THESIS

INVESTIGATING THE LINKS BETWEEN ACUTE GASTROINTESTINAL ILLNESS AND MENTAL HEALTH

GUT FEELINGS: INVESTIGATING THE LINKS BETWEEN ACUTE GASTROINTESTINAL ILLNESS AND MENTAL HEALTH
A REVIEW

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Abstract

Background: Psychiatric patients have been well documented to have higher rates of physical illness compared to the general population. Treatments of chronic illnesses such as functional gastrointestinal disorders are beginning to incorporate integrated care models to simultaneously address psychiatric and physical symptoms. This is based on recent research emphasizing the importance of the gut-brain axis. However, the intricacies of connections between infectious diseases and mental illness remain unclear. Diarrheal disease and depression account for a disproportionate amount of the total global burden of disease, being the second and fourth greatest contributors respectively. This highlights the need to investigate the possible links between the two, and interactions along the gut-brain axis in general.
Objectives: The objectives of this scoping review and thematic analysis was to explore what is known about infectious acute gastrointestinal illness and its relationship to depressive and anxiety symptoms. Ultimately, this review was intended to act as a case study of novel connections between infectious illnesses and mental illness.
Methodology: Following Arksey & O'Malley's framework, five databases (EMBASE, MedLine, PsychInfo, Global Health, HealthStar) were searched resulting in 1156 titles and abstracts. These were screened for inclusion and produced a total of 17 articles included for review and synthesis.
Results: Three major themes were identified: 1) Connections between physical and mental status within this context can occur via i) the microbiome, ii) the immune system, iii) the nervous system, and iv) the endocrine system; 2) Bidirectionality of the gut-brain axis is key in understanding cross-talk between symptoms; 3) Integration of care options might result in improved health outcomes.
Conclusion: These findings demonstrate that holistic and integrated interventions must be considered not only for chronic and mental illnesses, but also for infectious and mental illnesses, based on the connections between AGI and depressive and anxiety symptoms. More research is required, particularly with human subjects, in order to further understand the connections between the gut and brain. Incorporation of this knowledge into new treatment plans will allow clinicians to deliver more effective care to their patients who suffer from a dual burden of disease.

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This thesis would not have existed without my experiences in Nepal, Honduras, and inner city Hamilton. I dedicate this work to the marginalized and suffering: I hope to make a small impact in creating a more just and equal world.

"There, but for the grace of God, go I." – James Bradford

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List of abbreviations

AGI: acute gastrointestinal illness
CRF: corticotrophin releasing factor
HPA axis: hypothalamic-adrenal-pituitary axis
mhGAP: Mental Health Gap Action Programme
WHO: World Health Organization

Declaration of Academic Achievement

The following is a declaration that the content of the research in this document has been completed by Janet Hélène Zanin and recognizes the contributions of Dr. Tim O'Shea, Dr. Jeffrey Pernica, and Dr. Nick Kates in both the research process and the completion of the thesis.

Chapter one: Overview

The purpose of this chapter is to provide an overview of background information relevant to the scoping review and thematic analysis.

Introduction

The statement of 'no health without mental health' has been a launching point for global health movements that emphasize the interplay between psychoneurotic and other conditions.[1] There is growing evidence and awareness of the need to address whole persons and systems in order to create efficient and effective solutions that can address the root causes of issues, and not just the surface symptoms.[2]

Anxiety and depressive illnesses, as well as acute gastrointestinal illnesses, are two illnesses that affect individuals in all walks of life, regardless of circumstance. Psychiatric patients have been well documented to have higher rates of physical illness compared to the general population,[3–6] and chronic health conditions are well known to affect mental health of patients.[7] However, the intricacies of connections between specific infectious diseases and mental illness remain unclear.[4] Infectious diseases such as acute gastrointestinal illness (AGI) are being shown to have direct and indirect connections to psychiatric illnesses, particularly anxiety and depressive illnesses.[8] A holistic approach to health indicates the necessity of integrating knowledge from different specialties in order to treat the causes, rather than the just the symptoms of disease.[9,10] Investigating the connections between acute gastrointestinal illness and anxiety and depressive illnesses will thereby address health solutions that can target multiple diseases. This will encourage action to tackle upstream determinants in order to have a broad impact on population health.

In order to appropriately understand how acute infectious illness in the form of acute gastrointestinal illness could possible be linked to mental health in the form of anxiety and depressive illnesses, several areas must be explained: i) an overview of the current burden of disease for patients and health systems on a global scale, ii) current clinical perspective of anxiety and depressive illnesses, iii) pathophysiology of anxiety and depressive illnesses relevant to the thematic analysis, iv) current clinical perspective of acute gastrointestinal illness, v) pathophysiology of acute gastrointestinal disorders relevant to the thematic analysis, and vi) a brief understanding of the gut-brain axis in a chronic context.

A global health perspective

The global burden of anxiety and depressive illnesses is one of the highest of any non-communicable disease. Depressive disorders account for 3% of disability-adjusted life years, and are the second-leading cause of years-lived with disability at 8.2% of global records.[11] Anxiety and depressive illnesses primarily cause high morbidity, but mortality is an issue as well. This is attributed to suicide, which is the second leading cause of death in young adults (15-29 year olds).[12] Furthermore, health systems retain high costs due to the burden of anxiety and depressive illnesses, as individuals within primary care are associated with higher costs, after adjustment for medical comorbidity.[13] Depressive disorders are the primary target of the WHO Mental Health Gap Action Programme (mhGAP), as symptoms can be successfully controlled in about 70% of cases and cost is minimal at only two USD per month.[14]

Individuals with mental illnesses are more likely to have poor health outcomes due to diminished health-seeking behaviour,[15] decreased immune functioning,[16] as well as poor standards of psychiatric care.[15] In addition, mental illness is highly associated with poverty and criminal behaviour, although causal relationships are not determinable.[17] Interaction between

mental disorder and disability is complex and bidirectional: depression is a prospective risk factor for physical and social disability, which in turn mediate the course of depressive disorders.[18]

Advances in awareness of mental health issues have been improved, and it has resulted in increased understanding in clinical and societal settings.[19] The process of deinstitutionalization of persons with mental illness has begun in high income nations, however the majority of mental health budgets in low and middle income nations are still directed towards separate hospitals for psychiatric illnesses.[20] The understanding of mental illness resulting from a combination of factors that have physical and scientific basis is prevalent.[19] Nevertheless, low and middle income nations, as well as aid programs from high income nations, tend to focus on programs addressing infectious and reproductive health in isolation, with little regard for integration of mental health aspects.[21] For instance, 41% of countries do not have any policies related to mental health, and 25% of countries have no legislation on mental health.[22] Mental health conditions around the world are notoriously poorly understood. According to the WHO ATLAS study, 27% of countries have no system for collecting mental health indicators.[23] In addition, 65% of beds for mental health care are in separate hospitals,[23] meaning that it is difficult for systems to connect merely based on obstacles in physical space.

Treating mental illness effectively has several barriers. Many are based on access to human or physical resources, however many more are related to attitudes of patients, clinicians, and policy makers. Stigma around mental illness hinders the help-seeking behaviour of patients, can lead clinicians to ignore the possibility of mental illness in primary care patients, and prevents policy makers from instituting programs for mental illness.[24,25] When mental health is

considered in combination with physical health, positive primary and secondary benefits are experienced for both the patient and the community.[26]

Acute gastrointestinal illnesses also have a proportionally high burden of disease. According to the Global Burden of Disease Study, acute gastrointestinal illness of some form is the fourth leading cause of disability adjusted-life years lost at 3.6% of global records[27] and 1.5% of years-lived with disability.[28] While direct mortality is not high in most populations, diarrheal disease is the second leading cause of death in children under five.[29] Indirect mortality can occur through a number of other causal pathways, thus indirect mortality is likely much greater than direct mortality from acute gastrointestinal illnesses. The elderly are also at risk, as 85% of all deaths in hospital due to diarrheal disease are from elderly persons.[30] Morbidity is a large concern in adult populations, with four billion cases per year globally, and three cases per person per year.[31]

The epidemiology of acute gastrointestinal illness is complicated: pathogens can arise from a variety of sources, including bacterial, viral, or parasitic.[32] Transmission can result from animal to human, human to human, or environment to human, and is difficult to isolate. In addition, under reporting and the limited health seeking behaviour of patients further complicates the problem. The extraordinary variety of pathogens that can result in acute gastrointestinal illness and difficulty in obtaining diagnostic testing leads to underestimates in prevalence, incidence, and burden.[33]

Acute gastrointestinal illness has effects that reach farther than the course of the illness. These effects can be very different depending on the environmental conditions, namely high or low-income settings. AGI in children is a driver of the malnutrition pathway, which incorporates damage to intestinal epithelial cells,[34] disruption of the intestinal barrier,[34] severe acute

malnutrition, mal-absorption syndrome, and stunting.[35] Cognitive deficits are associated with these affects,[36] which can be a powerful predictor for reduced human capital.[37] This is much more common in low-income settings than in high-income settings.[36] Thus, aspects of acute gastrointestinal illnesses in low-income settings are different than in high-income settings in terms of causes and outcomes.

Children and adults with AGI can also go on to develop long-term gastrointestinal disorders, such as post-infective irritable bowel syndrome. Immunosuppression and increased susceptibility to further and various kinds of infections are also possible.[38]

Additionally, the economic impact of AGI is high. In high-income nations, it has been associated with over $1000 in direct and indirect costs per case,[39] and in low income nations it has been associated with approximately $85 in direct and indirect costs per case.[40] It is important to note that the costs per case are relative to the state of the economy and care available: costs per case will be lower in low income nations as typically less treatment is available. However the burden of the cost will be higher for patients and the health system for the same reasons. Overall, 6% of all disability-adjusted life years are attributed to poor sanitation and water management,[41] which is one of the largest risk factors for acute gastrointestinal illness.[42]

Treatment of acute gastrointestinal illness faces barriers: increased globalization and developing concerns regarding antibiotic resistance being among them.[43,44] While many low and middle-income countries have policies in place that address water, sanitation, and hygiene causes of acute gastrointestinal illness, several are poorly monitored and implemented.[45] Many organizations acting with little integration and oversight contribute to a lack of progress on the challenge of acute gastrointestinal illness.

Combined, anxiety and depressive illnesses as well as acute gastrointestinal illness share unique characteristics within global health systems: they are all high in morbidity, can have significant long-term sequelae, and are common in many different settings and regions. Often perceived as issues for different populations, the profound similarities in global disease burden sets the groundwork for the thematic analysis to follow showing the truly interconnected nature of these two illnesses.

Anxiety and depressive illnesses

Anxiety and depressive illnesses: Clinical perspective

The overlap of symptoms between anxiety and depressive illnesses means that they are frequently addressed together: up to 90% of patients with anxiety disorders have comorbid depression[46] and 85% of patients with depressive disorders can also experience symptoms of anxiety.[46] Typically, comorbidity of anxiety and depressive disorders ranges around 50%: one study in the United States found that lifetime comorbidity of anxiety and depressive disorders was approximately 59%[47]. Treatments are often similar: selective serotonin reuptake inhibitors and tricyclic antidepressants are used, as well as psychosocial interventions such as cognitive behavioural therapy.[48] Thus, due to their high comorbidity, it makes sense to consider anxiety and depressive disorders together on a research, policy, development, or advocacy front.

Nevertheless, there are distinctive diagnoses used for anxiety and depressive disorders and symptomatology. Anxiety disorders are generally characterized as resulting in feelings of excessive nervousness, including: separation anxiety disorder, selective mutism, specific phobia, social phobia, panic disorder, panic attack agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder, and unspecified anxiety disorder.[49]

Similarly, depressive disorders are affective disorders which result in depressed mood, and include several distinct types: disruptive mood dysregulation disorder, major depressive disorder, single and recurrent episodes, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.[49]

These definitions of anxiety and depressive disorders cover a wide variety of specific pathologies. This manuscript allows for inclusion of all of these illnesses in its definition of anxiety and depressive disorders, however most are non-specific.

Anxiety and depressive disorders: Pathophysiology summary

Anxiety and depressive illnesses work through several physiological mechanisms, not all of which are well understood. It is important to understand the basic processes of how emotion is regulated so that the implications of abnormalities are clear. There are several hypotheses of how anxiety and depression can arise: the monoamine deficiency hypothesis and the hypothalamic-pituitary-adrenal hypothesis will be discussed in detail due to their relevance to the thematic analysis.

The monoamine deficiency hypothesis is centred around the evidence that lowered levels of monoamines serotonin, norepinephrine, and dopamine are associated with anxiety and depressive symptoms.[50] Most anti-depressants and anxiolytic medications used in therapy today work on the basis of this theory.[51] The serotonergic system regulates sleep and pain sensitivity, and is found in the basal ganglia, frontal cortex, hypothalamus, and the limbic system of the brain. In the pathology of depressive symptoms, it fails to inhibit the stress response through a lower than expected response to stimuli.[52] The noradrenergic system regulates behaviour,

attention, as well as emotional responses to memory, and is most active in the pre-frontal cortex and amygdala. In the pathology of depressive symptoms, an elevated response to stimuli increases the stress response.[53] The dopaminergic system regulates motor function, memory, attention, and the reward systems of the brain. It is most active in the pituitary gland, nigostriatal, and mesocorticolimbic pathways. In the pathology of anxiety and depressive symptoms, lower levels of dopamine are present in the mesolimbic pathway.[54]

Another important pathway in the pathophysiology of emotion and mood regulation is the hypothalamic-pituitary-adrenal axis. The hypothalamic-pituitary-adrenal system is the body's response to stressful stimuli. Chronic activation results in excess secretion of corticotrophin releasing factor (CRF) in the paraventricular nucleus of the hypothalamus, which results in excess secretion of adrenocorticotropic hormone from the anterior pituitary gland. Circulation brings adrenocorticotropic hormone to the adrenal glands, which release glucocorticoids such as cortisol. Cortisol has many roles in the body, but in the context of the stress response, excess levels result in impaired immune functioning, and decreases levels of brain-derived neurotrophic factor.[55] Brain-derived neurotrophic factor is thought to play opposing roles in different areas of the brain: elevated levels occur in the nucleus accumbens, and depressed levels in the hippocampus. These levels result in the symptomatology of anxiety and depressive illnesses: sleep disturbances, impaired memory, motor retardation, and depressed mood. A low level of brain-derived neurotrophic factor is also associated with impaired neuroplastic processes and smaller hippocampal volume.[56] Chronic activation of the hypothalamic pituitary adrenal system reduces the inhibitory feedback loop that normally occurs, thus preventing regulation of the stress response.[57]

There are several areas of the brain that are key in the physiology of anxiety and depressive illnesses. It is necessary to be familiar with these regions in order to understand what activity or lack of activity might mean. These areas are largely part of the limbic system located deep in the central area of the brain, and they are responsible for reward systems, emotions, memory, and learning processes. The amygdala is a primary emotional regulation centre. The right hemisphere is associated with negative emotions such as fear, whilst the left is associated with reward-associated emotions such as happiness and anxiety. It can be further divided into the basolateral complex (lateral, basal, and accessory basal nuclei), basal ganglia (central and medial nuclei), and the cortical nuclei. Increased activity is present with anxiety or depressive symptoms.[58]

The amygdala projects to the hippocampus, which processes long-term emotional and spatial memory. It is shown to decrease in size with anxiety and depressive symptoms due to decreased neural connections. It is particularly sensitive to cortisol as it has many glucocorticoid receptors.[59]

While not part of the limbic system, the amygdala also projects to the thalamus, which receives sensory information and integrates it into the frontal and pre-frontal cortex. These are responsible for judgment and behaviour. The hypothalamus connects to the thalamus and the pituitary gland, and is divided into several nuclei that function in various ways to connect the endocrine and autonomic nervous system. Of interest in the physiology of anxiety and depressive systems are: the paraventricular nucleus, which releases corticotropic releasing hormone; and the nucleus accumbens, which is part of the mesolimbic dopaminergic pathway. These areas work in tandem to produce low mood or apprehension, and it is not fully elucidated how every pathway results in symptomatology.[58]

Taken together, understanding the regulatory pathways and related structures and functions of the brain give context for the thematic analysis.

