A NEW APPROACH TO SUFFERING IN LIFE-LIMITING ILLNESS: TOTAL PAIN AND THE HUMAN MICROBIOME

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Contents

EXECUTIVE SUMMARY

"Total pain" is the term used within hospice, palliative, and end-of-life care for pain which is overwhelming, complex, and which encompasses physical, psychological, social, and spiritual dimensions. Addressing total pain through a holistic approach is a central philosophy in caring for those with life-limiting illnesses. There continues, however, to be an entrenched divide in care treatments that either privilege a biomedical (e.g., benzodiazepines, SSRIs) or a psychosocial (e.g., social work, talk therapy, spiritual care) aetiology of suffering. The result is that an individual's total pain as they near the end of their lives often goes un- or under-treated, even within a multidisciplinary team approach. We wanted to investigate one innovative approach to this problem by exploring total pain within an anthropological lens of embodiment applied to human microbial ecology. This report is the initial output of an ongoing project exploring possible relationships between the gut microbiome and experiences of suffering in advanced life-limiting illness.

The gut microbiome[1] is the complex community of microorganisms that live in our digestive tracts. The gut microbiome is a central feature of a multi-directional

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[1] The gut microbiome is the combined intestinal microorganisms and genetic material of these microorganisms. In this report we focus solely on the bacteria within the gut microbiome, acknowledging that there are also viruses, fungi, and protozoa that constitute the gut microbiome, as well as other human microbiomes (e.g., mouth, skin, vaginal).

communication system linking the gastrointestinal tract and the brain, via neuroendocrine, immunological, and metabolic pathways, both directly and indirectly through a range of peptides, neurotransmitters, hormones, and other substances, collectively known as the brain-gut-microbiome axis (BGMA).

Through the BGMA, the gut microbiome is part of a larger unconscious system regulating cognitive function, mood, and other fundamental behaviour patterns including memory, sleep, and appetite, as well as more general behaviours, social interaction, and sociability, and even stress management, including resilience to environmental stressors. There is also research evidence establishing its involvement in human metabolism, nutrition, physiology, and immune function. Understandings about how these complex interactions happen is constantly expanding, in part due to next generation sequencing and the birth of metagenomics.

The microbiome has primarily a concern within medical and life sciences and only in the last few years has become a topic of interest to social scientists. The so-called 'microbial turn' in the social sciences and humanities has unlocked several possible fields of inter- and transdisciplinary study in which social science research may critically inform and respond to microbiome science. This emerging transdisciplinary however has not yet been taken up by social science researchers working on end-of-life issues. In this report we therefore map emerging BGMA research to give additional backing to the existing collaborative (and holistic) palliative care approaches for engaging with complex pain and, indeed, we believe our work extends the remit of consideration when addressing the sources of such pain. In this report we pay particular attention to research on the human intestinal microbiome.

This report brings together the findings of a transdisciplinary literature review which aimed to find and synthesize relevant research from a range of disciplines and approaches relevant to the concept of total pain. Rather than a conventional systematic review, we found that a flexible mixed methods approach was better at highlighting research in disparate fields that address components of total pain, albeit with numerous proxy terms. We have ordered our review by theme, offer a summary conclusion, and include several useful appendices.

Summary of key findings:

- Internal and external stressors, including early life experiences, are mediated by the BGMA and can combine over time to compromise our ability to maintain both physical and emotional stability. In doing so, they influence perceptions of, and habituated responses to, pain.

- Pain and negative affective states such as depression often co-present and activate common neurocircuitries and neurochemicals in the brain, many which involve the BGMA.
- The gut microbiome is often poorer in biodiversity for people with chronic illness, multimorbidity, physical frailty and mobility limitations, as well as those who live within institutions rather than in the community.
- Age brings negative changes to the gut microbiome (such as decrease in number and types), increased gastrointestinal issues, and changes to mobility and eating patterns. These changes may initiate or exacerbate neurodegeneration and associated diseases like Alzheimer's or Parkinson's and increase the likelihood of anxiety and depression.
- Medical treatments for serious illness, both in type (e.g., pharmacological, surgical) and location (e.g., institutional settings), may have unintended consequences on experiences of suffering and distress by affecting the gut microbiome.
- As individuals age, or when they experience life-limiting or critical illness, the gut microbiome may be implicated in the way that, over and above existing physical symptoms, they also suffer poorer affective health resulting in an overwhelming combination of experiences that can be described as total pain.
- Studies about the gut microbiome and its role as part of the BGMA demonstrate the integration of mind and body in a way that mirrors the holism of total pain.
- There is significant interest in designing interventions to support microbial health. These may be applicable in ways that could simultaneously reduce the complex physiological and emotional concerns that are often a part of life-limiting illnesses.
- This incudes nutritional interventions, speific pro-, pre, and/or post-biotic interventions, fecal transplants, and developing cost-effective and rapid tests for assessing microbiome-related health risks. It may also include attending to environmental conditions, early life experiences, and psychadelic therapies.
- Medical and life science research about the BGMA is fueling a paradigm shift in discussions of the human. If microbes are as involved as they seem to be in aspects of cognition, mood, and health, then we have to re-evaluate what it means to be human, and as a 'multispecies endeavour'.
- Bringing together different disciplinary approaches to the BGMA has ramifications for how we understand the environmental, biological, political, and social determinants of health, even at the end of life (including bio-inequalities at the end of life).
- Bringing ideas about total pain into contact with biomedical research concerning the microbiome provides a concrete example of how our biological and social selves are

intertwined and offers a radically new way of thinking about embodiment, suffering, and pain in life-limiting illness and at the end of life.

Our primary goal has been to summarize findings across a diversity of literature[2] to enable us to think about total pain in a new way. Publishing this report as an open access resource allows us to make our findings available to a wide audience. As our aim was to be exploratory in scope rather than systematic and exhaustive, it is designed to provide a foundation – a jumping off point – for further transdisciplinary thought and research. Given the ambitious scope of this report, our methodological 'messiness', and in the wish to provide a useful summary of existing key research, this document is best understood as a background report which details the results of a unique transdisciplinary literature review. It is not designed to be read as a linear narrative, but rather as a series of findings and considerations that can be explored based on interest. Each section is therefore hyperlinked to the table of contents. More formally, we conceptualise this report as an exploratory critical interpretive mixed methods scoping literature review, drawing from medical, life, and social sciences. We will be publishing further from the findings in this report, but we also feel the report itself represents a valuable resource which should be made freely available for others. We hope that it generates further interest in developing a truly transdisciplinary enviro-bio-psycho-social approach to experiences of distress and suffering in advanced life-limiting illness and at the end of life.

Methodology & Reading notes

Report structure

This report describes the methods and selected results from a critical interpretive exploratory mixed-methods transdisciplinary scoping literature review exploring the possible relationships between the gut microbiome and experiences of distress and suffering in advanced life-limiting illness. The review was exploratory across life and medical science literatures and informed by social science conceptions of pain, suffering, and embodiment, and included studies with a range of designs. We adopted both systematic and non-systematic approaches to identify key concepts and findings connecting the gut microbiome, the concept of 'total pain' or suffering, end of life/life-limiting illness, and embodiment. The original review was carried out between March and August 2019 and updated multiple times,

[2] We thank Dr Stuart Hanscombe (School of Social and Environment Sustainability, University of Glasgow) and Dr Douglas Briant (Department of biology, University of Victoria) for their review of this report. All errors are our own.

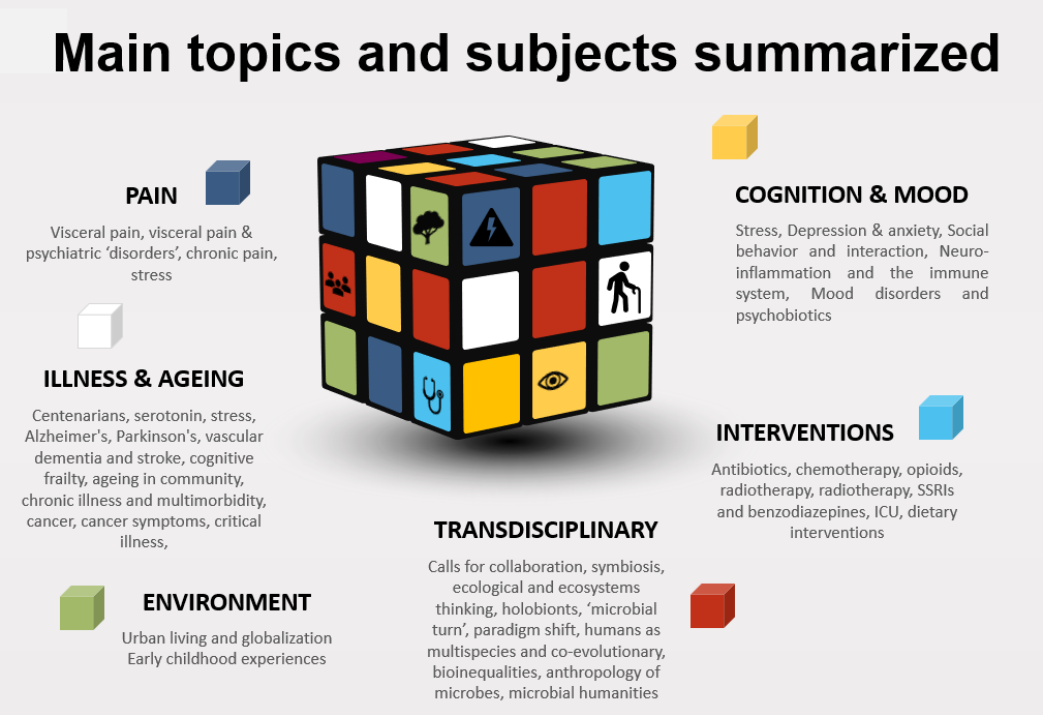

Figure 1: Main topics and subjects summarized, including proxy terms.

the last being in June 2023. We anticipate that potential readers will be interested in some sections more than others; at the same time some findings are relevant across themes. Some material and associated citations are therefore mentioned in multiple sections.

We do not, in this report, engage in a detailed discussion about the concept of total pain; however, however in the overall summary we do consider different aspects of total pain in relation to the microbiome. For those interested in knowing more about this concept, we direct readers to the open access article Total pain: origins, current practice, and future directions. We also do not detail the myriad mechanisms through which the brain-gut-microbiome-axis operates; there are several excellent overviews readily available elsewhere. Finally, we have divided the main results section of the report into six general subject sections, with 50 sub-sections overall. Each of these section and sub-sections are hyperlinked within the table of contents. Within each sub-section we offer summarized findings, at times almost verbatim, although also in conversation and/or in contrast with each other.

While there is a robust body of literature calling for interdisciplinary research between health and social sciences, there is little literature offering actual models or discussing the challenges of conducting *transdisciplinary* literature reviews. For this project, we quickly understood that we could not conduct a 'conventional' systematic review as our topic spanned diverse bodies of literature and disciplines, including both qualitative and quantitative research, and required numerous proxy terms which evolved over time. As a

result, our review was an iterative process, with methods evolving as the review progressed in order to better fit the identified evidence and literature.

Additionally, as we conducted this review over several different time periods with different people's involvement, we found it easiest to follow these summaries with the citations of the research specifically referenced in that section. While these citations are bit 'shaggy' due to updates by different people (i.e., use of numbering system) they are comprehensive within each section, and a full reference list is offered in Appendix Three. Given the size the of document, there is some overlap between topics and citations in some sections. Appendix One contains further details of our literature review methodology. We have also developed a glossary of scientific terms for readers which can be found in Appendix Two.

Pain

The gut microbiome, and the BGA, are essential for pain regulation and nervous system communication. Gut symbionts interact with sensory afferent neurons either directly, through secretion of metabolites or neurotransmitters, or indirectly, through first signalling to epithelial cells or immune cells, to regulate visceral, neuropathic, and inflammatory pain. [P5] The gut microbiota can therefore modulate nervous system functioning, including pain signalling pathways. [P3] Earlier studies addressed the direct and indirect connections between the microbiome and pain, primarily focusing on visceral abdominal pain, such as irritable bowel syndrome (IBS). More studies are beginning to address other forms of pain, including somatic pain and/or chronic pain, neuropathic pain, inflammatory pain, thoracic pain, fibromyalgia, migraine, and autoimmune-related pain in rheumatoid arthritis, as well as cancer-related pain, among others [1-5]. [P10] [P9] [P7] [P6] [P4] [U2] [U6] [U22]

Visceral pain

Visceral pain is pain related to the internal organs. Although often caused by a definable aetiology, unlike somatic pain (pain that occurs in damage to tissues such as the muscles, skin, or joints) visceral pain is often vague, happens intermittently, and can feel like a deep ache or pressure. [6] Diseases and disorders with increased visceral pain are associated with significantly reduced quality of life. [10] Studies in this area evidence how the microbiota dramatically impacts normal visceral pain sensation and the mechanisms mediating such sensations. Much of the research in this field involves animal models in which visceral hypersensitivity is consistently associated with changes in gut microbiota, caused by pathogenic bacterial infections, probiotic bacteria, or antibiotic drugs. [10] [11] Other studies found that increases in gut permeability, which can cause visceral pain in areas like the colon, are affected by factors including high-fat or high-fructose diets, alcohol consumption, vitamin A deficiency, and changes in the intestinal microbiome all of which can cause increased pain sensitisation. [6]

Chronic pain

Gut dysbiosis is involved in central sensitization of the nervous system, otherwise known as wind-up pain (where the pain signal becomes stronger and longer lasting), which can lead to chronic pain. [2] This increased pain sensitization may lead to visceral hypersensitivity. One review of the literature found that up to 80% of patients suffering from IBD experience acute pain, which dissipates when the underlying inflammation and tissue damage resolves. However, despite achieving endoscopic remission with no signs of

ongoing intestinal inflammation or damage, 30–50% of IBD patients in remission experience chronic abdominal pain, suggesting altered sensory neuronal processing in this disorder. [P12] Dysbiosis has also been linked to heightened cancer pain. [2] On the other hand, a review of osteoarthritis pain research in this field found that studies only weakly support a relationship between the gut microbiome and osteoarthritic pain. [P9]

