SOCIAL STRESS AND SEX-BIASED INFLAMMATORY DISEASES

SEX-BIASED EXPERIENCES OF SOCIAL STRESS AND THE ORIGIN OF SEX-BIASED INFLAMMATORY DISEASES AND MENTAL DISORDERS

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Abstract

Women are more susceptible to a range of detrimental diseases surrounding autoimmunity and inflammation, but the causes of this are largely unknown. Much of the current research investigating these patterns focus on a microscopic view of cellular and/or hormonal processes, but holistic perspectives incorporating sociology, psychology, physiology, and evolution are rarely considered. Through investigating interactions between a history of neglecting women's research, evolutionary origins of sex differences in the immune system, and the impacts of society's influences on stress, some sex-biased patterns of disease may emerge. The existing SS-SH-SS theory by Brown et al. (2022) describes the complex environmental, psychological, and biological mechanisms that interact to create a female sensitivity to stress-based inflammatory diseases. Using the foundations of this theory, in this study we used global disease and stress exposure data from the World Bank and Global Health Data Exchange project to investigate how the relationships between exposure to stress and prevalence of diseases differ by sex. Using principal component analysis and generalized linear mixed models, we demonstrated a complex relationship between certain stress factors and inflammatory diseases. Particularly, we found that levels of poverty, alcohol use and drug use had distinct, sex-specific impacts on rates of diseases that we studied. Female rates of disease were particularly sensitive to the changes in substance use and poverty, with an inverse relationship with poverty and a direct relationship with substance use. This study can serve as an example for investigating the correlates of sex-biased diseases and mental disorders, particularly about the role of sex-biased experiences of social stress in the origin of sex-biased mental illnesses.

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Chapter 1: Introduction

The nature of sex and diseases are not simple biological concepts, but instead are influenced by almost every part of the human condition. In order to provide the context necessary for this study, we have included a detailed review of some current research explaining: (1) sex differences in physiology and disease, including sex hormones, genetics of disease, and sociological impacts of disease, and mental disorders; (2) immunological system and disease, including neuroinflammation, autoimmune diseases, inflammatory diseases, and sex differences in immune regulation; (3) influences of stress, on disease and sex differences in stress; (4) evolution of sex differences and disease prevalence; and finally (5) the grand theory of sex-biased diseases and mental disorders. Through this chapter, we hope to provide the background of knowledge required to inform the reader of the current literature and provide context necessary for our project.

Chapter 1.1: Sex differences in physiology and disease

The distinctions between male and female physiology are less of a rigid box, and often considered more of a sliding scale between each sex characteristic. For example, “normal” serum progesterone levels in fertile human females range from >1 – 63.6 nmol/L depending on where they fall in their menstrual cycle and males’ levels range from >1 – 3.18 nmol/L, a range that clearly overlaps (Ferri, 2021). Due to this, wide variations of morphology and physiology appear within sexual traits in human populations (Morrow, 2015). Some of these differences in sexual characteristics are also present in non-sexual traits, either as purposeful or unintended consequences of sexual selection. These consequences play important roles in human diseases, especially diseases that show stark differences between males and females (Morrow, 2015). Sex differences in genetics play a large role in regulating many of the

differences seen between males and females in humans, like the vast complexities of the sex chromosomes, which will also be covered in this chapter. We will touch on the sex differences in the brain and neurological functioning that leads to mental disorders. Finally, we will discuss an important factor of sex differences in disease that is often disregarded in scientific literature, sociological impacts of health. We aim to establish the groundwork necessary to examine the intricate interconnections among the immune system, stress, evolution, and sex differences that we will explore in later chapters.

Genetic basis of sex-bias in diseases

One of the most robust and universal differences between sexes is the sex chromosomes. In humans most often, males have one X and one Y chromosome while females usually have two X chromosomes, although nondisjunction events cause many exceptions to this (Visootsak & Graham, 2006). Males, however, only have one copy of the X chromosome and this means that if they inherit one recessive deleterious gene, that recessive mutation will be expressed (Germain, 2006). There are many X-linked diseases that are only or almost only present in males. Hemophilia A is one example of this. This disorder arises when there is a mutation in the gene coding for Factor VIII on the X chromosome, a coagulation factor that aids with blood clotting (Konkle & Nakaya Fletcher, 2017). For those with Hemophilia A, injuries are slower to stop bleeding and blood can hemorrhage into joints and muscles (Konkle & Nakaya Fletcher, 2017). Another X-linked disease is Severe Combined Immunodeficiency disease (XSCID), which is caused from a mutation in the interleukin-2 (IL-2) receptor gamma subunit (Brooks et al., 1990). This receptor is involved in growth and differentiation of T and B cells throughout the body so with this disorder, many infants die prematurely, as they cannot fight off bacterial, viral, or fungal infections (Brooks et al., 1990). Additionally, in females, one X chromosome is silenced to prevent an excess of X-

related genes being expressed (Disteche & Berletch, 2015) but, an estimated 15% of genes escape X-inactivation (Carrel et al., 1999). They are not necessarily expressed the same way as if they were not silenced, but they are still being transcribed in some manner (Carrel et al., 1999), potentially leading to differences between males and females. X and Y chromosome genes influence brain development both inside and outside of the production of sex hormones (Ratnu et al., 2017). Even before gonadal development when sex hormones begin being produced in fetuses, more than 50 neurological genes are expressed differently in males and females (Dewing et al., 2003). This demonstrates the multifaceted effect of sex chromosomes on physiology and development through and apart from sex hormones. Clearly, the X and Y chromosomes have an important role in sex differences in disease.

Sex differences in mental disorders and neurological functioning

Exploring sex differences in mental illness and neurological functioning, including sociological factors, serotonergic and dopaminergic systems, and the gut-brain axis, reveals their complexities. Although there are many differences in sex presentation for specific diseases, there are some overarching general trends spanning across mental illnesses. Serotonin is an important neurotransmitter that is associated with many mental diseases. Although it is present throughout the body, it has vast effects on emotion, behaviour, and cognition in the brain (Lin et al., 2014). The serotonin system is effected differently in males and females, primarily through sex hormones (Spies et al., 2020). Evidence in non-human animals suggests that treatment with estradiol in ovariectomized females increases serotonin production in the brain (Rivera et al., 2009; Sánchez et al., 2013). These findings are not always consistent, though. An important family of enzymes within the serotonergic pathways are the monoamine oxidases (MAO). These are responsible for the breakdown of serotonin and many other crucial neurotransmitters (Jones & Raghanti, 2021). Recent evidence

suggests their involvement in various mental diseases is vast and complex, but also differs between sexes (Jones & Raghanti, 2021). Some mental illnesses, like major depressive disorder, are associated with higher neurological levels of MAO-A (Meyer et al., 2009), but generally, estrogen and MAO-A have a negative relationship (Spies et al., 2020). Research investigating sex differences in MAO-A and impacts of mental illness likely require thorough consideration of female hormonal changes throughout the menstrual cycle, pregnancy, and menopause to acquire more consistent findings (Spies et al., 2020).

Similar to serotonin in many ways, the dopaminergic system is also heavily involved in the presentation and development of many neurological and psychological disorders. Sex also influences the dopaminergic system through various means (Woodcock et al., 2020). Changes in estrogen levels, such as during the menstrual cycle, pregnancy, or menopause, are associated with vulnerability to substance use disorder, a mental illness primarily driven by the serotonergic system (Calipari et al., 2017). Progesterone is also thought to reduce the reward response of drug use (Lynch & Sofuoglu, 2010). The effects of testosterone are not consistent, but it is thought to play a role in the mesolimbic dopamine pathway (Hermans et al., 2010). MAO-A regulation is also influenced by the Sry gene (Wu et al., 2009), the sex determining region on the Y chromosome (Loke et al., 2015). The distinct effects of this regulation are unclear, but this sex-specific modulation could indicate some of the differences in mental disorders that involve the serotonergic and dopaminergic systems.

Additionally, the gut brain axis may influence some sex differences in psychiatric diseases. In childhood, diversity and balance of the gut microbiome is general similar in males and females, but once puberty begins and sex hormones differ significantly between sexes, gut bacteria change distinctly (Shobeiri et al., 2022). Many gut bacteria are able to produce and influence the production of chemicals involved in mental illnesses, (e.g. GABA is made by

Lactobacillus brevis and *Bifidobacterium dentium*) (Shobeiri et al., 2022). In fact, mice have shown alleviation of anxiety and depression-related behaviours after ingestion of a related strain of *Lactobacillus rhamnosus* (Bravo et al., 2011). The gut microbiome is also associated with many specific mental diseases and show sex-specific effects. Weakening the gut microbiome shows more extreme anxiety behaviour in females compared to male mice (Shobeiri et al., 2022). Specific differences in general bacterial families have also been observed. A study by Shobeiri et al. (2022) demonstrated that human patients with depression showed sex-specific microbiome differences compared to control groups. Depressed females tended to have higher levels of *Actinobacteria* than healthy females while depressed males had lower levels of *Bacteroidia* than healthy males. But depression status showed no relationship with *Actinobacteria* in males and showed no relationship with *Bacteroidia* levels in females. But fortunately, the gut microbiome doesn't just cause mental illness, it can also be manipulated to act as a protective factor against it (Murray et al., 2019). Research has found that ingesting probiotics during puberty can help to protect teens from depression and anxiety behaviours caused by exposure to stress (Murray et al., 2019).

Sex hormone receptors in the brain can also affect thoughts, emotions and behaviour potentially even in a self-reinforcing manner McEwen & Milner, 2017). In general, administering testosterone reduces emotional and fear-based responses to stimuli (Hermans, et al., 2006; Hermans, Putman, & van Honk, 2006). In females, luteal phases of the menstrual cycle, when progesterone is higher, tend to result in more emotional volatility and poorer emotion recognition (Sundström-Poromaa, 2018). Meanwhile, estradiol is thought to positively influence memory and cognition through the hippocampus (Shepherd, 2001). Estrogen receptors are present in cell nuclei of some nerve cells and affect the cholinergic, serotonergic, noradrenergic, and dopaminergic systems (McEwen, 2001). From this section,

it becomes clear that sex differences in mental illness and neurology are vast and complex, influenced by many biological and environmental systems.

Sex differences in sociological factors of diseases

In addition to genetic and sex hormone differences in physiology, a long history of patriarchal societies has led to men's health being viewed as the "normal" and women's health as the "exception". This has resulted in exacerbation of sex differences normally seen with disease presentation. One of the largest examples of this effect can be seen with cardiovascular diseases. Historically, cardiovascular diseases were considered primarily 'men's diseases', but, in reality, women tend to experience higher deaths from many such diseases (Sobhani et al., 2018). It's possible that this is influenced by men's cardiovascular diseases being the primary focus of scientific research for centuries (Bergami et al., 2022). Women's symptoms tend to present differently to men, commonly exhibiting nausea, heart palpitations, and shortness of breath while men tend to experience more chest pain. The higher rates of women's deaths could stem from delayed diagnosis and treatment because of their 'unusual' presentation of symptoms (Branyan & Sohrabji, 2020). The diagnostic criteria for several cardiovascular diseases are biomarkers, but often, standardized thresholds for diagnosis are not differentiated between males and females. For example, Troponins and CK-MB are two biomarkers sometimes used to diagnose ischemic heart disease and heart failure (Jacob & Khan, 2018). Women tend to have significantly lower levels of these than men, but the standard diagnostic criteria utilize men's levels as the standard (Sobhani et al., 2018). This results in many women with inflated Troponins and CK-MB are not flagged for concern. There is also a case to be made that woman are less likely to have a supportive partner at home that is willing and able to care for them after a cardiovascular event (e.g., stroke, heart attack) (Sobhani et al., 2018). This is also associated with a higher level of mortality. All this

being said, women tend to experience higher levels of inflammation, which is associated with increased risk of various cardiovascular diseases (Bergami et al., 2022).

Additionally, due to the immense influence of environmental factors on mental disorders, sociological differences can have a large effect on prevalence and severity of mental illnesses. In a study from Brazil, the gender gap in wages explained 17% of the increased risk of common mental disorders like anxiety and depression in women (Loret de Mola et al., 2020). Schooling level was also associated with a decreased risk of mental illness, and women around the world tend to receive less access to education than their male counterparts (Loret de Mola et al., 2020). Although the sociological factors of disease are less of a focus in most scientific literature, they are vital to comprehensively understand sex differences in disease that exist in human societies.