Acute gastrointestinal illness

Acute gastrointestinal illness: Clinical perspective

No standard definition of AGI has been presented in the medical literature.[60] It is generally a syndrome incorporating vomiting, diarrhea, or both in otherwise healthy persons in response to a pathogen. Symptoms can include diarrhea, nausea, vomiting, abdominal pain, abdominal cramps, and fever, which can be caused by a variety of different agents. Importantly, it is most often self-limited.[61] AGI has been characterized by several other terms in the literature: gastroenteritis, colitis, foodborne and waterborne gastrointestinal illness, and diarrheal disease are among a few.

Acute gastrointestinal illness can be caused by viral, parasitic, or bacterial pathogens.[60] Of the viral pathogens that can cause acute gastrointestinal illness, rotavirus is the most common in children, and norovirus is the most common in adults. Adenovirus and astrovirus are also common causes.[62] Bacterial infection is less common in AGI, and can be caused by a multitude of pathogens, including (but not limited to) *Campylobacter*, various diarrhoeagenic subtypes of *Escherichia coli*, *Salmonella*, *Shigella*, or *Vibrio cholerae* when it is attributed to environmental exposure.[63] Antibiotic use is also associated with *Clostridium difficile* colitis.[64] Less commonly, parasitic organisms can also cause acute gastrointestinal illness, including (but not limited to) *Giardia lambia*, *Cryptosporidium*, and *Entamoeba histolytica.*[65] Enteric diagnostics to determine the exact cause of AGI are rarely used in upper-income countries, let alone in resource-limited settings, and so it is difficult to distinguish between specific causative agents when reviewing the

literature. It is important to note that all of these illnesses fall under the definition of acute gastrointestinal illness that this manuscript employs.

Acute gastrointestinal illness: Pathophysiology

The areas of the gastrointestinal tract that are most frequently affected by acute gastrointestinal illness are the stomach, small intestine, and large intestine. Within these structures, several accessory systems interplay into the absorption of ingested nutrients and excretion of waste components. These structures are important to understand when discussing the potential linkages of the gastrointestinal system to mental health, whereas the basic concepts of digestion and absorption are not the focus of this manuscript.

One of the key features of the gastrointestinal tract is the intestinal epithelium, which is key in the pathophysiology of acute gastrointestinal illness. Although the epithelial structure is different in various parts of the gastrointestinal tract, key feature are present that are relevant to infective processes. Epithelial tissue provides an impediment to pathogenic bacteria, and is comprised of enterocytes, enterochromaffin cells, and gut-associated lymphoid tissue, all of which are connected by tight junctions. These tight junctions are important to prevent infection as they regulate the permeability of the intestinal barrier.[66] In addition, these intestinal epithelial cells work with the immune system. Gut-associated lymphoid tissue is firstly comprised of goblet cells, which form a mucous layer to prevent bacterial adherence.[66,67] A second component is microfold-cells, which transport bacteria across the intestinal barrier to Peyer's patches, which function as mucosal immune centres to recognize pathogenic antigens. After recognition of a pathogenic antigen, T-cells in Peyer's patches interact with B-cells and memory cells before stimulating the production of immunoglobulin A, the first antibodies of the innate immune

response.[66,67] These features of the epithelium work in concert to prevent infection, and when disturbed can result in acute gastrointestinal illness.[68]

One of the mediating systems of the gastrointestinal tract is the enteric nervous system, a division of the autonomic nervous system embedded in the mucosal lining. Interestingly, the enteric nervous system can function independently of the central nervous system and has been described as a second brain.[69–71] The myenteric plexus is involved in mechanical movements, while the sub-mucosal plexus coordinates secretion and absorption.[69,72] Together, these contain more neurons than either the peripheral or central nervous system.[72] Over 90% of the fibres in the vagal nerve, the primary conduit for connecting the central to the enteric nervous system, carry information from the gastrointestinal tract to the brain.[73] This is important for understanding how sensory information from the gastrointestinal system can influence the brain, more so than other peripheral sensory findings.

The gastrointestinal system is also heavily influenced by gut microbiome in the outer mucosal layer, which are groups of commensal bacteria that function to assist in digestion of substances that humans are unable to digest on their own.[74] Composition of the microbiome is highly individualized and dependent on factors such as genetics, diet, method of delivery of a neonate, metabolism, age, geography, antibiotic use, and stress.[75] It has been found that the gastrointestinal microbiome can vary even among healthy subjects, with specific niche specialization within and among individuals.[76] The microbiome is established in the postnatal period and subsequently develops over the first few years of life.[77] The microbiome contains as many as 10^{14} microorganisms[78] which comprise one hundred times more genes than the human genome.[78] The main phyla present are *Firmicutes*, *Bacteroides*, *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia*, however ratios are different for all individuals and

populations.[78] Thus, the composition of the microbiome is a good representation of environmental history, and contributes to individual differences in risk of illness, disease course, and treatment response.[79,80]

One of the many functions of the microbiome is prevention of infection[81]. Firstly, commensal bacteria compete for resources with pathogenic bacteria, and thus inhibit colonization of the gastrointestinal tract by other bacterial pathogens.[82] Secondly, commensal bacteria in the microbiome release microorganism-associated molecular patterns, such as lipopolysaccharides, through their assistance in the digestive process.[83] The microorganism-associated molecular patterns can activate host genes, for instance, pattern recognition receptors on the intestinal epithelial cells.[84] An example of pattern recognition receptors is toll-like receptors, which must be activated to allow for signaling cascades to the nuclear-factor-kappa-B pathway. This is the beginning of the innate immune response, namely T-cell activation.[85,86] In this way, the microbiome controls host reactions to pathogens.

Dysbiosis of the microbiome can arise from many different factors. Essentially, what must be understood in the context of the thematic analysis is that disruption of the microbiome could be a factor in the development of acute gastrointestinal illness, and subsequent immune activation.[87]

Another one of the accessory systems of the digestive tract is the enteroendocrine system. It works in concert with the enteric nervous system[88] and the mucosal immune system.[89] For instance, the myenteric plexus is in close contact with enteroendocrine cells, of which the most common are enterochromaffin cells.[90] These are located underneath the mucosa in the lamina propria, and are open to the lumen, and thus function as transepithelial signal transduction conduits. Ingestion of mechanical, chemical, or pathological stimuli will result in a signal

transduction cascade.[91] For instance, enterochromaffin cells release serotonin (5-HT) and activate peristaltic and secretory reflexes depending on the subtype of 5-HT receptor to which it binds. Dysregulation of these cells due to pathogenic stimulation can result in acute gastrointestinal illness through hyper-secretion of serotonin, which increases gut motility.[90]

These selected structures of the gastrointestinal tract are described in order to give context to the findings of the thematic analysis.

The gut-brain axis: Chronic perspective

Much of the research that has been done investigating the links between the gastrointestinal system and the brain has focused on chronic pathologies, mainly different forms of functional gastrointestinal disorders, such as irritable bowel syndrome, or inflammatory bowel diseases.

There has been an established association between brain and gut function within chronic gastrointestinal disorders, and recent research has focused on the exact mechanisms of gut-brain interaction. Several studies have elucidated that symptoms of functional gastrointestinal disorders, such as irritable bowel syndrome, are affected by stressful situations, and indeed, current clinical guidelines for treatment involve the use of selective-serotonin reuptake inhibitors in some cases.[92] Moreover, it has been shown that up to 90% of patients with irritable bowel syndrome have psychiatric comorbidity, most commonly anxiety and depressive disorders.[93–96] It has been found that anxiety and depressive disorders and associated stress causes persistent and severe symptoms of irritable bowel syndrome.[97,98]

The idea that chronic functional gastrointestinal disorders as associated with dysbiosis of the intestinal microbiome has emerged as a large research area over the past ten years. Human studies have shown that the relative abundance and diversity of the microbiome changes with

diagnosis of irritable bowel syndrome as compared to previous individual microbiome composition. Specifically, patients with irritable bowel syndrome[99–101] and adults with no diagnosed functional gastrointestinal disorder but with gastrointestinal pain have decreased amounts of *Bifidobacteria* phyla in the microbiome when compared to patients without as controls.[102] However, it is important to note that changes within the microbiome are not definitively causal of functional gastrointestinal disorders, and it is not fully elucidated as to what microbiome profiles, if any, are associated with illness.

Dysbiosis of the microbiome has also been found for inflammatory bowel diseases, such as ulcerative colitis.[103] Patients with depressive symptoms and chronic gastrointestinal disorders have been shown to have increased amounts of non-pathogenic *Escherichia coli* in the microbiome.[99] It has also been demonstrated that anxiety and depressive symptoms in healthy individuals could potentially result in altered microbiota composition:[91] specifically increased levels of *Enterobacteria.*[105] While no specific microbiome profiles have been labeled as characteristic for functional gastrointestinal disorders or mental illness, it has been suggested that the microbiome is a key point in the gut-brain axis.[106]

It has been well established that the autonomic nervous system is a mediator of visceral and central communication. Recent studies have found that women with irritable bowel syndrome and anxiety symptoms have lower vagal tone (parasympathetic activity)[107,108], as well as more visceral pain (sympathetic activity).[109] This indicates that the vagal nerve is a key communication pathway between the gut and the brain, potentially activated through normal viscerosensory processes.[110]

The hypothalamic-adrenal pituitary axis is a very important gut-brain communication pathway. It has been found that acute psychosocial stress in experimental conditions could lead

to an increase in gastrointestinal symptoms in patients with irritable bowel syndrome. These patients have sustained activity in the hypothalamic-adrenal-pituitary axis, as indicated by greater cortisol levels.[111] Activation of the hypothalamic-adrenal-pituitary axis occurs through pro-inflammatory cytokines, which can also feed into monoaminergic systems in the brain and increases noradrenaline production.[112] Ultimately, activation of the hypothalamic-adrenal-pituitary axis results in suppression of inflammatory processes in the gastrointestinal system.[113] Thus, the hypothalamic-adrenal-pituitary axis is a regulatory loop for the gut-brain axis mediated by the immune system.

The immune system is a mechanism for gut-brain communication on its own: elevated levels of macrophages in the mucosa of the intestine are associated with depression in irritable bowel syndrome patients.[114] Furthermore, post-infectious irritable bowel syndrome has been suggested to be related to psychological changes, as well as increased enterochromaffin cell and T-cell counts.[115] The immune system is also related to autonomic nervous system function: stimulation of the vagal nerve can potentially reduce intestinal inflammation through decreasing production of cytokines; and ablation of the vagal nerve increases intestinal inflammation through increased activation of the nuclear-factor-kappa-B pathway.[116] Thus, the immune system is one of the most pervasive methods for gut-brain communication.

Importantly, it must be understood that evidence for gut-brain communication is bidirectional: it is clear through all of these mechanisms described that the status of the gastrointestinal tract can influence the brain, but also that the status of the brain can influence the gastrointestinal tract. Infection and psychosocial distress are suggested as prospective risk factors for the development of irritable bowel syndrome.[117] Additionally, post-infectious irritable bowel syndrome is associated with increased anxiety and depressive symptoms.[118] This leads to

inquiries as to the state of the research of acute gastrointestinal infection with anxiety and depressive symptoms, and was key in the formulation of the research question for the thematic analysis.

Chapter one summary: Over-arching purpose of thesis

This chapter provided an overview of background information needed to understand the rational and purpose of the following scoping review. In chapter two, I investigate the status of the literature pertaining to the potential linkages between acute gastrointestinal illness and anxiety and depressive illnesses as a case study for how infectious disease and mental illness are related in a modern context. Research attention to the intricacies of how different disease states can interact is imperative to stimulate attention to holistic approaches in clinical practice and health systems. Advancing dialogue on how infectious states can affect mental status has implications across high, middle, and low-income nations within a global context. With the backdrop of the pathophysiology of anxiety and depressive illnesses and acute gastrointestinal illness, it is possible to understand how these disease states can interact.

Chapter two overview: Scoping review and thematic analysis

The purpose of this chapter is to provide the methodology and results of the scoping review and thematic analysis, and discuss implications of these findings.

Background and objectives

As far back as Charles Dickens' time, there was a sense that the mental and physical are related. Dickens' surly character of Scrooge in the classic *A Christmas Carol* states, "A little thing affects [the senses]. A slight disorder of the stomach makes them cheats."[119] Yet, the division between physical and mental is still present: physical and mental healthcare are separate silos in health care delivery models. For instance, 41% of countries do not have any policies related to mental health, and 25% of countries have no legislation on mental health.[22] In addition, 65% of beds for mental health care are located in separate hospitals,[23] meaning that it is difficult for systems to connect merely because of physical obstacles. Yet, psychiatric patients have been well documented to have higher rates of physical illness compared to the general population.[5,7,120]

The most recent global development initiative by the United Nations, the Sustainable Development Goals, acknowledges the importance of both acute gastrointestinal illness and mental illness. Specifically, Sustainable Development Goal target 3.3 aims to "Combat…water-borne diseases and other communicable diseases"[121] by 2030. Directly following, Sustainable Development Goal target 3.4 aims to "By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being."[121] Due to the global burden of disease of acute gastrointestinal illness, anxiety, and depressive illnesses, it follows that an increased knowledge base of the potential links between them would prove useful to improve health outcomes. Moreover, increased understanding of

how physical and mental illnesses are specifically related follows the Sustainable Development Goals ambition of "A world with equitable and universal access to quality education at all levels, to health care and social protection, where physical, mental, and social well-being are assured."[121]

To advance understanding of the field, it is useful to know the current state of the research. Currently, the extent of the research specifically regarding infectious gastrointestinal illness relations to mental health is unknown. To inform future research directions, it is appropriate to use a scoping review to synthesize the peer-reviewed literature and inform next steps. Thus, the objectives of this thematic analysis are as follows: to (i) synthesize the research on connections between acute gastrointestinal illness and anxiety or depressive illnesses globally; (ii) examine the major themes as to how acute gastrointestinal illness, anxiety and depressive illnesses are related as a case study for how mental illness and infectious disease are related; (iii) perform a gap analysis of the literature in this field to recommend areas of work needed; (iv) provide recommendations on how health systems can address the connections between infectious and mental illnesses.

Research Question

What is the current state of knowledge in the existing published, peer-reviewed literature about the potential associations between acute gastrointestinal illness and anxiety or depressive illness?

Research Methods

Scoping review framework

Arksey & O'Malley's framework[122] for conducting scoping reviews was used to understand the key concepts, and main types of evidence available in the research area. A

scoping review is used in areas that are broad, complex, and scarcely researched, and allows incorporation of a range of study designs. This design is thus appropriate for a novel and complex research area focused on different domains of health.