Chronic pain may also be associated with microglia, which are macrophages living in the central nervous system (CNS). Emerging research demonstrates that microglia respond to signals from the central nervous systems as well as the gastrointestinal tract and so affect the initiation and persistence of chronic pain. Based on established research linking interactions between microglia, pain and the microbiome, the combination of gut dysbiosis and microglial activation are likely to influence the pathogenesis of chronic pain. [5] [15] [U3] Research based on stool samples of twins suggests that chronic widespread musculoskeletal pain (CWP) is linked to decreased alpha diversity of the gut microbiome. This may be related to high dietary fat intake suggesting the possibility of dietary interventions for chronic pain that target the gut microbiome. [16]

Pain and psychiatric ‘disorders’

Interactions with emotional or stressful influences can modulate visceral sensitivity resulting in increased pain perception. Studies evidence a very high comorbidity between gastrointestinal disorders and neurologic, psychiatric, autoimmune, metabolic, and oncologic diseases. Of particular interest is the close link between 1) GI disruptions, pain, pain signalling, and visceral hypersensitivity, with stress and neuropsychiatric disorders. [1] [10] [13] The high comorbidity of visceral pain and psychiatric or affective “disorders” such as depression and anxiety are well documented in other contexts outside of microbiome research as well, but this research suggests potential common neurobiological pathways are involved in the aetiology of these disorders, such as the hypothalamic-pituitary-adrenal axis, or common neurochemicals like monoamines, cytokines, and neurotrophic factors. [12] For example, the neurotransmitter serotonin, which is involved in regulating mood, in cognitive functioning, and in processing signals involved in the experience of pain, is primarily manufactured in the gut. Serotonin may therefore be crucial in understanding experiences of pain, in particular when these experiences intersect with mood disorders, for example in IBS patients. [13]. IBS is also associated with altered psychological processes such as catastrophizing and hypervigilance to negative stimuli which, through the microbiome, could perpetuate perceptions of pain.[3] One empirical study explored how context-dependent interoceptive conditioning can turn benign interoceptive cues into predictors of visceral pain and found that key regions of the fear network were activated through mediation of the gut-brain axis. [S3]

This interaction between anxiety, depression, fear, and pain could be related to an individual's allostatic load as part of the process of allostasis in which the body attempts to maintain stability by reacting to and anticipating external and internal stress. Allostatic overload could lead to combined pain and psychiatric disorders. [12] Studies in this area share similarities with research linking gut dysbiosis and depression suggesting both chronic pain and depression may be affected by common metabolites such as SCFAs, amino acids and bile acids. [17] However, one empirical study with young men found that while there was a significant relationship between pressure pain thresholds and certain bacterial signatures, there was no significant correlation between psychological states and pain perceptions in subjects. [P11]

Early life experiences

Individuals interpret their physiological symptoms, including pain, in the context of cognitive schemas that develop over a lifetime. [3] At the same time, there is a growing recognition that the gut microbiome regulates pain and nociception, and that early-life stress produces a long-lasting impact on the gut microbiome. [F15] Chronic or early-life stress is crucial in potentiating visceral pain responses and its associated comorbidities, and the relation between the microbiome and neurodevelopment is implicated in the way that stress experienced in early life triggers long-term changes in visceral sensitivity to noxious stimuli [11] [18]. There is additional evidence to suggest that the gut-brain axis is involved in learnt responses to pain and fear of pain that intersect with stress and anxiety as well as increased defecatory urgency and visceral pain. [19] Evidence from early experiments with rats suggests it may be possible to reduce the higher levels of experienced pain associated with early-life stress by modulating the gut microbiome. [20]

Resilience to environmental stress seems to be heavily influenced by microbial composition. [2a] Such responses may be related to early-life experiences. Studies demonstrate that the early-life colonization of the gut microbiome is crucial for normal development of both the HPA axis and appropriate stress responses in subsequent stages of life. [3] At the same time, positive social interactions affect the activity and reactivity of stress circuits like the HPA axis. It is increasing recognition that there are a range of factors mediating the BGMA across the lifespan, including but surpassing early life experiences. [U1] [U23]

Stress

Stress alters the gut microbiota and plausibly this could contribute to stress-related changes in mood. Stress is implicated in the development and exacerbation of visceral pain

disorders, and chronic stress can modify central pain circuitry. In the brain there is a significant overlap in areas regulating the affective component of visceral pain and those mediating psychological stress (including emotional and cognitive centres of the brain). Stress involves the BGA through various routes: the HPA axis, intestinal permeability, the vagus nerve, and amygdala activation. [1][18] “Maladaptive” stress responses have been associated with an array of pathologies including functional gastrointestinal disorders, affective disorders, autoimmune, metabolic, and oncologic diseases. [21-22] Collectively, studies clearly evidence that stress can lead to long-term changes in the gut microbiota. Areas in the brain that are active during visceral pain overlap with those which process stress, often associated with visceral hypersensitivity. [7] Visceral pain responses may therefore be the result of various psychological, infectious, and other stressors which can disrupt the balance of the microbiome, and in turn be affected by dysbiosis. [8-10] Response to stress is due not only to the qualities of the stressor in relation to the microbiome, but also due to genetic factors, early-life experience, cognitive factors, and environmental support, as well as injury, disease, and medication. [21-22]

Biological sex

There is a lack of research into female health and the role of the gut microbiome. [U23] It appears from some studies that women may present certain pain conditions to health care providers more commonly than males, and females may also be more likely to have osteoarthritis, heart disease, cancer, and anxiety all which commonly co-present with pain. [U4] [U7] Higher sensitivity to pain is a common clinical symptom in postmenopausal females and the gut microbiota has been identified as changing during menopause and potentially contributing to multiple postmenopausal symptoms. [U4]U One empirical study explored how the gut microbiota and critical components of the gut-brain axis might influence electrical pain thresholds for males and females, and results indicated that that gut microbiota appeared a factor determining the physiological inter-sex differences in pain perception. [P3]

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Cognition and mood

Dysbiosis of the gut microbiome and dysregulated neuroimmune responses are common comorbidities of neurodevelopmental, neuropsychiatric, and neurological disorders. In this section, studies directly address the health of the BGA in relation to cognition and mood, as well as social behaviour, with a particular focus on depression. There is mounting data that gut microbiota is the source of a number of neuroactive and immunocompetent substances which shape the structure and function of brain regions involved in the control of emotions, sleep, appetite, memory, mood, cognition, behaviour, eating and substance abuse disorders, and physical activity. [M20] [M21] [M22] Microbial diversity and taxonomic compositions appears to be significantly changed for people with mood disorders compared with individuals who do not. This means there is frequent comorbidity between psychological and gastrointestinal disorders, which has long been clinically observed. [M14] For example, a large US study analysed fecal samples from a randomly selected population-based cohort of older adults and measured psycho-cognitive dimensions (cognition, mood, and personality) and key confounders. Sequencing results found a strong relationship between certain bacteria and specific psycho-cognitive traits. [M15] Another human study with more than two hundred women found a direct correlation between relative gut microbial diversity and overall structure and women's self-reports of positive or negative emotions and associated regulatory processes over a 6-month period. [U8] Gut microbes appear therefore to be a critical part of the unconscious system regulating cognitive function and fundamental behaviour patterns such as sense of self, social interaction, and stress management. [1] [2] There is even a new term to describe this: "disorders of gut-brain interaction". [M14]

Depression and anxiety

Depression is strongly associated with altered gut microbiota composition, generally in the form of reduced richness and diversity. [8] [10-13] [U20] For example a large population level study from the American Health and Nutrition Examination survey found that those with gastrointestinal symptoms were significantly more likely to have depressive symptoms. [M4] One potential point of crossover is the function of SCFAs, amino acid-derived metabolites and secondary bile acids when depression is comorbid with chronic pain. [14] Depression also been associated with dysbiosis and the inflammation of the CNS. [8] [14] One review of the literature found that most of the studies revealed that short-chain fatty acids-producing bacterial genera were decreased, while pro-inflammatory genera and those involved in lipid metabolism were increased in patients with depressive episodes. [M7]

Of particular importance seems to be neuro-inflammation processes and the immune system. Neuro-inflammatory responses are implicated in a number of psychiatric disorders, including anxiety and depression. An increasing body of evidence suggests a link between microglia (the brain and spinal cells which act as the main form of immune defence in the central nervous system) and the microbiota-gut-brain axis, with disruptions to a healthy gut microbiome having negative implications for many stress-related and neurodegenerative disorders. [6–8] D'Acquisto terms this new area of study between emotions, the immune system, and the BGA "affective immunology" [9].

There is also a correlation between the HPA axis activation and gut microbiota, which has a significant impact on the development of major mood disorders such as clinical depression. A review on studies of depression found that increased HPA axis activity was observed during chronic stress, which plays a key role in the pathophysiology of depression, and that overactivity of the HPA axis occurs in major depressive disorder. [M12] Other reviews highlight other key pathways between gut dysbiosis and major depression, including serotonin–tryptophan metabolism, neuroinflammation, and oxidative stress. [M18] However, while microbiome changes occur in patients with major depressive disorder, the mechanism behind such changes is unclear since depressive brain states can influence gut microbiota states, and the gut microbiota can modulate depressive states.

One particularly interesting clinical study considered the link between hypertension and depression in adults with cardiovascular disease through the perspective that humans are eukaryote-prokaryote "meta-organisms," such that cardiovascular disease dysregulation is conceptualized as a mosaic disorder involving dysbiosis of the gut. Through analysing fecal samples of patients diagnosed with hypertension plus depression, the researchers found a unique gut microbial ecology, which suggests a new type of hypertension – "depressive hypertension", which necessarily engaged with models from gastroenterology and psychiatry. [M19]

Clear preclinical evidence also supports a link between anxiety and the microbiome, although very few studies have examined the relationship between anxiety and the microbiome in clinical populations. [10] Episodes of depression and anxiety commonly follow the experience of stress, however not everyone who experiences stress develops a mood disorder. Stress-resilience (and its counterpart stress-susceptibility) are influenced by several psychological and biological factors, including the brain-gut-microbiome axis. [S1]

Early life trauma may prime the microbiome for changes in composition that facilitate a pro-inflammatory cascade and increase the risk of development of PTSD. [S5] Although the microbiome-gut-brain axis has been proposed as a mediator or moderator of PTSD risk and persistence of symptoms, clinical data directly delineating the gut microbiome's relationship to PTSD remain sparce. [S2] [S5] Early life trauma may prime the microbiome

for changes in composition that facilitate a pro-inflammatory cascade and increase the risk of development of PTSD. [S5] A study of frontline health care workers during the first waves of COVID-19 found that they had significantly disrupted microbial community structure, which persisted for at least half a year, and disturbed microbes were essential determinants of appearance and reappearance of PTSD symptoms. [S2] Research linking the gut microbiome to issues such as post-partum depression, post-traumatic stress disorder and anorexia nervosa is ongoing. [11]. From a broader perspective, beyond linking stress to depression and other behavioural changes within an individual's lifetime, the durable imprinting of experience onto the microbiome may even contribute to inter-individual or trans-generational transfer of phenotypes. [U20]

Major mood disorders

Empirical studies and systematic reviews of these studies in mice and humans has found that dysbiosis, leaky gut, endotoxemia and neuro-inflammation may contribute to the development of psychiatric disorders including clinical depression, schizophrenia, bipolar disorder, and obsessive compulsive disorder. [1] [3] [4] [M1] [M5] [M9] [M10] [M15] [M16] For example, in the United States, IBS is estimated to affect about 11% of the general population yet rates of comorbidity with psychiatric disorders range from 54 to 94% in those seeking treatment for IBS [M5]. Another meta-analysis of American population level data of IBS patients compared against healthy controls found a significantly increase in bipolar disorder in the IBS population. [M5] There appears to be robust evidence to an association between exposure to *T.gondii* and an increased risk of schizophrenia. [U10] One review found that fecal microbiota transplantation from patients with schizophrenia to mice induces schizophrenia-like behaviours. [M16]. Finally, a systematic review of literature on serious mental illness (SMI) found that all studies reported alterations in the gut microbiome of patients with SMI compared to non-psychiatric comparison subjects. [M13] The possible role of gut dysbiosis in psychiatric disorders is further supported by studies indicating increased levels of markers of intestinal inflammation in many individuals with schizophrenia and mood disorders. [U10] Medications for acute and long-term management of these disorders primarily rely on lithium, anticonvulsants, and atypical antipsychotics all which directly exhibit activity with the microbiome. [M5] [M16] There is increasing interest in studying the microbiome and clinically-define mental health issues, as well as broader mental health concerns, across the lifespan. [U9]

Social behaviour and interaction

The evolutionary formation of a complex gut microbiota in mammals has played an important role in enabling brain development and, perhaps, sophisticated social interaction. Microbes and the neurochemicals they produce have been associated with the development of sociability within evolutionary-based theories of the benefits of mutualism and reciprocity in social survival. For example, the brain's serotonergic system, which plays a key role in emotional activity, does not develop appropriately in the absence of microbes. [2] It is therefore likely that the immune signalling of the BGMA axis mediates social behaviour: for instance, cytokine-induced sickness behaviour is associated with social withdrawal, or, alternatively, social threat may lead to a proinflammatory immune response. [15] Further studies in mice have found germ-free mice had marked behavioural and cognitive deficits including issues with recognition and memory, sociability, anxiety, locomotion, and self-grooming. A study with humans found that participants' gut microbiome was compositionally and functionally altered in those with social anxiety disorder, and that this group had compromised intestinal permeability. [P2] One unusual study examined the relationship between loneliness and the human gut microbiome found that lower levels were associated with greater richness and diversity of the gut microbiome. [E8] Early research exploring the gut microbiome and the neuroendocrine mechanisms which regulate social behaviour suggests further research might yield therapeutic interventions for disorders characterised by disturbed social behaviour. [16] For example, early research suggests promoting the growth of certain bacteria is likely to improve emotional resilience to stress. [17]

Serotonin and other mood hormones

The microbiome has a role (both direct and indirect) in the production of several hormones within the body, including serotonin, dopamine, norepinephrine, cortisol, and GABA. [U14 Serotonin is a key hormonal neuromodulator involved in cognition, mood, and perception, and is particularly well researched, in part because it is almost exclusively made in the gut (more than 90%). Reviews of existing studies have found a key role of the neurotransmitter serotonin, which plays a critical role in both the gastrointestinal tract and in the brain. [M11] Serotonin is widely produced in the gut, with up to 90% of the body's supply being synthesized by enterochromaffin cells in the gastrointestinal tract. [F9]

