10.1002/14651858.CD010682.pub2
314. Bradley PM, Lindsay B, Fleeman N. Care delivery and self management strategies for adults with epilepsy. *Cochrane database Syst Rev*. 2016;2:CD006244. doi:10.1002/14651858.CD006244.pub3
315. Canadian Frailty Network. What is frailty? https://www.cfn-nce.ca/frailty-matters/what-is-frailty/.
316. Vaughan L, Corbin AL, Goveas JS. Depression and frailty in later life: a systematic review. *Clin Interv Aging*. 2015;10:1947-1958. doi:10.2147/CIA.S69632
317. Rodríguez-Mañas L, Féart C, Mann G, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci*. 2013;68(1):62-67. doi:10.1093/gerona/gls119
318. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146-56. doi:10.1093/gerona/56.3.m146

319. Paulson D, Lichtenberg PA. Vascular depression: An early warning sign of frailty. *Aging Ment Heal*. 2013;17(1):85-93. doi:10.1080/13607863.2012.692767
320. Arts MHL, Collard RM, Comijs HC, et al. Relationship between physical frailty and low-grade inflammation in late-life depression. *J Am Geriatr Soc*. 2015;63(8):1652-1657. doi:10.1111/jgs.13528
321. Pollok J, van Agteren JE, Carson-Chahhoud K V. Depression and frailty in old age: a narrative review of the literature published between 2008 and 2018. *Cochrane database Syst Rev*. 2018;12(12):CD012346-CD012346. doi:10.1002/14651858.CD012346.pub2
322. Berthold-Losleben M, Himmerich H. The TNF-alpha system: functional aspects in depression, narcolepsy and psychopharmacology. *Curr Neuropharmacol*. 2008;6(3):193-202. doi:10.2174/157015908785777238
323. Ting EY-C, Yang AC, Tsai S-J. Role of Interleukin-6 in Depressive Disorder. *Int J Mol Sci*. 2020;21(6):2194. doi:http://dx.doi.org/10.3390/ijms21062194
324. Farooq RK, Asghar K, Kanwal S, Zulqernain A. Role of inflammatory cytokines in depression: Focus on interleukin-1β. *Biomed Reports*. 2017;6(1):15. doi:http://dx.doi.org/10.3892/br.2016.807
325. Monteserin R, Brotons C, Moral I, et al. Effectiveness of a geriatric intervention in primary care: a randomized clinical trial. *Fam Pract*. 2010;27(3):239-245. doi:10.1093/fampra/cmp101
326. Apóstolo J, Cooke R, Bobrowicz-Campos E, et al. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a systematic review. *JBI database Syst Rev Implement reports*. 2018;16(1):140-232. doi:10.11124/JBISRIR-2017-003382
327. Dent E, Morley JE, Cruz-Jentoft AJ, et al. Physical Frailty: ICFSR International Clinical Practice Guidelines for Identification and Management. *J Nutr Health Aging*. 2019;23(9):771-787. doi:10.1007/s12603-019-1273-z
328. Medicine UNL of. Huntington disease. https://ghr.nlm.nih.gov/condition/huntington-disease. Published 2020.
329. Dale M, Maltby J, Shimozaki S, Cramp R, Rickards H. Disease stage, but not sex, predicts depression and psychological distress in Huntington's disease: A European population study. *J Psychosom Res*. 2016;80:17-22. doi:10.1016/j.jpsychores.2015.11.003
330. Martinez-Horta S, Perez-Perez J, van Duijn E, et al. Neuropsychiatric symptoms are very common in premanifest and early stage Huntington's Disease. *Parkinsonism Relat Disord*. 2016;25:58-64. doi:10.1016/j.parkreldis.2016.02.008
331. van Duijn E, Craufurd D, Hubers AAM, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *J Neurol Neurosurg Psychiatry*. 2014;85(12):1411-1418. doi:10.1136/jnnp-2013-307343
332. Wesson M, Boileau NR, Perlmutter JS, et al. Suicidal Ideation Assessment in Individuals with Premanifest and Manifest Huntington Disease. *J Huntingtons Dis*. 2018;7(3):239-249. doi:10.3233/JHD-180299
333. Epping EA, Mills JA, Beglinger LJ, et al. Characterization of depression in prodromal Huntington disease in the neurobiological predictors of HD (PREDICT-HD) study. *J Psychiatr Res*. 2013;47(10):1423-1431. doi:10.1016/j.jpsychires.2013.05.026
334. Bachoud-Lévi A-C, Ferreira J, Massart R, et al. International Guidelines for the Treatment of Huntington's Disease. *Front Neurol*. 2019;10:710. doi:10.3389/fneur.2019.00710
335. Read J, Jones R, Owen G, et al. Quality of life in Huntington's disease: a comparative study investigating the impact for those with pre-manifest and early manifest disease, and their partners. *J Huntingtons Dis*. 2013;2(2):159-175. doi:10.3233/JHD-130051
336. Mestre TA, van Duijn E, Davis AM, et al. Rating scales for behavioral symptoms in Huntington's disease: Critique and recommendations. *Mov Disord*. 2016;31(10):1466-1478. doi:10.1002/mds.26675
337. Epping EA, Paulsen JS. Depression in the early stages of Huntington disease. *Neurodegener Dis Manag*. 2011;1(5):407-414. doi:10.2217/nmt.11.45
338. 2 C and CF of A. The Facts About Inflammatory Bowel Diseases.

https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated IBD Factbook.pdf. Published 2014.
339. Bennebroek Evertsz' F, Thijssens NAM, Stokkers PCF, et al. Do Inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? *J Crohns Colitis*. 2012;6(1):68-76. doi:10.1016/j.crohns.2011.07.006
340. Tribbick D, Salzberg M, Ftanou M, et al. Prevalence of mental health disorders in inflammatory bowel disease: an Australian outpatient cohort. *Clin Exp Gastroenterol*. 2015;8:197-204. doi:10.2147/CEG.S77567
341. Lima FDV de, Ribeiro TC da R, Chebli LA, et al. Mood swings in patients with Crohn's disease: incidence and associated factors. *Rev Assoc Med Bras*. 2012;58(4):481-488.
342. Byrne G, Rosenfeld G, Leung Y, et al. Prevalence of Anxiety and Depression in Patients with Inflammatory Bowel Disease. *Can J Gastroenterol Hepatol*. 2017;2017:6. doi:http://dx.doi.org/10.1155/2017/6496727
343. Fuller-Thomson E, Lateef R, Sulman J. Robust Association Between Inflammatory Bowel Disease and Generalized Anxiety Disorder: Findings from a Nationally Representative Canadian Study. *Inflamm Bowel Dis*. 2015;21(10):2341-2348. doi:https://dx.doi.org/10.1097/MIB.0000000000000518
344. Choi K, Chun J, Han K, et al. Risk of Anxiety and Depression in Patients with Inflammatory Bowel Disease: A Nationwide, Population-Based Study. *J Clin Med*. 2019;8(5):654. doi:10.3390/jcm8050654
345. Kao L-T, Lin H-C, Lee H-C. Inflammatory bowel disease and bipolar disorder: A population-based cross-sectional study. *J Affect Disord*. 2019;247:120-124. doi:10.1016/j.jad.2019.01.014
346. Graff LA, Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis*. 2009;15(7):1105-1118. doi:10.1002/ibd.20873
347. Faust AH, Halpern LF, Danoff-Burg S, Cross RK. Psychosocial factors contributing to inflammatory bowel disease activity and health-related quality of life. *Gastroenterol Hepatol (N Y)*. 2012;8(3):173-181.
348. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. 2015;28(2):203-209. https://pubmed.ncbi.nlm.nih.gov/25830558.
349. Powell N, Walker MM, Talley NJ. The mucosal immune system: master regulator of bidirectional gut–brain communications. *Nat Rev Gastroenterol Hepatol*. 2017;14(3):143-159. doi:10.1038/nrgastro.2016.191
350. Dinan TG, Cryan JF. The Microbiome-Gut-Brain Axis in Health and Disease. *Gastroenterol Clin North Am*. 2017;46(1):77-89. doi:10.1016/j.gtc.2016.09.007
351. Mu C, Yang Y, Zhu W. Gut Microbiota: The Brain Peacekeeper. *Front Microbiol*. 2016;7:345. doi:10.3389/fmicb.2016.00345
352. Mikocka-Walus A, Ford AC, Drossman DA. Antidepressants in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2020;17(3):184-192. doi:10.1038/s41575-019-0259-y
353. Tabibian A, Tabibian JH, Beckman LJ, Raffals LL, Papadakis KA, Kane S V. Predictors of Health-Related Quality of Life and Adherence in Crohn's Disease and Ulcerative Colitis: Implications for Clinical Management. *Dig Dis Sci*. 2015;60(5):1366-1374. doi:10.1007/s10620-014-3471-1
354. Mikocka-Walus AA, Gordon AL, Stewart BJ, Andrews JM. ' Just to get it off my chest ': Patients' views on psychotherapy in inflammatory bowel disease. *Couns Psychother Res*. 2013;13(3):227-234. doi:10.1080/14733145.2012.730540
355. Hanlon I, Hewitt C, Bell K, Phillips A, Mikocka-Walus A. Systematic review with meta-analysis: online psychological interventions for mental and physical health outcomes in gastrointestinal disorders including irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;48(3):244-259. doi:10.1111/apt.14840
356. Stapersma L, van den Brink G, van der Ende J, et al. Illness Perceptions and Depression Are Associated with Health-Related Quality of Life in Youth with Inflammatory Bowel Disease. *Int*