According to the five-stage framework, the main research question was articulated and kept purposefully broad due to conceptual clarity achieved during study of key terms. Inclusion and exclusion criteria were developed and included the following: all study designs from dates ranging from January 1, 1980 – December 31, 2015 that were accessible via McMaster University library resources and written in English. Relevant articles were selected based on identification of key terms. Data characterization and charting was conducted with a data collection form to ensure a transparent and replicable methodology (see Table 1 in Appendix). Descriptive components extracted from each relevant study included: title, authors, location of study, year of publication, methodological design, purpose and aims of study, population characteristics, and key findings relevant to the research question. Risk of bias and related data was not evaluated, as it is not within the realm of a scoping review.[122] The fifth and final stage of the process collated and communicated the qualitative results from included studies. Consultation was not included as an optional final step of the research framework, as the objective of the question was to describe the current themes of the academic literature. Eliciting opinions of stakeholders such as clinicians, health policy analysts, or researchers was not pertinent to the objective of the study to determine the current state of knowledge of the apparent associations between acute gastrointestinal illness and anxiety or depressive illness. Reporting guidelines for scoping reviews have not been developed[123] thus the applicable reporting guidelines for a systematic review are followed, namely the Preferred Reporting Guidelines for Systematic Reviews and Meta-Analyses (PRISMA) checklist (item numbers: 1-4, 6-10, 17-21,

23-26).[124] For the thematic analysis portion of this scoping review, Braun & Clarke's (2006) process of familiarization, initial coding, searching for themes, defining and naming themes, and reporting was followed.[125]

Concept clarity

The search string for this review aims to characterize the published research investigating the links between infectious gastrointestinal pathology and mental illness globally. Thus, two broad categories of search terms related to i) acute gastrointestinal illness and ii) anxiety or depressive illnesses were included. The search string attempted to account for synonyms and various spellings, as well as word variations that were tailored to each bibliographic database.

Development of the Search String	
Question Components	**Search Terms**
Population: Global population	-
Exposure: Acute gastrointestinal illness	Acute gastrointestinal illness, gastroenteritis, colitis, gastrointestinal disease, diarrhea, diarrhoea, diarrheal disease, diarrhoeal disease, diarrheal illness, diarrhoeal illness, gastrointestinal infection, gut infection, foodborne illness, waterborne illness
Comparator: Occurrence of depressive or anxiety illnesses, disorders, or symptoms	Mental health, mental illness, mental disease, mental disorder, depression, depressive illness, depressive illness, depressive disorder, mood disorder, anxiolytic, anxiety, anxiety disorder
Outcome: Gut-brain axis connection	Gut-brain, brain-gut

Concept of acute gastrointestinal illness

Acute gastrointestinal illness is defined differently in each database, as there is no agreed upon definition in the literature.[60] It is essentially a syndrome incorporating vomiting, diarrhea, or both in otherwise healthy persons in response to a pathogen.[61] Other terms that are used to define acute gastrointestinal illness include gastroenteritis, stomach flu, specific bacterial, viral, and parasitic infections, diarrheal disease, food and water-borne illness.[60] In order to qualify for this scoping review and thematic analysis, a specific indication of infectious quality had to be stated in the study. Self-reporting or independent diagnoses of symptoms were both included, as long as acute quality was inferred.

Concept of anxiety and depressive illnesses

Anxiety and depressive illnesses were defined similarly in each database, although subject headings and leading literature were different. Through initial review of literature searches, it was determined that studies that indicated anxiety or depressive symptoms would be eligible for inclusion in this review. These were kept purposefully broad in order to capture any potential hits, as initial literature review indicated that few articles were published in the area.

Databases

Five research databases were identified in consultation with a McMaster University librarian specializing in the field of global health. These were: i) EMBASE; ii) Medline/PubMed, iii) HealthStar, iv) PsycINFO, v) Global Health and were chosen primarily based on the likelihood of containing literature related to the key terms of the research question. For instance, EMBASE (Excerpta Medica database) contains primarily biomedical and pharmacological studies, while HealthStar covers clinical and non-clinical aspects of health care delivery.[126] Medline/PubMed was chosen because of its widespread scope,[127] whereas PsycINFO focuses on

mental health, namely from a social science perspective.[128] Global Health focuses on public health at different levels of society from a biomedical perspective,[129] and was included to address the state of information for clinicians, health policy analysts, and researchers on an international level. The inclusion of these five databases attempts to address the research question from a multifaceted standpoint, which is key when attempting to communicate among differing medical disciplines. These databases were chosen as the broad content coverage and comprehensive tagging services were expected to yield the largest number of citations, as well as to compensate for imperfect search recall and citation error.

Relevance screening

A preliminary scan of articles retrieved from searches of Google Scholar identified terms that could be relevant to the search. Differing keywords and subject heading searches were used for each database based on their coding methods. Both keyword and subject heading searches were conducted for each database (see Figure 1 in Appendix). This strategy allowed a broad scope of consideration for included articles. Database searches were completed through OVID Technologies© in December 2015, and screened for inclusion based on titles and abstracts, erring on the side of inclusion when doubt occurs in order to increase sample size. For all discarded articles, reason for elimination was documented, and for all articles kept for further screening, the full text was obtained if available. Citation information and the abstract were downloaded into Microsoft Excel®. Secondary relevance screening encompassing full-text articles was done to confirm whether the article was relevant to the research questions and met the inclusion criteria. This broad method was used in order to capture any possibility for inclusion, beyond just title and abstract information. Once all articles were screened, a hand-search for ancillary sources was conducted by consulting the citation list of each article. Multiple

reports of the same study were linked together and counted as one unit, using the most recent or peer-reviewed version where applicable.

Citation management was conducted with Zotero® in collaboration with Ovid Technologies©, a web-based searching software that allows searches to be run across multiple databases.

Synonyms for concept domains were entered into the database as keywords or subject-headings on independent lines. Medical subject headings (MeSH) terms and Boolean connectors "OR" and "AND" were used to isolate potential articles. The Boolean connector "OR" was used between all related terms for both concept domains in order to capture articles under each of these subheadings. Finally, both concept domains were merged together with the Boolean operation "AND" to find articles that overlapped with both concept domains. Each database was searched line by line with the same pattern for combining concept domains.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were developed and were the following:

Selection criteria	
Inclusion	**Exclusion**
Method of research indicated	Opinion studies
Written in English	Written in any language other than English
Accessible via McMaster University library resources (online or print)	Full text not accessible via McMaster University library resources
Date range of January 1, 1980 – December 31, 2015	Dates before January 1, 1980; dates after December 31, 2015

Study references infectious gastrointestinal pathology	Study focuses on chronic gastrointestinal pathology or effects
Study references symptoms relating to anxiety and depressive illnesses OR pathways that can relate to anxiety and depressive illnesses	Study does not reference any pathology relating to anxiety and depressive illnesses

Rationale for inclusion of articles was as follows: reference of acute infectious gastrointestinal pathology AND symptoms relating to anxiety and depressive illnesses OR pathways that can relate to anxiety and depressive illnesses. Multiple study designs and populations were included, such as randomized control trials and observational protocols with both human and animal populations. Timing was chosen to ensure that recent data was captured, but also a sufficiently large quantity to show how the field has changed and evolved over a period of time.

Data Characterization

Data characterization and charting was conducted with a data collection form to ensure a transparent and replicable methodology. Key elements from full-text articles were extracted, however, risk of bias and related data was not evaluated. Key elements included any information relevant to the review questions, with a focus on general information over specifics. The data characterization form (see Table 1 in Appendix) included the following descriptive components: title, authors, location of study, year of publication, methodological design, purpose and aims of study, population characteristics, and key findings relevant to the research question. This form was pre-tested on 5% of relevant articles that comprised background reading to this project, in order to ensure that data charting was consistent and no relevant criteria were excluded.

Data Analysis

Data analysis resulted in frequency tabulations for types of study designs, years of publication, and the overall number of included articles (see Table 2 in Appendix). Qualitative analysis resulted in a narrative synthesis that divides the literature into common themes to determine important considerations for the future of physical and mental health care. The themes reflect concepts that describe the characteristics of the literature reviewed, and were refined until the dataset as a whole was exposed.

Limitations

Limitations of this study are that no grey literature search was conducted, as no reliable way to identify and obtain data from studies has been published or recommended.[130] Additionally, one reviewer undertook the scoping review and thematic analysis due to time and resource constraints. Five databases were searched as they were identified in consultation with a McMaster University librarian to be relevant, yet it is possible that searches in additional databases could meet the inclusion criteria. Finally, the small number of articles identified in the initial search could affect the interpretation of the synthesized findings. Additionally, most data is from countries in the Global North and/or the laboratory setting, thereby limiting its generalizability. It is important to note that included studies were not assessed for quality due to recommendations presented by Arksey & O'Malley's framework.[122]

Results

Five databases yielded an initial result of 1156 articles: 344 from EMBASE, 611 from Medline/PubMed, 126 from Health Star, 62 from PsycINFO, and 13 from Global Health. Following de-duplication and initial screening of titles and abstracts, 1117 articles were discarded and 39 articles were kept for further screening. Hand searching of citations resulted in

9 additional articles for screening, for a total of 48 articles screened in detail for inclusion. Results were combined into a single dataset. The final number that met all inclusion criteria was 17 articles (see Figure 2 in Appendix).

Primary reasons for elimination

The majority of articles were eliminated because study participants did not have an active infectious illness; many studies included individuals with chronic gastrointestinal pathology in the form of post-infectious irritable bowel syndrome. Furthermore, many studies were eliminated because infectious pathology was only briefly mentioned as a potential factor. Of the studies that met inclusion for infectious pathology, two were eliminated, as explicit relations to anxiety and depressive illnesses were not made clear. A flowchart of identified and eliminated articles, as well as the outcome of the hand-search of citations, for the final outcome of incorporated articles is included (see Figure 2 in Appendix). In addition, a descriptive component overview of the included studies is provided (see Table 2 in Appendix).

Descriptive components: authorship, geographical location, methodological design, years of publication

A total of sixty-five different authors contributed to at least one of the twenty included articles. Of these, six authors contributed to two articles, two each contributed to three and four articles, and one contributed to six articles. The nine authors who contributed to two articles are as follows, in alphabetical order: Collins, S.M.; Foster, J.A.; Li, W.; Lu, J.; & Verdú, E.F. The authors who contributed to three articles are Bercik, P. and Bailey, M.T.; while Gaykema, R. and Goehler, L.E. contributed to four articles. Lyte, M. contributed to six articles in total. This analysis reveals prominent scholars working to examine the linkages between acute gastrointestinal illness and anxiety and depressive illnesses. These individuals also represent key

figures that would be potential stakeholders for academic community consultation in follow up research. The authors for included articles are listed in detail (see Table 2 in Appendix).

The primary location of research investigating the linkages between acute gastrointestinal illness and anxiety and depressive illnesses are in the Global North, with only one article originating from a low or middle income country (Taiwan). Of the included articles, 70% of articles arose from North America, 18% from Europe, and 12% from Asia. Nine articles came from the United States specifically. The proportion of geographical locations of included articles by region is demonstrated (see Figure 3 in Appendix).

All studies used quantitative approaches, and three databases (Health & Retirement Study[131]; Danish National Hospital Registry[132], Danish Psychiatric Research Register[132]) were used in the two studies as data sources. Of the included articles, 76% of studies were randomized control trials, 18% were cohort studies, and 6% were cross-sectional studies. In addition, 76% of studies represented animal populations, and 24% of studies represented human populations. The methodological designs and types of population are described in detail (see Table 2 in Appendix). The proportion of study populations and proportions of methodological designs of included articles is also included (see Figures 4, 5 in Appendix).

All articles included in this scoping review and thematic analyses were published after 1998. The most common year of publication was 2013, with three articles published. Also of note is that two articles were each published in 2006, 2008, 2009, and 2010. In addition, 68% of the included articles were produced in 2008 or later (see Figure 6 in Appendix).

Synthesis of key findings

A synthesis of findings from this scoping review will be reported thematically, as it is an appropriate presentation of descriptive data. It is important to note that included studies were not

assessed for quality. The synthesis of key findings will be presented in three broad themes that combine qualitative and quantitative components of included analysis The themes are as follows: 1) Connections between physical and mental status within this context can occur via i) the microbiome, ii) the immune system, iii) the nervous system, and iv) the endocrine system; 2) Bidirectionality of the gut-brain axis is key in understanding cross-talk between symptoms; 3) Integration of care options might result in improved health outcomes.

Connections between mental and physical status

Connections between mental and physical status are the underpinning of the research between acute gastrointestinal illness and anxiety and depressive illnesses, as they comprised 49% of the code-applications in the analysis. Connections between the gastrointestinal tract and behaviour are mediated through four main pathways: the microbiome, the immune system, the nervous system, and the endocrine system.

Microbiome

Three studies addressed the microbiome route of mental and physical connections between acute gastrointestinal illness and anxiety and depressive illnesses. Park *et al.* (2009) examined the depressed gut in olfactory-bulbectomized male mice as a model of depression[133] and suggested that this model of comorbid anxiety and depression altered the phylogenetic ratios of the microbiome compared to controls: specifically by increasing the proportion of *Clostridia* and *Actinobacteria*, and decreasing the proportion of *Bacteroides.*[134]

Bailey & Coe (1999) observed that infant rhesus monkeys that underwent the psychological stressor of maternal separation had decreases in the *Lactobacilli* phyla in their microbiome after psychological stress. Following this, the monkeys were forty-five percent more likely to have gastrointestinal infections from *Shigella* and *Campylobacter*, however this was at a

sub-clinical level.[135] In addition, this was a dose-dependent relationship: lower *Lactobacilli* levels were associated with higher levels of pathogen shedding, however, it is important to note that this is not necessarily reflective of the severity of the disease.[135] Notably, this only approached statistical significance ($p=0.07$), however, it does suggest a trend that may have validity and should be considered.[135]

Bailey *et al.* (2010) observed that mice stressed by prolonged restraint, which is equivalent to a psychological stressor, had a 10,000-fold increase in *Citrobacter rodentium* levels over the physical stressor of food and water deprivation over control mice. Overgrowth of gram positive and negative bacteria in the small and large intestine occurred in mice that underwent the psychological stressor.[136] However, species diversity and richness were decreased with a reduction of the *Porphyromonadacaeae* phyla. Without infectious challenge, there was no change in any immune cytokine gene expression: interleukin-1β, tumour necrosis factor-α, interleukin-6, interferon-γ, or interleukin-10.[136] Infected mice that underwent psychological stressors had a ten-fold increase in tumour necrosis factor-α and increased immunoglobulin-A levels compared to infected mice that underwent a physical stressor, but not until nine days after stress-induced increase in *Citrobacter rodentium* levels had occurred.[136] This indicated that mucosal immune responses were not responsible for the increase in *Citrobacter rodentium* levels, and that psychological stressor was the primary causative agent.

These three articles indicate that disturbances of the microbiome could potentially result in increased likelihood of opportunistic gastrointestinal infection, and that psychological disturbances could potentially alter that environment to be more prone to infection. Possible mechanisms for this exist, including: increasing gastrointestinal permeability,[137] inhibition of gram-negative bacterial colonization through blocking attachment to gut binding sites,[138–140] and

reduced competition with commensal microbes.[82,141,142] While these pathways are potential ways for the gut-brain axis to communicate across the microbiome, none are proved causal and only associations are present at this current time in the research.