Serotonin also regulates inflammation and immunity by acting on serotonin receptors that are differentially expressed on immune cells. Interestingly, it appears that a specific bacteria found in the intestine can produce a state of well-being in animals (including humans) this is due to its ability to affect the level of serotonin in the brain. Indeed, this microorganism was described to play a role reducing the anxiety-related behaviour in mice, thus increasing the learning abilities of the animals [M21]. In turn, serotonin, as well as other

neurotransmitters such as noradrenalin, can modify the gut microbiota; through the development of novel compounds, including neuronal effectors, that can cross the intestinal barrier and reach the brain. [M21]

The relationship between the microbiome and hormones is also a focus of attention for those who are interested in how the microbiome may be related to aggression through (dys)regulation of testosterone, serotonin, cortisol, and norepinephrine.[U14]

Globalisation and urban living

Western dietary patterns high in carbohydrates, fats and processed foods have become increasingly common globally. There is a link metabolic link between inflammatory and cancer-associated gut microbes and a fat- and meat-rich diet. [A12] [SS13] Additionally, the homogenisation of diets affects gut microbiome diversity and consequently has ramifications for mental health as mediated by the BGMA. However, exposure to new and different microbiota through frequent foreign travel may also undermine normal microbiome responses. [15] Modern urban lifestyles without access to green space and with increased consumption of processed foods and diurnal disruption appear to be affecting dysbiosis, immune responses, and subsequent chronic inflammation in later life. [7]

A review of studies found evidence suggesting individuals residing in urban areas experience increased risk for depression due to exposure to noise, light and air pollution, housing quality, reduced diet quality, physical inactivity, economic strain and diminished social networks. [E6] Along with diet and stress, gut microbes are also profoundly affected by their environment, including exposure to plastics, pesticides, synthetic fertilizers, electronic waste, and food additives that release endocrine-disrupting chemicals (EDCs) into the environment and the food chain. There is increasing evidence that EDCs interact with gut microbiota. Emerging evidence indicates an association between exposure of EDCs and diabetes. [A11] [E1]

An interesting paper hypothesizes the role of the inflammation from dietary sources and hypocholesterolaemia mediated through BGA as a critical element of the ‘social environment’ influencing social behaviours, including social bonding, violence, and political extremism. [M8] As such, material changes at a societal level could affect cognition and social behaviour via the BGA. [15]

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Aging, advanced, life-limiting, and critical illness

Ageing is associated with broad changes in whole-body physiology that influences the gut microbiota–brain axis. Age-related changes in gut microbiota composition appear to involve marked changes in the microbiome, often leading to a reduction in microbial diversity. Ageing can be characterised in part by the reductions in the functioning of the enteric nervous system, gut motility, the permeability of the small intestine and alterations in

the mucosal defense system. These can lead to gastrointestinal diseases, including inflammatory problems, as well as cause changes in the gut microbiota. The incidence of some gastrointestinal diseases therefore increases with age, and prevalence of diagnosed gastrointestinal disorders is around 24% in people over 65. [1-2] Such changes reduce microbial richness and diversity in ways associated with worsening health and frailty. [3-6] Indeed, the processes of age-related dysbiosis and neurological decline may be linked because chronic low-grade inflammation as a result of dysbiosis is the basis for a broad spectrum of age-related pathologies in a process known as 'inflammaging". Ageing is also associated with the inability to accelerate a robust immune response, a condition known as immunosenescence. For example, inflammation can contribute to cognitive decline in the context of normal aging but also impact behaviour and neurological disorder, as well as decreased immune responses. [2-4] [7] At the same time, there is greater inter-individual variation in the microbiota of the elderly than that of younger adults and pronounced differences between frail elderly subjects and healthy elderly subjects. [7]

Age-related changes in the brain are most pronounced in the amygdala, hippocampus and frontal cortex, whose function is heavily dependent on serotonergic neurotransmission, potentially implicating microbiome-influenced changes in tryptophan metabolism. Altered serotonin systems could represent a common link with changes in sleep, sexual behaviour, and mood in the elderly, as well as disorders such as diabetes, fecal incontinence, and cardiovascular diseases. [2]

Aging as stress

Ageing and stress in the brain are comparable on both cellular and behavioral levels because the aged brain resembles the stressed brain and chronic stress can exacerbate cognitive issues during ageing. Data from mice indicate that ageing is accompanied by increased anxiety-like behavior, and indeed, the prevalence of anxiety disorders in elderly adults is considerably greater than in younger persons. Similarly, increased depressive-like behavior is associated with ageing in rodent studies. [8] Further, the risk of suicide increases with depression, and older persons who die by suicide is a significant issue in many countries, particularly among older men.

Centenarians

Some research suggests that centenarians may have gut microbiota that differ significantly from the general adult population, which in turn suggests that some bacterial species contribute to good health in old age. [1] This may be because while those in deep old age lose some important core aspects of their gut microbiome, they achieve a personal balance. Bearing in mind associations of gut dysbiosis and psychiatric problems, there is

evidence to suggest that the balanced microbiome of centenarians could be related to their delayed cognitive decline and low levels of reported anxiety and depression. [9]

Alzheimer's disease

Studies show that microbiota regulates neuronal plasticity, development, and pathologies, including Alzheimer's disease (AD). People with AD often have a less diverse microbiome with distinct compositional differences compared to a healthy microbiome. Studies suggest a causal link between dysregulation of the microbiota and systemic inflammation, which may initiate or exacerbate the neurodegeneration occurring in the brain as a result of AD, including abnormal inflammatory signals that could contribute to the deposition of amyloid protein and early dysfunction in the brains of AD patients. [3] [10] [11] [O3] [U15] More studies are needed to determine whether alterations to the make-up of the gut microbiome result in AD or whether dysbiosis is a consequence of more centralised neurodegeneration. [3-4]

Parkinson's disease

People diagnosed with Parkinson's disease (PD) often report early nonmotor-related symptoms such as depression, sleep disturbances, and constipation, which suggest gastrointestinal dysfunction occurs before more obvious motor symptoms. [4] [O2] [U15] PD is also associated with altered gut microbiome and symptoms such as leaky gut, constipation and hypersalivation. [12] Some therefore suggest the disease may begin in the gut and spread via the GBA [12] [13] – perhaps through inflammation and bacterial translocation as the result of gastrointestinal disturbances as indicated in pre-clinical and clinical studies. [3-4], [10-12] The total abundance of intestinal bacterial has been found to decrease during PD progression, with a low count of some bacteria associated with worsening of PD symptoms. [4] [O2]

Vascular dementia and stroke

Little research exists regarding vascular dementia and the microbiome. Yet the GBMA axis mediates the neuroinflammatory response after a vascular injury such as ischemic stroke, and studies have found dysbiosis in patients following a stroke. [3] Dysbiosis is also involved in both diabetes mellitus and obesity, often predisposing conditions for vascular dementia. The overall health of the gut microbiota may therefore be underlying vascular cognitive impairment. [5]

Cognitive frailty

The GBA is related to the development of hippocampus-dependent memory. Some research demonstrates that frail older people and those living with cognitive difficulties tend to have comparatively low diversity in their gut microbiome. [6] Interestingly, one study showed that elderly patients with mild cognitive impairment who undertook mindful awareness practice displayed improved cognitive impairment coupled with altered gut microbiome profile. [14]

Aging in community

Several studies demonstrate that older people living within the community demonstrate greater similarities of microbial diversity to younger adults than older people living in care facilities. [15] Such alterations, which are most obvious in older patients living in nursing homes, may be related to changes in diet and reduced mobility. [5] Diet certainly impacts indicators of frailty and poor health in long-term institutionalized people, while healthy older people have demonstrated increased brain volume and cognitive function when consuming a low-meat diet. [2]

Chronic illness and multimorbidity

Some research in humans suggests the microbiome may be influencing cognitive issues in people with chronic illnesses. [16] Other studies have confirmed that the fecal microbiota of older patients with frailty and multimorbidity, including mobility problems, have lower diversity and fewer microbes that are currently understood to be beneficial. Consistant alterations have been found linking diabetes and mental health issues, including mood disorders, where the onset of diabetes is show to directly affect the development of mental health disorders, including among older people. [O4]

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Cancer - Cause and Progression

Cancer is a multifactorial disease which often involves aspects related to the microbiome and the BGMA. Few microbes directly cause cancer, but many seem complicit in its growth, often acting through the host’s immune system; conversely, several have immunostimulatory properties. [U12] This can include the modulation of risk, etiology, progression, and treatment response. It is becoming increasingly clear that microbes play a key role in cancer in at least two ways. First, the microbiome (particularly in the gut) seems to determine some risk of developing sold tumour cancer, through interactions with immune pathways and inflammatory processes. [U11] Secondly, bacteria in tumours themselves can play a role in changing the microenvironment, and thereby interfering with host immunity and/or therapies. This includes an indirect influence on metastasis, which is the main cause of death when secondary tumours spread and colonise other parts of the body. [U11]

Dysbiosis is associated with carcinogenesis in many organs. In vivo and in vitro studies have revealed an association of specific microbiome signatures with individual cancers, and research suggests that changes in gut microbiota can be linked to the genesis

of, or association with, many cancers, including colorectal, gynecological, gastric, liver, pancreatic, breast, and gall bladder, among others. [A1] [A2] [A3] [A5] [A6] [A7] [A8] [U11]

The main link appears to be inflammatory. Microbiota may therefore influence cancer by encouraging inflammation responses and by facilitating tumour environments. [16], [19] [A3] Additionally, circulation of toxic metabolites may contribute to cancer onset or progression at locations distant from where a particular microbe resides, [A1] such as bone metastasis. [A4]

Within elderly populations cancer is often associated with underlying low-level chronic inflammation and age-related reductions in immune system function. Some meta-analysis of existing research suggests ageing gut microbiota may trigger inflammation and impair the immune system meaning microbiota may lie behind risk factors for developing cancer in older people, although the mechanisms are not fully understood. [20]

Cancer symptoms

Inflammation via the BGA appears to be involved in both the development of cancer and the experienced severity of its symptoms. Because of the influence of the gut microbiota on regulation of stress hormones and the immune system, alterations in gut microbiota may play an important role in symptoms experienced by people with cancer.

There is some evidence that mortality in cancer may be related to “microbiome mutiny” in which the primary cancer alters the ecosystem in the gut from mutualism to pathogenesis. This can lead to microbiome-induced inflammation which can cause wasting – often a direct cause of mortality in cancer patients. [20] For example, emerging evidence links the gut microbiome with symptoms such as cancer-related cachexia. [23] Cancer cachexia is associated with poor prognosis, and directly contributes to at least 20% of all cancer-related mortality. Cachexia limits therapeutic options because it enhances the toxic side effects of chemotherapy; in turn chemotherapy can also induce cachexia. [23] Other cancer-related symptoms involving the microbiome include nausea, vomiting and bloating in gastrointestinal cancers. [16]

Dysbiosis in cancer has also been linked to the co-development of several of the psychoneurological symptoms such as pain, anxiety, depression, fatigue, altered sleep patterns, and cognitive difficulties. [16] [23][17] [18] [23] [A3] [P1] One study found that patients with head and neck cancers, and with higher reported psychoneurological symptoms (PNS), showed a greater decrease in microbial balance and diversity during radiotherapy compared to patients with fewer PNS. [21] Another systematic review detailed how the gut microbiome offers a possible explanation of the mechanisms underlying PNS

and gastrointestinal toxicities which often co-present in women with gynecological cancers. [A3]

Interestingly, one study about cancer pain and fatigue asserts that while they are both part of a recognized “symptom cluster” that appears to be related through inflammatory cytokines to sickness behaviour, they found that evidence substantiating the link between pain and suffering is weak, where pain and suffering may have a direct association only at severe pain intensity. In their review they found that fatigue or tiredness, and not pain, was identified as the most prevalent and debilitating cancer symptom influencing suffering. [P1]

Critical illness

As with cancer, critical illness more generally can be typified by physiological alterations that seriously effect the environmental conditions and community make-up of the gut microbiome. [24] [25] [C1] [C2] [S4] Within hours of the initial insult of critical illness, there is progression from a commensal microbiome to a virulent “pathobiome”. [C5] Changes in the homeostasis maintained by the gut microbiome as a result of critical illness can be associated with increased inflammatory cytokine production, gut barrier dysfunction, and increased cellular apoptosis. [26] Reduced levels of health-promoting commensal bacteria and corresponding increases in pathogenic bacteria lead to dysbiosis and an increased risk of infection. These changes in the gut can potentially accelerate the progression of critical illness. [15] Indeed, changes in the “organ” of the microbiome can be understood as a form of organ failure in the way that it results in increased inflammation and susceptibility to infection, as well as increased risk of acute respiratory distress syndrome, multi-organ failure or sepsis. [15] [25] [27] [28] Patients with sepsis may also have further microbiome changes due to therapeutic interventions, including antibiotics, analgesics, and anesthetics. [C3] For those that survive sepsis, many will have sepsis-induced atrophy, loss of strength, and hindered regeneration, and rates of sepsis-induced myopathy have been linked with gut microbiota dysbiosis. [C4]

Additionally, some research suggests that the same alterations in gut microbiota may also lie behind the mild to severe confusion which sometimes presents in critically ill patients, as well as those with more chronic disease such as liver cirrhosis and diabetes. [25] Microbiota patterns of the critically ill may therefore be predictive of clinical outcomes including mortality. [C6] [C5] [C1] For example, one study of trauma patients found that there were differences in metabolic profiles between those who died or required lengthy ICU stays versus those who had shorter ICU stays and uninjured controls. [C1] One particularly compelling study even found that the composition of some fecal samples taken from ICU patients resembled those obtained from decomposing corpses. [29]

Surgery also impacts the gut microbiome, particularly serious surgery. For example, cardiopulmonary bypass, which allows for a still and bloodless field for heart surgery, also results in systemic inflammatory response syndrome, and there appears to be a correlation between a patient's gut microbiome composition and the degree of inflammatory response experienced following cardiac surgery. [O1] Microbial metabolism is affected by stroke, and evidence suggests that the gut microbiota can influence the severity of post-stroke infection. [3]

Hospital environments

Perhaps as no surprise, hospital environments have been associated with alterations in the gut microbiome, particularly those who are critically ill and those in the ICU. [U6] The gut microbiome can be understood as the "motor" that lies behind multi-organ disfunction syndrome which often underpins deaths in intensive care units (ICUs). [28] Nutrient deprivation, opioid use, vasoactive agents, gastrointestinal prophylaxis agents and liberal antibiotic use have been shown to impact the gut microbiome of ICU patients. [29] Critical illness often results in nutrient deprivation and a pseudo-starvation state which, combined with increased antibiotic use, is likely to affect the gut microbiome of ICU patients. [27] [29] Drug regimes and invasive procedures impact specific body functions and open up the body's natural barriers to infection and microbial entry which can lead to colonization by pathogenic elements. [27] Similarly, increased hygiene practices in ICU settings, as well as restrictive hospital food, inhibited bowel movements, and chemical treatments mean that both ICU patients and staff both show substantially altered gut microbiota. [25]

COVID-19 (SARS-CoV-2)

COVID-19 is an inflammatory disease and the severity of infection is associated with dysregulation of inflammatory immune responses, which in turn inhibits the development of protective immunity to the infection. Gastrointestinal manifestations and gut microbial alterations observed in SARS-CoV2–infected hospitalized patients have raised awareness of the potential role of intestinal mechanisms in increasing the severity of the disease. One early small empirical study of patients with either mild, severe, or critical COVID-19 symptoms found that dysbiosis occurred in the patients, and that changes to the microbial community with associated with severity and haematological parameters. [Co7]. A more sizable study examining composition of the gut microbiota in patients with COVID-19 found that those who were the sickest had the highest ratio of several inflammatory cytokines. Further, they found that the dysbiotic gut microbiota composition in patients still persisted 30

days after clearance of the virus. [Co8] A review of these and other empirical studies found that the gut microbiome appears to be associated with chronic inflammations in COVID-19 patients, and that existing inflammation in the body was the leading cause of an individual's poor prognosis. [Co1] A healthy microbiome could therefore be one of the factors responsible for lower case fatality ratio in COVID-19 patients.