J Behav Med. 2019;26(4):415-426. doi:http://dx.doi.org/10.1007/s12529-019-09791-6
357. Thompson RD, Craig A, Crawford EA, et al. Longitudinal results of cognitive behavioral treatment for youths with inflammatory bowel disease and depressive symptoms. *J Clin Psychol Med Settings*. 2012;19(3):329-337. doi:10.1007/s10880-012-9301-8
358. Mussell M, Böcker U, Nagel N, Olbrich R, Singer M V. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. *Scand J Gastroenterol*. 2003;38(7):755-762. doi:10.1080/00365520310003110
359. Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-Behavioural Therapy for Inflammatory Bowel Disease: 24-Month Data from a Randomised Controlled Trial. *Int J Behav Med*. 2017;24(1):127-135. doi:10.1007/s12529-016-9580-9
360. Neilson K, Ftanou M, Monshat K, et al. A Controlled Study of a Group Mindfulness Intervention for Individuals Living With Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2016;22(3):694-701. doi:https://dx.doi.org/10.1097/MIB.0000000000000629
361. Berrill JW, Sadlier M, Hood K, Green JT. Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. *J Crohns Colitis*. 2014;8(9):945-955. doi:10.1016/j.crohns.2014.01.018
362. Jedel S, Hoffman A, Merriman P, et al. A randomized controlled trial of mindfulness-based stress reduction to prevent flare-up in patients with inactive ulcerative colitis. *Digestion*. 2014;89(2):142-155. doi:10.1159/000356316
363. Peters SL, Muir JG, Gibson PR. Review article: gut-directed hypnotherapy in the management of irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41(11):1104-1115. doi:10.1111/apt.13202
364. Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. *Aliment Pharmacol Ther*. 2013;38(7):761-771. doi:10.1111/apt.12449
365. Muscat P, Chilcot J, Weinman J, Hudson J. Exploring the relationship between illness perceptions and depression in patients with chronic kidney disease: A systematic literature review. *J Ren Care*. 2018;44(3):174-185. doi:10.1111/jorc.12243
366. Nagler E V., Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3-5 chronic kidney disease: A systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). *Nephrol Dial Transplant*. 2012;27(10):3736-3745. doi:10.1093/ndt/gfs295
367. Nagler E V, Webster AC, Vanholder R, Zoccali C. Antidepressants for depression in stage 3–5 chronic kidney disease: a systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP)*. *Nephrol Dial Transplant*. 2012;27(10):3736-3745. doi:10.1093/ndt/gfs295
368. Palmer S, Vecchio M, Craig JC, et al. Prevalence of depression in chronic kidney disease: Systematic review and meta-analysis of observational studies. *Kidney Int*. 2013;84(1):179-191. doi:10.1038/ki.2013.77
369. Tzur Bitan D, Krieger I, Berkovitch A, Comaneshter D, Cohen A. Chronic kidney disease in adults with schizophrenia: A nationwide population-based study. *Gen Hosp Psychiatry*. 2019;58:1-6. doi:10.1016/j.genhosppsych.2019.01.007
370. Griva K, Lam KFY, Nandakumar M, Ng J-AH, McBain H, Newman SP. The effect of brief self-management intervention for hemodialysis patients (HED-SMART) on trajectories of depressive and anxious symptoms. *J Psychosom Res*. 2018;113:37-44. doi:https://dx.doi.org/10.1016/j.jpsychores.2018.07.012
371. Zalai D, Szeifert L, Novak M. Psychological distress and depression in patients with chronic kidney disease. *Semin Dial*. 2012;25(4):428-438. doi:10.1111/j.1525-139X.2012.01100.x
372. Tsai S-H, Wang M-Y, Miao N-F, Chian P-C, Chen T-H, Tsai P-S. CE: original research: The efficacy of a nurse-led breathing training program in reducing depressive symptoms in patients on hemodialysis: a randomized controlled trial. *Am J Nurs*. 2015;115(4):24-42.

doi:https://dx.doi.org/10.1097/01.NAJ.0000463023.48226.16
373. McIntyre RS, Danilewitz M, Liauw SS, et al. Bipolar disorder and metabolic syndrome: an international perspective. *J Affect Disord*. 2010;126(3):366-387. doi:10.1016/j.jad.2010.04.012
374. Ellingrod VL, Taylor SF, Dalack G, et al. Risk factors associated with metabolic syndrome in bipolar and schizophrenia subjects treated with antipsychotics: the role of folate pharmacogenetics. *J Clin Psychopharmacol*. 2012;32(2):261-265. doi:https://dx.doi.org/10.1097/JCP.0b013e3182485888
375. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis. *World Psychiatry*. 2015;14(3):339-347. doi:10.1002/wps.20252
376. Vancampfort D, Vansteelandt K, Correll CU, et al. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry*. 2013;170(3):265-274. doi:10.1176/appi.ajp.2012.12050620
377. Vancampfort D, Wampers M, Mitchell AJ, et al. A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. *World Psychiatry*. 2013;12(3):240-250. doi:10.1002/wps.20069
378. Carney R, Cotter J, Bradshaw T, Firth J, Yung AR. Cardiometabolic risk factors in young people at ultra-high risk for psychosis: A systematic review and meta-analysis. *Schizophr Res*. 2016;170(2-3):290-300. doi:10.1016/j.schres.2016.01.010
379. Emul M, Kalelioglu T. Etiology of cardiovascular disease in patients with schizophrenia: current perspectives. *Neuropsychiatr Dis Treat*. 2015;11:2493-2503. doi:10.2147/NDT.S50006
380. Bartoli F, Crocamo C, Caslini M, Clerici M, Carrà G. Schizoaffective disorder and metabolic syndrome: A meta-analytic comparison with schizophrenia and other non-affective psychoses. *J Psychiatr Res*. 2015;66-67:127-134. doi:10.1016/j.jpsychires.2015.04.028
381. Block A, Schipf S, Van der Auwera S, et al. Sex- and age-specific associations between major depressive disorder and metabolic syndrome in two general population samples in Germany. *Nord J Psychiatry*. 2016;70(8):611-620. doi:10.1080/08039488.2016.1191535
382. Singh Balhara YP, Jain R, Kuppili PP, Shukla A, Chawla N, Gupta R. Which Criteria to Use to Identify Metabolic Syndrome among Patients with Addictive Disorders?: Observations among Patients with Alcohol and Opioid Dependence Syndrome. *Indian J Endocrinol Metab*. 2018;22(4):565-568. doi:10.4103/ijem.IJEM_617_17
383. Butnoriene J, Steibliene V, Saudargiene A, Bunevicius A. Does presence of metabolic syndrome impact anxiety and depressive disorder screening results in middle aged and elderly individuals? A population based study. *BMC Psychiatry*. 2018;18. doi:10.1186/s12888-017-1576-8
384. Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;74(Pt B):277-286. doi:10.1016/j.neubiorev.2016.07.003
385. Licht CMM, de Geus EJC, van Dyck R, Penninx BWJH. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biol Psychiatry*. 2010;68(9):861-868. doi:10.1016/j.biopsych.2010.06.032
386. Licht CMM, de Geus EJC, Seldenrijk A, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. *Hypertens (Dallas, Tex 1979)*. 2009;53(4):631-638. doi:10.1161/HYPERTENSIONAHA.108.126698
387. Serretti A, Mandelli L. Antidepressants and body weight: a comprehensive review and meta-analysis. *J Clin Psychiatry*. 2010;71(10):1259-1272. doi:10.4088/JCP.09r05346blu
388. Lamers F, Burstein M, He J, Avenevoli S, Angst J, Merikangas KR. Structure of major depressive disorder in adolescents and adults in the US general population. *Br J Psychiatry*. 2012;201(2):143-150. doi:10.1192/bjp.bp.111.098079
389. Lasserre AM, Glaus J, Vandeleur CL, et al. Depression with atypical features and increase in

obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. *JAMA psychiatry*. 2014;71(8):880-888. doi:10.1001/jamapsychiatry.2014.411
390. Belin RJ, Greenland P, Allison M, et al. Diet quality and the risk of cardiovascular disease: the Women's Health Initiative (WHI). *Am J Clin Nutr*. 2011;94(1):49-57. doi:10.3945/ajcn.110.011221
391. Gade W, Schmit J, Collins M, Gade J. Beyond obesity: the diagnosis and pathophysiology of metabolic syndrome. *Clin Lab Sci*. 2010;23(1):51-55.
392. Rojo LE, Gaspar PA, Silva H, et al. Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. *Pharmacol Res*. 2015;101:74-85. doi:10.1016/j.phrs.2015.07.022
393. Mitchell AJ, Lord O, Malone D. Differences in the prescribing of medication for physical disorders in individuals with v. without mental illness: meta-analysis. *Br J Psychiatry*. 2012;201(6):435-443. doi:10.1192/bjp.bp.111.094532
394. Sundbøll J, Schmidt M, Adelborg K, et al. Impact of pre-admission depression on mortality following myocardial infarction. *Br J Psychiatry*. 2017;210(5):356-361. doi:10.1192/bjp.bp.116.194605
395. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: overview, mechanisms, and implications. *Dialogues Clin Neurosci*. 2018;20(1):63-73. https://pubmed.ncbi.nlm.nih.gov/29946213.
396. Shelton RC, Miller AH. Eating ourselves to death (and despair): the contribution of adiposity and inflammation to depression. *Prog Neurobiol*. 2010;91(4):275-299. doi:10.1016/j.pneurobio.2010.04.004
397. Sublette ME, Postolache TT. Neuroinflammation and depression: the role of indoleamine 2,3-dioxygenase (IDO) as a molecular pathway. *Psychosom Med*. 2012;74(7):668-672. doi:10.1097/PSY.0b013e318268de9f
398. Lopresti AL, Drummond PD. Obesity and psychiatric disorders: commonalities in dysregulated biological pathways and their implications for treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;45:92-99. doi:10.1016/j.pnpbp.2013.05.005
399. van Winkel R, Rutten BP, Peerbooms O, Peuskens J, van Os J, De Hert M. MTHFR and risk of metabolic syndrome in patients with schizophrenia. *Schizophr Res*. 2010;121(1-3):193-198. doi:10.1016/j.schres.2010.05.030
400. Amare AT, Schubert KO, Klingler-Hoffmann M, Cohen-Woods S, Baune BT. The genetic overlap between mood disorders and cardiometabolic diseases: a systematic review of genome wide and candidate gene studies. *Transl Psychiatry*. 2017;7(1):e1007. doi:10.1038/tp.2016.261
401. Malan-Müller S, Kilian S, van den Heuvel LL, et al. A systematic review of genetic variants associated with metabolic syndrome in patients with schizophrenia. *Schizophr Res*. 2016;170(1):1-17. doi:10.1016/j.schres.2015.11.011
402. Rogers GB, Keating DJ, Young RL, Wong M-L, Licinio J, Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Mol Psychiatry*. 2016;21(6):738-748. doi:10.1038/mp.2016.50
403. DE Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52-77. doi:10.1002/j.2051-5545.2011.tb00014.x
404. Mitchell AJ, Delaffon V, Vancampfort D, Correll CU, De Hert M. Guideline concordant monitoring of metabolic risk in people treated with antipsychotic medication: systematic review and meta-analysis of screening practices. *Psychol Med*. 2012;42(1):125-147. doi:10.1017/S003329171100105X
405. Laugharne J, Waterreus AJ, Castle DJ, Dragovic M. Screening for the metabolic syndrome in Australia: a national survey of psychiatrists' attitudes and reported practice in patients prescribed antipsychotic drugs. *Australas psychiatry Bull R Aust New Zeal Coll Psychiatr*. 2016;24(1):62-66. doi:10.1177/1039856215618521
406. Ijaz S, Bolea B, Davies S, et al. Antipsychotic polypharmacy and metabolic syndrome in

schizophrenia: a review of systematic reviews. *BMC Psychiatry*. 2018;18(1):275. doi:10.1186/s12888-018-1848-y
407. Breslau J, Leckman-Westin E, Yu H, et al. Impact of a Mental Health Based Primary Care Program on Quality of Physical Health Care. *Adm Policy Ment Heal Ment Heal Serv Res*. 2018;45(2):276-285. doi:http://dx.doi.org/10.1007/s10488-017-0822-1
408. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacol Off Publ Am Coll Neuropsychopharmacol*. 2011;36(12):2452-2459. doi:10.1038/npp.2011.132
409. Canada O. What is obesity? https://obesitycanada.ca/understanding-obesity/.
410. Lier HØ, Biringer E, Stubhaug B, Tangen T. Prevalence of psychiatric disorders before and 1 year after bariatric surgery: the role of shame in maintenance of psychiatric disorders in patients undergoing bariatric surgery. *Nord J Psychiatry*. 2013;67(2):89-96. doi:10.3109/08039488.2012.684703
411. Zhao Z, Okusaga OO, Quevedo J, Soares JC, Teixeira AL. The potential association between obesity and bipolar disorder: A meta-analysis. *J Affect Disord*. 2016;202:120-123. doi:10.1016/j.jad.2016.05.059
412. Baskaran A, Cha DS, Powell AM, Jalil D, McIntyre RS. Sex differences in rates of obesity in bipolar disorder: postulated mechanisms. *Bipolar Disord*. 2014;16(1):83-92. doi:10.1111/bdi.12141
413. Adams CE, Gabriele JM, Baillie LE, Dubbert PM. Tobacco use and substance use disorders as predictors of postoperative weight loss 2 years after bariatric surgery. *J Behav Health Serv Res*. 2012;39(4):462-471. doi:10.1007/s11414-012-9277-z
414. Bell CN, Walton QL, Thomas CS. Race and income moderate the association between depressive symptoms and obesity. *Prev Med An Int J Devoted to Pract Theory*. 2019;119:1-6. doi:10.1016/j.ypmed.2018.11.024
415. Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BW. Depression and obesity: evidence of shared biological mechanisms. *Mol Psychiatry*. 2019;24(1):18-33. doi:10.1038/s41380-018-0017-5
416. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: A meta-analysis of community-based studies. *Psychiatry Res*. 2010;178(2):230-235. doi:10.1016/j.psychres.2009.04.015
417. Bornstein SR, Schuppenies A, Wong M-L, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene-environment interactions. *Mol Psychiatry*. 2006;11(10):892-902. doi:10.1038/sj.mp.4001873
418. Hryhorczuk C, Sharma S, Fulton SE. Metabolic disturbances connecting obesity and depression. *Front Neurosci*. 2013;7:177. doi:10.3389/fnins.2013.00177
419. Roqué i Figuls M, Martínez García L, Martinez-Zapata MJ, Pacheco R, Mauricio D, Bonfill Cosp X. Interventions for treating overweight or obesity in adults: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2018;2018(12):CD010665. doi:10.1002/14651858.CD010665.pub2
420. Prost SG, Ai AL, Ainsworth SE, Ayers J. Mental Health Professionals and Behavioral Interventions for Obesity: A Systematic Literature Review. *J evidence-informed Soc Work*. 2016;13(3):305-330. doi:10.1080/23761407.2015.1031418
421. Mannan M, Mamun A, Doi S, Clavarino A. Is there a bi-directional relationship between depression and obesity among adult men and women? Systematic review and bias-adjusted meta analysis. *Asian J Psychiatr*. 2016;21:51-66. doi:10.1016/j.ajp.2015.12.008
422. Vannucchi G, Toni C, Maremmani I, Perugi G. Does obesity predict bipolarity in major depressive patients? *J Affect Disord*. 2014;155:118-122. doi:10.1016/j.jad.2013.10.035
423. Nousen EK, Franco JG, Sullivan EL. Unraveling the mechanisms responsible for the comorbidity between metabolic syndrome and mental health disorders. *Neuroendocrinology*. 2013;98(4):254-266. doi:10.1159/000355632
424. Szmulewicz AG, Samame C, Martino DJ, Strejilevich SA. An updated review on the neuropsychological profile of subjects with bipolar disorder. *Arch Clin Psychiatry*.

2015;42:139+.
425. Gálvez JF, Sanches M, Bauer IE, et al. Premorbid obesity and metabolic disturbances as promising clinical targets for the prevention and early screening of bipolar disorder. *Med Hypotheses*. 2015;84(4):285-293. doi:10.1016/j.mehy.2015.01.016
426. Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. *Acta Psychiatr Scand*. 2015;132(2):97-108. doi:10.1111/acps.12445
427. Daumit GL, Dickerson FB, Wang N-Y, et al. A behavioral weight-loss intervention in persons with serious mental illness. *N Engl J Med*. 2013;368(17):1594-1602. doi:10.1056/NEJMoa1214530
428. Baillot A, Saunders S, Brunet J, Romain AJ, Trottier A, Bernard P. A systematic review and meta-analysis of the effect of exercise on psychosocial outcomes in adults with obesity: A call for more research. *Ment Health Phys Act*. 2018;14:1-10. doi:10.1016/j.mhpa.2017.12.004
429. Lv N, Ajilore OA, Ronneberg CR, et al. The ENGAGE-2 study: Engaging self-regulation targets to understand the mechanisms of behavior change and improve mood and weight outcomes in a randomized controlled trial (Phase 2). *Contemp Clin Trials*. 2020;95:106072. doi:10.1016/j.cct.2020.106072
430. Gómez-De-Regil L, Avila-Nava A, Gutierrez-Solis AL, Lugo R. Mobile Apps for the Management of Comorbid Overweight/Obesity and Depression/Anxiety: A Systematic Review. *J Healthc Eng*. 2020;2020. doi:10.1155/2020/9317179
431. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation*. 2014;129(25 Suppl 2):S102-38. doi:10.1161/01.cir.0000437739.71477.ee
432. Köster L-S, Carbon M, Correll CU. Emerging drugs for schizophrenia: an update. *Expert Opin Emerg Drugs*. 2014;19(4):511-531. doi:10.1517/14728214.2014.958148
433. Torniainen M, Mittendorfer-Rutz E, Tanskanen A, et al. Antipsychotic treatment and mortality in schizophrenia. *Schizophr Bull*. 2015;41(3):656-663. doi:10.1093/schbul/sbu164
434. Correll CU, Detraux J, De Lepeleire J, De Hert M. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. *World Psychiatry*. 2015;14(2):119-136. doi:10.1002/wps.20204
435. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. *Eur Psychiatry*. 2010;25 Suppl 2:S12-21. doi:10.1016/S0924-9338(10)71701-6
436. Mason TB, Lewis RJ. Minority stress, depression, relationship quality, and alcohol use: Associations with overweight and obesity among partnered young adult lesbians. *LGBT Heal*. 2015;2(4):333-340. doi:10.1089/lgbt.2014.0053
437. Foundation P. What Is Parkinson's? https://www.parkinson.org/understanding-parkinsons/what-is-parkinsons.
438. Tagliati M, Chaudhuri K, Pagano G. Prevalence Of Non-Motor Symptoms In Parkinson's Disease: A Systematic Review With Meta-Analysis (P2.053). *Neurology*. 2014;82(10 Supplement):P2.053. http://n.neurology.org/content/82/10_Supplement/P2.053.abstract.
439. Pachana NA, Egan SJ, Laidlaw K, et al. Clinical issues in the treatment of anxiety and depression in older adults with Parkinson's disease. *Mov Disord*. 2013;28(14):1930-1934. doi:10.1002/mds.25689
440. Chen JJ, Marsh L. Depression in Parkinson's disease: identification and management. *Pharmacotherapy*. 2013;33(9):972-983. doi:10.1002/phar.1314
441. Akhmadeeva GN, Magzhanov R V, Tayupova GN, Baitimerov AR, Khidiyatova IM. Depression and Anxiety in Parkinson's Disease. *Neurosci Behav Physiol*. June 2018:1-5. doi:http://dx.doi.org/10.1007/s11055-018-0609-1
442. Kenangil G, Ozekmekci S, Sohtaoglu M, Erginoz E. Compulsive behaviors in patients with Parkinson's disease. *Neurologist*. 2010;16(3):192-195. doi:https://dx.doi.org/10.1097/NRL.0b013e31819f952b