Immune system

Three studies examined the connections between gastrointestinal infection, anxiety, and depressive illnesses that are mediated through the immune system. Bercik *et al.* (2009) addressed the effects of *Helicobacter pylori* infection in mice and observed that infection almost doubled tumour necrosis factor-α mRNA levels in the median eminence and the arcuate nucleus concurrent with increased feeding intervals associated with more anxious state.[143] Increased heart rate in infected mice was also evident, to further support anxious state. Persistent immune activation altered brain neurochemistry and the changes persisted for up to two months past eradication of infection.[143] The study by Bercik *et al.* (2009) indicates that not only may cytokines that communicate with the brain be activated by acute gastric illness and result in anxiety-like behaviour, but also that infection may result in longer-term sequelae.

Bercik *et al.* (2010) observed that mice experimentally infected with parasitic *Trichuris muris* in a case-control study had elevated levels of immune cytokines tumour necrosis factor-α and interferon-γ.[144] Elevated cytokines after infection were correlated with increased anxiety behaviours in the light-dark preference test and the step-down test; along with decreased brain-derived-neurotrophic factor mRNA in the hippocampus, and increased kynurenine/tryptophan ratio.[144] These findings suggest that neurological changes in systems that regulate mood occurred in concert with immune activation, although it does not elucidate the specific mediating mechanisms.

In the only study using human populations that examined immune system connections between acute gastrointestinal illness and mood, Benros *et al.* (2013) determined that the incidence rate ratio of gastrointestinal infection occurring with mood disorders in a case-series retrospective study is 1.62 with a 95% confidence interval from 1.60 to 1.64.[132] The study also determined that a positive history of an infection (as compared to absence of infection) was associated with an incidence rate ratio for mood disorder of 1.63 with a 95% confidence interval from 1.61 to 1.66.[128] Importantly, the risk of mood disorders increased in a dose-response relationship with the number of infections predating the mood disorder. Additionally, the risk of developing a mood disorder increased when closer in time to the period of infection with an incidence rate ratio of 2.70 with a 95% confidence interval from 2.60 to 2.80.[132] These were adjusted for substance use and family psychiatric history. Female sex and persons older than thirty years of age were independently associated with statistically significant increases in the incidence of mood disorder after infection.[132] The authors hypothesize that severe infections create a higher inflammatory response, which is more likely to influence the brain through increased blood-central nervous system barrier permeability. It is important to note that Benros *et al.* focuses more on systemic inflammation that affects the risk of mood disorders resulting from gastrointestinal infection, rather than a direct gut-brain connection. In addition, pro-inflammatory cytokines produced in response to infection can affect the tryptophan-kynurenine pathway that regulates serotonin production, thus affecting mood. It was also found that the elevated risk of mood disorders remained significant for more than 15 years after the last hospital contact.[132] Overall, this study speculates that infection can increase the risk of mood disorders, and that robustness of the immune response is somehow directly correlated to those risks. However, no causal relationship is attributable. Importantly, the article states that only hospital contacts are

included in the Danish national database, which was used as the source for the study information.[132] Thus, the conclusions may not be attributable for infections where hospital assistance was not pursued.

These three articles propose that the innate and systemic immune response is involved in both mood and infection response beyond a mere display of sickness behaviour, as evidenced by increased long-term risk and neurological changes. The exact mechanisms of how this occurs are only hypothesized within this sample.

Nervous system

Five studies investigated the nervous system pathways of connections between physical and mental status in the context of acute gastrointestinal illness and anxiety and depressive illnesses. Four studies in particular were conducted in a series over a period of ten years. Lyte *et al.* (1998) began by determining that sub-clinical infection in mice with *Campylobacter jejuni* increased anxiety-like behaviours in the elevated-plus-maze test ($p<0.05$).[145] Importantly, white blood cell count and interleukin-6 were not elevated; Peyer's patches were not enlarged, and sickness behaviour was not observed,[145] this seems to indicate that the mucosal immune system was not activated. Lyte *et al.* (2005) conducted a similar experiment with the same results with the infective agent *Citrobacter rodentium.*[146] Anxiety behaviour was significantly increased in the hole-board open field test after infection without activating the immune cytokines tumour necrosis factor-α, interferon-γ, and interleukin-12.[146] It was also found that vagal sensory ganglia were activated, as indicated by cFos protein presence.[146]

A follow-up study was conducted by Gaykema *et al.* (2003) that determined the brain areas activated by *Campylobacter jejuni* included the nucleus of the solitary tract, the lateral parabrachial nucleus, and the hypothalamic paraventricular nucleus.[147] The nucleus of the

solitary tract projects to the hypothalamic paraventricular nucleus in the forebrain. Once again, this occurred without immune activation, as indicated by the unchanged levels of interleukin-1β, tumour necrosis factor-α, and interleukin-6.[147]

Goehler *et al.* (2004) made inquiries regarding the exact pathway that *Campylobacter jejuni* infection uses to activate the brain to influence behaviour.[148] Using cFos protein presence as an indicator of activation, sensory neurons in the vagal ganglia, the nucleus of the solitary tract, the later parabrachial nucleus, and the ventrolateral medulla were activated in a time-dependent manner following local infection.[148] The level of activation between the vagal ganglia and the nucleus of the solitary tract was highly significant ($p<0.001$),[148] indicating that this likely could be the pathway that the infection used to access the central nervous system. In addition, serotonergic neurons were activated in the ventromedial medulla.[148] These activations were most robust within eight hours of initial infection,[148] indicating that the vagal nerve is one of the initial signals of the gut to the brain. Once more, interleukin-1β, tumour necrosis factor-α, and interleukin-6 were not activated.[148] Interestingly, enteric ganglion cells were not activated,[148] thus indicating that activation of the vagal ganglia was mediated by a different mechanism.

The final study in this series investigated the pathway of how *Campylobacter jejuni* infection communicates with the central nervous system to produce anxiety-like behaviour.[149] Using cFos protein presence as an indicator of activation, exposure to psychological stressor equivalent of the holeboard combined with *Campylobacter jejuni* infection produced activation in several key areas regulating anxiety behaviour.[149] Namely, the paraventricular hypothalamic nuclei, basolateral nuclei of the amygdala, and the bed nucleus of the stria terminalis were areas that responded to psychological and physical stressors.[149] Particularly, the level of activation in

the bed nucleus of the stria terminalis predicted the level of anxiety behaviour, thus indicating a dose-dependent relationship.[149]

These articles illustrate one mechanism by which acute gastrointestinal illness can influence anxiety or depressive illnesses is through activation of the vagus nerve endings, which are present throughout the gastrointestinal tract. Increased excitatory neuronal input to the paraventricular nucleus could be the primary cause for anxiety and depressive behaviour in response to infection. Furthermore, it supports the concept that mental and physical connections are valid, and not merely psychosomatic. Bottom up sensory information can change ongoing responses of top-down neural processing.

Endocrine system

The endocrine system in this section primarily refers to the hypothalamic-adrenal-pituitary axis, the prime regulator of the 'fight or flight' and stress response. The first study by Liansheng *et al.* (2011) examined how experimentally induced gastric irritation analogous to gastrointestinal infection via 0.1% iodoacetamide in male rats affected anxiety symptoms, as measured by the elevated plus maze, open-field, and light-box tests, and depressive symptoms, as measured by forced-swimming and sucrose preference tests.[150] Primarily, this article used neonatal rats to determine if gastric irritation at a key time period would affect long-term outcomes and the hypothalamic-adrenal-pituitary axis.[150] It was found that corticotropin releasing factor levels in the hypothalamic paraventricular nucleus and the amygdala were increased by 22% and 23% respectively in mice with gastric irritation undergoing psychological stressors, and that this effect remained through to adulthood.[150] In addition, corticosterone and adrenocorticotropic hormone levels increased by approximately 50% each while displaying anxiety and depressive activity.[150] This study indicates that early life episodes of gastrointestinal

illness could potentially induce a long-term predisposition to anxiety or depressive illnesses through increasing the activity of the hypothalamic-pituitary-adrenal axis.

Lin *et al.* (2011) investigated how maternal bacterial infection analogous to gastrointestinal infection simulated by prenatal lipopolysaccharide exposure would affect fetal development in relation to mental disorders using lipopolysaccharide to mimic maternal bacterial gastrointestinal infection.[151] It was found that adult offspring of infected mice had more anxiety-like behaviours and heightened stress responses as measured by the open field, elevated plus maze, and novelty induced hypophagia.[151] Female mice displayed more anxiety behaviours in all three tests ($p<0.05$).[151] Corticosterone increased more in female offspring of infected mice than in male or control mice; and the hypothalamic-adrenal-pituitary axis was hyperactive; thus limiting the ability to control the level of corticosterone.[151] Physiological changes in the brain included increased dopamine levels in the nucleus accumbens and decreased serotonin in the prefrontal cortex and hippocampus.[151] It was also found that serotonin ($5HT_{1A}$) receptors were decreased in the dorsal and ventral hippocampus.[151] The study correlates with Liansheng *et al.* (2011) in postulating that a critical window exists in fetuses later in pregnancy for neuronal development, and that bacterial products from maternal infection can induce phenotypical changes in the infant's hypothalamic-adrenal-pituitary axis that results in increased anxiety behaviours. It was not determined what mechanism caused the fluctuations of dopamine and serotonin,[151] but this result provides an interesting mechanism warranting further study to determine exactly how the hypothalamic-adrenal-pituitary axis influences these neurotransmitters in key mood regulation areas of the brain.

Luo *et al.* (2013) examined how experimentally induced gastritis analogous to gastrointestinal infection induced via 0.1% iodoacetamide influenced depression-like behaviour,

as measured by the sucrose preference test and anxiety-like behaviour, as measured by the elevated plus maze and open field test.[152] Results were intriguing; as it was one of the few studies that included gender. In their primary results it was found that only female rats experienced anxiety and depressive behaviour in response to gastritis, and that the hypothalamic-adrenal-pituitary axis in these rats was hyperactive. This was supported by corticotropin-releasing factor and corticosterone levels.[152] Importantly, the immune cytokines interleukin-6, tumour necrosis factor-α, and interferon-γ were not activated or significantly different between the genders or control mice;[152] and neither was mRNA of cFos in the hypothalamus,[152] indicative of vagal nerve activity. It was determined that gastritis increased the corticotropin releasing factor mRNA expression in the hypothalamus of female rats by approximately 71%,[152] and decreased plasma corticosterone levels by approximately 22%,[152] both of which were significant differences ($p<0.05$).[152] Sex hormones respective to gender was decreased in female mice, and increased in male mice, with gastritis.[152] These findings suggest that connections between acute gastrointestinal illness and anxiety and depressive illnesses can be mediated independently of the immune system or vagal nerve and could be sex dependent based on differing hormonal systems. The authors note that vagal nerve activity is typically present with acute stressors, whereas corticotropin releasing factor is expressed with more chronic stressors, such as was present in the seven-day testing period.[152] It is possible that female gender makes individuals more susceptible to gastritis, through decreased estrogen role in mediation of mood and inflammatory processes.

Bailey & Coe (1999) determined that infant rhesus monkeys that underwent the psychological stressor of maternal separation had elevated cortisol levels in addition to an altered microbiome when housed in a group area with unfamiliar individuals.[135] However, this was not a dose-dependent relationship with alterations in the microbiome.[135] Thus, while activation of the

hypothalamic-adrenal-pituitary axis was present in response to psychological stress, and the gastrointestinal tract was affected,[135] it is not clear whether the effects were long lasting or responsible for the alterations in the microbiome.

Based on these studies, gastritis can influence anxiety and depressive symptoms in a secondary and potentially long-acting manner through inducing a hyperactive hypothalamic-pituitary adrenal system that inhibits the negative feedback mechanism.

Bidirectionality of the gut-brain axis

The gut-brain axis can be viewed in three ways: as a top-down process, where the brain affects the gastrointestinal system; as a bottom-up process, where the gastrointestinal system affects the brain; or as bidirectional where both systems affect each other. Bidirectionality of the gut-brain axis was acknowledged as important in several studies, but was never explicitly discussed in the results. Nevertheless, there was a good sampling of articles from both perspectives to display that signaling is indeed top-down as well as bottom-up.

Four studies spoke about top-down processes, comprising 14% of the total themes in the sample. In particular, Rogers *et al.* (2013) found that individuals diagnosed with depressive disorders were 35% more likely to develop *Clostridium difficile* infection, when adjusted for age, gender, race, weight, functional bowel disorders, marital status, exposure to antibiotics, and socioeconomics.[131] A large sample of 16,781 patients makes the findings more generalizable.[131] Three other studies were comprised of animal populations, but supported the notion that biological changes are possible due to anxiety or depressive illnesses.[134–136]

Six studies addressed bottom-up processes, comprising a total of 21% of the total themes in the sample. Five were conducted using animal populations, and one by Benros *et al.* (2013) determined that gastrointestinal infection increased the risk of mood disorders by 65%, and did

so in a dose-response relationship even when adjusted for substance use and family psychiatric history.[132] This provides an important contrast to Rogers *et al.* (2013).

Within this sample, no studies explicitly studied both top-down and bottom-up processes in their results. However, nine out of ten of these studies acknowledged the importance of bidirectionality within the discussion. Most particularly, each of these nine cases, similar statements to: "It has been suggested that mechanisms underlying the brain-gut axis may be bidirectional,"[131] and that recognition is key to understanding the symptoms.

Integration of care options might result in improved health outcomes

Integration of care options was an important theme that resulted from this scoping review and thematic analysis. Addolorato *et al.* (2008) investigated how state (transitory) and trait (temperament) anxiety and depressive symptoms were related to gastrointestinal diseases.[153] Of importance to the research question in this review was that infection with *Helicobacter pylori* was highly associated with trait anxiety ($p<0.001$),[153] and also associated with state anxiety ($p=0.01$).[153] In a sample of 559 individuals infected with *Helicobacter pylori* in Italy, approximately 90% were affected by state anxiety and 18% were affected by depression.[153] Based on these and other results, Addolorato *et al.* (2008) comes to two primary conclusions: firstly, many individuals with gastrointestinal symptoms have issues with mental health which could be present as a co-factor, co-morbidity, or as the main reason for medical consultation.[153] Secondly, given these findings and the unclear nature of the primary clinical issue, "psychometric evaluation, other than… medical observation and exams, acquire a great value,"[153] and thus patients "should be managed by a team,"[153] with expertise or awareness in both areas. At this stage of research, team management is an idea that should be further explored to determine if there is evidence supporting its implementation.

Rahman *et al.* (2007) examined infants of mothers with post-natal depression in rural Pakistan for relative risk of developing diarrheal disease.[154] It was found that infants of mothers with depression were 2.3 times more likely to have greater than five diarrheal episodes per year,[154] irrespective of sociocultural factors such as nutrition, breastfeeding, female empowerment, gender, socioeconomic status, and health education.[154] It is not known whether maternal depression affects the infant's risk for diarrheal episodes directly, or if this is a result of an undetermined variable such as poor caretaking of the infant. Nevertheless, recommendations that arise from this study are twofold: that improving mental status can influence physical health positively,[154] and that the association between "major public health problems indicates a need for integrated and holistic interventions."[154]

Discussion: opportunities, future research need, and recommendations

The themes described above present a multi-faceted picture of the connections between the gastrointestinal system and the brain. One system alone is not responsible for the relationship, but it appears that differing systems could potentially be responsible at different temporal points: the vagus nerve could be implicated at very early onset of infection,[145–149] and at a later point, the microbiome[134–136] and endocrine system in the form of the hypothalamic-pituitary-adrenal system could be largely important.[135,150–152] If the hypothalamic-adrenal-pituitary axis or microbiome is disturbed, it seems it has the potential to create long-term changes to the central nervous system which can onset or predispose individuals to anxiety or depressive illnesses.[135,136,150,152] Variability in central nervous system outcomes after infection can reflect differences in exposure timing or robustness of immune response.[132]

When the immune system is activated, the presence of anxiety or depression can be confounded with sickness behaviour. Symptoms of sickness behaviour arise as an adaptive response to infection and include lethargy and loss of appetite, thus sharing features of depression.[155] This can be used to explain anxiety or depressive symptoms and discount the possibility of psychiatric illness. However, it has also led to a conclusion that cytokines and inflammatory factors may be involved in the pathophysiology of depression.[156] For instance, at elevated levels, tumour-necrosis-factor-α and interleukin-1β impair neuronal plasticity[157] and inhibit long term potentiation.[158] The highest concentrations of these receptors are in the hypothalamus, hippocampus, and cortex, which are also key areas of mood regulation.[156] Thus, elevated cytokines are theorized to affect brain development and memory formation in mood controlling centres of the brain, providing an indirect, but still valid, mechanism for how infection can create long-term depression.