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Medical treatments impacting the microbiome

The gut is the first point of contact between the body and many medications and/or treatments. A large proportion of medications therefore exhibit direct activity against commensal microbes that can alter the normal functioning of gut microbes, including antibiotics, chemotherapy and radiotherapy, immunotherapy, opioids, SSRIs and benzodiazepines, anticonvulsants, and proton pump inhibitors as few examples, as well as interventions such as total enteral nutrition (TPN).

Antibiotics

Frequent use of antibiotics is leading to antimicrobial resistance which via evolution increases the risk of aggressive and lethal pathogens. [1] Antibiotics are widely used in many countries and recent evidence indicates antibiotic-induced dysbiosis as an important factor for functional disorders. Antibiotics kill both pathogens and 'health-promoting' microbes, leading to dysbiosis which can affect organs well beyond the gut, including leading to neurotoxicity. [1] [2] An emerging body of research is also establishing that the use of antibiotics increases the risk of depression as well as anxiety, even after a single course. [T12] [T5] This may be a particularly problematic link as people with serious depression appear to be more vulnerable to infections. [T13]

As mentioned previously, early-life exposure to antibiotics has been shown to have long-term negative effects on visceral pain responses. [4] Similarly, antibiotic disturbance of the microbiome in mice caused immune system changes that may be linked to enhanced pain signalling. [4] For example, studies using rodents suggest antibiotics may attenuate neuropathic pain by altering gut microbiota and so depleting anti-inflammatory T-cells. [5]

One way we ingest continuous low-dose antibiotics is through meat consumption – including fish, as well as through exposure through pharmaceutical and other forms of human waste. [E1] One particularly interesting empirical study among healthy volunteers found acute and persistent effects of antibiotics on the gut microbiome before, during, and six months after exposure to four commonly used antibiotics. Invoking the concept of "antibiotic scarring", the authors found that most volunteers returned to pre-treatment species richness after two months, but with altered microbiome profile. More troublingly a subset of volunteers experienced a persistent reduction and shared compositional similarities with patients hospitalized in ICU. [T11]

Disruptions in the gut microbiome with antibiotics to prevent sepsis and septic shock have been implicated in organ dysfunction. [T1] An empirical study examined metabolic changes of the gut microbiome induced by critical illness and antibiotics in among ICU

patients, in conjunction with gut microbiome samples representing 16 different diseases. The result revealed an “infection-vulnerable” gut microbiome environment present only in critically ill patients treated with antibiotics. [T6] The authors suggest that antibiotic administration may impact essential functional activities in the gut related to immune responses more than critical illness itself, which might explain in part untoward effects of antibiotics in the critically ill.

Additionally, ICU antibiotics may lead to not only dysbiosis but also to mitochondrial failure by damaging cellular energy production. This may lie behind the inflammation-induced organ failure that so often causes death in ICUs. [1] At the same time antibiotics are a common front line medication, particularly in critical care settings. One American study found approximately half of ICU patients have an infection and more than 70% are undergoing some form of antibiotic regime, meaning that dysbiosis is often inescapable for critically ill patients. [3] [In a global study of 1265 ICUs, it was found that 75% of admitted patients received antibiotics during their hospital stay [32]. [5] However, in a human end-of-life care setting, a study found no difference in documented symptoms between patients who received antimicrobials as they neared death and those who did not, suggesting their effect at the end of life is limited. [6]

While there is a clear link between many antibiotics and dysbiosis, a few antibiotics can also act positively on gut microbiota, providing a so-called ‘eubiotic’ effect, by increasing abundance of beneficial bacteria, including visceral and neuropathic pain. [P10] Further, few studies have described antibiotic-induced disruptions of the bacterial microbiome in composition of other kingdoms such as virus, fungi, and protozoa, which has been shown to have significant modulation effects. [T4]

Chemotherapy

Chemotherapy is associated with alterations in immune system function and bacterial profile of the gut microbiome. [7] [A6] [T3] [T9] Gut microbiota can also modulate the efficacy and toxicity of chemotherapy, including chemotherapy resistance. [A1] [A6] High toxicity is a key reason for cancer treatment interruption. For example, up to 80% of patients undergoing cancer treatment experience chemotherapy-induced gastrointestinal toxicity (CIGT) and an individual’s gut microbiome appears to play a role in the severity of this toxicity. [8] [T3] [T9] Chemotherapy induced gastrointestinal mucositis, caused by inflammation, is commonly experienced by patients as symptoms such as nausea, vomiting, abdominal pain, and diarrhea, and carries risks of systemic infection. [7] [T3] [T9] Dysbiosis may explain blood-stream infections via the gut when its lining is compromised and may be attributable to changes in the microbiome caused by chemotherapy. [7] Some drugs used in chemotherapy treatment (e.g., platinum, vincristine, or toxoids)may cause chemotherapy-induced

peripheral neuropathy (CIPN), and one reports found that over 30% of cancer patients suffered from such severe CIPN-related pain that they were not receiving sufficient treatment dosages. [U22]

Existing research linking changes to gut microbiota with changes in CNS immunity and blood-brain barrier damage has led others to hypothesise links with chemotherapy-induced cognitive impairment. [9] An empirical study found that women who received chemotherapy for breast cancer reported statistically significant increases in cognitive difficulties and depression as well as increased gut dysbiosis according to fecal sampling when compared to cancer-free healthy controls. [10] Other review studies map out findings connecting chemotherapy and a disrupted gut microbiome with other common side effects such as fatigue, hot flushes, anxiety, and insomnia, as well as depression and cognitive impairment. [T9] Chemotherapy-related behavioural comorbidities and cognitive impairment might result from altered microbiota–gut–brain communication pathways including neuroinflammation compromising intestinal barrier integrity.

Because chemotherapy damages the intestinal mucosa and heavily disrupts the gut ecosystem, leading to gastrointestinal toxicity, long-term cancer survivors often suffer from late effects, including cognitive impairment and cardiovascular toxicity. [8] [T3] The findings from breast cancer survivors revealed that the patients mostly experienced memory loss and problems with attention, information processing, organization, and decision-making. [T3] Large cohort studies of cancer survivors have provided important evidence of chemotherapy induced effects on cognitive functioning, mainly in breast cancer but also in colorectal, ovarian, and testicular cancer and lymphoma. [T3]

Chemotherapy-induced peripheral neuropathy (CIPN) is another common adverse late effect in cancer survivors, which can persist to some degree in 20–40% of patients. Cardiovascular complications such as heart failure, myocardial ischemia, hypertension, thromboembolism, and arrhythmias are among the most life-threatening late toxicities of platinum-based chemotherapy and radiotherapy in cancer survivors. [T3] At the same time, high dose chemotherapy regimens prior to hematopoietic stem cell transplantation have shown improved patient outcomes regarding the decrease in infectious complications and graft versus-host-disease. [T3]

Radiotherapy

Radiation therapy is an essential component both curative and palliative therapies. Similar to chemotherapy, current evidence suggests that the microbiome influences radiotherapy efficacy as well as causing radiotherapy-induced gastrointestinal mucositis.

[A11] [12] In turn, radiation therapy significantly alters the species and distribution of intestinal microbiota. [A12]

Immunotherapy

The immune system plays a key role in cancer suppression. Immunotherapy is widely used as a treatment method in patients with various types of cancer. Gut bacteria can positively or negatively modulate the response to immunotherapy treatment in cancer. [A9] [A10] A comprehensive review found that specific bacteria species inhabiting the gastrointestinal tract can have a beneficial influence on the efficacy of immunotherapy. [A10]

Opioids

The gut microbiome is implicated in the responsiveness to opioids and their long-term efficacy. Opioids are linked to gut dysbiosis, disrupted intestinal barrier and increased inflammation. [11] [12] [U22] There is also a connection between opioids and an increased risk of sepsis, and studies have found reduced gut barrier integrity as a result of opioid treatment which can exacerbate viral infection or sepsis. [12] [T1] Opioids are commonly prescribed in ICU settings for pain management; additionally, the growing incidence of opioid use disorders increases the risk for infection-related hospitalizations. [T1] Furthermore, post-operative infections are a leading cause of sepsis in hospitalized patients, who are often maintained on opioids for pain management. It appears that while opioids shape the composition of the gut microbiome, in turn the microbiome has a key role in the development of opioid tolerance. Regulating the gut microbiome may therefore improve both opioid desirable and undesirable affects. [11] [12] [U6]

Statins and Proton Pump Inhibitors

Statins are extensively used as potential cholesterol-lowering agents. A comprehensive review of the literature examined the effects of statins on the gut microbiota based on the in-vitro and in-vivo experiments and clinical trials. The review found a mutual interaction between statins and the gut microbiota, so that the consumption of statins is associated with the decreased population of bacteria, which plays a pivotal role in lipid synthesis. [T2]

Proton pump inhibitors (PPI) are widely used to treat acid-related disorders of the upper gastrointestinal tract. A review of studies found that PPIs affect the composition of the intestinal microbiota; while they did not affect microbiological richness and diversity, they were associated with distinct taxonomic alterations (showing overgrowth of orally derived bacteria) [T7].

SSRIs and benzodiazepines

Microbiota alterations play a role in the aetiology of neuropsychiatric diseases and treatment regimens may adversely affect the gut microbiota profile leading to dysbiosis. [14] Serotonin reuptake inhibitors, commonly known as antidepressants, are a front line medication to treat used affective and anxiety disorders, most commonly depression. These medications are so ubiquitous that worldwide, annual usage is estimated to be ~10% in Western population. [T8] Reviews of studies on the antimicrobial effects of SSRIs show an antimicrobial effect of serotonin reuptake inhibitors on the gut microbiota. [T8] Some drugs now commonly used in psychiatry and neurology were originally used as antibacterial agents. [15] Very few studies concerning the gut microbiome and second generation antipsychotics (SGA) exists but, in rodents, SGA-induced dysbiosis can be linked to disturbances in body weight and metabolism through increased inflammation and decreased energy expenditure. [15]

At the same time, however, some antidepressants have been shown to effectively treat visceral pain. [4] The authors of an in vitro study showed that desipramine (a tricyclic antidepressant) can alter gut microbiota composition with the most potent antibacterial activity, but also note that lithium, valproate, and aripiprazole have been shown to increase microbial richness and diversity, whereas escitalopram, venlafaxine, fluoxetine, and aripraxole can increase gut permeability. [C7]

Total enteral nutrition

A perspective paper examined the long-standing assumption that the best way to feed those who are critically ill is by delivering fibre-free chemically defined sterile liquid food (TPN). [T10] The authors highlight the paradox of TPN, where its ability to completely bypass the intestinal track may also one of its major drawbacks, identifying the importance of fibre to the gut microbiota. They propose a redefinition of ‘surgical nutrition’ that includes the nutritional needs of the gut microbiota. [T10] Two other articles however argue the opposite, where ENT provides an increased mucosal barrier to correct gut hyperpermeability that often happens in critical illness [C2], and can reduce intestinal inflammation, with additions of fibre and fish oil. [C5] Interestingly, there was one paper from a nutrition journal where the authors considered how changes in eating and nutrition at the end of life as contributing to total pain in patients receiving palliative care. [T14]

Anesthesia & perioperative outcomes

A review study found significant evidence in animal models that demonstrate that the composition of the gut microbiome is affected by exposure to anesthetics, even with a

relatively short duration. [U6] These changes may be potent and lasting, even after a month. In turn it appears that composition of the gut microbiome affects sensitivity to anesthetics, which in turn influences recovery time. Early human studies show an association of the gut microbiome composition and postoperative outcomes such as pain (including chronic postoperative pain) and delirium (including delayed neurocognitive recovery). [U6] Interestingly, in animal models, manipulation of gut bacteria by antibiotics, probiotics, or fecal microbiome transplantation positively affected the incidence of postoperative delirium and pain.

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Microbiome interventions

There is an enormous interest in microbiota-targeted interventions, including prebiotic (fibre), probiotics (living organisms), and postbiotics (the end-products of probiotic bacteria, as inanimate bacterial cells and bacterial metabolites). The term 'psychobiotics' can encompass all three, and synbiotics contain both pre- and probiotics. Microbiota may also be repaired and dysbiosis may be eliminated by other methods like diet modification and fecal microbiota transplantation, and all such treatments may be prominent future treatments for a

range of conditions. There is also interest in treating the microbiome from a public health and health equity perspective, which is the topic of the section following this one.