Chapter 1.2: The immune system and inflammation

The immune system is a complex system that consists of two primary branches: the innate and adaptive immune responses. The innate immune system is set up to automatically defend against pathogens introduced to the body by preventing access to sensitive tissues, competing for space and resources and many broad-scale automatic responses to any threats (Alberts et al., 2002). The adaptative immune response acts slower and responds to a particular threat that is causing an issue, but it can be more powerful than the innate immune system because it has a high degree of specificity towards the threat. Both sides of the immune system are activated through inflammation. Inflammation is a broad-scale term that describes the body response to a threat. When a threat is detected, cellular and molecular pathways release chemicals called cytokines, which act as signals to other cells to trigger inflammation (Newton & Dixit, 2012). This immediate response is an increase in blood flow to the area to

bring in more immune cells and can result in higher temperatures, redness, swelling, and pain (Alberts et al., 2002). Some of the first cells to act on an invading pathogen are macrophages and then neutrophils which are both phagocytes, meaning they engulf and break down pathogens entering the body (Alberts et al., 2002). These cells release more cytokines to bring in additional help (Newton & Dixit, 2012).

The immune system is very effective at preventing major illness the majority of the time, but it does tend to go overboard and damage healthy tissue when waging an attack on a potential infection. This is not of concern when the immune response lasts a short period of time and then relaxes, allowing the tissues to heal. But this is not always what happens. Inflammation can become chronic where the immune response can continue over a longer period of time (Blach-Olszewska & Leszek, 2007). The exact causes of why immune responses become chronic is unknown, but some of the effects of this can be severely damaging.

Neuroinflammation

Neuroinflammation is an inflammatory response that happens specifically in the brain. Neurons can be very vulnerable to the immune system, so long-term inflammation can be disastrous to neural tissue (Glass et al., 2010). In the brain, glial cells act as support for other neurons and are also the primary immune cell within the brain. These cells can act to upregulate or downregulate neuroinflammation depending on the signals they receive. They primarily do this through releasing various cytokines (Almeida et al., 2020). Some of these cytokines directly influence the regulation of tryptophan, a precursor of serotonin (O'Connor et al., 2009), which could be a direct mechanism of neuroinflammation's impact on psychiatric disorders (Mukhara et al., 2020). Glial inflammation is activated through M1 or M2 mechanisms. The M1 responses are pro-inflammatory and upregulate cytokines like TNF-α and interleukin (IL)-6 (Tang & Le, 2016). In contrast, M2 responses are anti-

inflammatory and allow for tissue repair and growth periods through cytokines like IL-10 and TGF-β (Tang & Le, 2016). The activation of these mechanisms are great signals for levels of neuroinflammation in the body.

Autoimmune diseases

Autoimmune diseases occur when the immune system targets an antigen that is part of the host's body and launches an inflammatory response against it. This results in many autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), Grave's disease, type 1 diabetes, Hashimoto's thyroiditis, etc. (Cheesman, 2019). Autoimmune disorders are almost all female-biased with some exceptions including type 1 diabetes, although about 25% of people with type 1 diabetes have a comorbid autoimmune disorder which is female-biased (Rogers et al., 2020). The reasons for the female-bias in autoimmune diseases are unknown, but there are many indicators that the female immune system is stronger than males, potentially through the roles of sex hormones and genetics as outlined above.

Rheumatoid arthritis (RA) is an autoimmune disease characterized by swelling, pain, and reduced mobility of the joints (Rindfleisch & Muller, 2005). It's a relatively common disease and ranges from prevalence rates of around 8 to 45 cases per 100,000 people but is much more common in females than males throughout the world (Vos et al., 2020). The disease is caused by the identification of "self" antigens as foreign and dangerous by the immune system, which then act to upregulate inflammatory factors to neutralize the threat. The stimulating antigen is continually present, so the immune cells are consistently reactivated (Souto-Carneiro et al., 2020).

The mechanism causing such a stark sex difference in RA prevalence is not known, but it is widely suspected to be caused by sex-specific immunological differences. One study

researching sex differentially expressed genes in RA patients found a significant difference in IL-4 gene expression (Yu et al., 2020). Interestingly, IL-4 was expressed the lowest in males with RA, slightly higher in females with RA, and highest in healthy controls. IL-4 is generally considered to be an anti-inflammatory cytokine by preventing overactive inflammatory responses (Weckmann & Alcocer-Varela, 1996). In the case of RA, IL-4 prevents bone resorption near affected joints (Miossec et al., 1994) and downregulates apoptosis of synovial cells (Relić et al., 2001) through its anti-inflammatory effects.

Inflammatory diseases

While autoimmune diseases tend to receive more attention regarding the impact of a robust immune system of illness, there are a significant number of diseases characterized by inflammation in their advancement that are frequently overlooked. There is no set definition for an inflammatory disease, but it generally describes a disease where inflammation is a main cause of the symptoms or disease progression. This does not necessarily need to be the body attacking its own cells, like an autoimmune disease, but could be an overreaction to a pathogen or injury that results in detriment to the body.

Sex differences in immune regulation

Current research has uncovered significant differences between male and female physiology, although there is still much to discover. Firstly, sex hormones have large influences on many aspects of human biology. Testosterone and estrogen are known to modulate immune functioning, although the specific details of how they do this and their effects have been mixed (Foo et al., 2017). Testosterone is likely to suppress immune functioning, as expected by the SS-SH theory (Singh et al., 2021). This could play a large part in the male susceptibility to many infectious diseases and cancers. For example, amebic liver abscess is a parasitic disease that has a much higher prevalence rate in men, even though exposure rates to

the parasite are actually higher in females (Thi et al., 2002). The risk of developing this disease is directly proportional to the changes in serum testosterone levels that males experience over their lifetimes (Bernin & Lotter, 2014). This provides strong evidence of testosterone playing a role in the development and susceptibility of this disease. Of course, the relationship between testosterone and diseases overall is not cut-and-dry, there are significant influences of many other factors that determine disease prevalence differences in sex. Regardless, testosterone likely plays a part in this complex system. Estrogen, on the other hand, seems to increase some immune functions and decrease others, depending on the dose, sensitivity of the individual, type of cell, specific estrogen receptor present, and more (Khan et al., 2012). This can have such extreme effects as upregulating cytokines associated with the development of some auto-immune diseases, like lupus (Kassi & Moutsatsou, 2010), and a potential treatment method for others by, for example, reducing inflammatory brains lesions on patients with multiple sclerosis (Gold & Voskuhl, 2009). Pre- and post-menopausal women have decreased M2 (anti-inflammatory) immune activation and heightened M1 (pro-inflammatory) activation, potentially hinting that estrogen may prevent the downregulation of the M2 pathway (Toniolo et al., 2015). Estrogens are also negatively associated with C-reactive protein, a common marker of inflammation (Sproston & Ashworth, 2018). Conversely, estrogen has also been found to positively impact some pro-inflammatory pathways. It is thought to increase the production of IgM and IgG antibodies (Grimaldi et al., 2002) and increase the release of pro-inflammatory cytokines from T-cells (Neigh et al., 2016). Estrogen administration has been found to increase production of micro RNAs related to systemic lupus erythematosus (SLE), a common autoimmune disease (Khan et al., 2015). In response to these contradictory findings, some suggest that estrogens may upregulate immune responses at low levels, but suppress inflammation at high concentrations (Mukhara et al., 2020).

In addition to sex hormones, the number of X chromosomes an individual possesses is suspected of influencing their immune functioning. X chromosomes contain many genes that have either direct or indirect effects on the immune system. Females, with two X copies, were once thought to silence one chromosome to regulate the dosage of X chromosome-genes between sexes, otherwise they would output twice the dose of X chromosome gene product than males, but recent findings indicate otherwise (Berletch et al., 2010; Gartler & Riggs, 1983). It appears that copies of some genes may avoid inactivation, leading to a higher dosage of these genes in females than in males (Bianchi et al., 2012). Given the presence of immune genes within the X chromosome, the effects of genes avoiding inactivation may explain some of the immunity differences between males and females (Libert et al., 2010). Females expressing two copies of immune genes may result in a stronger immune system than males with only one copy. In addition, males do not have the added protection of two X chromosomes to defend against deleterious recessive genes. If males inherit a deleterious mutation in their X chromosome, that mutation will be expressed throughout the entire body. Females on the other hand, have a second, likely non-mutated copy of that gene that may be able to make up for the mutation in the other chromosome. Once again, given that many immune genes exist on the X chromosome, males are more susceptible to experiencing severe immunological effects of X-linked mutations.

Additionally, non-human animals who may have different sex-determining genetic strategies also show sex-biased immune responses (Klein & Flanagan, 2016). Mammals, who generally follow the same XY sex-chromosome pattern as humans, generally show stronger innate immune responses (Gal-Oz et al., 2019) and higher circulating white blood cells in females than males (Nunn et al., 2009). Birds' sexes are determined differently, by Z and W sex chromosomes where females have two different ones and males have two copies of the Z chromosome. One study measuring almost 2000 birds from 97 species found consistent

evidence of female-biased immunity including higher agglutination rates, total white blood cell, lymphocyte, and heterophil counts than males (Vincze et al., 2022). Insects show inconsistent sex-differences in immunological functioning. Some insects, like drosophila, show XX-XY sex-chromosomes (Salz & Erickson, 2010), while others, especially those in eusocial structures, have no sex chromosomes, but instead a haploidiploid sex-determination strategy (Gempe et al., 2009). The queen has two different copies of a *complementary sex determiner (csd)* gene and is responsible for laying the eggs in the colony and produces either fertilized or unfertilized eggs (Beye et al., 2003). The small number of unfertilized eggs become haploid male drones, responsible for mating with the queen, while all the rest must also have different *csd* genes and become worker females (Gempe et al., 2009). Across all these different sex-determination routes, robust differences in male and female reproductive strategies still contribute to sex-specific physiological and genetic traits influencing the immune system and development of disease (Kelly et al., 2018; Klein & Flanagan, 2016).

Additionally, other types of sex-biased expression of genes are incredibly common. A meta-analysis of 2500 samples identified many genes that are differentially expressed in males and females, especially in the brain (Mayne et al., 2016). In one study, sex-specific transcriptome differences were noted in 144 immune-related genes (Bongen et al., 2019). Notably, female-associated genes tended to be expressed in higher levels in CD4+T cells, while male-associated genes were more expressed in myeloid cells. The major histocompatibility (MHC) complex is a vital protein responsible for helping the immune system determine which cells are healthy and belong to the 'self', and which cells are infected, cancerous, or otherwise abnormal and need to be destroyed.

Astrocytes, key neuronal immune cells, also show key differences between sexes in their responses to sex hormones. When exposed to estradiol, female mice upregulated

progesterone synthesis in astrocytes in the hypothalamus (Kuo et al., 2010). Male mice, on the other hand, do not show any change in progesterone with the same treatment of estradiol (Kuo et al., 2010). Furthermore, recent research has begun to suggest strong relationships between astrocyte functioning and psychiatric illnesses, like schizophrenia (Chang et al., 2021). The effects of sex hormones on astrocyte functioning and the relationships between astrocytes and psychiatric illnesses could explain one facet of sex differences in some diseases. Sex hormones play multifaceted roles in the body and likely influence the prevalence, susceptibility, and onset of many diseases.

The specific mechanisms that are responsible for sex differences in immunity are likely complicated and a combination of many factors. That being said, it is not the specific biological processes involved that are being investigated in our research. Instead, we are looking at the *evolutionary pressures* that have led to these mechanisms, and the pattern of effects they have caused in males and females.

Chapter 1.3: Stress factors and their impacts

Both microscopic stress (on a cellular level) and macroscopic stress (on an individual level) play important roles in activating different systems in the body to respond to certain stimuli. Within cells, stress causes cascades of enzyme reactions to take an appropriate response measure to that specific stressor. Similar processes occur on an organism level, but hormones, instead of intracellular enzymes, act in a cascading effect to address the stress. In vertebrates, this complex neuroendocrine system is described as the hypothalamus-pituitary-adrenal (HPA) axis (Denver, 2009). Stress responses are common in many animals, and have been well studied in some model organisms, like mice, but for the purposes of this study, we will largely be focusing on stress in humans. Through the release of corticotropin releasing factor

(CRF), organisms change their physiology and behaviour to keep themselves safe and healthy (Denver, 2009). On a short-term basis, stress is incredibly beneficial by upregulating both the innate and adaptive immune systems (Dhabhar, 2014). Stress becomes problematic when it advances to a chronic state. Long-term stress exposure results in immune dysregulation and low-grade chronic inflammation (Dhabhar, 2014). In the 21st century, humans report experiencing high levels of stress during a large portion of their lives (World Health Organization, 2001). One unfortunate result of this has been predominant mental distress and mental illness. Many mental illnesses are thought to be caused by both experiences of stress and genetic predisposition. Given that stress is so closely associated with both mental disorders and immune regulation, sex differences in immune functioning are likely to affect stress's impact on the body and mind.