443. Chan Y-LE, Bai Y-M, Hsu J-W, et al. Post-traumatic stress disorder and risk of Parkinson disease: A nationwide longitudinal study. *Am J Geriatr Psychiatry*. 2017;25(8):917-923. doi:10.1016/j.jagp.2017.03.012
444. Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J. Detecting depression in Parkinson disease: A systematic review and meta-analysis. *Neurology*. 2016;87(4):426-437. doi:10.1212/WNL.0000000000002898
445. Ahn S, Lee J, Chu SH, Sohn YH. Uncertainty and depression in people with Parkinson's disease: A cross-sectional study. *Nurs Health Sci*. 2017;19(2):220-227. doi:10.1111/nhs.12332
446. Perrin AJ, Nosova E, Co K, et al. Gender differences in Parkinson's disease depression. *Parkinsonism Relat Disord*. 2017;36:93-97. doi:10.1016/j.parkreldis.2016.12.026
447. Aarsland D, Påhlhagen S, Ballard CG, Ehrt U, Svenningsson P. Depression in Parkinson disease--epidemiology, mechanisms and management. *Nat Rev Neurol*. 2011;8(1):35-47. doi:10.1038/nrneurol.2011.189
448. Wen M-C, Chan LL, Tan LCS, Tan EK. Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. *Eur J Neurol*. 2016;23(6):1001-1019. doi:10.1111/ene.13002
449. D'Souza T, Rajkumar AP. Systematic review of genetic variants associated with cognitive impairment and depressive symptoms in Parkinson's disease. *Acta Neuropsychiatr*. 2020;32(1):10-22. doi:10.1017/neu.2019.28
450. Birchall EL, Walker HC, Cutter G, et al. The effect of unilateral subthalamic nucleus deep brain stimulation on depression in Parkinson's disease. *Brain Stimul*. 2017;10(3):651-656. doi:10.1016/j.brs.2016.12.014
451. Wu P-L, Lee M, Huang T-T. Effectiveness of physical activity on patients with depression and Parkinson's disease: A systematic review. *PLoS One*. 2017;12(7):e0181515. doi:10.1371/journal.pone.0181515
452. van der Kolk NM, King LA. Effects of exercise on mobility in people with Parkinson's disease. *Mov Disord*. 2013;28(11):1587-1596. doi:10.1002/mds.25658
453. Jin X, Wang L, Liu S, Zhu L, Loprinzi PD, Fan X. The Impact of Mind-body Exercises on Motor Function, Depressive Symptoms, and Quality of Life in Parkinson's Disease: A Systematic Review and Meta-analysis. *Int J Environ Res Public Health*. 2019;17(1):31. doi:10.3390/ijerph17010031
454. Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA*. 2020;323(6):548-560. doi:10.1001/jama.2019.22360
455. Yang S, Sajatovic M, Walter BL. Psychosocial interventions for depression and anxiety in Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2012;25(2):113-121. doi:10.1177/0891988712445096
456. Canada G of. Chronic Respiratory Diseases. https://www.canada.ca/en/public-health/services/chronic-diseases/chronic-respiratory-diseases.html. Published 2019.
457. Vanfleteren LEGW, Spruit MA, Groenen M, et al. Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(7):728-735. doi:10.1164/rccm.201209-1665OC
458. Garvey C, Criner GJ. Impact of Comorbidities on the Treatment of Chronic Obstructive Pulmonary Disease. *Am J Med*. 2018;131(9S):23-29. doi:10.1016/j.amjmed.2018.05.002
459. Spitzer C, Gläser S, Grabe HJ, et al. Mental health problems, obstructive lung disease and lung function: findings from the general population. *J Psychosom Res*. 2011;71(3):174-179. doi:10.1016/j.jpsychores.2011.03.005
460. Regvat J, Žmitek A, Vegnuti M, Košnik M, Šuškovič S. Anxiety and depression during hospital treatment of exacerbation of chronic obstructive pulmonary disease. *J Int Med Res*. 2011;39(3):1028-1038. doi:10.1177/147323001103900338
461. Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. Anxiety and depression-Important psychological comorbidities of COPD. *J Thorac Dis*. 2014;6(11):1615-1631. doi:10.3978/j.issn.2072-1439.2014.09.28

462. Kim HF, Kunik ME, Molinari VA, et al. Functional impairment in COPD patients: the impact of anxiety and depression. *Psychosomatics*. 2000;41(6):465-471. doi:10.1176/appi.psy.41.6.465
463. Laurin C, Moullec G, Bacon SL, Lavoie KL. Impact of anxiety and depression on chronic obstructive pulmonary disease exacerbation risk. *Am J Respir Crit Care Med*. 2012;185(9):918-923. doi:10.1164/rccm.201105-0939PP
464. Abrams TE, Vaughan-Sarrazin M, Van der Weg MW. Acute exacerbations of chronic obstructive pulmonary disease and the effect of existing psychiatric comorbidity on subsequent mortality. *Psychosomatics*. 2011;52(5):441-449. doi:10.1016/j.psym.2011.03.005
465. Pooler A, Beech R. Examining the relationship between anxiety and depression and exacerbations of COPD which result in hospital admission: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2014;9:315-330. doi:10.2147/COPD.S53255
466. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. *Eur Respir J*. 2011;37(2):264 LP - 272. doi:10.1183/09031936.00051110
467. Yin H-L, Yin S-Q, Lin Q-Y, Xu Y, Xu H-W, Liu T. Prevalence of comorbidities in chronic obstructive pulmonary disease patients: A meta-analysis. *Medicine (Baltimore)*. 2017;96(19):e6836. doi:10.1097/MD.0000000000006836
468. Matte DL, Pizzichini MMM, Hoepers ATC, et al. Prevalence of depression in COPD: A systematic review and meta-analysis of controlled studies. *Respir Med*. 2016;117:154-161. doi:http://dx.doi.org/10.1016/j.rmed.2016.06.006
469. Hung Y-H, Cheng C-M, Lin W-C, et al. Post-traumatic stress disorder and asthma risk: A nationwide longitudinal study. *Psychiatry Res*. 2019;276:25-30. doi:10.1016/j.psychres.2019.04.014
470. Scott KM, Saha S, Lim CCW, et al. Psychotic experiences and general medical conditions: a cross-national analysis based on 28 002 respondents from 16 countries in the WHO World Mental Health Surveys. *Psychol Med*. 2018;48(16):2730-2739. doi:http://dx.doi.org/10.1017/S0033291718000363
471. Hanania NA, Müllerova H, Locantore NW, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med*. 2011;183(5):604-611. doi:10.1164/rccm.201003-0472OC
472. Long J, Ouyang Y, Duan H, et al. Multiple Factor Analysis of Depression and/or Anxiety in Patients with Acute Exacerbation Chronic Obstructive Pulmonary Disease. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1449-1464. doi:10.2147/COPD.S245842
473. Bodescu M-M, Turcanu AM, Gavrilescu M-C, Mihăescu T. Respiratory rehabilitation in healing depression and anxiety in COPD patients. *Pneumologia*. 2015;64(4):14-18.
474. Tselebis A, Pachi A, Ilias I, et al. Strategies to improve anxiety and depression in patients with COPD: a mental health perspective. *Neuropsychiatr Dis Treat*. 2016;12:297-328. doi:10.2147/NDT.S79354
475. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirology*. 2013;18(1):61-70. doi:10.1111/j.1440-1843.2012.02255.x
476. Murali Mohan B V, Sen T, Ranganath R. Systemic manifestations of COPD. *J Assoc Physicians India*. 2012;60 Suppl:44-47.
477. Eagan TML, Ueland T, Wagner PD, et al. Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. *Eur Respir J*. 2010;35(3):540-548. doi:10.1183/09031936.00088209
478. Rose S, Paul C, Boyes A, Kelly B, Roach D. Stigma-related experiences in non-communicable respiratory diseases: A systematic review. *Chron Respir Dis*. 2017;14(3):199-216. doi:10.1177/1479972316680847
479. Xueli S. *Psychiatry*. Higher Education Press; 2013.
480. Howard C, Hallas CN, Wray J, Carby M. The relationship between illness perceptions and panic in chronic obstructive pulmonary disease. *Behav Res Ther*. 2009;47(1):71-76. doi:10.1016/j.brat.2008.10.004