Critical illness

Probiotic therapy may prevent infections by restoring non-pathogenic flora, which inhibits overgrowth of pathogens, modulating local and systemic immune response, and improving gut barrier function. [1] Probiotics are associated with a significant reduction in ICU-acquired infections. Several studies show clear benefits of probiotic therapy for several disease states, including reducing infections such as pneumonia in intubated, mechanically ventilated patients, although the processes involved come with their own risk of invasive infection. [2] Another study using fenugreek to ameliorate abdominal bloat common in intubated patients (due to enteral nutrition) found that multiple symptoms of abdominal bloating decreased significantly. [F4] While a systematic review of previous clinical trials of probiotic therapy in ICU suggested a lower incidence of nosocomial infection and clinical outcomes, a multicentre, randomised, placebo-controlled clinical trial did not result in a significant difference in days alive and out of hospital to Day 60. [F5] Other systematic reviews find conflicting or low-quality evidence and conclude that probiotics do not appear to have an effect on mortality or a range of other symptoms. [F6] However, one review study highlighted the potential of next-generation sequencing may be a cheap, fast, and reliable method for early detection among patients suffering from severe sepsis and at risk of organ failure. [C8]

Cancer

Microbiome patterns may be used as a marker for cancer diagnosis, a prognostic marker for cancer survival, and a predictive marker for treatment response. [A1] Probiotics using commensal bacteria may have beneficial effects on the microenvironment of tumours and assist in anti-cancer therapies through changes to the gut microbiome profile. Probiotics may also improve small intestinal bacterial overgrowth, alleviating gastrointestinal cancer-related symptoms and reduce the toxic effects of chemotherapy and radiotherapy like diarrhoea or nausea. [3] Interestingly, the use of bacteriotherapy in human and preclinical studies of chronic liver disease and hepatocellular carcinoma has been shown to successfully modify the microbiota composition, reducing overall inflammation and fibrosis. [A7] Consequently, pre-treatment microbiome profiling and therapeutic modulation of the microbiome may play an increasingly significant role in both palliative and curative radiotherapy interventions. [13] [A11]

Probiotics using commensal bacteria may have beneficial effects on the microenvironment of tumours and assist in anti-cancer therapies through changes to the gut microbiome profile. Probiotics may also improve small intestinal bacterial overgrowth, alleviating gastrointestinal cancer-related symptoms and reduce the toxic effects of chemotherapy and radiotherapy like diarrhoea or nausea. [3] One study with melanoma patients receiving immunotherapy found that higher dietary fibre from diet (not pre-biotic) had significantly improved progression-free survival than those who also took a probiotic. [A9] Ultimately, however, whilst there is growing evidence in mouse models, there is a major discrepancy and lack of evidence within clinical trials that support the use of prebiotics and probiotics to improve chemotherapy and immunotherapy outcomes. [A6]

Pain

Many studies on pain management are beginning to show promising results. [P6] Since the microbiome is associated with functional bowel disorders, pre- and probiotic approaches to modifying its microbial balance are likely to be important in future treatments for visceral pain, including pre-emptive treatments for chronic pain. [4] Additionally, improved management of dysbiosis in early life may improve changes in pain responsiveness in later life and probiotics appear to alter painful responses established during infancy. [4] [5] By affecting microbiota-immune interactions, probiotics can potentially alter emotional responses and pain perception, some of which is related to the opioid and cannabinoid systems. [3] [6] [U22]

Cognitive behavioural therapy (CT) in another intervention showing some promise. A study investigated whether baseline brain and gut microbiome parameters in people with IBS symptoms predict CT response (reduction of self-reported symptoms) and whether this response is associated with changes in the brain-gut-microbiome axis. Researchers found that those who had reduced reports of symptoms was associated with positive changes in functional and structural connectivity of brain networks, as well as changes in gut microbiota, compared to those who did not have reduced reports of symptoms [F8] Another study a with adult rats found that both probiotics and non-absorbable antibiotics markedly attenuated extreme sensitivity to pain. [F15]

Other physical illnesses

The microbiota may present a therapeutic target for the treatment of cardiovascular diseases, such as stroke. There is some limited pre-clinical evidence to suggest that probiotic strains can ameliorate the neurological damage caused by stroke. [7] A study with hemodialysis patients reporting severe gastrointestinal symptoms and reporting a low quality

of life found used a probiotic intervention and found that after treatment the gut microbiomes and gastrointestinal issues significantly improved which positively affected their quality of life. [F13] On the other hand, probiotic use has come into question due to some studies finding a potential adverse effect of probiotic use in ICU patients. [C3]

Mood disorders

Review studies evidence that psychobiotics can alter mental processes, improve cognitive impairment, mood disorders, and reduce stress responses. [5] [9] [F2] [M2] [M3] Both probiotic and prebiotic treatments have been shown to reduce depressive-like behavior in rodents and humans. [8] One empirical study explored changes in common to both obesity and depression following the use of psychobiotics and phylonutrients and demonstrated psychological indices as well as stress markers were significantly improved. [3] Other studies highlight that probiotics for constipation have been found to improve mood, reduce anxiety, depression, anger and hostility – and emotional improvement can be seen in both ill patients and healthy individuals. [M15] Moreover, positive effects on patients' emotional state have been demonstrated in both self-perception and the perception of those around them. [11] However, a systematic review on the use of psychobiotic interventions on anxiety in youth, found minimal efficacy of psychotics. [F1]

Interestingly, one study exploring the relationship between the BGMA, inflammatory pathways, and symptoms of severe mental illness first developed a 'gut-brain-axis questionnaire' alongside physical tests. [F7] Use of the survey among those with active psychosis and healthy controls found that such a transdiagnostic analysis was able to link psychotic symptoms to gut hypomotility, and it was able to predict medical comorbidity and systemic inflammatory conditions. In another study, the use of chamomile as a prebiotic was used to successfully improve cognitive reactivity to sad mood in people with Chron's disease. [F12] A small study among healthy people who reported moderate levels of psychological stress were compared with a control group, and following probiotic supplementation there was a significant increase in populations of 'good' bacteria in the supplement group and psychological indices were significantly improved. [F14] Reaction to stress may also be attenuated by probiotics; one meta-analysis of stress responses in rodents found that probiotic supplements significantly reduced 'immobility response' within forced water tests. [F15] A review of preclinical and clinical trials regarding the use of pro-, pre-, and post-biotics in depressive disorders finds that in many instances there are improvements in mood as well as changes in biochemical parameters. [F16] However, an empirical test with hamsters found that low dose probiotic administration significantly increased social avoidance and decreased social interaction, which was associated with a reduction in microbial richness. [F17]

Dietary interventions

Dietary interventions appear to be one of the most promising treatments for dysbiosis and associated poor health, due to its safety and is more beneficial than drug-based therapies. [A11] [A13] [M8] Targeting diet and other lifestyle factors often has a significant indirect impact on the microbiota.[10] Dietary interventions, including probiotic foods and wholefoods as well as avoiding certain elements like fat and sugar alter the gut microbiome and so improve inflammatory responses already linked to chronic disease including cancer. [12] [13] Dietary modulation of the microbiota could also promote healthier ageing [14], including the use of a FODMAP diet (restriction of short-chain fermentable carbohydrates). [U22] Reducing fat and added sugar in the diet could decrease polyamine production within the gut microbiome in ways that could improve chronic pain and reduce CNS sensitization. [15] Emerging research into the endocannabinoid system and relation to the microbiome may also be relevant in dietary interventions. [6]

FMT

Fecal microbiota transplantation (FMT) has now been determined to be an effective treatment for patients with IBS. [F23] There are also a significant number of empirical studies which have investigated if fecal microbiota transplantation (FMT) supports beneficial change in people with depression and anxiety, in both rodent and human studies. For example, one study found that FMT from people with depression or not resulted into mice found in a change to the rodents' behaviour and intestinal taxa, [F20] and another found similar transference among people with rheumatoid arthritis to rodents, where the mice subsequently exhibited depression-like behaviours, systemic inflammation, and abnormal composition of microbiota. [F21] Human studies are underway, with promising results such as a FMT study where people with IBS, depression, and anxiety had reduced symptoms across all three after treatment from healthy donors. [F22] While FMT is commonly used for recurrent *C. difficile* infection, it is also increasingly being considered for obesity, allergies, neurological and behavioral disorders, and multiple bowel and immune-mediated disorders. [U5]

Psychedelics

Psychedelics have regained popularity as therapeutic agents for stress-related disorders. Lasting impacts to mood and behavior have been documented with micro-dosing, which do not have the characteristic central psychedelic responses but have been theorized to be driven through peripheral mechanisms, perhaps mediated by gut microbes or microbe related metabolite mechanisms. [F9] Psychedelics such as LSD and psylocibin appear to

diverge from other drugs of abuse as they have reported anti-inflammatory properties. Whether alterations of neurotransmitters or immune status, there are few studies of psychedelics on the microbiome. The promising anti-inflammatory properties of psychedelics and the direct interaction with host serotonergic system make this class of drug appealing to study in conjunction with the microbiome to modify host behavior. [F9] In the context of terminal illness, psychedelic treatment appears to be a safe and effective treatment option for existential distress, depression, or anxiety. [F10]

Non-Western therapies

There are some studies indicating the benefits of non-Western therapies in 'recalibrating' the microbiome after illness. For example, acupuncture appears to affect the abundance and structure of the microbiome. [U16] An increasing number of studies have been conducted on traditional Chinese Medicine, gut microbiome, and their interplay [U17], as well as Ayurvedic-based interventions. [U18] [U19]

External factors influencing the microbiome

As well as endogenous factors like genes, sex and age, the gut microbiota is influenced by many external factors such as method of neonate delivery, diet (including breast-feeding), illnesses and the medicines used to treat them, sleep patterns, and environmental exposure to microbes, viruses, and toxins. These factors are often risk factors for a range of health conditions but their influence on the gut microbiome is complex and varies between people [16] Diet, emotional and behavioural practices, socioeconomic status, and habits such as smoking or alcohol consumption can affect emotional and immunological responses, and these effects relate to the gut microbiome. [17] For example, dietary habits have been linked to dementia development via the GBA axis and inflammatory responses. [13] Existing research linking the microbiome and Alzheimer's disease, or Parkinson's' disease suggests that neurotoxicity may be the result of environmental stressors affecting the gut microbiome via channels such as air pollution and dietary consumption of heavy metals and pesticides. [18] Early life stress, and experiences throughout life can also trigger long-term changes to microbiome. [10] [19] In one particularly interesting review, results of epidemiological studies showed that exposure to nature ('green prescriptions') had a positive impact in reducing the risk of neuropsychiatric disorders, demonstrating the plausibility of biophysiological mechanisms, including microbial transfers from the natural environment. [U21]

At the same time, it is imperative to critically question existing promises and framings of for-profit microbiome-based interventions. One interesting study of 27 the websites of

companies offering direct-to-consumer personalized nutrition based on the microbiome, finding that companies simultaneously positioned the gut microbiome, as simple and accessible yet also complex and inaccessible [U13].

Microbial diversity

Many of the studies highlight the difficultly of designing effective interventions when microbial diversity is still so poorly understood. The gut microbiome interacts with other microbiomes and so should not be assumed as primary but understood as interrelated with others, such as the skin or lungs. [20] Each body habitat contains specific microbial taxa and constitutes a highly specialized niche with its own microbial profile, community dynamics, and interaction with host tissue. [21] Furthermore, there is no single 'typical' microbiome that represents good physical and mental health since the microbiota profiles of healthy individual vary significantly. Instead, the ideal microbiome is a relative term: just because a healthy adult is accepted as a control subject in various studies it does not mean that they possess the ideal microbial ecosystem. Few studies describe how these disruptions impact the composition of other kingdoms such as viruses, fungi, and protozoa. [T4] Indeed, there are also questions concerning what truly defines dysbiosis. One large study combining global datasets on gut microbiome variation found a 14-genera core microbiota and identified 664 genera but was unable to represent all possible gut diversity. [22] The Human Microbiome Project similarly found that the uniqueness of an individual's microbiota profile relative the wider community seemed stable over time while variation of diversity and abundance between healthy individuals is wide. Variation over time and between individuals was often defined by strong niche specialisation, including between different regional microbiomes in the same individual, which was specific, functionally relevant, and personalized. [23] However, new technologies are moving the field into genomic and metagenomic spheres, including the use of ultrafast-read mapping, and machine learning-assisted processes which continue to accelerate the rate of discovery. [F11]

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Inter- and transdisciplinary approaches

Medical and life sciences: calls for collaboration

Some authors within the life and medical science studies reviewed here call for collaborations across disciplines, but only included other life and medical science disciplines. For example, Ghaisas and colleagues suggest the ‘complex and dynamic nature’ of the microbiome and its relationship with its human host requires collaborations between microbiology, neurobiology, biochemistry, immunology, gastroenterology, genetics, epidemiology, pharmacology, and toxicology. [1] Similarly, McFall-Ngai and colleagues call for collaboration within the sub-disciplines of biology. [2] Other authors also approach natural sciences, mathematics, computer science, and engineering. For example, Grice and Segre demonstrate alliances between computer science and experimental biologists. [3]

Others were more advanced in their interdisciplinary collaboration and the need for transdisciplinarity. For instance, Allen and colleagues at the APC Microbiome Institute in Ireland collaborate across the departments of Psychiatry, Behavioral Neuroscience, and Anatomy. Collectively their body of publications and research indicate that multidisciplinary work on the brain–gut–microbiota axis benefits from collaboration across a range of specialists to explore the potential interrelation between physiological phenomena with

emotion, cognition, society, and culture. [4] Within the life and medical sciences, the calls for, and interest in, building transdisciplinarity that is truly collaborative rather than merely carried out in parallel are most strongly evidenced within the literature published in psychology journals. In many instances this interest is exemplified through use of transdisciplinary theories such as symbiosis, ecology, and the holobiont to model human-microbial relations, concepts with are discussed further below.

Medical and life sciences: mutualism

Most of the literature within life and medical sciences either explicitly or implicitly modeled the relationship between humans and microbes as a form of "mutualism". However, focus tended only to be on the physiological aspects of the BGMA, and the gut-brain was often modelled as two separate but related organs. At the simplest level of complexity, many of the studies we reviewed acknowledged that the host–microbiota interaction is a complex and dynamic symbiosis, affected by many factors. However, while these studies might reference environment, diet, and the host's genetic composition, these were usually acknowledged as an aside. The primary focus was on the physiological relationship between the gut microbiome and specific outcomes, as well as concern for causative elements or origins (i.e., in the brain, or in the gut, or in other systems such as the immune system).

Medical and life sciences: ecological and ecosystems thinking

Other authors employed more complex ecological or ecosystems understandings that necessarily require an interdisciplinary method, seeing the brain and gut as inseparable elements of a complex system of nerves, microbes, and cells. For example, McFall-Ngai and colleagues take a broad biological view of the microbiome, situating it as a form of ecosystem. [2] Although their sense of interdisciplinarity is restricted to the life sciences, they argue that an ecological perspective permits an understanding of the human microbiome as nested within communities and assemblages of microbes, fungi, plants, and animals that exist within and alongside each other. Any such ecosystem, whether a gut microbiome or a planetary biosphere therefore requires attention to the complex relationships between its elements in order to promote health and predict underlying structures and activities.