Definitions of stress

Some of the first biological recognitions of stress were by Selye (1956). Selye performed experiments by injecting ovarian fluids into other organs and observed the resulting body reaction. He noticed a relatively consistent response even once he switched to using extracts from other body organs and even toxic solutions. These responses were the enlargement of cortical kidney tissues, atrophy of immune structures and ulcer development in the stomach and duodenum. He named this response "general adaptation syndrome" and described the instigators of this syndrome as "evocative agents" (Selye, 1950). Eventually, Selye settled on the definition: "Stress is the non-specific response of the body to any demand made upon it" (Selye, 1950). It may seem counter-intuitive to define stress as a "response" rather than a "trigger" causing a response, but in actuality, stress is a reaction or feeling that comes from exposure to some external prompt, or *stress factor*, as we will refer to it henceforth.

Cohen et al. (1997) expanded on Selye's framework and described stress as "environmental demands [that] tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease" (Cohen et al., 1997, pg. 3). By understanding stress itself, we can finally begin to investigate the relationships between stress and other aspects of physiology.

Stress and disease

Stress is strongly linked to inflammation and disease. When exposed to acute stressors, biological activation of the immune response is intended to help fight off a potential threat, but when a stressor is continuous, the immune system causes chronic inflammation in specific areas or throughout the body which creates detrimental effects (H.-R. Kim et al., 2012).

Chronic psychological and social stress is associated with many diseases. For example, stress is a risk factor for late-onset Alzheimer's disease by inducing inflammation that prevents microglia from supporting synapses (Piirainen et al., 2017). This prevents microglia from preventing the accumulation of amyloid beta, causing even more inflammation (Piirainen et al., 2017). Additionally, irritable bowel patients exposed to psycho-social stress had worse symptoms (Pigrau Pastor, 2019). Additionally, differences in cell and cytokine passage through the blood brain barrier has also been associated with psychiatric illnesses like depression, bipolar disorder, and schizophrenia (Dion-Albert et al., 2022). This is especially pertinent in regards to the effects of stress on psychological symptoms. Chronic social stress in mice may induce heightened blood brain barrier leaking, and allow for increased inflammatory cytokines in the brain (Menard et al., 2017). This is also associated with an increase of depressive symptoms. Clearly, stress has important implications in the physiology of disease, especially mental illnesses.

Specific mental illnesses investigated

Our study investigates five diseases, four of which are mental illnesses. In this section, we will provide a detailed breakdown of the classification and research behind each of these mental illnesses.

Schizophrenia and psychotic disorders

Psychotic disorders are considered some of the most severe mental disorders and include several illnesses such as schizophrenia, schizoaffective disorder, delusional disorders, and more (American Psychiatric Association, 2022). Schizophrenia is described as at least two of: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, and negative symptoms for at least one month that causes significant dysfunction in livelihood (American Psychiatric Association, 2022). Other psychotic disorders within this category include organic psychoses, where the symptoms are caused by an organic factor (e.g., drugs) and alcoholic hallucinosis, where an individual experiences chronic hallucinations caused by long-term alcohol dependency (American Psychiatric Association, 2022). There is also schizoaffective disorder, which is similar in symptoms to schizophrenia but with strong affective features instead of psychotic features. Additionally, delusional disorder describes delusions that could be considered feasible or reasonable although not real. Finally, there are other axis II disorders which involve personality disorders such as schizotypal personality disorder, where a person is eccentric, socially isolated or withdrawn and has odd beliefs (American Psychiatric Association, 2022).

In general, schizophrenia has higher prevalence in males than females, and males have an onset earlier in life (between 16-25) with fewer males diagnosed after 30 (Castle & Buckley, 2015). Females have three approximately equal peaks in onset at ages 16-25, 46-55, and 66-75 (Castle & Buckley, 2015). Additionally, females with schizophrenia tend to have more

manageable symptoms, lower requirement for antipsychotic medication, and a better prognosis than males (X. Li et al., 2022; M. V. Seeman, 2020). This difference may be caused in part by estrogen, which is hypothesized to have anti-psychotic properties thanks to its effects on dopaminergic pathways in the brain.

Trauma and stress have been strongly linked with schizophrenia, especially when it occurs at a young age (Popovic et al., 2019). Childhood trauma has been associated with impaired working memory, executive functioning, verbal learning, and attention capabilities in schizophrenia patients (Popovic et al., 2019). In females, scores in the Childhood Trauma Questionnaire (Bernstein et al., 2003) has been correlated with severity of schizophrenia symptoms before treatment, but not in males (Haug et al., 2015).

In addition to trauma, schizophrenia also has a strong link to inflammation. Like with ASD, maternal infections during pregnancy are associated with a diagnosis of schizophrenia in the offspring (A. S. Brown, 2006) and linked with developmental abnormalities, especially in the dopaminergic system (Vuillermot et al., 2010). It is thought that neuroinflammation could disrupt mirror social behaviours, which encourage positive social interactions between individuals (A. S. Brown & Meyer, 2018). Although higher inflammatory markers are associated with schizophrenia in both sexes, there are some differences between them. Females with schizophrenia tend to have higher average inflammatory markers (like high-sensitivity C-reactive protein and interleukin-6) (Lee et al., 2019). They also tend to have greater sleep disturbances compared to males. Other studies have indicated that females with schizophrenia have a positive correlation of inflammatory cytokines with the number and severity of their symptoms (specifically alpha-1-antitrypsin, B lymphocyte chemoattractant BLC, and interleukin-15) while males had a positive correlation of prolactin and testosterone with schizophrenia symptoms (Ramsey et al., 2013).

Additionally, there is some evidence that gene transcription differences between sexes could lead to the sex discrepancy in prevalence. A study measuring genes that were highly expressed in various key neurodevelopmental stages in life found that over half of these genes had sex differences in expression (Jiao et al., 2019). Of the genes that have been previously linked to a higher risk of schizophrenia through GWAS studies, males tended to express these genes earlier in development than females (Jiao et al., 2019).

In conclusion, the physiological components of schizophrenia, although still poorly understood, suggest a strong association with inflammation and potential sex differences in gene expression. As we transition to the next section, we will explore the complexities of bipolar disorder and its distinct manifestations.

Bipolar disorder

Bipolar disorder is a mental illness characterised by cycles of depression and mania (in type I) or hypomania (type II). Mania is a mental state of arousal where a person may become abnormally energetic, irritable, impulsive, and may sometimes involve experiences of psychosis, where one loses touch with reality (American Psychiatric Association, 2022). Hypomania is similar to mania, but the symptoms tend to be less severe and the patient is less disrupted in their ability to function (American Psychiatric Association, 2022). Mania tends to be more extreme and can often lead to serious consequences like loss of employment, strained relationships, run-ins with the law, injury or health risks, and/or hospitalization.

Bipolar disorder has similar prevalence between sexes, although the disorder symptoms tend to present differently. Manic periods usually involve more depression and anxiety-related symptoms in females, while in males, symptoms are more likely to be motor or psychosis-related (Arnold, 2003). Importantly, although the sex-bias for this disease is approximately equal, female-dominant symptoms are often considered clinically atypical while more

common symptoms in males are considered the norm (Bhattacharya et al., 2011). This could indicate underdiagnosis of females that are not being represented by the current diagnostic criteria. Females tend to experience an earlier onset of bipolar disorder, interestingly opposing the trend seen in schizophrenia where males are often diagnosed earlier in life.

From a neurological perspective, bipolar patients tended to have less activation to emotional stimuli in various brain regions making up cognitive-emotional pathways (Fleck et al., 2018). The structures themselves seemed similar between bipolar patients and control groups but the reaction to stimuli in the frontal, medial temporal, and limbic modules differed (Fleck et al., 2018) It also seems like the prefrontal cortex modulates changes in other brain regions that likely play a role in controlling emotion in people with bipolar disorder (Strakowski et al., 2005). Interestingly, some sex differences in healthy brains seem to reverse in patients with bipolar disorder. Specifically, male adolescent bipolar patients had larger left supramarginal gyrus regions while female adolescent patients had larger right inferior parietal lobe volumes. In general, bipolar patients of both sexes had generally smaller left supramarginal gyri and right inferior parietal lobe volumes than control adolescents (Mitchell et al., 2018). Additionally, glial cell gene expression in males and females tend to differ by sex. Males tended to show higher expression of glial-cell-related genes in the dorsolateral prefrontal cortex than females (Zhang et al., 2020). This difference in gene expression was strongly correlated with experiences of psychosis, even when controlling for sex (Zhang et al., 2020). Bipolar patients who experienced less suicidality also had lower gene expression of some microglial genes in the same brain region, the dorsolateral prefrontal cortex, in both males and females (Zhang et al., 2020). From a broader neurostructural perspective, female bipolar patients have been found to have smaller, more asymmetrical brains compared to control groups, while males tended to have larger, more symmetrical brains (Mackay et al., 2010).

Inflammation likely also plays a role in bipolar disorder. In general, bipolar patients have higher rates of inflammatory cytokines which indicate higher baseline inflammation (Modabbernia et al., 2013). Patients have also been found to have higher levels of some cytokines during periods of mania than during depressive periods, and even lower levels during periods with little or no symptoms at all (Modabbernia et al., 2013). Conversely, other studies have indicated lower circulating lymphocytes, an important immune cell, in bipolar patients experiencing mania (Abeer et al., 2006). Overall, people with bipolar disorder are more likely to experience inflammatory comorbid diseases than the general population (Eaton et al., 2007). There are some sex differences in inflammation for bipolar patients, although less differences than some other mental illnesses.

In summary, bipolar disorder shows distinct symptom variations between males and females, suggesting the need for gender-informed diagnostic criteria. Neurological differences and the role of inflammation further contribute to this complex disorder.

Depressive disorders

Major Depressive Disorder (MDD) is described by extended periods of low mood, lethargy, irritability, numbness, weight gain or loss, and changes in sleeping and eating habits. These periods often occur multiple times throughout the life, and most commonly begin in adolescence (American Psychiatric Association, 2022). MDD is generally much higher prevalence in females than males.

MDD has been strongly linked to heightened inflammation, but the exact mechanisms are still unknown. In pregnant mothers, higher levels of inflammation, measured through inflammatory cytokines, were correlated with depressive symptoms (Zhang et al., 2020). Those cytokines were also associated with heightened behaviours of negative emotion (e.g., fear, more crying, irritability, etc.) in infants (Zhang et al., 2020). Many mouse model studies

have been conducted linking inflammation to depressive behaviours, including lipopolysaccharide (LPS)-induced sickness behaviours, which describe depression-like symptoms brought on after exposure to cell membrane components of gram-negative bacteria (Caldarone et al., 2000). The bacteria themselves don't cause an infection, as only their membrane is injected into the mice, but the strong immune reaction causes general heightened inflammation, likely leading to these depressive behaviours (Caldarone et al., 2000). Males in particular show more sickness-behaviours when exposed to LPS, while females tend to show higher levels of serum corticosterone, often considered a stress hormone (Caldarone et al., 2000).

Genetics also play a major role in MDD. GWAS studies have identified more than 100 genes that may influence depression, but each likely has a very small effect, largely complicating the disease (Dunn et al., 2020). Other, more specific studies, indicate some genes have slightly larger effects, such as one haplotype of the gene FK506-binding protein 5 (Dunn et al., 2020). This gene had a large association with experiences of suicidality and was present in 47% of tested study participants (Yin et al., 2016). While MDD shows high heritability in both sexes through twin studies, it seems to be more heritable in females than males, where the relative risks are 42% and 29% respectively (Kendler et al., 2006). In more specific searches, homozygous recessive individuals in five genetic markers on chromosomes 17 and 19 demonstrated higher depressive symptoms than heterozygous or homozygous dominant individuals (Kang et al., 2020). Surprisingly, males were particularly vulnerable to the effects of the recessive alleles compared to females (Kang et al., 2020).

Finally, experiences of stress and trauma are strongly associated with the development of MDD. Many mouse model studies indicate chronic mild unpredictable stress leads to depressive symptoms (Willner, 2017). Although experimental studies causing stress to

humans are unethical and cannot be conducted, research indicates that individuals that experience higher levels of stress in their lives naturally are more likely to develop depressive symptoms as well. Importantly, the relationships between trauma exposure and depressive symptoms differ widely by sex. In mice, females develop depressive symptoms when exposed to chronic, mild stress more than two weeks earlier than males do (Hodes et al., 2015). Stress can also induce blood-brain-barrier (BBB) dysfunction, which may be further linked to depression symptoms. Specifically, stress-induced BBB dysfunction has been shown to result in tight junction protein loss between cells, which may increase the access of inflammatory cells and cytokines in the prefrontal cortex of female mice but the nucleus accumbans in male mice (Dion-Albert et al., 2022). Finally, childhood trauma is also linked to susceptibility of MDD with corticotropin-releasing hormone receptor-1 gene variants (Heim, 2009). The presence of this specific allele is associated with decreased cortisol response in males, while females with this allele had even higher levels of cortisol after stress experiences than females without the allele (Heim, 2009). Interestingly, the allele seemed to have little or no effect on people if they did not experience childhood trauma and only affected those who did (Heim, 2009). In conclusion, the association between depressive disorders and heightened inflammation, genetic factors, and sex-specific vulnerabilities highlights the multifaceted nature of their etiology. As we delve into the realm of anxiety disorders, we will explore the intricate interplay between brain structure, stress, trauma exposure, and sex differences, shedding light on the distinct mechanisms underlying these prevalent mental health conditions.