481. Chan SMH, Selemidis S, Bozinovski S, Vlahos R. Pathobiological mechanisms underlying metabolic syndrome (MetS) in chronic obstructive pulmonary disease (COPD): clinical significance and therapeutic strategies. *Pharmacol Ther*. 2019;198:160-188. doi:10.1016/j.pharmthera.2019.02.013
482. Usmani ZA, Carson K V, Cheng JN, Esterman AJ, Smith BJ. Pharmacological interventions for the treatment of anxiety disorders in chronic obstructive pulmonary disease. *Cochrane database Syst Rev*. 2011;(11):CD008483. doi:10.1002/14651858.CD008483.pub2
483. Alexopoulos GS, Sirey JA, Banerjee S, et al. Two behavioral interventions for patients with major depression and severe COPD. *Am J Geriatr Psychiatry*. 2016;24(11):964-974. doi:10.1016/j.jagp.2016.07.014
484. Valenza MC, Valenza-Peña G, Torres-Sánchez I, González-Jiménez E, Conde-Valero A, Valenza-Demet G. Effectiveness of controlled breathing techniques on anxiety and depression in hospitalized patients with COPD: A randomized clinical trial. *Respir Care*. 2014;59(2):209-215. doi:10.4187/respcare.02565
485. Usmani ZA, Carson K V, Heslop K, Esterman AJ, De Soyza A, Smith BJ. Psychological therapies for the treatment of anxiety disorders in chronic obstructive pulmonary disease. *Cochrane database Syst Rev*. 2017;3(3):CD010673. doi:10.1002/14651858.CD010673.pub2
486. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim care Respir Med*. 2015;25:15026. doi:10.1038/npjpcrm.2015.26
487. Bereza BG, Troelsgaard Nielsen A, Valgardsson S, Hemels MEH, Einarson TR. Patient preferences in severe COPD and asthma: a comprehensive literature review. *Int J Chron Obstruct Pulmon Dis*. 2015;10:739-744. doi:10.2147/COPD.S82179
488. Gale NS, Duckers JM, Enright S, Cockcroft JR, Shale DJ, Bolton CE. Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? *BMC Pulm Med*. 2011;11:20. doi:10.1186/1471-2466-11-20
489. Malpass A, Feder G, Dodd JW. Understanding changes in dyspnoea perception in obstructive lung disease after mindfulness training. *BMJ open Respir Res*. 2018;5(1):e000309. doi:10.1136/bmjresp-2018-000309
490. Hatzenbuehler ML, Phelan JC, Link BG. Stigma as a fundamental cause of population health inequalities. *Am J Public Health*. 2013;103(5):813-821. doi:10.2105/AJPH.2012.301069
491. Frischknecht U, Beckmann B, Heinrich M, et al. The vicious circle of perceived stigmatization, depressiveness, anxiety, and low quality of life in substituted heroin addicts. *Eur Addict Res*. 2011;17(5):241-249. doi:10.1159/000328637
492. Major B, O'Brien LT. The social psychology of stigma. *Annu Rev Psychol*. 2005;56:393-421. doi:10.1146/annurev.psych.56.091103.070137
493. Mickelson KD. Perceived stigma, social support, and depression. *Personal Soc Psychol Bull*. 2001;27(8):1046-1056. doi:10.1177/0146167201278011
494. Corrigan PW, Larson JE, Rüsch N. Self-stigma and the "why try" effect: impact on life goals and evidence-based practices. *World Psychiatry*. 2009;8(2):75-81. doi:10.1002/j.2051-5545.2009.tb00218.x
495. Corrigan P. How stigma interferes with mental health care. *Am Psychol*. 2004;59(7):614-625. doi:10.1037/0003-066X.59.7.614
496. Katz IT, Ryu AE, Onuegbu AG, et al. Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis. *J Int AIDS Soc*. 2013;16(3 Suppl 2):18640. doi:10.7448/IAS.16.3.18640
497. Frank C, Zamorski MA, Colman I. Stigma doesn't discriminate: physical and mental health and stigma in Canadian military personnel and Canadian civilians. *BMC Psychol*. 2018;6(1):61. doi:10.1186/s40359-018-0273-9
498. SBR O. *Advancing the Integration Conversation: A Report to the Toronto Central LHIN*. Toronto; 2016. http://www.torontocentrallhin.on.ca/~/media/sites/tc/TC LHIN

Docs/Resources/Advancing the Integration Conversation Report and Appendix.pdf?la=en.
499. Committee CPSA and MH. *Collaboration for Addiction and Mental Health Care: Best Advice*. Ottawa; 2014.
500. Van't Veer-Tazelaar P, Smit F, van Hout H, et al. Cost-effectiveness of a stepped care intervention to prevent depression and anxiety in late life: randomised trial. *Br J Psychiatry*. 2010;196(4):319-325. doi:10.1192/bjp.bp.109.069617
501. van't Veer-Tazelaar PJ, van Marwijk HWJ, van Oppen P, et al. Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. *Arch Gen Psychiatry*. 2009;66(3):297-304. doi:10.1001/archgenpsychiatry.2008.555
502. Wood E, Ohlsen S, Ricketts T. What are the barriers and facilitators to implementing Collaborative Care for depression? A systematic review. *J Affect Disord*. 2017;214:26-43. doi:10.1016/j.jad.2017.02.028
503. Overbeck G, Davidsen AS, Kousgaard MB. Enablers and barriers to implementing collaborative care for anxiety and depression: a systematic qualitative review. *Implement Sci*. 2016;11(1):165. doi:10.1186/s13012-016-0519-y
504. Kates N, Mazowita G, Lemire F, et al. The evolution of collaborative mental health care in Canada: A shared vision for the future. *Can J Psychiatry / La Rev Can Psychiatr*. 2011;56(5):1-10.
505. Fleury M-J, Farand L, Aubé D, Imboua A. Management of mental health problems by general practitioners in Quebec. *Can Fam Physician*. 2012;58(12):e732-8, e725-31.
506. Pass LE, Kennelty K, Carter BL. Self-identified barriers to rural mental health services in Iowa by older adults with multiple comorbidities: qualitative interview study. *BMJ Open*. 2019;9(11). doi:http://dx.doi.org/10.1136/bmjopen-2019-029976
507. Canada MHC of. *Changing Directions, Changing Lives: The Mental Health Strategy for Canada*. Calgary, AB https://www.mentalhealthcommission.ca/sites/default/files/MHStrategy_Strategy_ENG.pdf.
508. Ashcroft R. Inadequate performance measures affecting practices, organizations and outcomes of Ontario's family health teams. *Healthc Policy*. 2014;10(1):86-96. https://pubmed.ncbi.nlm.nih.gov/25410698.
509. Steele LS, Durbin A, Sibley LM, Glazier R. Inclusion of persons with mental illness in patient-centred medical homes: cross-sectional findings from Ontario, Canada. *Open Med*. 2013;7(1):e9-e20. https://pubmed.ncbi.nlm.nih.gov/23687535.
510. Leventhal, H., Meyer, D., & Nerenz D(. In S. Rachman (Ed.), Contributions to Medical Psychology. In: New York: Pergamon Press.; 1980:7–30.
511. Leventhal, H., Nerenz, D. R., & Steele DJ. Handbook of Psychology and Health. In: Hillsdale, NJ: Lawrence Erlbaum Associates; 1984:219– 252.
512. Gustin ANJ. Shared Decision-Making. *Anesthesiol Clin*. 2019;37(3):573-580. doi:10.1016/j.anclin.2019.05.001
513. Katon W, Guico-Pabia CJ. Improving quality of depression care using organized systems of care: a review of the literature. *Prim care companion CNS Disord*. 2011;13(1). doi:10.4088/PCC.10r01019blu
514. Farrar S, Kates N, Crustolo AM, Nikolaou L. Integrated model for mental health care. Are health care providers satisfied with it? *Can Fam Physician*. 2001;47:2483-2488.
515. Hughes K, Bellis MA, Hardcastle KA, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Heal*. 2017;2(8):e356-e366. doi:10.1016/S2468-2667(17)30118-4
516. A new direction in depression treatment in Minnesota: DIAMOND program, Institute for Clinical Systems Improvement, Bloomington, Minnesota. *Psychiatr Serv*. 2010;61(10):1042-1044. doi:10.1176/ps.2010.61.10.1042
517. Assari S, Lankarani MM. Race and Ethnic Differences in the Associations between Cardiovascular Diseases, Anxiety, and Depression in the United States. *Int J Travel Med Glob*