These articles all acknowledge the potential contribution of the immune system, but many showed that inflammatory cytokines were not activated in cooperation with the anxiety or depressive behaviour.[136,145–148,152] This shows that the association of emotional disturbance with infection goes beyond systemic effects of the inflammatory state. Several theories arise as a mechanism for how emotional state and gastrointestinal infection are related: alterations in gut permeability allow translocation of bacterial products to systemic circulation,[68,137,159,160] competition for binding sites occurs between pathogenic and commensal bacteria,[161–163] tryptophan metabolism is altered by bacterial products,[162,164,165] and changes in the composition of the commensal microbiome in the gastrointestinal tract[8,166–169] to name a few. These are present and further elucidated in patients with comorbid psychiatric conditions and chronic gastrointestinal disorders. For instance, female patients with irritable bowel syndrome were

found to have more tryptophan converted to kynurenine, rather than serotonin, and were two times more likely to have anxiety or depression.[170] In addition, patients with irritable bowel syndrome[99–101] and adults with gastrointestinal pain have decreased amounts of *Bifidobacteria* phyla in the microbiome,[102] which also occurs with psychiatric symptoms of depression. Understanding that there could be pathways other than the immune system that contribute to gut-brain connections is important as a paradigm shift to creating holistic treatment. Each pathway must be considered as important on its own, but also in relation to the others.

Research that collects data on variables relating the gut and the brain would do well to acknowledge the bidirectionality of the gut-brain axis. Conducting analysis on data from population databases from both directions would be of benefit. For instance, Rogers *et al.* (2013) and Benros *et al.* (2013) both used data from national registers (Health & Retirement Study;[131] Danish National Hospital Registry[132] and Danish Psychiatric Research Register[132] respectively). This data can be analyzed from both a gut-brain, and a brain-gut perspective. For instance, Rogers *et al.* (2013) could have used the same data to determine not just the relative risk for individuals diagnosed with depressive disorders to develop *Clostridium difficile* infection,[131] but also the relative risk for patients with *Clostridium difficile* infection to develop emotional distress. Similarly, Benros *et al.* (2013) could have determined the incidence rate ratio of developing infection with diagnosis of mood disorder, in addition to the incidence rate ratio of developing mood disorder with diagnosis of infection. While separate studies may address both directions along this axis, they are developed with different populations and sample sizes. Considering the bidirectionality of the gut-brain axis within one study would provide invaluable evidence of the importance of both a top-down and bottom-up consideration in the process of health systems design and patient treatment.

The results of this scoping review and thematic analysis reveal that the research into the intersection of acute gastrointestinal illness and mental status is in the extremely early stages. There are many opportunities that arise as a result, primarily that further, novel research can be done with an action-oriented mindset.

Conducting more studies with human populations is the most important next step. Animal models can attempt to approximate human populations, however especially when looking at mental and emotional health, it is not possible to approximate disease conditions. Further epidemiological evidence and studies examining the longitudinal and prospective outcomes of both AGI-mood and mood-AGI connections are also necessary. Confirmation of human mechanisms aligning with what animal studies have described is necessary before treatment paradigms may be shifted.

Further studies in more global communities are also recommended. Currently, only one study within this sample came out of a low or middle-income country. While certain associations between acute gastrointestinal illness and mental health are suggested in the Global North or laboratory settings, these may not necessarily be supported in very different areas of the world. For instance, different cultures understand mental illness in different ways: the relevance of psychiatric knowledge and evidence has been disputed in non-Western nations.[171] In contrast, it might become apparent that associations are more robust in low-income settings, due to the increased risk or prevalence related to social determinants of health. It is necessary to raise skills and capacity in diverse areas of the world, and the narrow scope of origin does not reflect any progress in this area. More of a global context is required as a basis to human studies in this field. In doing so, actions arising from research can be implemented in multiple settings, potentially preventing health disparities.

There were very few studies that examined gender differences, even among animal populations. Most studies using animal models used solely male mice, although a few investigating maternal links obviously did not.[135,151,154] Of the human studies that are available, few were analyzed fully with respect to gender. For instance, Addolorato *et al.* (2008) found that female gender was associated with higher levels of all measures of psychological distress, but did not elucidate the differences in proportion of *Helicobacter pylori* infection[153]. The high prevalence of anxiety and depressive illnesses in women[11] and the findings of a few preliminary studies that show female sex changes emotional responses to infection[132,151–153] mean that this avenue must be explored in greater detail.

A few reflections must be made for the inclusion of certain aspects of the literature sample. Firstly, two studies used the bacterium *Helicobacter pylori* as their infective agent.[143,153] It is important to note that this infection is usually chronic, and is not always self-limiting.[172] Nevertheless, it provides an important human study within the sample, and both studies examined patients within a short period from initial infection. This warrants inclusion under the definition of acute gastrointestinal illness used in this scoping review and thematic analysis.

In addition, several studies studied a maternal/neonate population with acute gastrointestinal illness and mood alterations in different individuals.[135,151,154] Nevertheless, the inclusion of a post-natal depression or maternal infection setting is relevant for two reasons: firstly, infants obtain their gastrointestinal microbiota from mothers during the birth and labour process.[173] Secondly, most infants obtain all of their nutrition from their mothers through breastfeeding in the first few months of life.[174] Thus, many of the same mechanisms as discussed in the connections between physical and mental status are still present. However, it is also important to note that there are obvious differences between gastrointestinal illness and mental

illness in the neonatal period versus other periods in life. There are additionally many confounding variables that could be presented when looking at links between illness in one person and illness in another, so any conclusions derived from these studies must not be viewed as causative, only interesting correlations that must be examined further.[135,151,154]

While effective treatments are known for most acute gastrointestinal illnesses, anxiety, and depressive illnesses,[14,175] understanding the intersections between these illnesses can change therapeutic techniques. Through the results of this scoping review, the microbiome appears to be a novel area that can be targeted with pharmaceutical interventions. The leading candidate appears to be probiotics, which is theorized to be able to adjust the microbial composition, thereby potentially off-setting the long-term negative effects of infection, or the propensity to succumb to infection.[176] It also offers a route for personalized treatment unique to each individual person.[177]

Probiotic supplementation is being pursued in the field as a therapeutic approach that can alleviate symptoms of both functional gastrointestinal disorders and mental illness.[178,179] Supplementation with lactic acid bacteria, specifically *Lactobacilli*, *Bifidobacteria*, *Enterococci*, *Streptococci,* and *Bacilli* has been associated with positive outcomes. For instance, supplementation with *Lactobacilli* showed 'adequate relief' from symptoms in diarrhea-predominant irritable bowel syndrome 48% of the time.[180] In addition, animal studies have found that the use of probiotics reduces anxiety symptoms, as evidenced by altered central expression of GABA receptors[181] and reduced corticotrophin releasing factor levels in the amygdala.[182] It is thought that probiotics exert these effects by rebalancing the microbiome to promote intestinal barrier function and thus mediate pathways of the gut-brain axis.[176] However, probiotic

supplementation is still experimental and not a standard clinical treatment for functional gastrointestinal disorders or mental illness.[176]

While integration of care options was only a major theme in two articles, it provides an opportunity to look forward and consider the way that the medical community can react to biomedical research. Integrated care is an ambiguous term in the medical literature, and synonyms include care management, coordinated care, and holistic care.[183] In the context of this review, integrated care refers to the organizational process of coordination that seeks to achieve continuous and holistic care tailored to the patient. Integrated care is shown to have improved patient's outcomes in several areas including quality of life, patient satisfaction, and clinical adherence.[183] For health systems, this has effectively resulted in fewer emergency room visits and fewer hospitalizations.[184] Integrated care has primarily been a phenomenon of the Global North, however recent interventions in low-middle income nations of the Global South have used the concept of specialist program integration into primary care to address specific health problems in a better and more cost-effective manner.[185,186] In the Global North, integrated care options typically target chronic illnesses[187]: several common examples are combining treatment for diabetes,[188] cardiac conditions (hypertension, coronary artery disease, congestive heart failure),[187,189] respiratory conditions such as asthma and chronic obstructive pulmonary disease,[190] and in some cases pain management. Integrated care clinics exist for consideration of the mental health aspect for chronic disorders such as cardiac conditions[191] and irritable bowel syndrome.[192,193] These have arisen due to the acknowledged connections between mental health, such as stress, and the physical outcomes of these illnesses. As knowledge grows about the biological and social connections of infectious illness and mental status, proof of concept is present that treating chronic physical illnesses in conjunction with mental illness results in better

outcomes for patients and societies.[187,194–196] Going forward, it makes sense to consider this adjustment of health systems as the connections between acute gastrointestinal illness and anxiety and depressive illnesses are further elucidated.

Infectious diseases and mental illness programs and treatments have largely been divided into distinct pathways, with the exception of studies regarding syphilis and neural complications of HIV/AIDS.[197] In the later stages of the HIV/AIDS epidemic, lessons were learned that found incorporating mental health treatment into HIV treatment had several positive effects. For instance, Farber *et al.* (2013) found that only three months after incorporating mental health services into community based HIV care, significant reductions of perceived self and others stigma occurred.[198] Schumacher *et al.* (2013) found that integrating depression and anxiety screening and group therapy into an HIV/AIDS treatment centre detected high comorbidity prevalence rates of approximately 80%, and that significant reductions of depression score occurred.[199] Furthermore, a systematic review and meta-analysis by Sin and DiMatteo (2013) found that depression treatment increased adherence to anti-retroviral therapy in HIV/AIDS patients by 83%.[200] This model shows that integrating care for infectious and mental illnesses can have extremely positive outcomes in both areas. The first steps in establishing holistic and patient-centered treatment in those with acute gastrointestinal illness and mental distress should involve breaking down barriers and increasing the continuity of care between health professionals. Key suggestions are to increase communication systems between health care providers to coordinate patient care.[201] Primary care providers can have an important role in collecting health information and acting as a point of contact for patients.[202,203] However, it is suggested that specialists and allied health professionals can have a role in collaboration as well, by working with each other as well as with primary care providers.[204,205] Medical education can

have a role in this as well, by exposing providers in certain sectors to areas that could be intimately connected with their own practice, but may be overlooked.[206,207] In sum, a shared knowledge base of providers is the first step to allow professionals to treat a whole person, and respond broadly and adequately to each patient issue.

The early stages of this research provide an opportunity for the medical community to be proactive, rather than reactionary. If disease burdens can influence each other through biological and psychosocial connections, then it is necessary to understand these mechanisms to thoroughly treat the causes, rather than the symptoms of illness.

Conclusion

These findings demonstrate that holistic and integrated interventions must be considered not only for chronic and mental illnesses, but also for infectious and mental illnesses, based on the connections between AGI, depressive and anxiety symptoms. More research is required, particularly with human subjects, in order to further understand the connections between the gut and brain. In addition, consideration of bidirectionality is important, as most studies chose a top-down or bottom-up approach with which to approach their findings. Incorporation of this knowledge into new treatment plans will allow clinicians to deliver more effective care to their patients who suffer from a dual burden of disease.

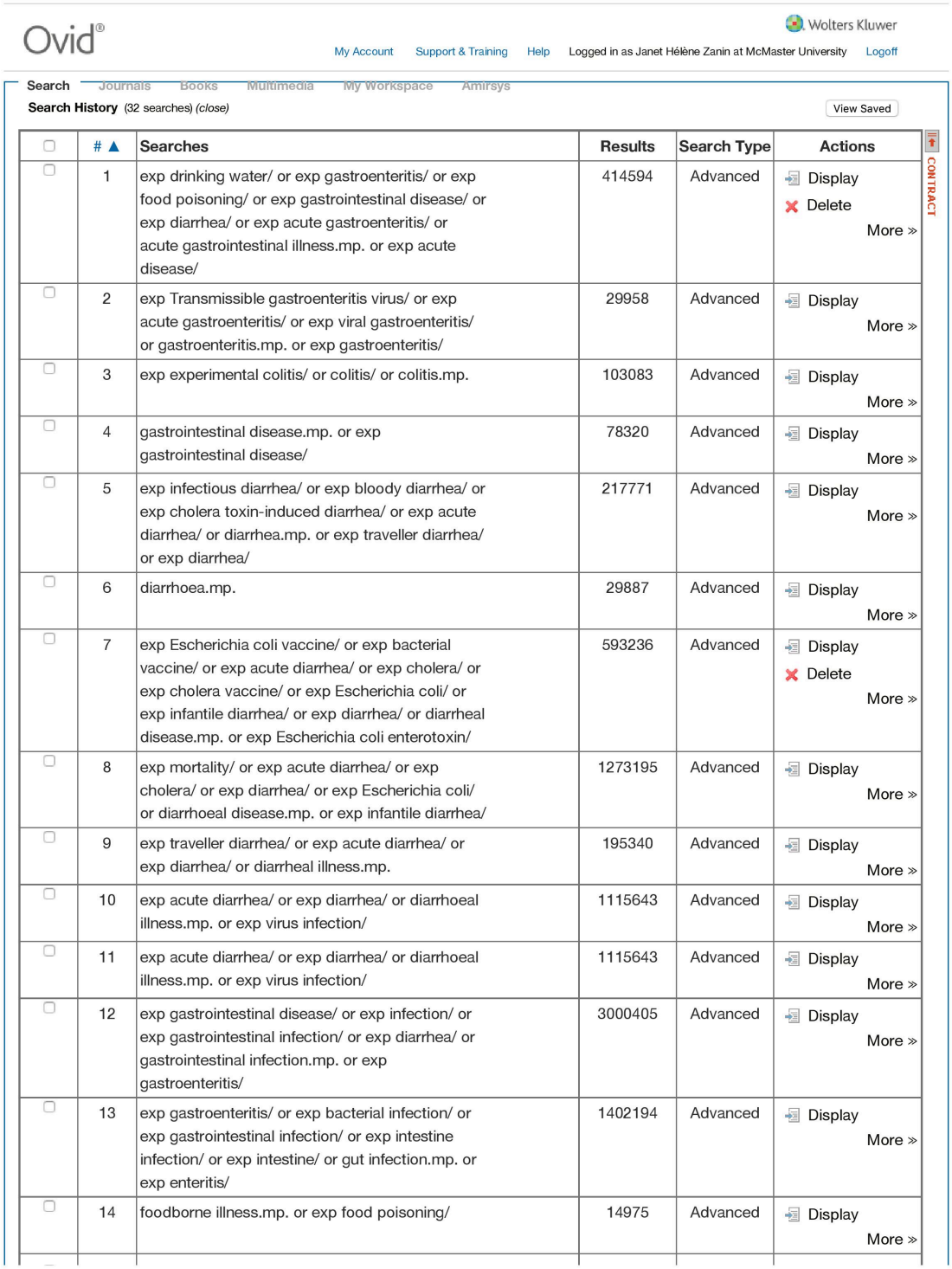
Appendix

Table 1: Data characterization form

Name of Article:	
Authors:	
Year:	
Citation:	
Theme:	
Chapter:	
Type of Study/ Research Methods:	
Key Information:	
Gaps in Research:	