Others did not necessarily invoke the terms ecological or ecosystem, yet still highlight the mutual constitution of mind and body through the microbiome, with attention to affect, emotion, and the immune system [5], which might require a biopyschosocial model of the BGMA, [6] or generate new scientific areas of research like "affective immunology". [7] Another term coined within the literature is 'psychoneuroendocrineimmunology' (PNEI) which a term to understand psychological and biological systems as mutually coordinated,

including the role of the microbiome, HPA, and immune systems meditating across these systems. [SS2]

Some life and medical science authors did identify the need for integrated responses to the social contexts which influence complex interactions of the BGMA. The authors of a position paper on the human gut microbiome and health inequalities considered various pathways through which environmental exposures could contribute to health inequities, including environment, diet, medication use, housing conditions, and social network characteristics. [E2] The authors call for 'ecological approaches' to promoting stable and resilient microbiome communities, achieved through environmental policy interventions, in collaboration with epidemiology and health-focused fields in the social sciences, along with front line health care providers. [E2] Other public health scholars are joining this call, where the interdependency between ecosystems needs to be considered 'ecological determinants' of health, and therefore raising necessary questions about health equity, where a 'microbiome first' approach can be used to develop new approaches to public health priorities, address bio-inequalities, and reduce human suffering (particularly from non-communicable disease). [E3] [E9] A particularly interesting critique of microbiome research by a transdisciplinary group of researchers (led by a physician) introduces the idea of 'ghost variables' in human microbiome research, where the function of racial and other taken-for-granted variables are framed as problematic and requiring of interrogation. [SS3]

Medical and life sciences: holobionts

In a special edition of Culture, Medicine, and Psychiatry, the editors propose the notion of 'embodied belonging' to gain a more nuanced understanding of the entanglements of the political, social, and affective dimensions of belonging and their effects on health, illness, and healing, where humans as fundamentally enabled with other life forms, including bacterial. [E7] This 'entanglement' was conceptualized by a few authors through the concept of "holobionts". Holobionts is a term coined by the biologist Lynn Margulis in 1991 to emphasise the interconnectedness and multiplicity of organisms. At the highest level of complexity, some life and medical science authors in this review incorporated the above ecological or ecosystems thinking through invoking the concept of holobionts to describe the totality of the host and its microorganisms as a multi-species organism, superorganism, and/or "collective self". [2] [3] [5] [8-11] By blurring the borders between otherwise clearly defined organ systems, the holobiont concept is useful for understanding the many levels of interaction between the host and its microbiome. A few authors provided further detail or description of their understanding of this commensurability, such as Dietert and Dietert who define holobionts as 'human DNA + microbiota + life events + across generations'. [12] In this understanding mammals are 'superorganisms' composed of both mammalian and

microbial cells interlinked to affect health where humans are inextricably connected to the environment in ways that helps to both define and sustain them.

Palacios-Garcia and Parada compare holobiont understandings of the gut microbiome to ideas of 4E-cognition. 4E stands for a model of cognition that an embodied, embedded, and extended phenomenon that is enacted which has gained popularity in cognitive science, with the authors suggesting the microbiome and holobiont understandings offer a biogenic understanding of cognition – a holobiont theory of mind. [11] [SS10]

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Social sciences and humanities: the microbial turn - a paradigm shift

As well as the large amount of literature from the medical and life sciences, a limited but provocative body of research addresses the brain-gut axis and gut microbiome from a social science and humanities perspective. These pieces often describe how the extent, diversity, and functional relevance of the microbiomes living in our bodies necessitates calls for a fundamental rethinking of how we approach our understanding of what it means to be human within and across all sciences. These contributions are predominantly from physical anthropology, medical humanities, and the history of medicine (as well as interdisciplinary and transdisciplinary coauthors highlighted in the previous section).

For example, there is a growing body of sociological research which interprets the recent life and medical science perspectives that frame the BGMA as indicating a paradigm shift in our understanding of the body. The central interest is how this new perspective challenges the dualism that divides biological (physical, organic, somatic) and psychological (thoughts and emotions) areas of concern and, indeed, that such dualism is becoming a ‘non-scientific’ position to hold. Here focus is given to how microbiome research demonstrates that we are connected to the environment in a way that helps to both define and sustain the completed human, and that the extent to which humans appear to be interrelated with other organisms in a complex natural ecology both undermines reductive materialist approaches and grounds consciousness in physical phenomena. [1-4] Understanding the self as biological and social is seen as requiring microbiome research that is co-designed by transdisciplinary teams in order to address global health inequalities, as well as to contribute to more ontological academic debates. [16]

Interest in this field consequently has been framed as part of a ‘microbial turn’ that requires further examination of the political ecology of Western health research and care. The environmental geographer Jamie Lorimer positions this microbial turn in the context of the wider ‘material turn’ within social science that considers how nonhumans, including animals and inanimate objects, affect social practices and systems of power. [5] This is an approach prevalent for example in social science research concerning entanglements between nutrition, well being, agriculture, and the natural world such as climate change. [SS6] Others point to ‘post-anthropocentric’ turn in the humanities, including but surpassing attention to the human microbiome. [SS4] Such interpretations are informed by Foucauldian concerns for embodiment and science and technology studies, [5] as well as being understood in terms of relational biology. [6]

Seeing humans as multispecies holobionts situates us within larger ecological systems of other organisms that together build and evolve themselves in response to their environments. [8-10] For example, our symbiotic relationships with the microbes in and on our body mean human cells have not needed to evolve certain genetic traits that our commensal bacteria provide. [11] Evolutionary perspectives like this hold the possibility to ‘depauperate’ biomedical approaches. [10] The critical medical humanities scholar Grace Lucas uses the microbiome to link ideas of embodiment in phenomenology to understandings of mental health. [8] The psychologist Leigh Smith and Emily Wissel, a nursing scholar, use recent neuropsychological approaches to argue that the microbiome supports existing social science perspectives that foreground the role of affect in physiology, selfhood, and interpersonal behaviour. [4]

Awareness of humans as multispecies also offers ways of bringing together conventional biomedicine with holistic approaches such as the One Health agenda or ideas of syndemics which include human health within wider conceptions of the shared health or illness of interactive populations. [12] The microbiome therefore offers a vector for troubling, as the communications scholar Andrea Casal puts it, “notions of the self as bounded, universal and autonomous [which become] increasingly difficult to maintain”. [9]

The plasticity of the gut microbiome might mean it offers the possibility of targeted public health interventions informed by such social science research. Amato and colleagues argue for a multidisciplinary approach to the study of health inequalities which incorporates research into the microbiome alongside epidemiology and the social sciences. This collaboration could result in health policy interventions which combine targeted interventions for known gut microbiome traits as well as ecological approaches which maintain microbiota stability and resilience, where future research would also take into account differences in gut microbiome community based on cultural or socioeconomic factors. [14]

These connections across disciplines therefore allow unique insight into how perturbations in the microbiome can be linked to health inequalities based on socioeconomic status, race, gender, and identity. For example, the human geographer Beth Greenhough and colleagues have set out a social science research agenda on the human microbiome which identifies areas for future research concerning 'the implications of the human microbiome for human health, public health, public and private sector research and notions of self and identity'. [19] Rather than simply a response to existing microbiome research, they want to position social science as a collaborator within new interdisciplinary approaches, attending to areas such as the role of commercial interest in ongoing microbiome research and knowledge production, issues of citizenship and identity (what they call 'molecular politics'), or issues of environmental governance – and making sure that future research is socially relevant and conscious of cultural norms and ideas. [19] Others articulate that studies of comorbidity need be broadened to include sociological consideration of over-medication in humans, fertilisers and pesticides in agriculture, and preservatives and antibiotics in the food industry. [12] Lucas argues that the microbiome is useful for realigning the current framing of mental health within a bio-psycho-social paradigm, where biology, psychology, and social sciences each take a 'vertical disciplinary cut'. [8] She instead suggests a horizontal slice that considers the entanglements between these disciplines when considering how the GBA cuts across environmental, behavioural, and physiological factors and changes, and includes long-term responses.

Some authors argue the microbiome therefore represents an important new area for expanding conversations about structural and environmental health inequalities, and that social science can bring discussion of political and cultural issues to microbial discourse which predominantly ignores issues of socioeconomic advantage and vulnerability. [1-4] [9] [13]. Physical anthropologist Katherine Amato and colleagues frame recent scientific work on the microbiome as a new way of conceptualising how environmental factors influence health inequalities in both responding to and perpetuating structural inequalities created by racism and other forms of discrimination. Since the microbiome is affected by diet, housing conditions, access to outdoor space, circadian rhythm, pollution and stress, the gut microbiome of minoritized populations is likely to reflect and intersect with structural discrimination and inequality. [14] In another example, the sociologist Gabe Ignatow uses emerging microbiome research to discuss possible causal pathways in the body for social bonding, violence, and political extremism. [6] In *the Journal of Physiological Anthropology*, Alan Logan adds concerns for heating and environmental stress, suggesting that microbiome research needs to be linked with work on both mental health inequalities and environmental justice. [13] In another example, Stefan Ecks uses the anthropological concept of "syndemics" in relation to dysbiosis to frame a case study of how issues of

access to fresh food and the iatrogenic effects of polypharmacy within a deprived area of the UK exacerbate the co-occurrence of dysbiosis and depression, or what he terms polyiatrogenesis. [15] The microbiome therefore offers social science new ways of conceptualising bioinequalities [9] as well as eco-psychotropics. [13] For these scholars, a transdisciplinary disciplinary approach is required to evaluate the intersection of 'matter and mind' represented by understandings of health and well-being informed by microbiome research. However, care is needed as such research could revolutionise Cartesian assumptions but could also privilege a physical, biological location for all conditions through overemphasis on the corporeal. [8]

Microbial anthropology & sociological approaches

Anthropological interest in the microbiome has led some to call for a new "anthropology of microbes" in which scientific microbiome research and various subfields of anthropology collaborate on research which has the potential to transform how we understand terms like community, individual, or the human. [16] Fuentes goes further and suggests all health research should be guided by anthropological approaches that recognise the complex conceptual and methodological toolkits ('ontological tendrils') required to 'develop a fuller, if somewhat messier, understanding of the human' that is both informed by and informs microbiome research. [10]

The microbiome also represents potential new ways of theorising existing concepts over and above embodiment and affect, such as grounding Pierre Bourdieu's idea of the *habitus* as flexible and responsive within the body's symbiotic relationship with its microbiome. [6] Ignatow asserts that sociologists interested in culture and cognition should consider the implications of microbiome research for the theoretical grounds of cognitive sociology. [SS5] For example, nutritional indexes could be used methodologically in survey research or methods can be inspired by nutritional psychiatry or social psychology. It appears that the fields of anthropology and sociology now must acknowledge the ways in which the microbiome forces an individual human to be understood as multispecies, [5] which fundamentally reorientates the relationship between life and social sciences.

Another example of this sort of approach is taken up in the emerging fields of anthropological genetics and evolutionary medicine which attempts to recover the origins of diseases to contribute to current public health initiatives. The biological anthropologist Molly Fox and colleagues use current research into the microbiome and Alzheimer's Disease alongside studies of the microbiome of non-industrialised communities to propose that historical changes to the human microbiome caused by developments such as the Agricultural and Industrial Revolutions and post-industrial globalisation have reduced microbiota diversity and enhanced pathogenic virulence. [17] They suggest that Alzheimer's

Disease is therefore more common as a result of the evolution of the microbiome alongside such historical factors. Similar research into the evolution and diversity of different human groups, past and present, and the influences of diet and genetics on interpersonal microbiome variation and health are likely to become more prominent in anthropological genetics. [18]

Anthropological perspectives also hold the potential to relativize norms of dysbiosis based on models of a white Westernised middle class. [13] [SS3] These perspectives could also problematize the nascent consumer culture of food and supplements surrounding the BGMA in which the desirable self-management of the gut microbiome is only accessible to certain demographics [8] and commercial interests risk restricting research and therapeutics to lucrative markets, further disadvantaging others. [13]

The conceptual work and material studies discussed in this review have enabled social scientists to literally structure humans as a multispecies endeavour – finding that entanglement with our companion species means that 'the human' is necessarily, and always has been, 'more than human'. For some, the microbiome challenges the definition and perceptions of 'self' through its involvement in the immune system, the brain, and the genome which, due to microbial influence, cease to be uniquely 'our' own. [7-8] The anthropologist Amber Benezra, using Donna Haraway's idea of 'kinship' as relational (rather than merely hereditary or claimed), asserts that microbes are kin - made of and making environments, across generations. [SS1] However, others are cautious about unproblematic use of the concept, highlighting that 'there is no innocence in these kin stories' where relations are not necessarily always synergistic; a caution which has significant implications for research into the human microbiome. [SS4]

Microbial humanities

Rees and colleagues advocate for a new field of 'microbial humanities' which recognises how the microbiome challenges conventional distinctions between the natural sciences and the arts and humanities. By undermining distinctions between the non-human and the human, such collaborative work would work towards an 'integrated understanding of what it means to be human, after the illusion of the bounded, individual self. The human is more than the human'. [7] [SS12] For example, one innovative study, called the 'Shit! Project', consisted of a series of experimental workshops using moving, making, and doing with food to assist people with serious gut disease and their families to envision and then preform healthier relationships with their gut microbiome. [SS11]

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Summary conclusion

The human genome consists of about 23,000 genes; our gut microbiome alone has *millions* of genes, with more being sequenced as our analytical tools become more precise. Well over 90% of bacteria in the human body reside in the large intestines, with a collective weight greater than our brains. We now know that the human microbiome is fundamentally involved in communication across nervous, immune, and endocrine pathways, leading to the term brain-gut-microbiome axis in an attempt to encapsulate the multitude of relationships between them. Consequently, many now consider the human gut microbiome as of such critical importance that it is best conceptualized as a 'invisible' organ of the body, and increasing attention is given to the apparently central role of the gut microbiome in regulating health and well-being.