Heal. 2014;2(3):107-113.
518. Fredriksen-Goldsen KI, Cook-Daniels L, Kim H-J, et al. Physical and Mental Health of Transgender Older Adults: An At-Risk and Underserved Population. *Gerontologist*. 2014;54(3):488-500. doi:10.1093/geront/gnt021
519. Fredriksen-Goldsen KI, Emlet CA, Kim H-J, et al. The Physical and Mental Health of Lesbian, Gay Male, and Bisexual (LGB) Older Adults: The Role of Key Health Indicators and Risk and Protective Factors. *Gerontologist*. 2013;53(4):664-675. doi:10.1093/geront/gns123
520. Heidari S, Babor TF, De Castro P, Tort S, Curno M. Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use. *Res Integr peer Rev*. 2016;1:2. doi:10.1186/s41073-016-0007-6
521. Keuken DG, Haafkens JA, Hellema MJ, Burgers JS, Moerman CJ. Incorporating a gender perspective into the development of clinical guidelines: a training course for guideline developers. *Implement Sci*. 2007;2:35. doi:10.1186/1748-5908-2-35
522. Health C for A and M. *Best Practice Guidelines for Mental Health Promotion Programs: Children (7-12) and Youth (13-19)*. Toronto; 2014.
523. Victoria Jeffries, Amanda Slaunwhite, Nicole Wallace, Matthew Menear, Julia Arndt, Jennifer Dotchin, Kathy GermAnn SS. *Collaborative Care for Mental Health and Substance Use Issues in Primary Health Care: Overview of Reviews and Narrative Summaries*. Ottawa; 2013. https://www.mentalhealthcommission.ca/sites/default/files/PrimaryCare_Overview_Reviews_Narrative_Summaries_ENG_0.pdf.
524. Pawson R. *The Science of Evaluation: A Realist Manifesto*. Leeds: University of Leeds; 2013.
525. Pawson, R. and Tilley N. *Realist Evaluation*. Sage Publications Ltd.; 1997.
526. de Leeuw E. Engagement of Sectors Other than Health in Integrated Health Governance, Policy, and Action. *Annu Rev Public Health*. 2017;38:329-349. doi:10.1146/annurev-publhealth-031816-044309
527. Shankardass K, Muntaner C, Kokkinen L, et al. The implementation of Health in All Policies initiatives: a systems framework for government action. *Heal Res Policy Syst*. 2018;16(1):26. doi:10.1186/s12961-018-0295-z
528. Newfoundland G of. The Way Forward: Better Outcomes: Take a Health-in-All-Policies Approach. https://www.gov.nl.ca/thewayforward/action/adopt-a-health-in-all-policies-approach/. Published 2020. Accessed August 26, 2020.
529. Kershaw P. A "health in all policies" review of Canadian public finance. *Can J Public Health*. 2020;111(1):8-20. doi:10.17269/s41997-019-00291-4
530. Exworthy M. Policy to tackle the social determinants of health: using conceptual models to understand the policy process. *Health Policy Plan*. 2008;23(5):318-327. doi:10.1093/heapol/czn022
531. Kickbusch I, Williams C, Lawless A. Making the most of open windows: establishing health in all policies in South Australia. *Int J Health Serv*. 2014;44(1):185-194. doi:10.2190/HS.44.1.k
532. Kingdon JW. *Agendas, Alternatives, and Public Policies. Second.* Glenview, IL: Pearson Education Inc.; 2011.
533. Diallo T. *Pan-Canadian Meeting on Health in All Policies (HiAP): Québec City, October 9, 2019. Report*. Montreal; 2020. http://www.ncchpp.ca/docs/2020-health-in-all-policies-pan-canadian-meeting-report.pdf.
534. Plsek PE, Greenhalgh T. Complexity science: The challenge of complexity in health care. *BMJ*. 2001;323(7313):625-628. doi:10.1136/bmj.323.7313.625
535. BJ Holmes, Bev J, A Best, Allan, H Davies, D Hunter, MP Kelly, M Marshall JR-M. Mobilising knowledge in complex health systems: a call to action. *Evid Policy*. 2017;13(3):539–60.
536. Bauer MS, Weaver K, Kim B, et al. The collaborative chronic care model for mental health conditions: from evidence synthesis to policy impact to scale-up and spread. *Med Care*. 2019;57 Suppl 1(10 Suppl 3):S221-S227. doi:10.1097/MLR.0000000000001145
537. Tuohy C. *Remaking Policy: Scale, Pace and Political Strategy in Health Care Reform*. Toronto: University of Toronto Press; 2018.

538. Tuohy CH. What's Canadian about Medicare? A Comparative Perspective on Health Policy. *Healthc Policy*. 2018;13(4):11-22. doi:10.12927/hcpol.2018.25497
539. Unions CF of N. *Canadian Federation of Nurses Unions: Environics Research Poll: "Attitudes Toward Healthcare", Conducted between January 9-21, 2019, Prepared for CFNU, January 25, 2019.*; 2019. https://nursesunions.ca/wp-content/uploads/2019/02/Environics-CFNU-Report-Jan-25-19_FINAL.pdf.
540. Canada H. *Https://Www.Canada.ca/En/Health-Canada/Corporate/about-Health-Canada/Public-Engagement/External-Advisory-Bodies/Implementation-National-Pharmacare/Final-Report.Html.*; 2019. https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/implementation-national-pharmacare/final-report.html.
541. CM Flood, Colleen M BT. Fragmented Law & Fragmented Lives: Canada's Mental Health Care System (July 28, 2020). In: *Law and Mind: Mental Health Law and Policy in Canada*. Toronto: LexisNexis; 2017.
542. Reiter JT, Dobmeyer AC, Hunter CL. The Primary Care Behavioral Health (PCBH) Model: An Overview and Operational Definition. *J Clin Psychol Med Settings*. 2018;25(2):109-126. doi:10.1007/s10880-017-9531-x
543. Sunderji N, Polaha J, Ratzliff A, Reiter J. A walk on the translational science bridge with leaders in integrated care: Where do we need to build? *Fam Syst Health*. 2020;38(2):99-104. doi:10.1037/fsh0000501
544. Leutz WN. Five laws for integrating medical and social services: lessons from the United States and the United Kingdom. *Milbank* Q. 1999;77(1):77-110, iv-v. doi:10.1111/1468-0009.00125
545. Hollander MJ, Prince MJ. Organizing healthcare delivery systems for persons with ongoing care needs and their families: a best practices framework. *Healthc* Q. 2008;11(1):2,44-54. doi:10.12927/hcq.2013.19497
546. Kodner DL. All together now: a conceptual exploration of integrated care. *Healthc* Q. 2009;13 Spec No:6-15. doi:10.12927/hcq.2009.21091
547. Hughes G, Shaw SE, Greenhalgh T. Rethinking Integrated Care: A Systematic Hermeneutic Review of the Literature on Integrated Care Strategies and Concepts. *Milbank* Q. 2020;98(2):446-492. doi:10.1111/1468-0009.12459
548. Kodner DL, Spreeuwenberg C. Integrated care: meaning, logic, applications, and implications--a discussion paper. *Int J Integr Care*. 2002;2:e12. doi:10.5334/ijic.67
549. Armitage GD, Suter E, Oelke ND, Adair CE. Health systems integration: state of the evidence. *Int J Integr Care*. 2009;9:e82. doi:10.5334/ijic.316
550. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract*. 1998;1(1):2-4.
551. Stevenson HM, Williams AP, Vayda E. Medical politics and Canadian Medicare: professional response to the Canada Health Act. *Milbank* Q. 1988;66(1):65-104.
552. Tuohy C. *Accidental Logics: The Dynamics of Change in the Health Care Arena in the United States, Britain, and Canada*. Oxford University Press; 1999.
553. Friedsen E. *Profession of Medicine: A Study of the Sociology of Applied Knowledge*. University of Chicago Press; 1988.
554. Mechanic D. Sources of countervailing power in medicine. *J Health Polit Policy Law*. 1991;16(3):485-498. doi:10.1215/03616878-16-3-485
555. Hafferty FW, Light DW. Professional dynamics and the changing nature of medical work. *J Health Soc Behav*. 1995;Spec No:132-153.
556. Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. *Ann Fam Med*. 2014;12(6):573-576. doi:10.1370/afm.1713
557. Jiwani I, Fleury M-J. Divergent modes of integration: the Canadian way. *Int J Integr Care*. 2011;11(Spec 10th Anniversary Ed):e018. doi:10.5334/ijic.578
558. Roth I, Thompson-Lastad A, Thomas AU. The Quadruple Aim as a Framework for Integrative Group Medical Visits. *J Altern Complement Med*. 2020;26(4):261-264.

doi:10.1089/acm.2019.0425
559. Morgan A, Ziglio E. Revitalising the evidence base for public health: an assets model. *Promot Educ*. 2007;Suppl 2:17-22. doi:10.1177/1025382307014002070 1x
560. ANTONOVSKY A. The salutogenic model as a theory to guide health promotion. *Health Promot Int*. 1996;11(1):11-18. doi:10.1093/heapro/11.1.11
561. Joseph S SS. Positive psychology in the context of salutogenesis. In: *The Handbook of Salutogenesis*. Springer; 2017.
562. M Eriksson MM. The Sense of Coherence and Its Measurement. In: *The Handbook of Salutogenesis*. Springer; 2017.
563. Van Bortel T, Wickramasinghe ND, Morgan A, Martin S. Health assets in a global context: a systematic review of the literature. *BMJ Open*. 2019;9(2):e023810. doi:10.1136/bmjopen-2018-023810
564. M Hills, S Carroll SD. Assets based interventions: Evaluating and synthesizing evidence of the effectiveness of the assets based approach to health promotion. In: *Health Assets in a Global Context*. Springer; 2010.
565. Campbell C. Social capital, social movements and global public health: Fighting for health-enabling contexts in marginalised settings. *Soc Sci Med*. 2020;257:112153. doi:10.1016/j.socscimed.2019.02.004
566. Justin Avery Aunger, Ross Millar, Joanne Greenhalgh, Russell Mannion, Anne Marie Rafferty HM. Why do some inter-organisational collaborations in healthcare work when others do not? A realist review. *BMC Syst Rev*. 2020.
567. Matcham F, Galloway J, Hotopf M, et al. The Impact of Targeted Rheumatoid Arthritis Pharmacologic Treatment on Mental Health: A Systematic Review and Network Meta-Analysis. *Arthritis Rheumatol (Hoboken, NJ)*. 2018;70(9):1377-1391. doi:10.1002/art.40565
568. *Dementia: Assessment, Management and Support for People Living with Dementia and Their Carers*. London; 2018.
569. Woltmann E, Grogan-Kaylor A, Perron B, Georges H, Kilbourne AM, Bauer MS. Comparative effectiveness of collaborative chronic care models for mental health conditions across primary, specialty, and behavioral health care settings: systematic review and meta-analysis. *Am J Psychiatry*. 2012;169(8):790-804. doi:10.1176/appi.ajp.2012.11111616
570. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1-s106. doi:10.1136/gutjnl-2019-318484
571. Barone P, Erro R, Picillo M. Quality of Life and Nonmotor Symptoms in Parkinson's Disease. *Int Rev Neurobiol*. 2017;133:499-516. doi:10.1016/bs.irn.2017.05.023
572. Avari JN, Alexopoulos GS. Models of care for late-life depression of the medically ill: Examples from chronic obstructive pulmonary disease and stroke. *Am J Geriatr Psychiatry*. 2015;23(5):477-487. doi:10.1016/j.jagp.2014.06.004
573. Scarpioni R, Ricardi M, Albertazzi V. Secondary amyloidosis in autoinflammatory diseases and the role of inflammation in renal damage. *World J Nephrol*. 2016;5(1):66-75. doi:10.5527/wjn.v5.i1.66
574. Orem DE, Taylor SG. Reflections on nursing practice science: the nature, the structure, and the foundation of nursing sciences. *Nurs Sci Q*. 2011;24(1):35-41. doi:10.1177/0894318410389061
575. Grande G, Romppel M, Vesper J-M, Schubmann R, Glaesmer H, Herrmann-Lingen C. Type D personality and all-cause mortality in cardiac patients--data from a German cohort study. *Psychosom Med*. 2011;73(7):548-556. doi:https://dx.doi.org/10.1097/PSY.0b013e318227a9bc
576. Naughton MJ, Weaver KE. Physical and mental health among cancer survivors: considerations for long-term care and quality of life. *N C Med J*. 2014;75(4):283-286. doi:10.18043/ncm.75.4.283
577. Beckie TM, Beckstead JW, Schocken DD, Evans ME, Fletcher GF. The effects of a tailored cardiac rehabilitation program on depressive symptoms in women: A randomized clinical