Anxiety disorders

Anxiety disorders fall into a category of illnesses categorized by the DSM-V that includes generalised anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder,

post-traumatic stress disorder (PTSD), social anxiety disorder, and specific phobias (American Psychiatric Association, 2022). Generalized anxiety disorder (GAD) is described as difficult to control, high levels of baseline anxiety occurring for the majority of days over at least 6 months about various different events or activities. Next, obsessive compulsive disorder (OCD) involves obsessions, which are reoccurring and persistent thoughts, causing distress and often subsequent compulsions, which are repetitive behaviours or mental acts that ease distress from obsessions but are not realistically connected to the event or problem or are excessive (American Psychiatric Association, 2022). Panic disorder involves intense acute feelings of fear or discomfort with a sudden onset, shortly reaching a peak and then resolving. The fears from the attacks or apprehensions for future attacks cause severe distress and disrupt livelihood (American Psychiatric Association, 2022). Next there is post-traumatic stress disorder (PTSD) which results after exposure to actual or threatened death, serious injury, or sexual violence either directly or indirectly. It involves reoccurring and distressing memories, dreams, or dissociative reactions associated with the event leading to attempts to avoid any related stimuli of the traumatic event (American Psychiatric Association, 2022). There is also social anxiety disorder where a person experiences a disproportionate fear of social events where they may experience scrutiny by others that causes avoidance of social situations and difficulty functioning (American Psychiatric Association, 2022). Finally, specific phobias are various immediate and extreme fears of an object or situation that is not proportional to the danger of this object or event in reality. This often leads to avoidance behaviours and causes significant distress in important areas of functioning in an individual's life (American Psychiatric Association, 2022).

Surprisingly, there seems to be limited structural differences that have been found between the brains of anxiety disorder patients and control patients. Some few differences include higher volume in gray matter in the dorsal striatum in patients with social anxiety disorder

(Bas-Hoogendam et al., 2017). Additionally, there may be sex-specific differences in brain structure that are not noticeable when not stratifying by sex. One study found no differences between GAD patients' and control patients' brains but when modulating by sex, males with GAD had significant increased volume of the right ventral diencephalon, while females did not (Harrewijn et al., 2020). This indicates a need for further research investigating sex differences in the brain structure of anxiety disorder patients.

Existing research has shown strong connections between anxiety and inflammation, but much of the existing research clumps depressive and anxiety symptoms together, especially in animal model studies. Inflammation can be upregulated by stress through cortisol to protect an individual from an injury or an infection, but if that stress continues long-term or there is not a resolution, that stress can become chronic (Michopoulos et al., 2017). There is very little surprise that chronic exposure to stress and trauma positively impact anxiety symptoms. But interestingly, stress impacts anxiety symptoms differently in both sexes. When exposing mice to chronic low levels of stress, males experienced early, sudden weight loss and a decreased preference for sucrose after just one week, while females showed gradual continuous weight loss and loss of sucrose preference over time (Dong et al., 2020). Both sexes also demonstrated differences in hormones and inflammatory biomarkers. Males had decreases in monoamine neurotransmitters, some inflammatory cytokines (TNF-alpha and IL-Beta) while females showed greater activation of the hypothalamic-pituitary-adrenal (HPA) axis, higher adrenocorticotropic hormone (Dong et al., 2020), and a reduction in a key hormone in hunger signalling (proopiomelanocortin) mRNA levels in the pituitary gland (Miller et al., 2022). Although the females experience more of a change, both sexes showed decreased sensitivity of the HPA axis to acute stress after exposure to chronic variable stress (Miller et al., 2022).

When investigating humans, a study researching low-income, high-risk adolescents in South Africa were assessed for PTSD and depression symptoms (Hiscox et al., 2021). For these teenagers, PTSD was higher in females, even when controlling for the amount of trauma exposure (Hiscox et al., 2021). After controlling for differences in PTSD symptoms, there was no noticeable difference in depression between males and females (Hiscox et al., 2021). This may indicate a much deeper connection between depression and anxiety and their interactions with stress and trauma exposure. Finally, younger females tend to report more exposure to stress than their male counterparts and higher sensitivity to those exposures, especially regarding peer interactions (Hankin et al., 2007). Another study showed adolescent males experiencing higher levels of lower-intensity chronic stress, while females had higher overall and interpersonal stress (Hankin et al., 2007). This may indicate a heightened female exposure to social stressors that may be particularly impactful for the development of mental health disorders. Anxiety disorders, including generalized anxiety disorder, obsessive-compulsive disorder, and post-traumatic stress disorder, significantly impact individuals' lives. While limited structural differences have been found in the brains of anxiety disorder patients, the role of stress, trauma, and inflammation cannot be overlooked.

Sex differences in stress

Although it is now well established that inflammation plays a complex role in many mental illnesses (Costello et al., 2019; Firth et al., 2019; Goldsmith et al., 2016; Strawbridge et al., 2015), responses can differ widely between sexes. For example, females have been shown to experience more severe depressive symptoms than males when treated with interferons, a cytokine that promotes inflammatory anti-viral action, during an infection (Koskinas et al., 2002; Udina et al., 2012).Unfortunately, many seemingly contradictory results have been found that muddy the relationship between the immune and neurological systems. For

example, some clinical trials treating mental illness with anti-inflammatory agents show promising results, while others show no difference after treatment (Eyre et al., 2015; Kohler et al., 2014). Additionally, some researchers found exposure to chronic stress was associated with an increase of T-regulatory cells which serve to control the immune system and prevent overreaction (H.-R. Kim et al., 2012; Schmidt et al., 2016). But another study found a decrease in lymphocyte T regulatory cells, specifically, after chronic psychosocial stress (Schmidt et al., 2010). Interestingly, most of the mice-model studies that found primarily neutral or immunosuppressive effects of psychosocial were only including males in their experiments (Ajmone-Cat et al., 2019; Langgartner et al., 2019; Sarjan & Yajurvedi, 2018; Schmidt et al., 2016). This may indicate an uninvestigated sex-dependent response, a facet that our study aims to address.

Stress factors investigated in this study

In our study, we used six measures of stress: Alcohol use, bullying victimization, child and maternal mortality, childhood sexual assault, drug use, and poverty. The reasoning for the inclusion of each of these factors will be covered in *Chapter 2: Methodology*. Here, we will provide a relevant summary of the literature related to sex differences, inflammation, and disease interactions with each of our stress factors.

Alcohol and drug use

The use of alcohol and illicit drugs are common throughout the world, but have differing effects based on the sex, wealth, and stress experiences of the person using them. Males have been found to have higher general drug use rates of almost every illicit drug, but even so, the effects of drugs on females can be substantially different (CBHSQ, 2016). The behaviours of females in different stages of drug use also differ from males. Females tend to start using at lower doses, but escalate to addiction quicker, and experience higher risk of relapse to

addiction than males (Becker & Hu, 2008). Some research also suggests that estradiol increases the motivation to take some drugs, like cocaine (Becker & Hu, 2008). Due to heightened responsibility in the home and higher standards of behaviour in public in women, it is possible that increased drug use has higher social consequences on women than men (Becker et al., 2016). This could serve to drug use in females, but potentially also increase the consequences of ingesting those drugs in people who still choose to do so. It is also worthwhile to consider the impact of incapacitation on the safety of females in comparison with males. While both are vulnerable to danger in this state, drunk or high females are much more likely to experience assault than males (Abbey, 2002). The impacts of trauma of this kind can have tremendous impacts on the body, including the inflammatory system, potentially demonstrating one cause of the female sensitivity to drug use.

In general, alcohol use disorders are higher in males, but the rate of increase has been much higher in females recently. Interestingly, females are more sensitive to the effects of alcohol use than males. Investigations as to what is causing this difference in sexes have not been conclusive. In males, chronic alcohol use is associated with decreases in testosterone and estradiol levels (La Vignera et al., 2013), while females experience the opposite (Muti et al., 1998). This split in alcohol's effects on sex hormones may contribute to the differences in the effects of alcohol on disease rates. Although it's unlikely to just be one factor, it is very possible that the social, psychological, and physical stress that people experience from alcohol use is more impactful in the bodies of women, resulting in higher rates of disease. Interestingly, the three diseases with similar effects of alcohol use are the three female-biased illnesses included in the study. This may further indicate the importance of stress factors like alcohol use on the sex differences of inflammatory disorders. Future investigation of alcohol and drug use with other autoimmune diseases and male-biased diseases would be helpful to clarify this relationship.

In regards to the interactions between substance use and inflammation, illicit or recreational drugs that are used vary wildly in their effects on the body, and therefore their effects on the immune system. A ketamine analog was found to upregulate pro-inflammatory cytokines in mice (Wang et al., 2017), and injection drug users have been found to have higher rates of systemic inflammation than non-injection drug users (Piepenbrink et al., 2016). While other drugs like Salvia (*Salvia divinorum)* (Coffeen & Pellicer, 2019), a hallucinogenic drug from Mexico, and marijuana (*Cannabis sativa*) (Alshaarawy et al., 2019) are both associated with slight anti-inflammatory effects. Alcohol consumption also shows a mix of effects on inflammation. A study of HIV patients associated heavy alcohol use with high inflammatory cytokines (So-Armah et al., 2019), and a study exposing patients to the common cold found those that regularly consumed moderate levels of alcohol were less likely to develop disease symptoms from an infection (Cohen et al., 1993). It seems that ethanol activates the innate immune system, leading inflammatory mediators and cytokines in the cerebral cortex, resulting in neuroinflammation (Alfonso-Loeches et al., 2012). There are also important sex differences in the effects of alcohol on inflammation. While chronic alcohol use is associated with neuroinflammation in both sexes, the effect is larger in females than in males (Alfonso-Loeches et al., 2010). This could be an effect of estrogen. A rat-model study found that fetal male microglia and astrocytes exposed to alcohol produced more inflammatory cytokines than females, but when exposed to varying levels of estrogen during development, anti-inflammatory effects were found in males, while pro-inflammatory effects were found in females (Loram et al., 2012). Not all of the effects of alcohol are pro-inflammatory. One study found that acute moderate alcohol use is linked with decreased inflammatory cytokine production when exposed to bacterial stimulation 16 hours after alcohol consumption (Szabo, 1998). This does not necessarily contradict the pro-inflammatory effects of alcohol other studies have found. It is possible that shortly after alcohol consumption, there is an anti-

inflammatory effect, but longer-term use results in pro-inflammatory effects. In addition to the relationship between drug and alcohol use with inflammation, the use of substances can also be linked to psychological and social stresses.

Many people consume substances socially, and others use them in response to stressful life experiences. Marginalized groups, such as African Americans (Mulia et al., 2008), Asian Americans (Chae et al., 2008; Gee et al., 2007; Yoo et al., 2010), Latin-Americans (Mulia et al., 2008)(Mulia et al., 2008), and people in the LGBTQIA+ community (McCabe et al., 2010) who experienced discrimination consumed much more alcohol than people not experiencing discrimination. The rates of alcohol consumption also increased with added discriminatory exposure. Additionally, the National Epidemiologic Survey on Alcohol and Related Conditions showed a clear positive relationship with the number of stressors a person experiences within a year and their alcohol consumption amount (Dawson et al., 2005). It also differs by sex, where each additional stressor predicts an increased frequency of heavy drinking of 24% in males and 13% in females. Notably, this increase is only true for heavy drinking episodes. Moderate drinking frequency actually decreased with increases in stress levels (Dawson et al., 2005). If the higher relationship between alcohol consumption and disease rates in females were only attributable to females drinking more alcohol in response to stress, we would expect to see a stronger association between drinking and stress in females than males. Considering that males actually have higher drinking rates when exposed to greater stress levels, it's likely that there's more to this relationship. We predict that the influence of the immune system, heightened by stress, is a big contributor to the relationship between substance use and disease in females.

The reasons that people stress-drink also differ by sex. Females report drinking to deal with social and health related stressors, while males report drinking more for job-related and legal

stressors (Dawson et al., 2005). People with incomes below the poverty line have exacerbated effects of these job-related stressors, demonstrating an impact between poverty, alcohol, and stress. But it is of note that wealthier countries have generally higher rates of alcohol and drug consumption, muddying the relationship between disease, stress, substance use, and poverty.