This review began by mapping how the microbiome may be involved in pain signalling within a larger brain-gut-microbiome axis (BGMA), and how this axis relates to visceral pain and psychological stress overlap; a combination which in conjunction with advanced life-limiting illness can be conceptualized as total pain. Unsurprisingly, there were no direct references in the literature to relationships between the gut microbiome and total pain, although several partial physical proxies were available such as pain, visceral pain, and chronic pain. In terms of total pain, we can see from these studies that pain and negative affective states such as depression and anxiety often co-present and activate common neurocircuitries and neurochemicals in the brain. The frequent comorbidity of pain and psychiatric disorders in cases such as IBS-related pain can be debilitating and affect quality of life in ways that echo total pain by combining to be more than the sum of their parts. Similarly, the microbiome may be involved in the accumulation of painful experiences. This may be through mediating internal and external stressors which combine over time to drain our ability to maintain both physical and emotional stability in, for example, allostatic overload. Alternatively, there is also evidence that the BGMA may play a role in habituated responses to, and perceptions of, pain based on early life experiences. Both perspectives support the importance of the totality of a person's experience, as is assumed in conceptualisations of total pain. Finally, the review shows an important relationship between experiences of pain and gastrointestinal issues, including those related to diet, which are common near the end of life, perhaps indicating that historic eating patterns or the shift to institutional food could exacerbate end-of-life pain.

The studies found a strong association between physical pain and negative affective states such as anxiety and depression, highlighting that these states are frequently 'comorbid' with physiological symptoms. However, none of the research defined the various negative affective states addressed as 'suffering' or in themselves as a form of 'pain'.

Importantly, however, many of the studies went beyond depression and anxiety to consider how the gut microbiome through the BGMA is part of a larger unconscious system regulating cognitive function, mood, and fundamental behaviour patterns including memory, sleep, and appetite, as well as more general behaviours such as social interaction and sociability, and even stress management, including potential resilience to environmental stressors. More broadly, socio-economic and lifestyle factors, including those established through urban living or globalisation, seem to influence affective health through the (dys)regulation of the BGMA.

These studies show the inextricable inter-constitution between mind and body in a way that mirrors the holism of the total pain concept; for example, mental health seems to be linked to the body's inflammatory responses and the immune system. Although complicated by lack of consistent language to describe different affective conditions, the studies reviewed here suggest that perceptions of self, others, and environment are shaped by microbiome health and dysbiosis. Given this close connection, some authors advocated a more interdisciplinary approach to understanding the interrelationship between pain, cognition, and mood, which echoes the interdisciplinary ethos of the total pain concept. This approach may also be a fruitful and unique approach to exploring and addressing the effects of structural (bio)inequalities which are often exacerbated at the end of life.

Since total pain is used to describe experiences of suffering unique to the end of life, research on the microbiome and the BGA in aging and illness were also relevant. Age brings negative changes to the gut microbiome (such as decrease in number and types), increased gastrointestinal issues, and changes to mobility and eating patterns. Studies included here again highlighted the causal link between dysregulation of the microbiota and systemic inflammation, which may initiate or exacerbate the neurodegeneration in aging and age-related diseases such as Alzheimer's' Disease, Parkinson's Disease, and other forms of dementia. Moreover, ageing more generally brings increased likelihood of chronic diseases and multi-morbidity which are experienced by the body as stress, meaning a higher chance of compromised affective health through, for example, great prevalence of anxiety and depression. At the same time, ageing should not be pathologized since studies on the gut microbiome of centenarians indicates some age-related changes can be positive.

Similarly, symptoms and mortality associated with critical illness more generally could be exacerbated by changes or responses in the gut microbiome and are therefore relevant in linking the gut microbiome with suffering as the end of life nears. Studies indicated that the gut microbiome is poorer in biodiversity for people with chronic illness, multimorbidity, physical frailty and mobility limitations, as well as those who live within institution rather than in the community. Inflammation via the BGMA is also potentially involved in both the development of cancer and the experienced severity of its symptoms, such as pain,

depression, fatigue, sleep disturbance, and cognitive issues. As individuals age, or when they experience life-limiting or critical illness, these studies suggest that the gut microbiome may be implicated in the way that, over and above physical symptoms, people at the end of life also suffer poorer affective health and overwhelming combinatory experiences that can be described as total pain. By implication, we might be able to design interventions to support microbial health and mitigate dysbiosis that would simultaneously reduce common physiological symptoms from cancer (e.g., pain, lack of appetite, fatigue) as well as symptoms of depression or cognitive issues (such as “chemo brain”) by treating them as related expressions of the same problem. One place to start might be the medical/institutional environment and its impact on the gut microbiome. Studies included here demonstrate how hospital and in particular the ICU care might negatively impact the gut microbiome in ways that could simultaneously exacerbate critical illness and affect patients emotionally.

The medical treatments we give to people who are aging, who have multi-morbidity, and/or have advancing life-limiting or critical illness (all profiles common as people near the end of life) appear to have unintended consequences on experiences of distress and suffering. The studies reviewed here show how common treatments such as antibiotics and more aggressive treatment like chemotherapy, radiotherapy, or opioids negatively impact the microbiome in ways that may be shaping experiences of pain. Perhaps most challengingly, many of the studies evidence that pharmacological treatments designed to ameliorate affective distress in the form of anxiety or depression may increase long-term symptoms in as much as they function as antibacterial agents. However, not all agree, with some saying that use of SSRIs can positively moderate pain experiences. Understanding how pain can be mediated by the BGMA may therefore expose how experiences of suffering at the end of life may be exacerbated through iatrogenesis in ways not previously considered.

There is much promise in the use of pre- and probiotic treatments which may be relevant to addressing many of the symptoms that are collectively described as total pain, especially those related to gastrointestinal issues. Such treatments may help to mitigate suffering that arises from serious illness and secondary related infections. Through the BGMA, interventions that rebalance dysbiosis hold the potential to improve emotional wellbeing, sometimes via side effects of drugs which target physical symptoms. Dietary interventions and psychobiotics may in particular offer fairly simple intervention possibilities, preferable over more invasive treatment like fecal transplant therapy. At the same time, research suggesting that the influence of diet on inflammatory and pain responses may be long-term makes this conclusion difficult while also affirming some of the relevance of individual history implied by conceptualisations of total pain. Additionally, at this point, most studies into pre- and probiotics are with mice; inter- and intra-personal microbial diversity in

humans is an emerging area of research concerning a very complex intersectional environment. Further study is needed to initiate more concrete interventions involving dietary interventions, environmental factors, and personalised approaches.

This review has found that the human microbiome may be an essential component of the pathogenesis of multiple types of pain. However, despite the availability of various pain management methods, findings also evidenced that there still a great need for research on factors contributing to pain and suffering, and for novel therapies. The microbiome is influenced by both physical and non-physical issues and so requires expertise from a range of specialisms within and beyond medicine. Some of the literature that we reviewed within the medical and life sciences was concerned with interdisciplinary and transdisciplinary approaches to the microbiome. In its efforts to address total pain, end-of-life care commonly also utilises multidisciplinary teams. The emerging microbiome research gives additional backing to a collaborative approach to conceptualizing total pain and, indeed, extends the remit of consideration when addressing the source of such pain.

In turn there is an increasing turn in the medical and life sciences to call for collaborative work that understands people not simply as individual humans but as symbiotic partners with the microbial communities that populate their body. Such symbiosis requires ecological thinking and to conceptualize humans in ways which question our sense of ‘self’ in complex and challenging ways. If microbes are as involved as they seem to be in aspects of cognition, mood, and health, then we will have to re-evaluate humans as holobionts - a multispecies endeavour comprising the human cells that make up the body as well as the fauna and flora that live in and on it. Total pain might consequently be seen not only as a descriptor for the complex suffering of an individual, but as that of a holobiont defined by its microbiota (and its relationship with other forms of life), personal life history, and surrounding environments.

Emerging research within medical and life sciences about the microbiome within the BGMA is also fuelling a paradigm shift in discussions of the human within the social sciences and humanities. Such thinking has ramifications for how we understand the environmental, social, and cultural determinants of health, including at the end of life. We intend to synthesize the results in this report more fully and to use our findings to explore the case for greater attention to issues concerning the microbiome in the treatment and care of people with life-limiting illnesses. Indeed, the ‘microbial turn’ unlocks several possible fields of inter- and trans-disciplinary study in end-of-life care. Those of us interested in embodiment and total care in relation to the end of life, suffering, and/or the concept of total pain must now seriously consider the emerging and revolutionary implications that the microbiome offers.

Limitations

In theory, the connections to be described here seem relatively straightforward: the gut communicates with the brain through various pathways and in turn the brain communicates with the gut, and the gut microbiota has a key role mediating this relationship. However, different studies describe different communication pathways (or similar pathways using different names), and there was overlap between different pathways (perhaps because some substances secreted by the gut microbiota have roles across many pathways). Even the term ‘brain-gut-mocrobiome axis’ was not consistent, and a very large number of relationships, hypotheses and interactions were proposed. Importantly, descriptions were often written with the purpose of justifying potential relationships (for example, between Alzheimer’s disease and the gut microbiota).

Various additional limitations regarding the available evidence were often highlighted by authors, including issues with adopted study designs, failures to acknowledge that the gut microbiome contains organisms other than bacteria, and that the human body hosts other microbiomes. Most available empirical studies were carried out with rodents and translating findings is challenging. For example, there is rarely an equivalent in human studies to the germ free mice often used in experiments, and clinical trials based on interventions that target the microbiome in humans are currently less conclusive.

Researchers in the field noted the continued uncertainty surrounding the mechanisms underpinning many relationships between the microbiome and a range of health conditions (and potential microbe-based treatment). Further research is needed, for instance, to support claims about the etiology of affective disorders (e.g., depressions, anxiety) being mediated by the microbiome: it is not clear, for example, whether visceral hypersensitivity is a cause of or a response to stress-related emotional states, or how this relationship interacts with more accepted systems of sensitization. Future research is also needed on less explored interactions such as that between the gut microbiome and the endocannabinoid system which, through linking aspects of the immune system, is similarly implicated in pain and inflammation.

Additional uncertainty exists over what constitutes a healthy gut microbiota, and which features of dysbiosis are implicated in health conditions. There are limitations to the current research in this area due to, for example, reliance on stool samples which ignore bacteria from the small intenstine. Similarly, data on the microbiome often exhibits a lower degree of correlation and/or unexplained variance compared to more available biometircs like sex, body temperature, or blood pressure. Additionally, there are some bacteria that may be beneficial, netural, or pathogeic depending on the relationships to other bacteria and envrionmental conditions. Finally, there is still limited understanding of the long-term impact

of early life influencers (such as maternal microbiota transfer and diet), as well as other socio-economic, environmental, and/or epigenetic influences.

Conducting this transdisciplinary review has been challenging for several additional reasons. While there is little research explicitly linking total pain with the microbiome, our proxy terms and quadrants yielded a huge number of initial results, not all of which added to our understanding. Methodologically, our initial systematic methods yielded few relevant results and we instead relied heavily on targeted Google Scholar searches. Sorting through the results was very time consuming, and there were multiple authors working over different time periods, resulting in a temporally segregated citation process. At the same time, the field of microbiome science is expanding so rapidly that many of the potential correlations and implications discussed are inconclusive meaning theories based on initial results may not be borne out by long-term studies. However, while much of the research include here is based on proxy terms, many publications explicitly or implicitly indicated bidirectional relationships between different aspects of suffering which mirror different components of total pain. We therefore believe there is more than enough evidence of relevant relationships to justify a new approach to total pain and to call for further transdisciplinary research that links issues of distress and suffering in life-limiting disease with the microbiome.

Appendix 1: Methodological Considerations

While there is a robust body of literature calling for transdisciplinary research between health and social sciences, there is little literature discussing the benefits and challenges of conducting transdisciplinary literature reviews. For this project, we did not want to conduct a conventional systematic review or even a scoping review as our topic spanned diverse bodies of literature, including both qualitative and quantitative research, and required numerous proxy terms. Our goal was rather to explore how researchers from different fields have connected the microbiome to pain/suffering, embodiment, and the end of life/life-limiting illness - or taken an interdisciplinary approach to these concerns. As a result, our review was an iterative process, with methods evolving as the review progressed to better fit the identified evidence. While the resulting review involved a flexible exploratory methodology, we have tried to make the review process as transparent as possible, primarily so that our work contributes to a field in which there is little formal guidance or discussion about how to conduct this kind of transdisciplinary study.

Methodological influences

We found four articles that were useful to our thinking and informed our methodological approach, and which we discuss here in relation to our own study 'methodology'. [1]–[4] Dixon-Woods and colleagues advocate an 'interpretive synthesis' methodology which acknowledges that systematic approaches can be detrimental to theory-building. Instead, they call for a creative, inductive, and interpretive approach, conceptual in both process and output, where the main product is theory instead of data aggregation, although theory which must be grounded in the data reported. [1] They also discuss a 'critical interpretive synthesis' of a complex, broad range of literature in which sampling boundaries shift over time and a low inclusion threshold is maintained to avoid missing relevant concepts. [2] We followed their data extraction process in which formal extraction was not necessarily relevant for all papers; at times markers were used to highlight important aspects of the document 'in situ'. This was, necessarily, a generative rather than a conclusive process in which the goal was to record sections which seemed fruitful. However, other readers may have drawn different conclusions or highlighted different sections.

Montuori provides an evocative discussion of transdisciplinary literature reviews [3], asserting the importance of considering knowledge as an 'ecology of ideas… a vast web of relationships interconnected' (p.45-6). A transdisciplinary review therefore requires a 'rich description' that acknowledges complexity and systems thinking. We began from this position, exploring the network of potential interconnections between the human microbiome,

the BGA, pain, advancing life-limiting illness, and affective issues a across life, medical, and social sciences. Importantly, Montuori recommends that if work on the desired topic is scarce, reviews should explore work with the closest 'family resemblance' to the topic. [3] Hence although the lead author is a social scientist, we have privileged the biomedical literature where the most research has been done on the relationship between microbiome, pain, and affective 'disorders'. At the same time, like Dixon-Woods, Montouri sees these types of literature reviews as a critical self-reflective creative process that recognises how disjunctive thinking can separate what is related, and can naturalize certain discourses (or silences), an approach which chimes with wider social science approaches. We therefore grounded our approach through his four dimensions of transdisciplinary inquiry: 1) Inquiry-based rather than discipline-based; 2) integrating rather than eliminating the inquirer from the inquiry; 3) meta-paradigmatic rather than intra-paradigmatic; and 4) applying systems and complex thought rather than reductive/disjunctive thinking. [3]

We also considered the very detailed "heuristic reflective tool" for reviewing literature in transdisciplinary research for sustainability proposed by Gaziulusoy and Boyle. [4] However, while relevant to our work, we found it too prescriptive for our exploratory purposes.