Figure 1: Keyword and subject heading search terms

EMBASE



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2	exp Transmissible gastroenteritis virus/ or exp acute gastroenteritis/ or exp viral gastroenteritis/ or gastroenteritis.mp. or exp gastroenteritis/	29958	Advanced	Display, More »
3	exp experimental colitis/ or colitis/ or colitis.mp.	103083	Advanced	Display, More »
4	gastrointestinal disease.mp. or exp gastrointestinal disease/	78320	Advanced	Display, More »
5	exp infectious diarrhea/ or exp bloody diarrhea/ or exp cholera toxin-induced diarrhea/ or exp acute diarrhea/ or diarrhea.mp. or exp traveller diarrhea/ or exp diarrhea/	217771	Advanced	Display, More »
6	diarrhoea.mp.	29887	Advanced	Display, More »
7	exp Escherichia coli vaccine/ or exp bacterial vaccine/ or exp acute diarrhea/ or exp cholera/ or exp cholera vaccine/ or exp Escherichia coli/ or exp infantile diarrhea/ or exp diarrhea/ or diarrheal disease.mp. or exp Escherichia coli enterotoxin/	593236	Advanced	Display, Delete, More »
8	exp mortality/ or exp acute diarrhea/ or exp cholera/ or exp diarrhea/ or exp Escherichia coli/ or diarrhoeal disease.mp. or exp infantile diarrhea/	1273195	Advanced	Display, More »
9	exp traveller diarrhea/ or exp acute diarrhea/ or exp diarrhea/ or diarrheal illness.mp.	195340	Advanced	Display, More »
10	exp acute diarrhea/ or exp diarrhea/ or diarrhoeal illness.mp. or exp virus infection/	1115643	Advanced	Display, More »
11	exp acute diarrhea/ or exp diarrhea/ or diarrhoeal illness.mp. or exp virus infection/	1115643	Advanced	Display, More »
12	exp gastrointestinal disease/ or exp infection/ or exp gastrointestinal infection/ or exp diarrhea/ or gastrointestinal infection.mp. or exp gastroenteritis/	3000405	Advanced	Display, More »
13	exp gastroenteritis/ or exp bacterial infection/ or exp gastrointestinal infection/ or exp intestine infection/ or exp intestine/ or gut infection.mp. or exp enteritis/	1402194	Advanced	Display, More »
14	foodborne illness.mp. or exp food poisoning/	14975	Advanced	Display, More »

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☐	15	exp communicable disease/ or exp water contamination/ or exp gastroenteritis/ or waterborne illness.mp. or exp food contamination/	100885	Advanced	Display More »
☐	16	mental health.mp. or exp mental health/	208202	Advanced	Display More »
☐	17	mental illness.mp. or exp mental disease/	1735354	Advanced	Display More »
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☐	19	mental disorder.mp. or exp mental disease/	1732904	Advanced	Display More »
☐	20	exp inbreeding depression/ or exp involutional depression/ or exp Self-rating Depression Scale/ or exp Depression Anxiety Stress Scale/ or exp agitated depression/ or exp bipolar depression/ or exp Montgomery Asberg Depression Rating Scale/ or exp Beck Depression Inventory/ or exp perinatal depression/ or exp endogenous depression/ or exp central nervous system depression/ or exp Zung Self Rating Depression Scale/ or exp Cornell Scale for Depression in Dementia/ or exp Death Depression Scale/ or exp major depression/ or exp treatment resistant depression/ or exp Geriatric Depression Scale/ or exp experimental depression test/ or exp masked depression/ or exp Hamilton Depression Rating Scale/ or depression.mp. or exp atypical depression/ or exp ST segment depression/ or exp long term depression/ or exp depression assessment/ or exp depression/ or exp reactive depression/ or exp "mixed depression and dementia"/ or exp Edinburgh Postnatal Depression Scale/ or exp recurrent brief depression/ or exp "Hospital Anxiety and Depression Scale"/ or exp "mixed anxiety and depression"/ or exp postoperative depression/ or exp depression inventory/ or exp Calgary Depression Scale/ or exp late life depression/ or exp organic depression/ or exp puerperal depression/ or exp Center for Epidemiological Studies Depression Scale/	530073	Advanced	Display Delete Save Auto-Alert RSS Feed
☐	21	depressive illness.mp. or exp depression/	357596	Advanced	Display More »
☐	22	depressive disorder.mp. or exp depression/	359577	Advanced	Display More »
☐	23	exp reactive depression/ or mood disorder.mp. or exp depression/ or exp mood disorder/ or exp mental disease/ or exp mood/	1743669	Advanced	Display More »
☐	24	anxiolytic.mp. or exp anxiolytic agent/	175884	Advanced	Display More »
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	25	exp Self-rating Anxiety Scale/ or exp Hamilton Anxiety Scale/ or anxiety.mp. or exp anxiety assessment/ or exp experimental anxiety test/ or exp anxiety/ or exp anticipatory anxiety/ or exp performance anxiety/ or exp State Trait Anxiety Inventory/ or exp unconditioned response anxiety test/ or exp generalized anxiety disorder/ or exp anxiety disorder/ or exp Liebowitz Social Anxiety Scale/ or exp separation anxiety/ or exp Death Anxiety Scale/ or exp Anxiety Sensitivity Index/ or exp anxiety neurosis/ or exp "Hospital Anxiety and Depression Scale"/ or exp Beck Anxiety Inventory/ or exp Social Interaction Anxiety Scale/ or exp "mixed anxiety and depression"/ or exp conditioned response anxiety test/ or exp Depression Anxiety Stress Scale/	342224	Advanced	Display Delete Save Auto-Alert RSS Feed
☐	26	anxiety disorder.mp. or exp anxiety/ or exp anxiety disorder/	291053	Advanced	Display More »
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☐	29	gut brain.mp.	936	Advanced	Display More »
☐	30	brain gut.mp.	1429	Advanced	Display More »
☐	31	29 or 30	2305	Advanced	Display More »
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3	colitis.mp. or exp Colitis/	60299	Advanced	Display More »
4	gastrointestinal disease.mp. or exp Gastrointestinal Diseases/	810422	Advanced	Display More »
5	exp Diarrhea/ or diarrhea.mp.	83473	Advanced	Display More »
6	exp Diarrhea/ or exp Escherichia coli/ or diarrhoea.mp. or exp Rotavirus Infections/ or exp Gastroenteritis/	460537	Advanced	Display More »
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8	exp Escherichia coli Infections/ or exp Rotavirus Infections/ or exp Diarrhea, Infantile/ or exp Diarrhea/ or exp Gastroenteritis/ or diarrhoeal disease.mp. or exp Escherichia coli/	459258	Advanced	Display More »
9	exp Escherichia coli/ or exp Escherichia coli Infections/ or exp Gastroenteritis/ or exp Gastrointestinal Diseases/ or exp Diarrhea/ or gastrointestinal infection.mp. or exp Helicobacter Infections/	1097669	Advanced	Display More »
10	exp Gastroenteritis/ or gut infection.mp. or exp Diarrhea/	208286	Advanced	Display More »
11	foodborne illness.mp. or exp Foodborne Diseases/	17595	Advanced	Display More »
12	exp Gastrointestinal Diseases/ or exp Foodborne Diseases/ or waterborne illness.mp. or exp Gastroenteritis/	824779	Advanced	Display More »
13	mental health.mp. or exp Mental Health/	129451	Advanced	Display More »
14	exp Mental Disorders/ or exp Stress, Psychological/ or mental illness.mp. or exp Bipolar Disorder/	1104045	Advanced	Display More »
15	mental disorder.mp. or exp Mental Disorders/	1021195	Advanced	Display More »

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☐	20	anxiolytic.mp. or exp Anti-Anxiety Agents/	64477	Advanced	Display More »
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☐	23	exp Microbiota/ or gut brain.mp.	6782	Advanced	Display More »
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☐	25	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	1832742	Advanced	Display More »
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☐	3	colitis.mp. or exp Colitis/	26640	Advanced	Display More »
☐	4	gastrointestinal disease.mp. or exp Gastrointestinal Diseases/	439107	Advanced	Display More »
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☐	6	exp Escherichia coli/ or exp Diarrhea/ or diarrhoea.mp. or exp Dysentery, Bacillary/ or exp Escherichia coli Infections/	87368	Advanced	Display More »
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☐	10	exp Diarrhea/ or diarrhoeal illness.mp.	25105	Advanced	Display More »
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	19	mental disorder.mp. or exp Mental Disorders/	782195	Advanced	Display More »
	20	exp Depression/ or exp Long-Term Synaptic Depression/ or exp Cortical Spreading Depression/ or exp Depression, Postpartum/ or exp Depression, Chemical/ or depression.mp.	190128	Advanced	Display More »
	21	exp Bipolar Disorder/ or exp Depressive Disorder/ or depressive illness.mp. or exp Depressive Disorder, Major/ or exp Depression/	154545	Advanced	Display More »
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	25	anxiolytic.mp. or exp Anti-Anxiety Agents/	28144	Advanced	Display More »
	26	exp Manifest Anxiety Scale/ or exp Test Anxiety Scale/ or Anxiety/ or exp Anxiety, Separation/ or exp Anti-Anxiety Agents/ or exp Anxiety Disorders/ or anxiety.mp.	167028	Advanced	Display More »
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☐	5	diarrhea.mp. or exp Diarrhea/	1307	Advanced	Display More »
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☐	10	exp Diarrhea/ or diarrhoeal illness.mp.	274	Advanced	Display More »
☐	11	exp Gastrointestinal Disorders/ or exp Infectious Disorders/ or exp Gastrointestinal System/ or gastrointestinal infection.mp.	58947	Advanced	Display More »
☐	12	exp Parasitic Disorders/ or exp Microorganisms/ or exp Gastrointestinal System/ or exp Infectious Disorders/ or exp Gastrointestinal Disorders/ or gut infection.mp.	59703	Advanced	Display More »
☐	13	exp Food/ or foodborne illness.mp.	11289	Advanced	Display More »
☐	14	waterborne illness.mp.	3	Advanced	Display More »
☐	15	mental health.mp. or exp Mental Health/	162564	Advanced	Display More »
☐	16	mental illness.mp. or exp Mental Disorders/	498509	Advanced	Display More »
☐	17	exp Psychiatry/ or exp Mental Disorders/ or exp Mental Health/ or exp Neurology/ or mental disease.mp.	568381	Advanced	Display More »
☐	18	mental disorder.mp. or exp Mental Disorders/	491564	Advanced	Display More »

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☐	19	exp Major Depression/ or exp Treatment Resistant Depression/ or exp "Depression (Emotion)"/ or exp Postpartum Depression/ or exp Recurrent Depression/ or exp Beck Depression Inventory/ or exp Zungs Self Rating Depression Scale/ or exp Reactive Depression/ or exp Atypical Depression/ or exp Endogenous Depression/ or exp Anaclitic Depression/ or depression.mp. or exp Spreading Depression/ or exp "Long-term Depression (Neuronal)"/	250020	Advanced	Display Delete Save Auto-Alert RSS Feed
☐	20	exp Bipolar Disorder/ or exp Emotional States/ or exp Major Depression/ or exp "Depression (Emotion)"/ or depressive illness.mp. or Pathophysiology/	330147	Advanced	Display More »
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☐	22	exp Major Depression/ or exp Bipolar Disorder/ or exp "Depression (Emotion)"/ or exp Anxiety/ or depressive disorder.mp. or exp Anxiety Disorders/	243491	Advanced	Display More »
☐	23	mood disorder.mp. or exp Affective Disorders/	135057	Advanced	Display More »
☐	24	exp Anxiety/ or anxiolytic.mp.	60835	Advanced	Display More »
☐	25	exp Separation Anxiety/ or exp Anxiety Sensitivity/ or anxiety.mp. or exp Social Anxiety/ or exp State Trait Anxiety Inventory/ or exp Generalized Anxiety Disorder/ or exp Anxiety Disorders/ or exp Anxiety/ or exp Taylor Manifest Anxiety Scale/ or exp Performance Anxiety/	212412	Advanced	Display Delete Save More »
☐	26	anxiety disorder.mp. or exp Anxiety Disorders/	72593	Advanced	Display More »
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☐	29	brain gut.mp.	107	Advanced	Display More »
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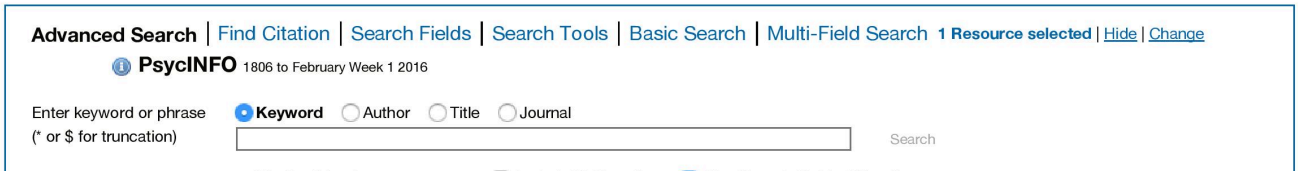
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	# ▲	Searches	Results	Search Type	Actions
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	2	exp Transmissible gastroenteritis virus/ or exp gastroenteritis/ or gastroenteritis.mp.	9109	Advanced	Display More »
	3	colitis.mp. or exp colitis/	7814	Advanced	Display More »
	4	gastrointestinal disease.mp. or exp gastrointestinal diseases/	57690	Advanced	Display More »
	5	diarrhea.mp.	27842	Advanced	Display More »
	6	exp diarrhoea/ or diarrhoea.mp. or exp travellers' diarrhoea/	33096	Advanced	Display More »
	7	diarrheal disease.mp. or Escherichia coli.od. or parasites.sh. or Giardia duodenalis.od. or protozoa.od. or Entamoeba histolytica.od. or Vibrio cholerae.od. or Rotavirus.od. or diarrhoea.sh. or protozoal infections.sh. or bacteria.od. or viral diseases.sh. or Shigella.od. or bacterial diseases.sh.	466548	Advanced	Display Delete Save More »
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	10	diarrhoeal illness.mp. or diarrhoea.sh. or drinking water.sh. or bacterial diseases.sh. or gastrointestinal diseases.sh.	164373	Advanced	Display More »
	11	gastrointestinal infection.mp. or bacterial diseases.sh. or helminths.sh. or viral diseases.sh. or gastrointestinal diseases.sh. or Salmonella.od. or Escherichia coli.od. or infections.sh. or gastroenteritis.sh. or Entamoeba histolytica.od. or diarrhoea.sh. or Cryptosporidium.od. or parasites.sh.	491907	Advanced	Display Delete Save More »
	12	gut infection.mp. or Trichinella spiralis.od. or Cryptosporidium parvum.od. or experimental infections.sh. or parasites.sh. or helminthoses.sh.	184629	Advanced	Display More »
	13	foodborne illness.mp. or Salmonella.od. or	312040	Advanced	Display