Bullying victimization

Experiencing bullying is a hurtful scenario that can take decades to emotionally or mentally heal from. In general, both people who experience bullying victimization and those who perpetrate bullying are more likely to have a history of abuse and family history of mental illness (Ezeokoli-Ashraph et al., 2019). These effects are not equal in males and females. Males tend to be involved in bullying (either as a victim or perpetrator) than females, but female bullying tends to be emotional or relational, while males tend to engage in physical bullying (Yang et al., 2022). Following this trend, females experience more emotional difficulties when bullied than males who experience more behavioural difficulties (S. Kim et al., 2018). Importantly, it seems that females generally experience more mental health consequences of bullying victimization than males (Eyuboglu et al., 2021). In fact, females who experience childhood bullying are more likely to die by suicide as an adult, even when controlling for depressive symptoms, while males' rates of suicide after bullying are dependent on depression. A possible cause of this is differences in inflammation caused by the stress of experiencing bullying (Klomek et al., 2009). As adults, females who have been bullied have higher average levels of C-reactive protein, one measure of inflammation, than females who haven't experienced bullying (Baldwin et al., 2018). Males, on the other hand, don't show this trend.

Child and maternal mortality

Child and maternal mortality (CMM) rates are closely intertwined with experiences of stress. Research shows that increased stress exposure predicts heightened risk for maternal morbidity (Lawrence et al., 2019) and that the death of a mother during childbirth contributes to poor physical and mental health for the partner and children of the deceased (Zhou et al., 2016). Child and maternal mortality rates are also very closely tied to racial and gender-based discrimination. Countries with higher gender equality rates, through measures like education levels, employment and governance opportunities, child marriage rates and more, have lower risks of CMM (Bagade et al., 2022). Racial disparities in maternal mortality are wide, including in high-income countries. In the United States, Black women experience approximately 3x the rate of maternal mortality during childbirth than White women (Hoyert, 2023). The causes of this are multifaceted, but include general higher poverty rates for Black women, racial bias in healthcare practices, and higher exposure to social and environmental risks (Taylor, 2020). Considering that women are the people directly affected by this risk of death, the impact it has is different in both sexes. Men whose partners die through maternal mortality deal with high amounts of psychosocial stress of losing their loved one, and the stress of being a single parent. Of course, this assumes a heterosexual monogamous relationship that does not accurately reflect every single person's situation, but it does represent the majority of relationship dynamics. The remaining children of a mother who dies during childbirth can be male or female and are exposed to the trauma of losing their mother. Traumatic losses such as these early in life can have detrimental long-term effects far into adulthood (Bagade et al., 2022). Finally, the racial and class discrimination that contributes to these higher rates of maternal mortalities affect both males and females, but the sex discrimination only affects women. Clearly the impact of child and maternal mortality is multi-faceted and affects males and females very differently.

Childhood sexual assault

Childhood sexual assault (CSA) is unfortunately common in most countries around the world. Many studies have linked a history of childhood sexual assault with mental and physical health risks in adults (Coid et al., 2001). Experiencing CSA also tends to associate with higher risks of being abused as an adult, too. Adults who were sexually abused as children are twice as likely to experience intimate partner violence and have poorer health during and after pregnancy (Barrios et al., 2015). Adverse childhood experiences of any kind have been found to predict both domestic and peer violence (Zietz et al., 2020). These effects are not equal for males and females. Considering that childhood sexual assault is more commonly experienced in females (Gilbert et al., 2009), it is probable that the global impact of this experience effects females more than males. But even of those individuals that experience childhood sexual assault, females tend to experience more severe mental consequences than males (Sari Gokten & Saday Duman, 2016), although not all studies have found this difference (Mersky et al., 2013). This effect could stem from the impact of childhood sexual assault on inflammation. Childhood sexual assault has been positively associated with inflammatory markers like interleukin-6 and tumor necrosis factor-alpha (Baumeister et al., 2016). CSA has far-reaching effects on the mental and physical well-being of survivors, with a higher prevalence and more severe consequences observed among females, potentially linked to the inflammatory impact of these traumatic experiences.

Poverty and wealth

Current literature finds rates of autoimmune diseases higher in wealthier countries, which would seem counter intuitive given the higher rates of stress faced by people in impoverished countries. One explanation for this is the *hygiene hypothesis*. This hypothesis posits that people exposed to infectious diseases and diverse pathogens (potentially through less robust

hygiene practices) have lower rates of autoimmune diseases and allergies (Rook, 2009). This exposure to diverse pathogens during development desensitizing the immune system, can result in less sensitive immune responses to potentially allergenic compounds (Rook, 2009). Poorer countries generally have higher rates of infectious diseases and less robust hygiene practices, likely due to lower education levels and lower access to resources. The hygiene hypothesis would predict that these locations would see lower rates of autoimmune diseases (e.g., type 1 diabetes, multiple sclerosis) and allergies, which is indeed reflected in the data (Bach, 2002; Rook, 2009). It may seem that a genetic difference in populations could explain this varied rate of disease, but Silman et al. (1993) found through monozygotic twin studies, only around 15-30% of RA is attributable to genetics. In further evidence to the importance of environmental factors in the development of autoimmune diseases, studies following immigrants travelling from lower-autoimmune-incidence places to higher-autoimmune-incidence places find that rates of autoimmune diseases in these migrant populations rapidly approach the rates of disease in the general population in these locations, particularly by generation one (Bodansky et al., 1992).

The hygiene hypothesis has been highly scrutinized, though, as seemingly contradictory studies have found that infections can trigger autoimmune diseases for some people (Vatanen et al., 2016). Overzealous immune reactions to pathogens can kick start people's immune systems into reacting to antigens naturally occurring within the body, causing autoimmune diseases. Some have adjusted this hypothesis to say that it is particularly exposure to harmless or even helpful diverse microbes during development that lead to lowered rates of autoimmune and allergenic reactions instead of exposure to any microbes, including harmful ones (Vatanen et al., 2016).

In conclusion, our study examines several stress factors that may play a role in the development of inflammatory disorders. We have explored the literature and provided an overview of each stress factor, including alcohol and drug use, bullying victimization, child and maternal mortality, childhood sexual assault, and poverty. These stress factors provide a foundation for our study, and their interactions with inflammation and disease will be further investigated in the subsequent chapters.

Chapter 1.4: Evolution of sex-biased diseases and mental disorders

For much of human history, our largest concerns looked nothing like those present today. Daily threats involved escaping predators, fighting disease, and maintaining relationships with our closely knit social circles, often limited to our immediate families. Over time, our physiology evolved to best respond to these environments. The more energy and resources our bodies could dedicate to fighting infection, fending off predators, or healing an injury, the more likely we were to survive and pass on those genes to the next generation. Ultimately, each of these processes were likely activated by stress–either on microscopic levels (by pathogens) or macroscopic levels (by injury)—and resulted in a rush of inflammatory agents that, over time, changed our bodies' energy allocation to best react to the threat at hand (Okin & Medzhitov, 2012).

Although the responses that we experience towards threats can help us survive, they work by dominating the body's resources. While sometimes necessary, this can be detrimental when there are other energy-costly biological functions that we want to perform. Males are especially susceptible to this, as the energy they require for sexual selection is often immense (Darwin, 1871). From an evolutionary perspective, female individuals of a species are likely to invest more energy and resources into oocyte development, gestation, and offspring rearing

than males (Henshaw et al., 2019). The result from this trend is females being pickier with their mating partner and having a relatively consistent rate of reproduction (Kokko & Jennions, 2008). Males, on the other hand, generally pass on their genes if they can access females to mate with. Depending on the species, different traits or characteristics are seen as attractive to females, so males who are most successful with these traits/behaviours succeed in getting to mate. Over many generations, males with the strongest/most extreme traits are selected for in the population (Berglund et al., 1996). Much of the time, the traits/behaviours that are selected for require a lot of energy, time, and/or expose the organism to increased danger (Berglund et al., 1996). These costly traits/behaviours are still worthwhile for males, as living a longer life is useless if a male can't access any females to mate with (Bonduriansky et al., 2008). For this reason, males may have selected for weaker inflammatory responses in order to balance their energy expenditure between survival and reproduction. Although females usually invest more energy into developing and rearing offspring, their relatively steady rate of reproduction and easily accessible mates mean that a longer lifespan is much more beneficial to females than males (Bonduriansky et al., 2008). Therefore, females may have been selected opposite to males to develop a stronger immune system.

This sex-specific reproduction description is simplified and generalized to animals across an evolutionary timescale of hundreds of millions of years. It does not represent the unique familial relationships that individual species or groups of species may form, but instead represents the background of mating principles and practices. It should be noted that males may provide valuable resources for offspring in some species, which would increase selective pressure for longevity in those males. In other animals, though, females are solely responsible for all rearing efforts of offspring. For the purposes of this study, we are mainly considering a generalization of male and female reproduction strategies that compares selective pressures

as a product of large gamete size and child rearing being more commonly female responsibilities.

Over the last few thousand years, rapid advancements in technology have radically transformed our everyday lives. Although our cultures may have evolved quickly, biological evolution is temporally limited (Darwin, 1859). Because of this, our physiology is un-ideal for our present society. We are less likely to experience infection than our ancestors, and better equipped to treat it using modern medicine, so the strong immune system that females developed may overreact to stresses and cause harm. Likewise, we are living much longer lives now, but males' prioritization of early life reproductive fitness may leave them more susceptible to late-life disease. Many diseases that plague humanity today reflect these evolutionary pressures.

Females consistently have a longer average lifespan than males, regardless of location and males tend to experience higher prevalence of most diseases (Austad & Fischer, 2016). But some select diseases are significantly higher in females than in males. These diseases tend to show key similarities surrounding increased levels of inflammation (Austad & Fischer, 2016), and links have been found that relate sex hormones with both inflammation and stress (Cutolo & Straub, 2020; Slavich & Sacher, 2019). It has been largely accepted that stress plays a role in immune responses, but the specific response differences by sex are largely unknown.

Health research on causes of sex-differences has largely focussed on genetics and physiology and a formal sexual selection-based theory giving rise to gender differences in disease prevalence has been described as the *Sexual Selection-Sex Hormone* (SS-SH) theory by Singh et al. (2021). This two-part theory describes male predisposition to many diseases and disorders as an effect of their reproductive-focused evolution. The predominance of late-life

diseases in males likely caused increased rates of antagonistic responses to male-driven mutations by females in order to promote their sex-specific fitness ideal (Singh et al., 2021). These evolutionary antagonistic responses between males and females have likely resulted in many of the sex differences in physiology that we see today.

Chapter 1.5: The grand theory of sex-biased diseases and mental disorders

The concepts discussed thus far have resulted in the development of the Sexual Selection-Sex Hormone- Social Stress (SS-SH-SS) Theory initially proposed by Singh et al. (2021) and expanded by Brown et al. (2022). This theory brings together the reasons why there are sex-biased diseases and underlines how sexual selection has pushed for females to develop stronger immune systems and males to develop weaker immune systems through sexual development, sex hormones, sex-specific genetic and transcriptome differences. Singh et al.'s (2021) SS-SH Theory did not consider how stress plays a role in sex-biased diseases, but we know that, in today's society, stress is such a huge part of our daily lives and also how our bodies function, fight, and develop diseases. Especially when mental disorders are considered, there are no illnesses that are separate from stress because of how intertwined stress and neurological functioning are. Solely using sexual selection and sex hormones to map differences in sex-biased mental disorder prevalence rates, cannot represent the whole story because it misses a critical component - sex-biased experience. The theory was expanded to include these vital components of psychological and social stress to become a combined SS-SH-SS Theory (Brown et al. 2022).

The combined SS-SH-SS theory describes how stress interacts with immune predispositions to create the sex differences in disease prevalence that we see today. Because females are predisposed to a more robust immune response, their exposure to stress has a stronger impact

on inflammation and this causes diseases related to inflammation and autoimmunity to have higher prevalence rates. At the same time, this same process causes infections and cancers to have lower prevalence rates in females. Males are less predisposed to inflammatory diseases, like many mental illnesses and autoimmune disorders, but are subsequently more predisposed to cancers and infections. The psychosocial stress component of this theory covers a three-part mechanism of how stress may impact the established theory, where 1) females may be biologically predisposed to be physically sensitive to stress. If exposed to the same type and level of stress, females will exhibit a higher immune response and more disease from that. 2) Sexes are exposed to the same environmental level of stress but females perceive it to be more extreme, so bodily systems react to it as if it is environmentally higher levels of stress. 3) Females are exposed to overall more stressors that impacts their immune responses in a more robust manner. These three mechanisms are not separate, but all three play a role together to impact the sex prevalence of different diseases.