trial. *Int J Nurs Stud*. 2011;48(1):3-12. doi:https://dx.doi.org/10.1016/j.ijnurstu.2010.06.005
578. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. *Psychol Health*. 2015;30(11):1361-1385. doi:10.1080/08870446.2015.1070851
579. Bonsaksen T, Lerdal A, Fagermoen MS. Trajectories of illness perceptions in persons with chronic illness: An explorative longitudinal study. *J Health Psychol*. 2015;20(7):942-953. doi:10.1177/1359105313504235
580. Health NCC for D of. *Foundations: Definitions and Concepts to Frame Population Mental Health Promotion for Children and Youth*.; 2017. https://nccdh.ca/index.php?/resources/entry/foundations-definitions-and-concepts-to-frame-population-mental-health-prom.

Appendix A: Search Strategy

The purpose of the search strategy is to: 1) obtain literature about common physical and mental health co-morbidities that outlines their prevalence and incidence across the lifespan and among priority populations and equity-seeking groups (scoping review); and 2) obtain literature about common physical and mental health co-morbidities and effective strategies in which to prevent and mitigate them across the lifespan and among priority populations and equity-seeking groups (rapid realist review).

Working Definitions

Comorbidity: the co-occurrence of at least one mental and at least one physical disease or disorder in the same person, regardless of the chronological order in which they occurred or the causal pathway linking them[9]. For the purposes of this project, multimorbidity would be considered as inclusion criteria for comorbidity.

Non-communicable conditions: Physical health conditions as indicated by the WHO's top 20 leading causes of disease burden and other global burden of disease estimate studies that include diabetes, cardiovascular and chronic respiratory diseases, rheumatoid arthritis, osteoarthritis, inflammatory bowel disorders, kidney disease, neurological conditions (Alzheimer's disease, dementia, Parkinson's disease).

Mental health conditions: Depressive and anxiety disorders, bipolar and related disorders, schizophrenia spectrum and other psychotic disorders, obsessive-compulsive and related disorders, trauma- and stressor-related disorders, substance use and addictive disorders, and feeding and eating disorders.

Where applicable, the most recent edition of the International Classification of Diseases will be used to screen for the NCDs and mental health conditions. For the mental health conditions, however, it is anticipated that older versions will need to be used. In addition, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Revision IV and 5 will be used.

Populations: Women/men, immigrant, refugee, ethnocultural and racialized (IRER) communities, First Nations, Inuit and Métis, 2SLGBTQ+, linguistic minorities, rural, low income, aging (>65 years).

Databases: MEDLINE, EMBASE, CINAHL, PsycInfo, Sociological Abstracts, and EBM Reviews Multifile

Search Limiters: English language, full texts, human, January 2010–

[9] Benjamin G. Druss & Rosalynn Carter. Mental disorders and medical comorbidity. 2011. Robert Wood Foundation

1. Searches of Academic Databases

Search 1: Broad Mental and Physical Health Terms

Code A	Concept (Broad Terms)	Code B	Concept (Complementary Terms)
BT1	Multimorbid* or Comorbid*	CT1	Psychiatr* or psychol* or mental*
		CT2	Prevalence or incidence

Search 2: Search of Non-communicable Diseases

Code A	Concept (Mental Health)	Code B	Concept (Physical Health)
MH1	Depress* or affective disorder	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke*
			or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*
MH2	Anxiety*	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*

Code A	Concept (Mental Health)	Code B	Concept (Physical Health)
MH3	Bipolar* or Manic*	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*
MH4	Schizophr* or Schizoaff*	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*

Code A	Concept (Mental Health)	Code B	Concept (Physical Health)
MH5	Psychos* Psychot*	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or Amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*
MH6	Obsessive-compulsive or neurosis	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*

Code A	Concept (Mental Health)	Code B	Concept (Physical Health)
MH7	Trauma* or PTSD or post-traum* or stressor	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or Amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH0	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*
MH8	Substance* or addict* or compuls* drug abuse or drug dependence	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*

Code A	Concept (Mental Health)	Code B	Concept (Physical Health)
MH9	Feeding dis* or eating dis* or anor* or Bulimia or Binge Eating Disorder	PH1	Hyperten* or high blood pressure
		PH2	Cardiovasc* or heart* or coronary* or myocar* or stroke* or cerebrovas* or ischem*
		PH3	Respir* or asthma or lung dis* Or pulmon* or COPD or dyspnea or emphys* or bronchitis
		PH4	Arthr* or osteoarthr* or rheumatoid arthr* or spondylarthr* or musculoskeletal*
		PH5	Diabetes or diabetes mellitus
		PH6	Bowel* or colitis* or ulcerative colitis or crohn's
		PH7	Neoplas* or tumor or cancer or malignan*
		PH8	Neurocogn* or neurol* or dementia or amnestic or Alzheim* or Parkin* or epilepsy
		PH9	Kidney dis* or urol* or nephr* or renal dis*
		PH10	Obes*
		PH11	Metabolic Syndrome
		PH12	Frail*

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Search 3: Broad Mental and Physical Health Terms with Priority and Equity-Seeking Populations

Code A	Concept (Comorbid)	Code B	Combine With Priority Groups
CM1	Multimorbid* or comorbid*	PG1	Disadvan* or hard-to-reach or marginalise* or marginalize* or vulnerable or socioeconomic or inequalit* or inequit* or unequal*
		PG2	Emigrant* or foreign* or foreign born or immigrant* or migrant* or im/migrant* or refugee*
		PG3	Ethni* or ethnic minorit* or minority population* or race* or racial* or racial minorit* or visible minorit*
		PG4	Aged or aging or elder* or old age* or older or senior* or frail*
		PG5	Countryside or remote or rural
		PG6	Education* or litera* or illitera*
		PG7	Income* or poor or poverty
		PG8	Sex* or women
		PG9	Aborig* or Indig* or First Nations or Inuit or Métis
		PG10	2SLGBTQ+ or GLBT or Person* or Non-Heterosexual* or sexual or minorities or gay or gender minor* or Lesbian or bisexual or homosexual or queer or pansexual
		PG11	Canada and French Quebec and English

2. Grey Literature Searches

1) Theses/dissertations:
   - Proquest Dissertations and Theses
   - Theses Canada Portal
   - Networked Digital Library of Theses and Dissertations (NDLTD)

2) Conference proceedings/papers:
   - PapersFirst
   - ProceedingsFirst

3) International, national & provincial non-profit organizations (addressing the identified disease groups and priority populations)
   a. International
      - World Health Organization
      - Mental Health International
      - Mental Health Foundation: UK - https://www.mentalhealth.org.uk/
      - MIND UK https://www.mind.org.uk/
      - International Research Community on Multimorbidity
      - Equally Well – Australia - https://www.equallywell.org.au/

- Equally Well – New Zealand - https://www.tepou.co.nz/initiatives/equally-well-physical-health/37
- Equally Well - UK - https://equallywell.co.uk/

b. National
- Alzheimer's Society of Canada
- Anxiety Disorders Association of Canada
- The Arthritis Society of Canada
- The Asthma Society of Canada
- Autism Canada
- Canadian Centre on Substance Use and Addiction
- Canadian Diabetes Association
- Canadian Frailty Network
- Canadian Hypertension Society
- Canadian Lung Association
- Canadian Mental Health Association
- The Centre for ADHD Awareness, Canada
- Crohn's and Colitis Canada
- Heart and Stroke Foundation of Canada
- Metabolic Syndrome Canada
- Mood Disorders Society of Canada
- Obesity Canada
- OCD Canada
- Parkinson Canada
- Schizophrenia Society of Canada
- Diabetes Canada
- Cardiac Health Foundation of Canada
- Huntington Society of Canada
- Kidney Foundation of Canada
- The Centre of Excellence for Women's Health (for relevant studies using sex and gender-based analysis)

c. Provincial non-profit organizations
- Provincial chapters of national non-profit organizations listed above
- Provincial non-profits (e.g., National Organization of Immigrant and Visible Minority Women of Canada)
- Medical Psychiatry Alliance (https://www.medpsychalliance.ca/)