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		Clostridium perfringens.od. or bacterial diseases.sh. or viral diseases.sh. or gastroenteritis.sh. or food contamination.sh. or food poisoning.sh. or foodborne diseases.sh. or Escherichia coli.od.			Delete More »
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☐	15	mental health.mp. or exp mental health/	17115	Advanced	Display More »
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☐	17	mental disease.mp. or mental health.sh. or mental disorders.sh.	30569	Advanced	Display More »
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☐	25	anxiety disorder.mp. or anxiety.sh. or depression.sh. or mental disorders.sh.	33979	Advanced	Display More »
☐	26	gut brain.mp.	206	Advanced	Display More »
☐	27	brain gut.mp.	120	Advanced	Display More »
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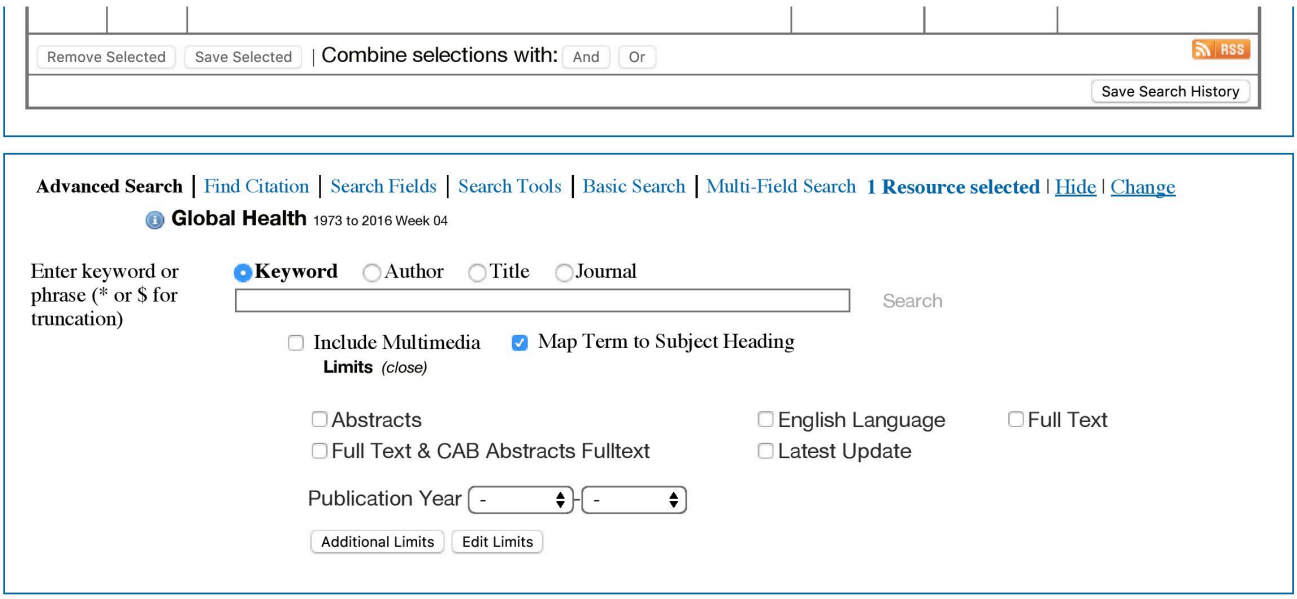
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Figure 2: PRISMA flowchart

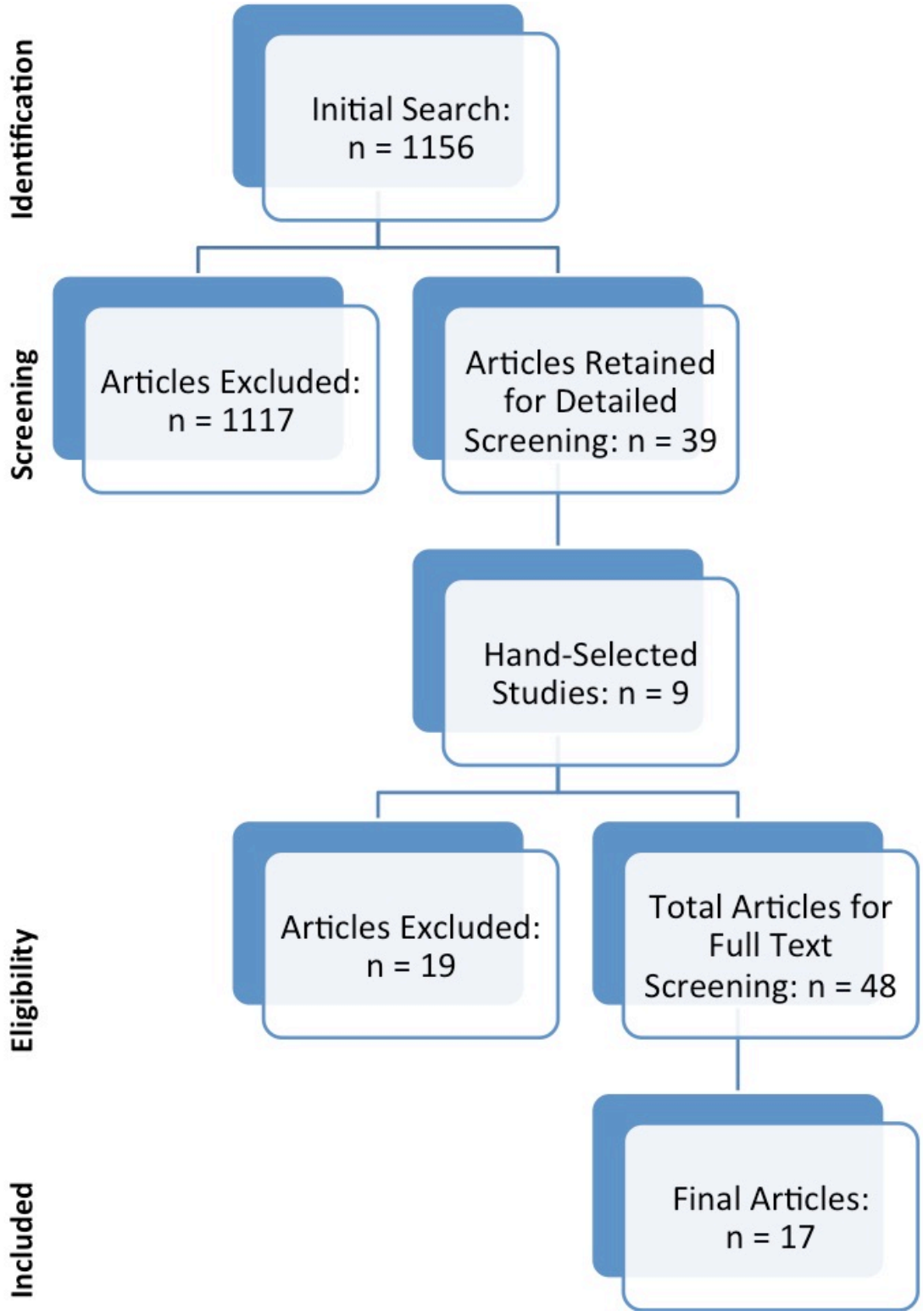


Table 2: Summary of included articles

Number	Title	Authors	Year Published	Database of origin	Location	Methodological Design	Study Purpose	Primary Themes
1	Anxiogenic effect of subclinical bacterial infection in mice in the absence of overt immune activation.	Lyte, M. Varcoe, J. J. Bailey, M.T.	1998	Medline/PubMed, PsycINFO	United States	Clinical randomized control trial with animal populations	To examine whether subclinical, per-oral infection could affect behaviour in the absence of immune system involvement	Nervous system Bottom up signaling
2	Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys	Bailey, M.T. Coe, C.L.	1999	Hand Search	United States	Clinical randomized control trial with animal populations	To determine whether psychological disturbance can influence the stability of indigenous microflora	Microbiota system Hypothalamic-pituitary-adrenal axis Top down signaling
3	Brain response to cecal infection with *Campylobacter jejuni:* analysis with Fos immunohistochemistry	Gaykema, R.P.A. Goehler, L.E. Lyte, M.	2003	Medline/PubMed, PsycINFO	United States	Clinical randomized control trial with animal populations	To test that specific areas in the brain respond to local gut infections	Nervous system Bottom up signaling
4	Activation in vagal afferents and central autonomic pathways: Early responses to intestinal infection with *Campylobacter jejuni*	Goehler, L.E. Gaykema, R.P. Lyte, M.	2004	Medline/PubMed, PsycINFO	United States	Clinical randomized control trial with animal populations	To test the hypothesis that local infection in the gut activates vagal sensory neurons	Nervous system
5	Induction of anxiety-like behaviour in mice during the initial stages of infection with the agent of murine colonic hyperplasia *Citrobacter rodentium*	Lyte, M. Li, W. Opitz, N Gaykema, R.P.A Goehler, L	2006	Medline/PubMed, PsycINFO	United States	Clinical randomized control with animal populations	To determine the early effects of infection on behavioural response and examine potential pathways by with *Citrobacter rodentium*-induced signals reach the brain	Nervous system Bottom up signaling

	diarrhoeal illness: A cohort study	Lovel, H. Creed, F.				cohort with human populations	postnatal depression in mothers and diarrhoeal illness in their first year of life in a low income country	
7	State and trait anxiety and depression in patients affected by gastrointestinal diseases: psychometric evaluation of 1641 patients referred to an internal medicine outpatient setting	Addolorato, G. Mirijello, A. D'Angelo, C. Leggio, L. Ferrulli, A. Abenavoli, L. Vonghia, L. Cardone, S. Leso, V. Cossari, A. Capristo, E. Gasbarrini, G	2008	Hand Search	Italy	Observational cross sectional study with human populations	To evaluate state and trait form of anxiety and current depression in patients affected by gastrointestinal diseases	Integration of care options
8	*Campylobacter jejuni* infection increases anxiety-like behaviour in the holeboard: Possible anatomical substrates for viscerosensory modulation of exploratory behaviour	Goehler, L.E. Park, S.M. Opitz, N. Lyte, M. Gaykema, R.	2008	Medline/PubMed, PsycINFO	United States	Clinical Randomized control trial with animal populations	To identify brain regions that may serve to integrate exteroceptive and interoceptive challenges and potentially mediate the effects of immune-related viscerosensory modulation of anxiety-like behaviour	Nervous system connections Bottom up signaling
9	Role of gut-brain axis in persistent abnormal feeding behaviour in mice following eradication of *Helicobacter pylori* infection	Bercik, P. Verdú, E.F. Foster, J. A. Lu, J. Scharringa, A. Kean, I. Collins, S.M.	2009	Hand Search	Canada	Clinical randomized control trial with animal populations	To investigate the role of the gut-brain axis in gastric dysfunction during and after chronic *Helicobacter pylori* infection	Immune system Bottom up signaling
10	Examination of the depressed gut reveals changes in microbiota and serotonin levels	Park A.J. Blennerhassett P. Denou E.	2009	EMBASE	Canada	Randomized control trial with animal populations	To further characterise the exact influence of pre-existing psychological	Microbiota system Top down signaling

		Bercik P. Collins S.M.					perturbations on the basal state of the gastrointestinal tract	
11	Stressor exposure disrupts commensal microbial populations in the intestines and leads to increased colonization by *Citrobacter rodentium*	Bailey M.T. Galley J.D. Dowd S.E. Lyte M.	2010	Medline/PubMed, PsycINFO	United States	Clinical randomized control trial with animal populations	To investigate the impact of the stress response on enteric infection	Immune system Top down signaling
12	Chronic gastrointestinal inflammation induces anxiety-like behaviour and alters central nervous system biochemistry in mice	Bercik, P. Verdú, E.F. Foster, J. A. Macri, J. Potter, M. Huang, X. Lu, J.	2010	Medline/PubMed, PsycINFO	Canada	Clinical randomized control trial with animal populations	To investigate whether chronic gut inflammation alters behaviour and brain biochemistry and examine the underlying mechanisms	Immune system Bottom up signaling
13	Gastric but not cutaneous irritation in the neonatal period programs adult rats into depression-like behavior depression, which is accompanied by upregulation of hypothalamic CRF expression and reversed by a CRF1 receptor antagonist.	Liu L. Bhargava A. Li Q. Sapolsky R. Pasricha P.J.	2011	EMBASE	United States	Clinical randomized control trial with animal populations	To determine the specificity of gastric irritation and possible mechanisms underlying increased depression and anxiety-like behaviours	Hypothalamic-adrenal-pituitary axis Bottom up signaling
14	Prenatal lipopolysaccharide exposure increases anxiety-like behaviours and enhances stress-induced corticosterone responses in adult rates	Lin, Y.L. Lim, S.Y. Wang, S.	2012	EMBASE	Taiwan	Clinical randomized control trial with animal populations	To examine anxiety and stress responses of maternally infected offspring and neurophysiological changes in the brains	Hypothalamic-adrenal-pituitary axis Bottom up signaling
15	Autoimmune diseases	Benros, M.E.	2013	Hand Search	Denmark	Observational	To estimate the effect	Immune

	and severe infection as risk factors for mood disorders: a nationwide study	Waltoft, B.L. Nordentoft, M. Ostergaard, S.D. Eaton, W.W. Krogh, J. Mortensen, P.B.				prospective cohort study with human populations	of autoimmune disease and infections on the risk of developing mood disorders	system Bottom up signaling
16	Experimental gastritis leads to anxiety-and-depression-like behaviours in female but not male rats	Luo, J. Wang, T. Liang, S. Hu, X. Li, W. Jin, F.	2013	EMBASE	China	Clinical randomized control trial with animal populations	To examine the effects of experimental gastritis on anxiety and depressive-like behaviour	Hypothalamic-adrenal-pituitary axis Bottom up signaling
17	Depression, antidepressant medications, and risk of *Clostridium difficile* infection	Rogers, M.A.M. Greene, M.T. Young, V.B. Saint, S. Langa, K.M. Kao, J.Y. Aronoff, D.M.	2013	PsycINFO	United States	Observational longitudinal cohort study with human populations	To evaluate whether depression or the use of anti-depressants altered the risk of developing *Clostridium difficile* infection	Top down signaling Bottom up signaling Bidirectional signaling

Descriptive components of included articles

Figure 3: Proportion of the geographical locations of included articles by region