Chapter 1.6: Objectives

In this study, we seek to investigate how variation in stress level correlates with female-biased diseases in global populations to determine if the female susceptibility to these diseases may be caused in part by exposure to stress and/or trauma. The SS-SH-SS theory predicts that females have developed a stronger immune system through antagonistic evolution to protect themselves from the male drive for reproduction but have higher susceptibility originating from sexual hormones and social stress. With the higher rate of chronic social stress in current society, women are particularly vulnerable to an array of inflammatory and autoimmune diseases. We are looking to explore 5 diseases' prevalence rates in 198 countries in both males and females and compare these to stress factors. These

include 3 female-biased illnesses: rheumatoid arthritis, MDD, anxiety disorders, 1 sex-equal prevalence illness: bipolar disorder, and 1 male-biased mental illness: schizophrenia.

Chapter 2: Methodology

In our study, we aim to investigate the relationships between sex-biased inflammatory diseases with psychosocial exposure to stress. In doing so, we collected 26 years of prevalence rates of diseases and exposures to stress in hundreds of countries. Using these data, we conducted a series of generalized linear mixed models (GLMMs) to evaluate how the influence of stress differs between sexes. Next, we conducted a principal component analysis (PCA) to explore the relationships between stress factors. Finally, we created a series of new GLMMs where the predictor variables are the principal components from the earlier analysis. In doing each model, we aim to investigate the sex differences in diseases influenced by stress exposure.

Chapter 2.1: Data collection

Disease data

Data for this study was acquired from The Global Burden of Disease Study (Vos et al., 2020; GBD) and the World Bank. Using the Global Health Data Exchange (GHDx) results tool (Institute for Health Metrics and Evaluation (IHME), 2021), age-standardized MDD, combined anxiety disorders, bipolar disorder, schizophrenia, and rheumatoid arthritis prevalence rates per 100,000 people in males and females were collected from 204 countries for each year from 1990-2019. The GBD study used government censes, telephone surveys, mailed surveys, individual meetings, and hospital data with DSM- and WHO-validated metrics of diagnosis to calculate the prevalence of illness in each country. They then compiled this data from all the sources and used sex ratio analyses, age-sex splitting, and bias correction analyses, where applicable, to determine the prevalence rates for each country, sex, and year. Although mental illnesses are of particular focus for us, they are extraordinarily

complex in the two-way interactions between disease prevalence and stress factors. We are intending to study the indirect effects of stress on disease through inflammation, but there is existing literature that highlights a direct cause of mental illness from stress factors. For example, people who experience some mental illnesses are more likely to self-medicate with drugs and alcohol than the general population (Swendsen et al., 2010). For these reasons, we decided to initially investigate rheumatoid arthritis, our inflammatory non-mental illness, as a baseline. For the purposes of our model, we are assuming that there are fewer two-way interactions between our stress factors directly leading to rheumatoid arthritis, and rheumatoid arthritis directly causing an increase in stress factors than most mental illnesses.

Stress factor data

To determine the stress factors to use in this project, we searched current literature to find validated assessments of stress and trauma. We evaluated the questions of each assessment to determine exposures that were considered stressful or traumatic and compared between all the assessments. If particular exposures were listed in multiple assessments, they were considered primary contenders of stressful events in our study. The assessments used were the Traumatic Life Events Checklist, Stressful Life Events Screening Questionnaire, Happiness Report, Stress Module of Patient Health Questionnaire (Beutel et al., 2018), Bernstein Childhood Trauma Questionnaire (Bernstein et al., 2003), and Perceived Stress Scale (Schneider et al., 2020). We also included large sample-size studies assessing links between psychosocial stress factors and diseases to further determine common experiences of stress (Johansson et al., 2013; Öhlin et al., 2004; Rosengren et al., 2004; Von Korff et al., 2009). From this, we determined common themes of stressful events and, when necessary, translated them to more generalizable experiences of stress (e.g., widowhood becomes death of spouse). We then searched publicly available data from the GBD database to find similar

or exact matches of global records of each stress factor. The final list of available stress factors for use in our study included childhood exposure to stress (childhood sexual abuse, bullying victimization), social stress affecting an adult's self, friends and/or family (child and maternal mortality, loved-one with addiction to drugs or alcohol), and societal injustices and access to resources (country wealth). These stress factors are either measured in summary exposure value (SEV) or in prevalence rate per 100,000 people. SEV is a metric developed by the GBD study and it represents the relative risk of experiencing a certain stressor and the risk of harm that experience may cause. It is given as a percentage, where 0% is no chance of exposure and/or no negative consequence of the experience.

Data from the World Bank covers income through GDP per capita. The data from The World Bank was collected primarily by income surveys conducted by individual governments supplemented by trade, industrial, and agricultural censes. Income from the World Bank is measured in Gross Domestic Product (GDP) Purchasing Power Parity (PPP) per capita (in 2011 international $) from the years 1990 – 2015 in 201 countries. GDP per capita is calculated by dividing the GDP PPP of each country by the population mid-year.

Given that World Bank data is only available between 1990-2015, mental illness prevalence data from years 2016-2019 will not be included. Additionally, the statuses of various countries are not consistent between data sources, so countries that are included in one databank and not the other were also removed. These countries are Niue, North Mariana Islands, Guam, American Samoa, South Sudan, Tokelau, and Taiwan. Many of the countries included in the dataset are labelled with different official country titles, so those will be modified to be consistent between both datasets.

Data cleaning

Each disease and stress factor were mean-centered and scaled by standard deviation in order to allow for fair comparisons using metrics of different units (e.g., stress factors in prevalence rate per 100,000 people vs. summary exposure value). Additionally, a logarithm base-10 function was applied to transform GDP per capita. When dealing with wealth, the larger the values, the less difference each dollar makes. For example, a change of $1000 in a country with an average GDP per capita of $5000 represents a 20% change, whereas the same monetary change to a country with a GDP per capita of $50,000 only represents a 2% change. By log-transforming the values, we lessened the change in value of a single dollar.

Chapter 2.2: Data analysis

Hypothesis

The aim of this study was to examine the relationship between stress factors and diseases, focusing on the potential differences between males and females. Specifically, we sought to determine whether varying levels of stress contribute differently to the prevalence of diseases in males **vs.** females. Considering the known associations between mental illnesses, inflammation, and heightened immune responses in females, our hypothesis posited that increased stress would have a greater impact on disease prevalence in females compared to males.

Descriptive statistics

Before creating our disease models, we first investigated the data to determine their structure and patterns. This is necessary as the assumptions used in many statistical models require specific criteria to be met with the data. If these assumptions do not hold, we must transform

the data or the model to remedy these discrepancies and keep the models as accurate and appropriate as possible.

Outliers

Each disease showed country outliers in both males and females. For the purposes of this study, outliers were defined as datapoints that fall outside of the interquartile range, described in Equation 1. For MDD, six female and eight male outlier locations were identified. Anxiety disorder outliers were more numerous, with 13 female outlier locations and 16 male outlier locations. Interestingly, there was only one outlier for both males and females with bipolar disorder, and that was New Zealand. Schizophrenia had 4 outlier locations in females and 7 in males. Finally, there were 4 locations in females and 12 in males with rheumatoid arthritis. A break down of each outlier for each disease can be found in Table A. 1.

$$Outliers = \ q_{0.25} - 1.5 \cdot IQR;\ q_{0.75} + 1.5 \ \cdot IQR \quad (1)$$

Equation 1: Calculating outliers, where q0.25 refers to the maximum value of the first quartile, q0.75 refers to the minimum value of the last quartile, and IQR, which refers to the interquartile range, calculated by subtracting q0.25 from q0.75.

Difference in disease variances between sexes

To reduce the violations of the expectations that come with a linear model, an awareness of the difference in variable variances in important. To do this, we conducted a series of Cleveland dot plots (Cleveland & McGill, 1984) and density plots (Brandon, 1996) to visualize the difference in spread for each disease (Figure 1). To quantify this assessment, Levene's tests for homogeneity of variance were used (Levene, 1960). Each disease showed significant heterogeneity with a p-value < 2.2e-16 (Table 1). Visually, the plots showed a considerable difference in spread between females and males for most diseases except for

bipolar disorder and schizophrenia which showed a spread that was approximately equal. That being said, both males and females showed unusual patterns in the data for these same two diseases, even though they matched each other. There seemed to be 3 separate peaks in density in the bipolar data, and 2 peaks in the schizophrenia data. This could violate the expectation that the data forms a simple normal distribution. To address some of the concerns regarding variance discrepancies between sexes, we decided to include sex as a dispersion parameter in our modelling for our diseases.

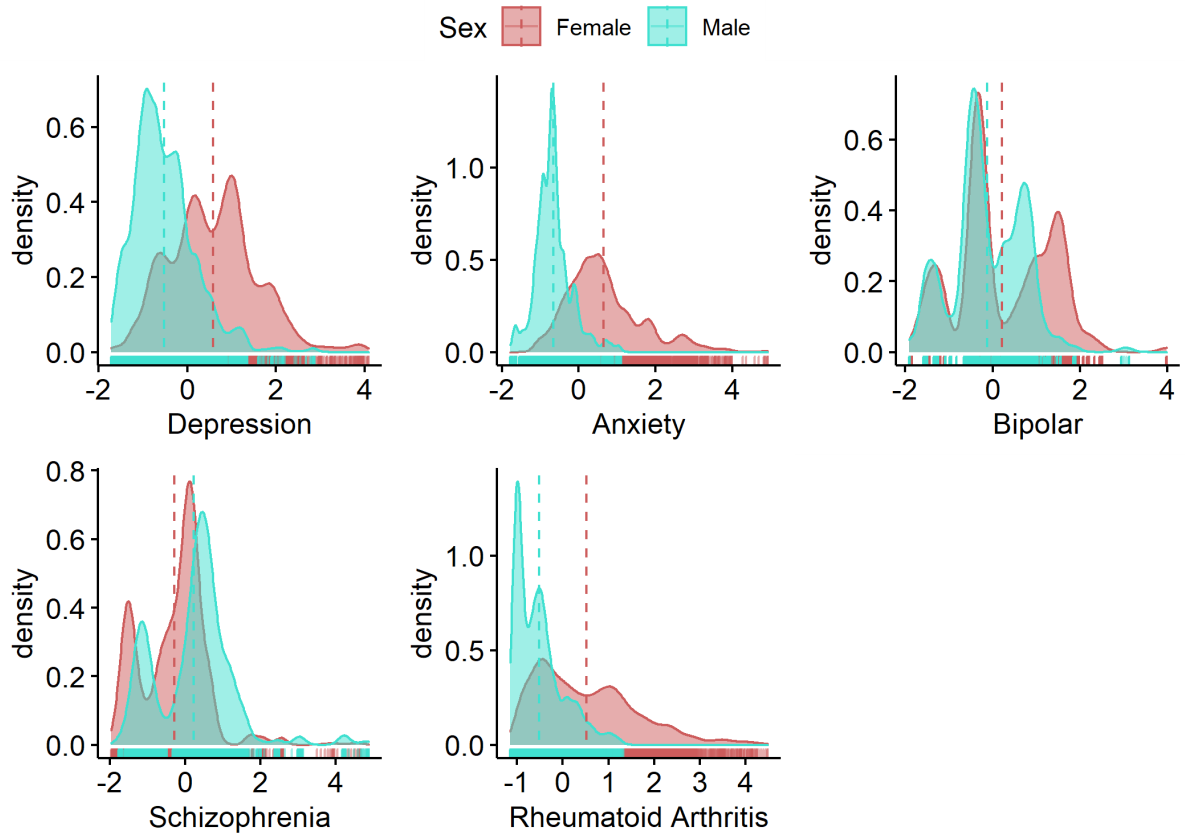

Figure 1: The distribution of scaled mean-centered data for each disease in males and females.

Table 1. Results of Levene's test for homogeneity of variance comparing differences in the variation of data in males and females.

Disease	F value	p-value
Depression	625.02	< 2.2e-16
Anxiety	1721.4	< 2.2e-16

Bipolar	816.26	< 2.2e-16
Schizophrenia	36.172	< 2.2e-16
Rheumatoid Arthritis	2524.4	< 2.2e-16

Substantial heteroskedasticity was observed for each disease between sexes. To account for this, we added sex as a dispersion parameter for our models. This accounts for differences in the spread of data for both sexes in the creation of the model.

Predictor correlation

One expected complication that we encountered was multicollinearity between predictors. We expected to find a relationship between countries with higher childhood sexual abuse and higher uses of alcohol and drugs, for example. Many of these predictors do not exist in a vacuum, and people who experience stressful situations may be more predisposed to face more stressful experiences in the future. To assess this, we evaluated the correlation pairs for each predictor variable with one another (Table 2). None of the correlations were higher than 70%. We determined that correlations of this level were not a large concern for our dataset and that we could move on with our model selection.

Table 2: Correlation matrix between predictor variables. 1.00 indicates perfect correlation and 0 indicates no correlation.