We are keenly aware that a transdisciplinary approach requires further consideration regarding integration between different disciplines, including empirical, experiential, and initiative types of knowledge, as well as qualitative and quantitative data, theoretical and practical knowledge. Importantly, however, the aim of this review was not to design a new methodological framework, but a much more modest proposal to explore a range of literature to inform our thinking about experiences of suffering at the end of life from a transdisciplinary perspective. Therefore, given the newness of the study's inquiry, we made a collective decision to be informed by different methodological approaches, while not limiting the review to any of them. If pressed, we characterize our methodology as exploratory critical interpretive mixed-methods literature scoping review, drawing from medical, life, and social sciences.

Our goal was to use empirical evidence in a way that allowed for an evaluation a paper's 'usefulness' to our original concern about the relationship between the BGA, the microbiome, and aspects of suffering relevant to the concept total pain in advanced life-limiting illness. There was no explicit attempt to seek generalisation of results; we aimed for credible (as opposed to valid in a positivistic sense) evidence in order to establish further lines of inquiry in a new area. This was a critical and reflective approach, and we root our synthesis within the benefits and limitations of existing research, as well as the limitations of our own evolving methods.

Review process

The process for carrying out this review comprised several steps. The first step was to read and summarise key background literature selected by the first author to inform the development of search parameters. This literature was chosen by the primary as these papers had collectively inspired the research question. This literature encompassed a diversity of social, life, and medical sciences perspectives (often transdisciplinary) which addressed some relationship between the microbiome, total pain and/or suffering, life-limiting illness, and/or embodiment. Then, methodological papers were sought out which described different literature review frameworks in order to inform our methods. [1]–[4]

An initial list of search terms was prepared for discussion and refined after considerations of four areas/quadrants to be investigated in the review, which included: 1) end of life and/or life-limiting illness, 2) total pain and/or suffering, 3) embodiment and 4) the gut microbiome (Figure 1). Proxy terms were developed from an initial scan of the literature (Box 1). As the study crosses a range of disciplines, searches were carried out in several search platforms and databases including Ovid, Cochrane Library, Anthrosource, BioOne, SciencOpen, SCOPUS, Web of Science, ProQuest and EBSCO. The review looked for relationships between quadrants, identifying links between different disciplines. The search strategy was amended to include proxy terms corresponding to each quadrant. Databases were searched in April 2019. Results were last fully updated in early 2022 and a rapid scan of literature was completed in June 2023. While previously we had included articles on any combination of quadrants, for the updated searches it was decided that the microbiome had to be addressed. Consequently, the update was only concerned with work on the microbiome and any other quadrant published since the initial searches were conducted.

Our analytic approach identified recurring commonalities within and across the literatures to generate themes (which we have structured as section headings and sub-headings). Publications describing relationships between a minimum of two quadrants were eligible for inclusion. Additionally, we included 1) publications which referred to the microbiome and interdisciplinary or “novel” approaches and 2) publications describing methodologically innovative review frameworks encompassing inter/transdisciplinarity. There were no restrictions regarding publication date or investigated populations (human or non-human). We were particularly interested in reviews/overviews as opposed to intervention studies, but no publications were excluded solely because of their study design. Hence, books, book chapters, guidelines, overviews, essays, commentaries, quantitative and qualitative studies were all eligible for inclusion. Only publications in English were included.

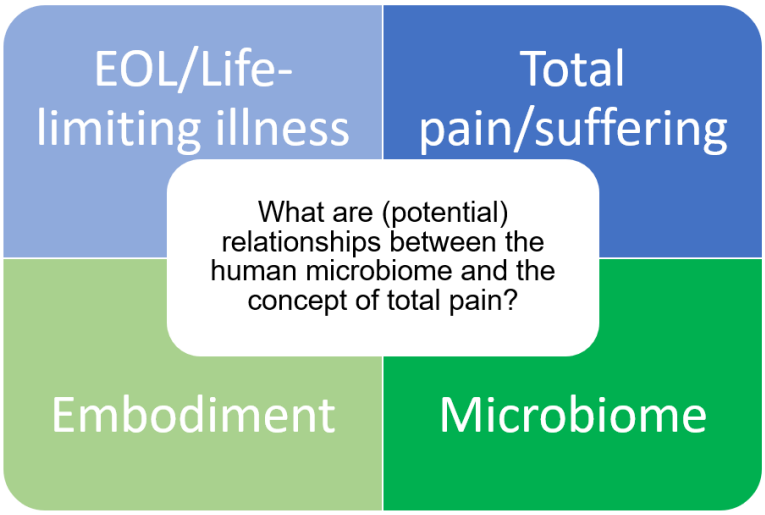

Figure 1. Research quadrants

proxy terms for end of life
• Ageing (including centenarians, cognitive decline, cognitive frailty, frailty, dementia, and other neurodegenerative conditions such as Alzheimer's Disease, Parkinson's Disease and Multiple Sclerosis, poor health, life-limiting conditions, HIV, CNS conditions, chronic diseases • cancer, cancer treatment (chemo), terminally ill patients, terminal or terminal pain, terminal care, incurable malignant disease • critically ill; palliative care; illness; serious illness; death
proxy terms for total pain
• psychiatric disorders (including anxiety and depression), mood, mood disorders, mental health, stress, emotion, CNS conditions, cognition, psychology, affect, psychological factors • pain, visceral pain and chronic pain • suffering; distress; spiritual aspect/religion; existential suffering • sociability and social behaviours • fatigue, sleep disturbances; quality of life; cancer symptoms
proxy terms for embodiment
• environment, social environment, culture, and social behaviour • the "human condition", the human self, self and completed self (n=4); holobiont and multispecies; bodily experience; pain experience
proxy term for the microbiome
• BGMA/GBMA/BGA • homeostasis

Box 1. Proxy terms

Database searches yielded some relevant results but often constrained by disciplinary boundaries. We therefore conducted additional targeted Google Scholar searches with some of the most productive proxy terms in order to identify literature not

found in the systematic searches. The key background literature identified by first author was then added to the list of included studies and checked for any articles that had been previously read but had not been identified by any searches. Hence, the final list of included literature derived from three sources: systematic searches, targeted Google searches, and initial core references. The data extraction process was carried out through both formal data extractions procedures where deemed beneficial (the article had substantial use value) and the methodology of Dixon-Woods and colleagues in reading and highlighting pdf copies (when looking for confirmatory or new information).

Please feel free to contact the lead author if you would like further information about our review methods.

Key texts

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Appendix 2: Glossary of terms

Term	Definition
Autonomic Nervous System (ANS)	The autonomic nervous system is regulated by the hypothalamus and controls involuntary functions of internal organs. It comprises sympathetic (spinal nerves) parasympathetic (the cranial nerves, especially the vagus nerve) nerves and the enteric nervous system. (https://qbi.uq.edu.au/brain/brain-anatomy/peripheral-nervous-system/autonomic-nervous-system;https://www.nature.com/articles/nrgastro.2016.107.pdf)
Brain-Gut-Axis, Gut-Brain-Axis	Bidirectional communication between the CNS and the ENS, with a cross-talk between the endocrine (HPA axis), immune system and ANS." Its role is to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms such as immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling.[1]
Chronic illness	Health condition or disease that is persistent or otherwise long-lasting in its effects or a disease that comes with time. The term chronic is often applied when the course of the disease lasts for more than three months. Chronic and life-limiting conditions are often similar, often end in critical conditions and mark end of life
Central Nervous System (CNS)	The CNS comprises the brain and the spinal cord.
Cortisol	Cortisol is a steroid hormone produced in the adrenal glands. Its secretion is controlled by the HPA axis. Cortisol has several roles and is connected to stress responses.
Critical illness	Life-threatening condition, can be end point of chronic or life-limiting illness(es) or serious trauma.
Cytokines	Proteins secreted by cells in the immune system that work as chemical messengers (https://study.com/academy/lesson/what-are-cytokines-definition-types-function.html).
Dysbiosis	Condition in which the normal composition, structure and function of the microbiome has been disrupted/disturbed and which is considered as detrimental to the host (human or other)[2-4]
Eco-biotic o eco-psychotropic	Terms proposed by Logan to replace the term psychobiotics[5]
Embodiment	Various definitions, but usually refers to how the body and its interactive processes, such as perception or cultural acquisition through the senses shape the development of the human functioning. Lived experience.
End of life	A poorly defined concept, but usually The months and days before death, where irreversible decline is often evident.
Enteric Nervous System (ENS)	Part of the ANS, it comprises an interconnected network of over 100 million neurons. The ENS is uniquely equipped with microcircuits that allow it to control gastrointestinal behaviour independently from CNS input. Several neurotransmitters, signalling pathways and anatomical properties are common to the ENS and CNS. (https://www.nature.com/articles/nrgastro.2016.107.pdf)
Faecal microbiota transplantation	Treatment in which subjects are colonised with faecal matter (usually from a healthy donor or from a population of interest)[2, 6]
Holobiont	All organisms in a given ecosystem; i.e. a host (human or other) and its microbiomes. It is also called a superorganism[6, 7]

Hologenome	The host and microbial genomes in a holobiont[8]
Hypothalamic-Pituitary-Adrenal (HPA) axis	The HPA axis is the endocrine core of the stress system. Its activation results in the release of corticotropin-releasing factor from the hypothalamus, adrenocorticotropic hormone from the pituitary and cortisol (corticosterone in rats and mice) from the adrenal glands[3]
Immune system	First line of response to invaders or tissue injury. It answers to danger signals by recruiting immune cells to the injury site, inducing inflammation and activating the adaptive immune system. The luminal gastrointestinal surface is one of the largest common surface areas between host and environment. The immune system is critical in maintaining immune tolerance to commensal microbes, whilst ensuring the rapid immune response against invading pathogens[9]
Inflammaging or Inflamm-ageing	Chronic, low grade, progressive increase in inflammatory response typical of the elderly[3, 6, 10]
Life-limiting illness	In absence of other considerations will shorten life, terminal - result in death, where it is expected that death will be a direct consequence of the specified illness. Such illnesses may include, but are not limited to cancer, heart disease, chronic obstructive pulmonary disease
Metabolites	Resulting from metabolism (modulated by bacteria), these products/substances are essential for host health[11]. They include bile acids, choline and short-chain fatty acids (SCFAs)[3]
Metagenome	All the genetic material in an environment; i.e. genomes of all individual organisms[7]
Microbiome	The collective genome of all microorganisms in a microbiota[2-4, 6, 12, 13]
Microbiota	A collection of microorganisms (viruses, bacteria, fungi, archaea, and protozoa) in an environment/ecosystem/living host (human or other)[4, 6, 7, 12]
Mutualism	A mutually beneficial relationship (in this case, between the host and the microbiota)
Neuroendocrine system	The neuroendocrine system comprises neuroendocrine cells (nerve cells and hormone-like cells of the endocrine system) spread throughout the body. They receive messages from the nervous system and respond by making and releasing hormones that control many body functions (https://www.cancer.ca/en/cancer-information/cancer-type/neuroendocrine/neuroendocrine-tumours/the-neuroendocrine-system/?region=on)
Nociceptor	A receptor that is preferentially sensitive to noxious stimuli or stimuli that would become noxious over time[14]
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Pain is always subjective[14] Central pain: initiated or caused by a primary lesion/dysfunction in the CNS[14] Neurogenic pain: initiated or caused by a primary lesion/dysfunction/temporary perturbation in the peripheral or CNS[14] Neuropathic pain: initiated or caused by a primary lesion/dysfunction in the nervous system[14] Nociceptive pain involves the activation of pain receptors by a stimulus that normally causes pain stimulus. Two types: Somatic pain: pain from receptors in tissues (skin, muscles, skeleton, joints, and connective tissue) are activated. Visceral pain: pain from internal organs and is generally described as dull, diffuse, poorly localized and characterized by hypersensitivity to stimulus

Pathobionts	Typically, benign endogenous microbes that expand as a result of dysbiosis and can elicit pathogenesis in the host[2, 7]
Prebiotics	Nutrients (such as fibers) that promote the growth of bacteria that confers health benefits to the host[2, 4, 6, 7]
Probiotics	Live microbes that can confer health benefit to the host (by preserving or restoring symbiosis) when administered in appropriate quantities[2-4, 6, 7]. They are often administered as dietary supplements or as food products, such as yogurt[13]
Psychobiotics	Interventions targeting the microbiome with the aim to support mental or brain health[6]
Serotonin	Serotonin (5-HT) is a neurotransmitter that plays a role in mood, anxiety and depression[15]. It is produced from tryptophan and is mostly found in the GI tract (90% - the remaining 10% is found in the brain)[16]
Short-Chain Fatty Acids (SCFAs)	Neuroactive bacterial metabolites of dietary fibres that can modulate brain and behaviour[3]
Stress	The process by which a stimulus/stressor disrupts internal homeostasis resulting in a physiological response (the stress response) aiming at returning to a state of homeostasis[17]
Stress response	Complex combination of behavioural, neuronal and endocrine responses that occur after exposure to a threat and prepare the organism to cope with the stressor and maintain homeostasis. Chronic or inappropriate activation triggers the pathophysiology of several medical and psychiatric disorders. A stress response involves the activation of the HPA axis[3, 17]
Supraorganism	An organism comprising both microbial and human cells, as well as microbial and human genes, with the number of microbial components vastly exceeding the number of human components[18]
Symbiosis	Relationship between two or more organisms that live close together. There are three types of symbiosis: mutualism, commensalism and parasitism (https://learn.genetics.utah.edu/content/microbiome/symbiosis)
Synbiotics	A combination of prebiotics and probiotics with the aim to optimise treatment[2, 6, 7]
Total pain	A concept of pain that includes physical, psychological, social, emotional and spiritual elements[19]
Tryptophan	An essential amino acid that produces serotonin[20]
Vagus nerve	This is a cranial nerve(X) that connects the brain to the body. It is a major component of the autonomic nervous system and regulates organ functions (including gut motility). Activation of the vagus nerve has been shown to have anti-inflammatory capacity. About 80% of nerve fibres are sensory, conveying information from the body to the CNS; approximately a fifth are dedicated to GI-CNS communication[3, 21]
γ-Amino Butyric Acid (GABA)	Main inhibitory neurotransmitter in the brain, it plays a role in the regulation of movement, blood pressure, heart rate, and pain perception. It has also been implicated in anxiety and depression[16]

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