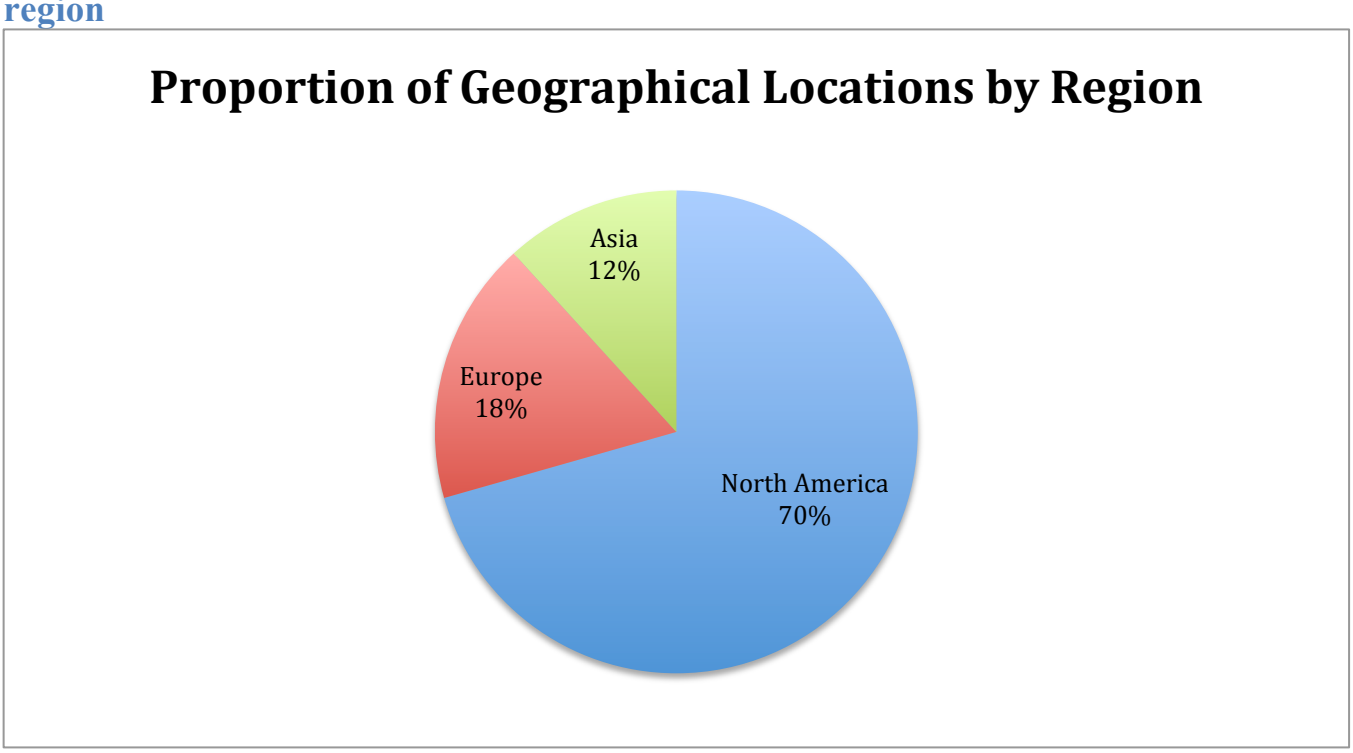


Figure 4: Proportion of the population types of included articles

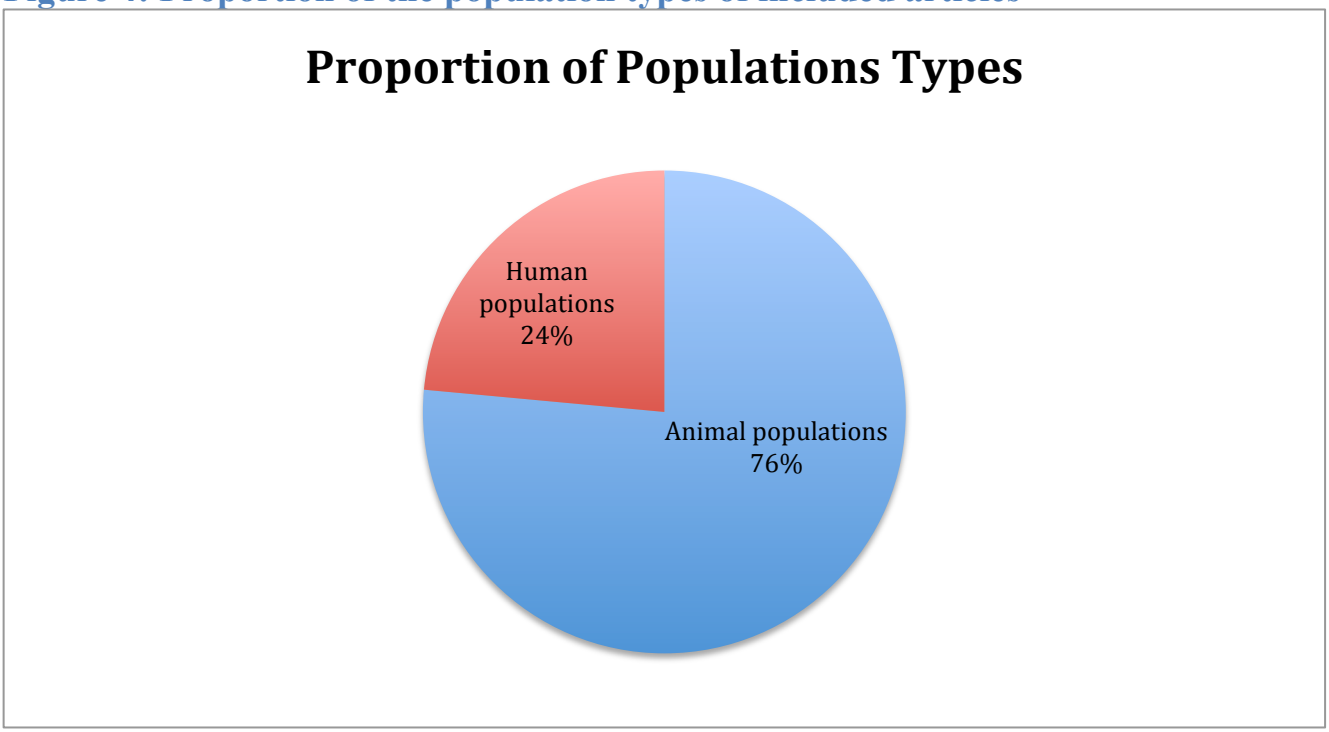


Figure 5: Proportion of the study designs of included articles

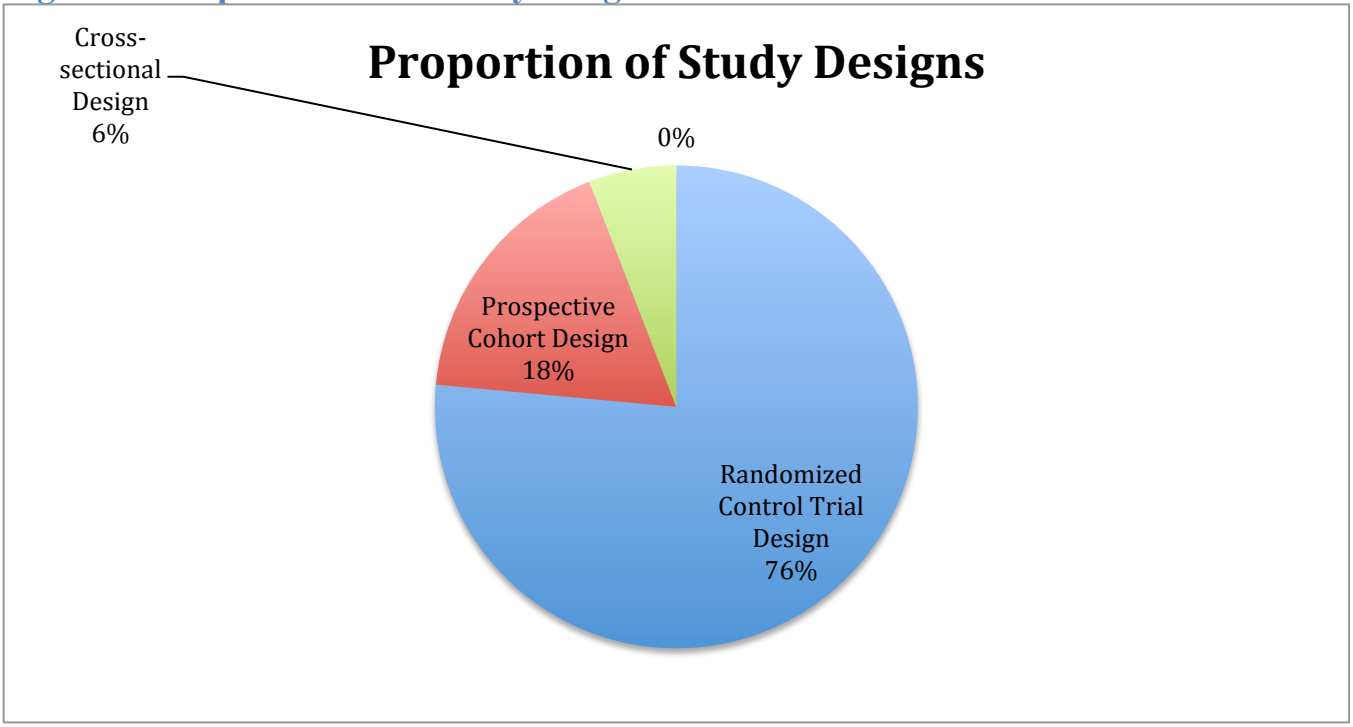


Figure 6: Number of articles published per year

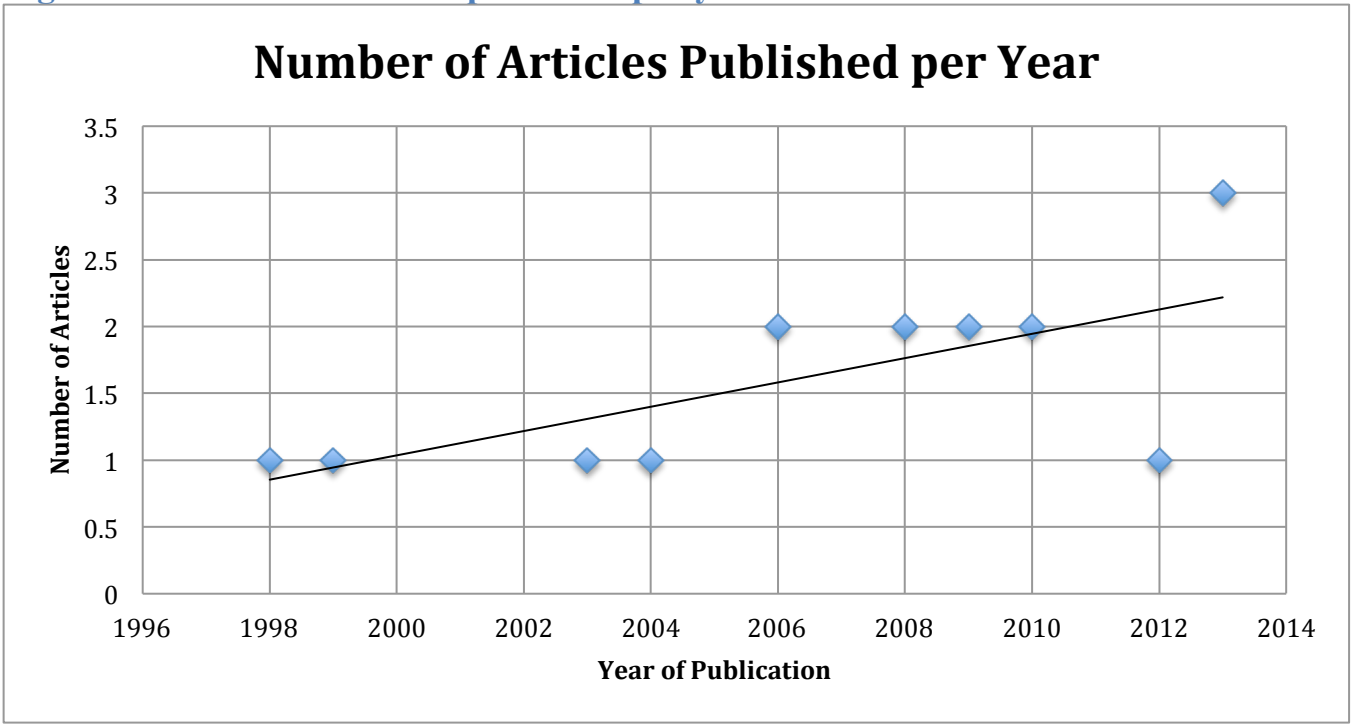
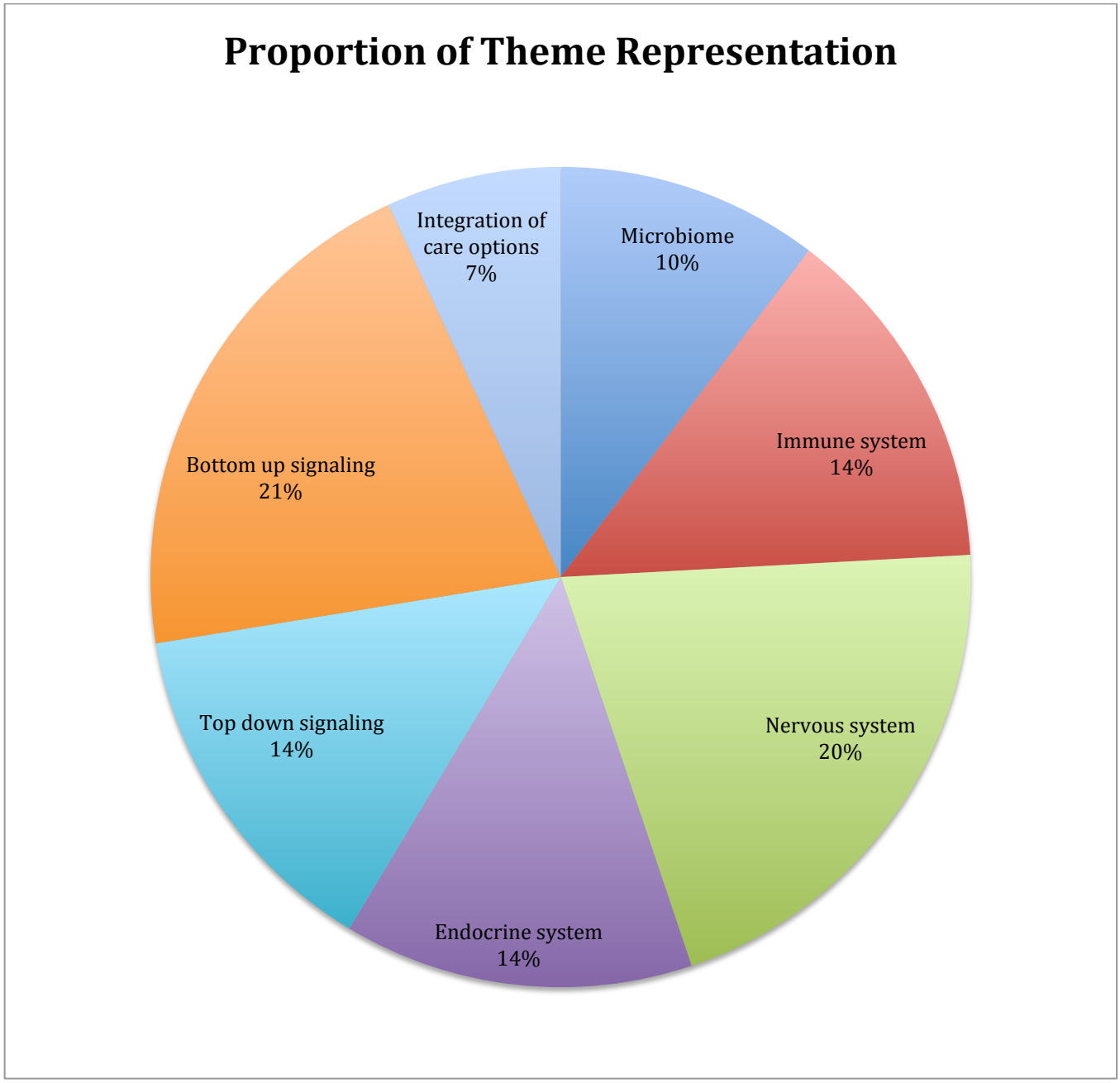


Figure 7: Proportion of themes represented in the literature



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