	Alcohol Use (AU)	Bullying Victimization (BV)	Child and Maternal Mortality (CMM)	Childhood Sexual Abuse (CSA)	Drug Use (DU)	Log of GDP per capita (LogGDP)
AU	1.00	0.22	-0.61	-0.11	0.56	0.44
BV	0.22	1.00	-0.30	-0.02	0.19	0.11
CMM	-0.61	-0.30	1.00	0.16	-0.37	-0.34

CSA	-0.11	-0.02	0.16	1.00	-0.16	-0.27
DU	0.56	0.19	-0.37	-0.16	1.00	0.45
LogGDP	0.44	0.11	-0.34	-0.27	0.45	1.00

Error correlation structure

We are using multiple years' data in our analysis, so we expected to see a relationship between successive years, where a value is more likely to be similar to another value from the next or previous year, than one with 15 years in between. To try and combat any bias from this structure, we chose to add Year as a fixed effect term in our model and to include a term of (1 | Year) as a random effect to allow for small random fluctuations in the levels of disease for each year.

Generalized linear mixed models

The generalized linear mixed models (GLMMs) are used to determine linear relationships between predictor variables (in our case, stress factors and sex), and response variables (diseases) in complex scenarios. Mixed models allow for fixed and random effects, which are necessary when each data point is not entirely independent from one another.

The final component of the data analysis was the model selection and completion using R version 4.1.2 (R Core Team, 2021) using the package 'glmmTMB' (M. E. Brooks et al., 2017). The first model that we created was rheumatoid arthritis, the female-biased disease that we used as a 'control' because we assume this disease is influenced less by two-way interactions between our included stress factors and our mental illnesses. After RA, the mental illnesses were modeled.

Rheumatoid arthritis model

Within this section, we will explain the process of determining our first model, the comparison of slight variations of this original model, and the selection of the best-fitting model that we created.

The fixed effects of the model are an interaction between sex with each of the stress factors, and year. The primary purpose of the model was to determine the effects of stress as a whole on disease, not necessarily the effects of each stress factor individually, nor the effect of just sex on each disease (Equation 2). Year was included in the main effects of the model because disease prevalence changed slightly over time. Likely due to technological advancements, international aid to less-wealthy countries, and cultural shifts, disease rates slowly decreased over time, and this was accounted for by including year as a main effect in the model. The random effects included (1 + Sex + -Log of GDP | Location), which serves to allow for slight random variations in disease prevalence rates by location for each sex and the wealth of each country Additionally, having the "1" term before the pipe allows some random variation in the initial rates of disease for different countries. We also added (1 | Year) which accounts for small fluctuating changes in disease variation over time and (1 | Region) which serves to allow for some interactions between countries that share a general region and considers that these may experience higher rates of similarity due to shared culture, environment, resources, etc. This initial model is represented in Equation 2.

Equation 2. Generalized linear model predicting disease from the interactions of sex and stress factors. In the term Zb_j, Z refers to a known design matrix and b_j refers to an unknown vector of random effects parameters. ϵ_{ij} refers to the variance equation. The subscript 'i' indicates the value for each location and the subscript 'j' indicates the value for each sex. AU stands for alcohol use, BV stands for bullying victimization, CMM stands for child and maternal mortality, CSA stands for childhood sexual abuse, DU stands for drug use, and NegLogGDP refers to the log10 of GDP per capita for each country multiplied by -1.

$$Disease_{ij} = \beta_0 + \beta_1\, sex_{ij} + \beta_2 AU_{ij} + \beta_3 BV_{ij} + \beta_4 CMM_{ij} + \beta_5 CSA_{ij} + \beta_6 DU_{ij}$$
$$+ \beta_7 NegLogGDP_i + \beta_8 sex_{ij} AU_{ij} + \beta_9 sex_{ij} BV_{ij} + \beta_{10} sex_{ij} CMM_{ij}$$
$$+ \beta_{11} sex_{ij} CSA_{ij} + \beta_{12} sex_{ij} DU_{ij} + \beta_8 sex_{ij} NegLogGDP_i + Zb_j + \epsilon_{ij}$$

After creating the primary model, we created 3 models with slight variations on this, to compare and contrast. Model 1 was considered to be the base model, which was explained above. Model 2 was similar to model 1, but the random effect term (1 + Sex + NegLogGDP | Location) had "diag" added to it. This creates a covariance structure where only the diagonal of the matrix of this term is considered, attempting to reduce any issues with covariance within this term. Next, model 3 was similar to model 1 but a new term using autoregression correlation structure of AR1(Years + 0 | Years1) was included. Any particular data for a year is more likely to be similar to the year just before or after it than the value from a year 15 years away. For that reason, there is non-independence between subsequent years' data. Adding an autoregression covariance term aims to address this. It creates a matrix of linearly decreasing correlation values for every subsequent time point before and after any other time point (time here being years). Years1 is a vector of just the number "1" for every single row in the dataset. The purpose of this vector is to allow for a global relationship between the values of each disease prevalence rate and the autoregression1. This creates a covariance matrix where the parameter of this term is increased by a power of 1 each step away from the diagonal of the matrix. Finally, model 4 was almost identical to model 3, but instead of using (Years + 0 | Years1), the covariance term was (Years + 0 | Region).

Upon running each model, we found model 3 (base model with an added ar1 covariance random effect term with (Years + 0 | Years1) did not converge and was ultimately determined to not be a viable model to continue forward with. Using the remaining 3 models, we calculated the small-sample corrected Akaike information criterion (AICc) (Akaike, 1973;

Hurvich & Tsai, 1989), difference in AICc between the model with the lowest AICc and each of the others (Delta_AICc), the weight of the AICc (AICcWt) and loglikelihood density of each model (Table 3). AIC is a calculation of the log maximum likelihood estimate of the model (a measure of the goodness of fit of the data) subtracted by the number of covariance parameters (Equation 3.1). Subtracting by the number of parameters attempts to account for overfitted models by penalizing models with excessive terms. AICc uses the value of AIC but adjusts for a smaller sample size as one of the assumptions of AIC is an infinite sample size (Equation 3.2). Delta AICc represents the difference between the model with the lowest AICc and each other model. AICc weight is the amount of predictive power that each model contains compared to the predictive power of all of the models combined (AICcWt). The loglikelihood density is log transformation of an estimate of the probability each observed datapoint falls within the predicted model in a limit as dx goes to zero.

Table 3. Assessment of model fit using AICc, Delta AICc, Weights of AICc, and log likelihood density. Weights describes the amount of variation of the data that each model accounts for compared to one another.

Model name	k	AICc	Delta_AICc	AICcWt	LogLikelihood density
Model 1: base	26	-27464.0	2034.5	0	13758.1
Model 2: base + added "diag" to the (1 + sex + negLogGDP | location) random effect	23	-27176.9	2321.6	0	13611.5
Model 4: base + added (ar1 (Years + 0 | Region))	28	-29498.5	0	1	14777.3

Equation 3. Equations of Akaike information criterion (AIC), and small-sample corrected Akaike information criterion (AICc),

$$AIC = -2\,LL + 2k \tag{3.1}$$

$$AICc = -2\,LL + 2k + \frac{2k(k+1)}{n-k-1} \tag{3.2}$$

Model 4 had the lowest AICc, lowest Delta AICc, an AICc weight of 1, and highest loglikelihood density, so it was selected as the best model going forward.

Next, we performed a series of chi-square tests to assess the effect of each interaction term on the model to see if it was worth keeping. Bullying victimization was shown to potentially be unnecessary so model 5 was created to compare model 4 with and without this variable. Ultimately, including bullying victimization in the model ended up resulting in a slightly lower AIC so once again, model 4 was determined to be the most successful model.

To assess the model quality and determine if further adjustments should be made, we conducted a series of tests using the DHARMa package (Hartig & Lohse, 2022). This package contains diagnostic functions to assess how well our model output fits the assumptions used it its creation. First, we determined that the number and range of model outliers fell within the predicted range for our data. Then, we tested the uniformity of the model and found that the centre of the model and the highest values of the model significantly deviated from the theoretical expectations of normal distribution. Although this may be a problem for some models, because of the large sample size of this dataset, we did not determine this dispersion to be an immediate cause for concern. Next, we investigated the model dispersion and found the frequency of the simulated residuals formed a normal curve, and the fitted model did deviate from the theoretical dispersion. The distribution family of our model was gaussian and in this structure, the variance is not a factor of the mean, unlike other distribution families, like poisson, for example. Due to this reason, we determined that

the extent of dispersion discrepancy between our model simulated residuals and the theoretical estimates were acceptable.

Mental illness models

After creating the ideal model for our main disease of study, rheumatoid arthritis, the models for the other diseases were also created using the final RA model as a basis. For schizophrenia and bipolar disorder, the models with an autoregression 1 covariance structure with "region" resulted in non-convergence, so we instead used "1" and the models converged with a low AICc and high loglikelihood. Both the MDD and anxiety models converged without issue with the exact same structure as the RA model.

Once determining that all the models successfully converged, we used the DHARMa package again to conduct a series of diagnostic tests to find any glaring problems with our models. The diagnostic evaluations of the models looked very similar to the RA model. The output of the diagnostics can be found in Appendix 1 – Figures 1 – 4. Although some of the diagnostic evaluations showed signs of overdispersion, the model is set up with a gaussian distribution which does not have overdispersion as a possibility.

Principal component analysis

Next, we conducted a PCA to investigate any further relationship between predictors and/or between diseases. To do this, values of alcohol use, bullying victimization, child and maternal mortality, childhood sexual abuse, drug use, and GDP per capita were used as variables in a PCA. From these, 6 principal components were created that represented the variation between these variables. We found that the first 5 principal components contained over 90% of the variation, so we decided to drop principal component 6.

With these components, we conducted a generalized linear mixed model predicting rheumatoid arthritis though the 5 principal components and year interacting with sex. We used 1|Year and 1|Region as random variables and including sex as a dispersion variable. We assessed the model by creating simulated residuals to test uniformity, outliers, dispersion, quantiles, and temporal autocorrelation. The uniformity of the model was no different from the expected normal distribution in the middle area of the values, but significantly deviated from the expected pattern at both ends. Although this does bring up a level of concern, the amount of data that we have protects against a lot of the negative effects of conducting models with a non-normal distribution. Our outliers and dispersion tests showed no signs of concern. The quantile assessments of this model were very different from the expected values, very similar to the test that we conducted without creating the PCA. Finally, the temporal autocorrelation showed no significant deviation from the expectation. We also conducted the same generalized linear mixed models with the four mental illnesses in order to compare these results.

Chapter 3: Results

Chapter 3.1: Generalized linear mixed model results

In this chapter, we will demonstrate the interesting connections between diseases and stress factors, and their interactions with sex. We will begin by describing the RA model, as it acts as our makeshift 'control', then compare these results to each of the four mental illness models. Then, we will describe the PCA results and explain how the principal components impacted each disease.

Rheumatoid arthritis (RA)

The RA model showed distinct relationships between stress factors in males and females. The coefficients of the model were almost all significant but many of the effects were very small. All the parameter coefficients are listed in Table 4 and visualized in Figure 2 - Figure 4.

Table 4. Generalized linear mixed model output for predicting rheumatoid arthritis prevalence rates. AU stands for alcohol use, BV stands for bullying victimization, CMM stands for child and maternal mortality, CSA stands for childhood sexual abuse, DU stands for drug use, and -LogGDP represents the log of GDP per capita multiplied by -1. Within the p-value column, significant values (where a = 0.05) have '' listed next to the values.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	0.549	0.115	4.759	1.94 e-06 *
Sex (male)	- 1.209	0.058	- 20.721	< 2 e-16 *
AU	0.074	0.016	4.676	2.92 e-06 *
BV	0.003	0.007	0.417	0.677
CMM	- 0.055	0.010	- 5.290	1.22 e-07 *
CSA	- 0.010	0.016	- 0.593	0.553
DU	0.084	0.007	12.586	< 2 e-16 *

Year	0.010	0.001	19.337	< 2 e-16 *
-LogGDP	- 0.105	0.020	- 5.365	8.14 e-08 *
Sex:AU	- 0.071	0.016	- 4.538	5.69 e-06 *
Sex: BV	0.019	0.007	2.620	0.009 *
Sex:CMM	- 0.088	0.020	- 4.470	7.82 e-06 *
Sex:CSA	0.058	0.021	2.796	0.005 *
Sex:DU	- 0.082	0.007	- 12.302	< 2 e-16 *
Sex:Year	- 0.005	0.000	- 20.917	< 2 e-16 *
Sex:-LogGDP	0.066	0.009	7.176	7.18 e-13 *