4) Government departments or agencies (international and national)
- Ministries of Health (federal and provincial), including departments of chronic disease and primary care
- Provincial and regional health authorities (Vancouver Coastal Health and others in BC and Canada)
- Public Health Agency of Canada

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia
- Health Quality Council, Saskatchewan
- Institute for Clinical Evaluative Sciences (ICES), Ontario
- Institute of Health Economics (IHE), Alberta
- Agency for Healthcare Research and Quality (AHRQ), USA
- Public Health Ontario

5) National & provincial healthcare provider associations (international and national)
    - Canadian Medical Association
    - Canadian Psychiatric Association
    - Canadian Psychological Association
    - Canadian Nurses Association
    - Canadian Physiotherapy Association
    - Canadian Association of Occupational Therapists
    - Dietitians of Canada
    - Provincial chapters of associations listed above

The grey literature checklist Grey Matters, developed by the Canadian Agency for Drugs and Technologies in Health (CADTH), and the New York Academy of Medicine's Grey Literature Report will also be mined for organizations relevant to the review. Although some grey literature sources may use standardized subject headings to index their publications, the vast majority rely on information being extracted by keyword. In general, keywords from the detailed strategy in the table below will be used to query the identified sources, providing for context dependent modification.

6) Cited reference checking (reference mining and snowballing)

Useful supplementary strategies for unearthing relevant studies are referencing mining and snowballing, techniques that are two sides of one coin. Reference mining involves combing through bibliographies and reference lists of key articles to find similarly relevant literature. Snowballing involves the use of a cited reference database such as Web of Science, or a parallel feature in Google Scholar and other databases to determine who has cited the article in question.

7) Personal contacts

For discovering the most current literature, works that have yet to be indexed or even works in progress, working through personal contacts are an effective method. As the search evolves, we will compile a list of relevant key authors to follow up with.

Background:

Purpose of the search strategy: 1) obtain literature about common physical and mental health co-morbidities that outlines their prevalence and incidence across the lifespan and among priority populations and equity-seeking groups; and 2) obtain literature about common physical and mental health co-morbidities and effective strategies in which to prevent and mitigate them across the lifespan and among priority populations and equity-seeking groups. The following will be applied to the abstract screening:

1. Does the abstract refer to at least one of the following mental health conditions:

- Depressive disorders (includes major depression, depression)
- Bipolar and related disorders (includes Manic depressive)
- Anxiety
- Schizophrenia spectrum (Schizoaffective)
- Psychotic disorders (includes psychosis)
- Obsessive-compulsive disorders (includes neurosis)
- Trauma- and stressor-related disorders; example post-traumatic stress disorder
- Substance use and addictive disorders (includes compulsive disorders, drug abuse, drug dependence, gambling)
- Feeding and eating disorders (includes anorexia, bulimia, binge eating disorder)

AND

2. Does the abstract refer to at least one of the following physical health conditions:

- Diabetes (includes diabetes mellitus)
- Cardiovascular (includes hypertension or high blood pressure, myocardial infarction, coronary heart disease, stroke, cerebrovascular accident, ischemic heart disease)
- Chronic respiratory diseases (includes asthma, lung disease, pulmonary, chronic obstructive pulmonary disease, COPD, dyspnea, emphysema, bronchitis)
- Arthritis (rheumatoid arthritis, osteoarthritis, spondyloarthritis, musculoskeletal arthritis)
- Inflammatory bowel disorders (includes colitis, ulcerative colitis or crohn's)
- Cancer (neoplasm, tumor; all types)
- Kidney disease (includes nephritis, renal disease)
- Obesity
- Metabolic syndrome
- Frail or frailty
- Neurocognitive conditions: dementia, amnestic, amnesia, Alzheimer's disease, dementia, Parkinson's disease, epilepsy

Note: abstract may refer to multimorbidities or comorbidities and be specific about the health conditions; in this case select it and it will be screened at the full text review

3. Does the study focus on adults (18 years+)

4. Is the abstract written in English?

Exclude: Traumatic brain injury, studies of children and adolescents (include adults 18 years+), exclude animal studies

Search includes all study types: intervention, epidemiology, qualitative

Added Inclusion and Exclusion Criteria for Full Text Screening

The following mental and physical health condition combinations had a high level of search hits.

1. Depression and diabetes
2. Depression and cardiovascular disease or hypertension
3. Depression and Alzheimer's dementia or dementia
4. Depression and cancer
5. Depression and respiratory conditions
6. Depression and arthritis
7. Anxiety and cardiovascular disease
8. Anxiety and cancer

The following criteria were applied:

1. Select intervention, systematic reviews/meta-analyses, cohort studies, qualitative studies (exclude retrospective, case-control, cross-sectional, case series, case studies, letters to editor, narrative reviews)
2. Select studies that include at least one of the following priority or equity seeking populations.

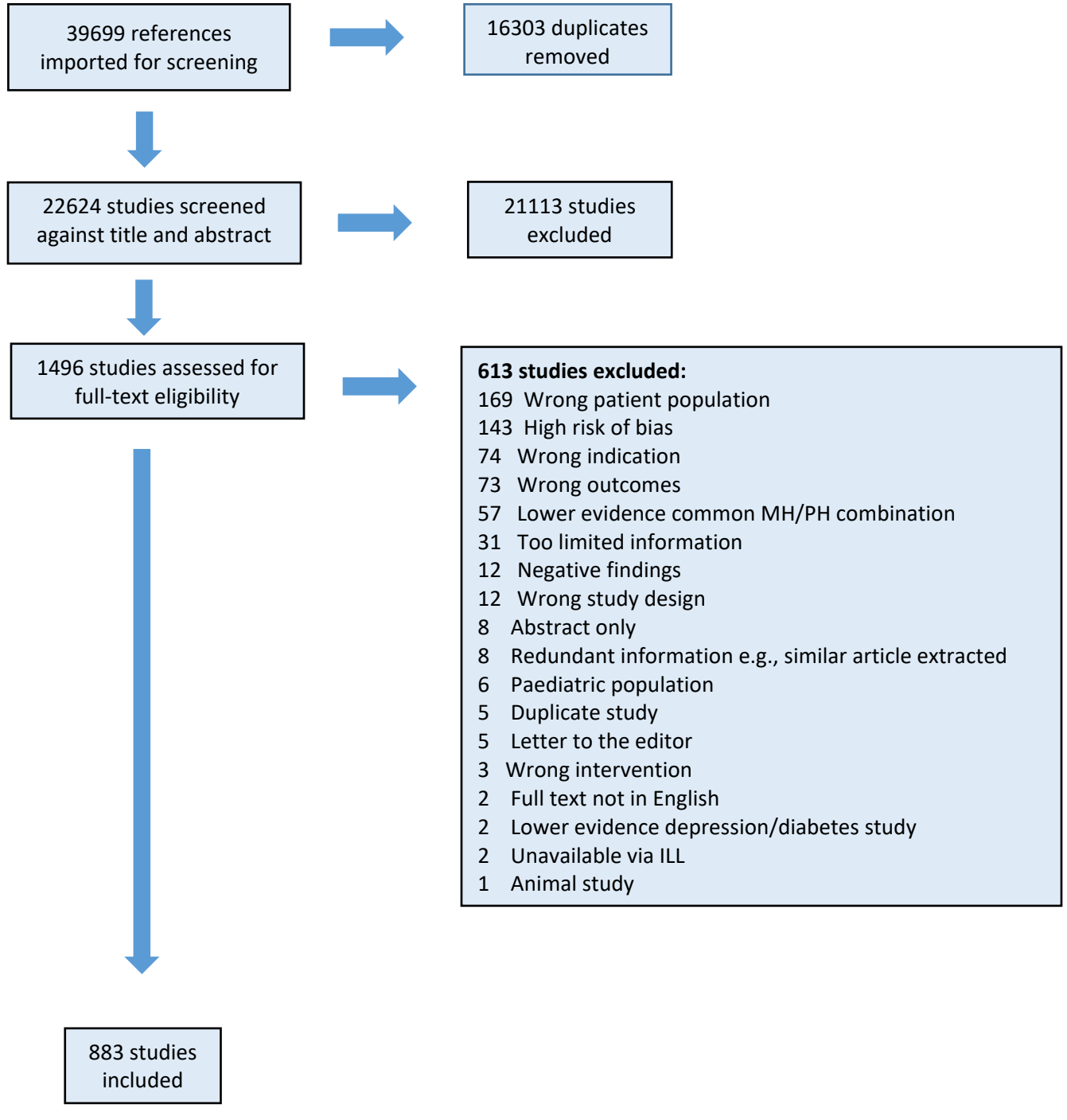
Additional criteria for all studies:

Exclude studies:

- Where factors such as depression and/or anxiety symptoms are a secondary outcome variable, or part of another construct (e.g., quality of life, patient outcome measures) or not discussed in any depth
- Where primary mental and physical health comorbidities are not the main construct
- Validation studies of measurement tools where depression and anxiety are a subscale

Appendix B: Search Strategy Results

PRISMA Results



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