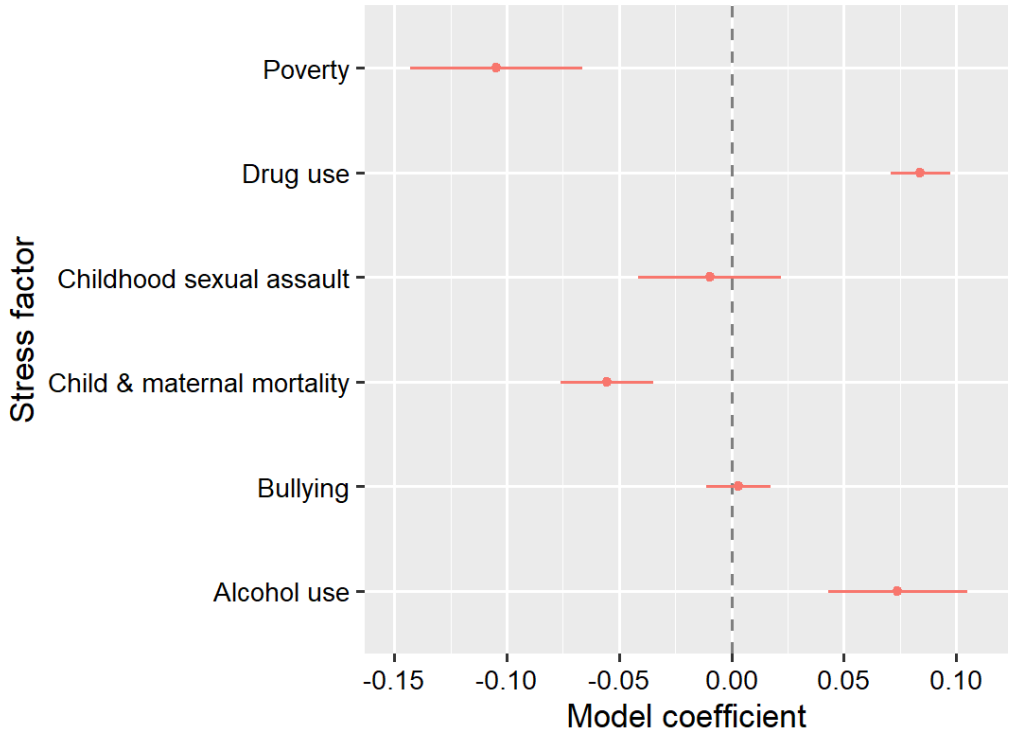

Figure 2. Effects of stress factors on rheumatoid arthritis prevalence rates independent of sex.

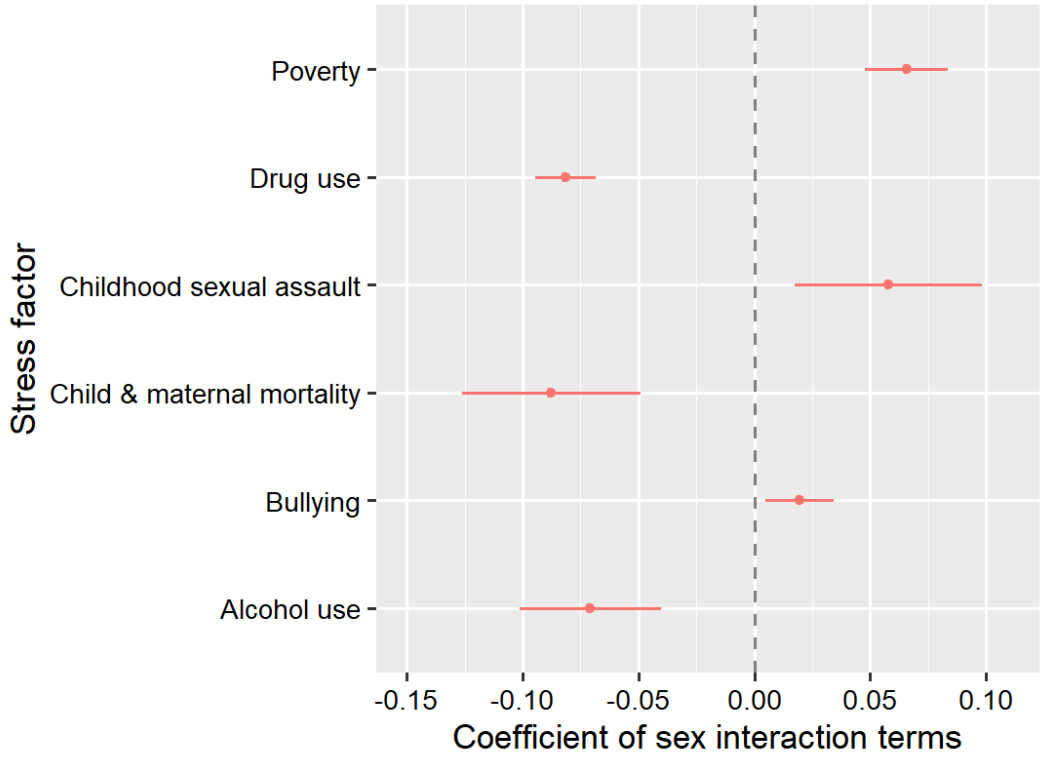

Figure 3. Sex differences in the effects of stress factors on rheumatoid arthritis prevalence rates. These values represent the difference between the female coefficients and the male coefficients.

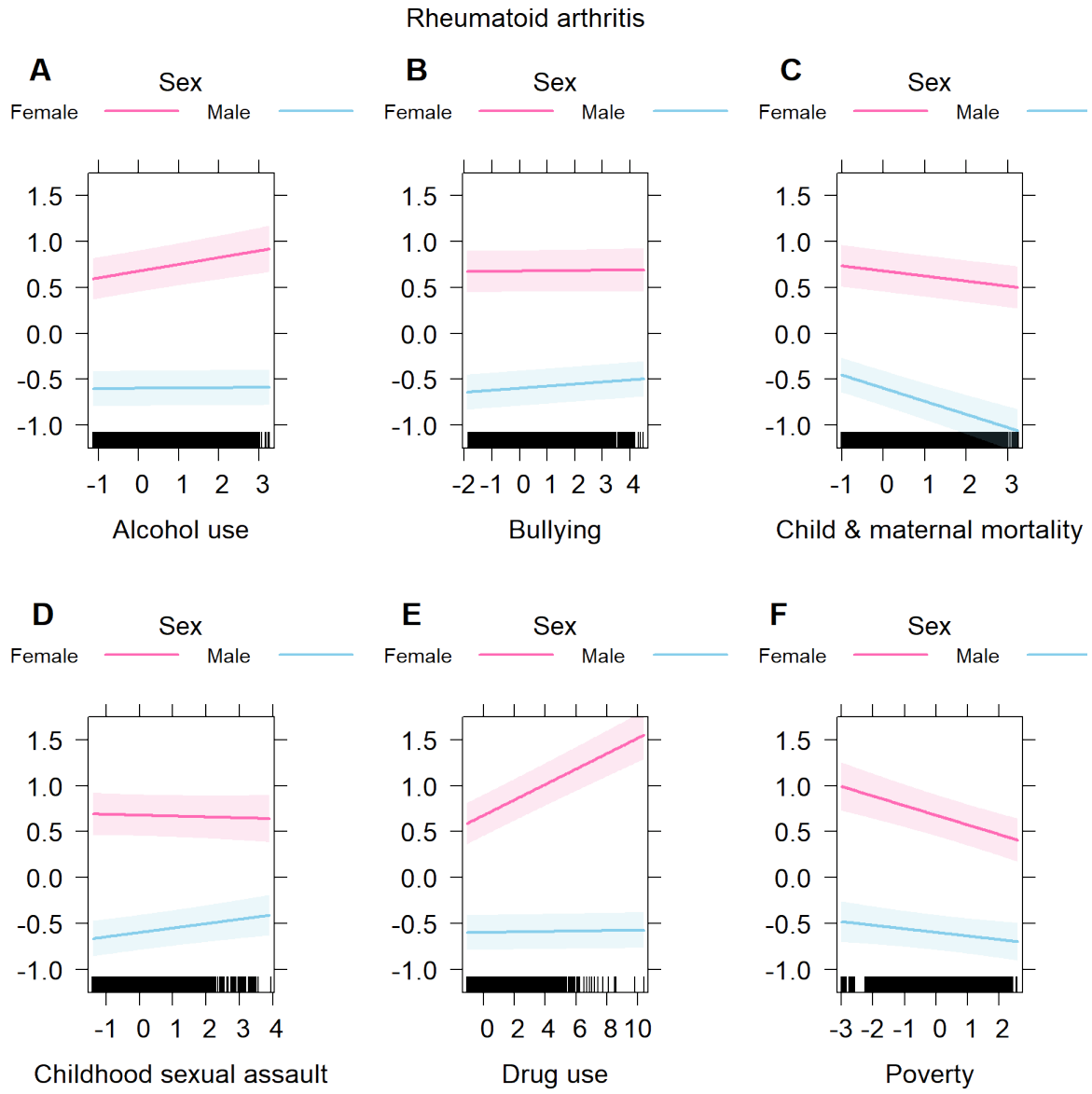

Figure 4. The sex-specific effects of stress factors on rheumatoid arthritis. The stress factors are alcohol use (A), bullying victimization (B), child and maternal mortality (C), childhood sexual assault (D), drug use (E), and the natural logarithm of GDP per capita multiplied by -1 (F).

Aside from the differences in sexes, GDP per capita was one of the strongest influences on disease rate. Paradoxically, in our model, an increase in wealth was associated with higher rates of disease. Both drug use and alcohol use were positively associated with increased disease rates as well.

Mental illnesses

Major depressive disorder

Apart from child and maternal mortality, increased rates of stress were associated with increased levels of depression for every stress factor in females (Figure A. 1). Males showed slight increases in depression with increases in alcohol use, bullying, childhood sexual assault, a strong increase in depression with child and maternal mortality, and slight decreases in depression with drug use and poverty.

Anxiety disorders

The effects of male anxiety rates change remarkably little with increases in stress compared to females. They experience slight increases in anxiety with higher alcohol use, bullying, child and maternal mortality, and childhood sexual assault, while slight inverse relationship between anxiety disorders with drug use and poverty rates (Figure A. 2).

Bipolar disorder

The effects of each stress factor on bipolar disorder are relatively minor and contain a lot of uncertainty. There is almost no effect of each stress factor in females while males experience a little bit more association, including an inverse relationship between each of alcohol use, bullying, childhood sexual assault, drug use, and poverty with bipolar disorder, while a positive relationship with bipolar and child and maternal mortality rates (Figure A. 3).

Schizophrenia

Males show higher overall rates of schizophrenia but the interactions with sex and each stress factor with schizophrenia differ. Both males and females have a similar rate of increased schizophrenia with increases of alcohol use, bullying and childhood sexual assault. With

child and maternal mortality, male rates of schizophrenia drastically decline with increased stress, and female rates decline a very small amount (Figure A. 4). Drug use also shows an interesting relationship. Males experience a large decline in rate of disease with higher drug use, but females show the opposite, where higher drug use is strongly associated with increased schizophrenia. Finally, the effects of poverty on schizophrenia rates are the most extreme out of all the stress factors. Both males and females show a very strong negative relationship between poverty and schizophrenia, but females decline slightly less than males do.

Chapter 3.2: Principal component analysis results

Before describing the results from each model, we will first consider the relationships between our stress factors that are outlined by our PCA as seen in Figure 5. Principal component 1 (PC1) represented 42% of the variation in rates of RA after previous combinations of the principal components (Figure 6), with positive higher weighting of alcohol and drug use, and negatively by child and maternal mortality and poverty. We interpret this as representations of wealthier countries with higher rates of substance use. The second principal component (PC2) is primarily represented by just two factors: childhood sexual assault and bullying victimization. These are both strongly negatively associated with PC2, so we are interpreting this component as countries with positive childhood experiences. Principal component 3 (PC3), like PC2, is primarily influenced by childhood sexual assault and bullying victimization, but this time it's positively influenced by CSA and negatively influenced by bullying. We consider PC3 to represent countries with high adult-caused childhood adverse experiences, but low peer-to-peer childhood adverse experiences. Principal component 4 (PC4) is very interesting because it represents countries with lower rates of poverty, but higher rates of child and maternal mortality. Of all countries, the USA has the

highest level of PC4 in the world. Other countries that have high rates of PC4 include South Africa, Botswana, Greenland, and Gabon. These countries tend to have high rates of healthcare inequality. In the USA and South Africa, these disparities likely stem from economic status and racial differences in healthcare access. Unlike the US, in South Africa, about a third of the maternal and infant deaths are attributable to pre-existing, treatable conditions that do not receive care before a birth takes place (Mabaso et al., 2014). Other areas, like Greenland, have high disparities between access to healthcare in rural/remote vs. urban settings (Houd et al., 2022). Because of these factors, we are considering PC4 to be a measure of healthcare inequality. Finally, principal component 5 (PC5) is strongly represented by countries with low poverty and low drug use. Usually, high-income countries have higher rates of drug use, but this component represents countries that defy that trend. We consider PC5 a measure of high-income, low-drug-use countries. Our interpretations of each principal component are listed in Table 5.

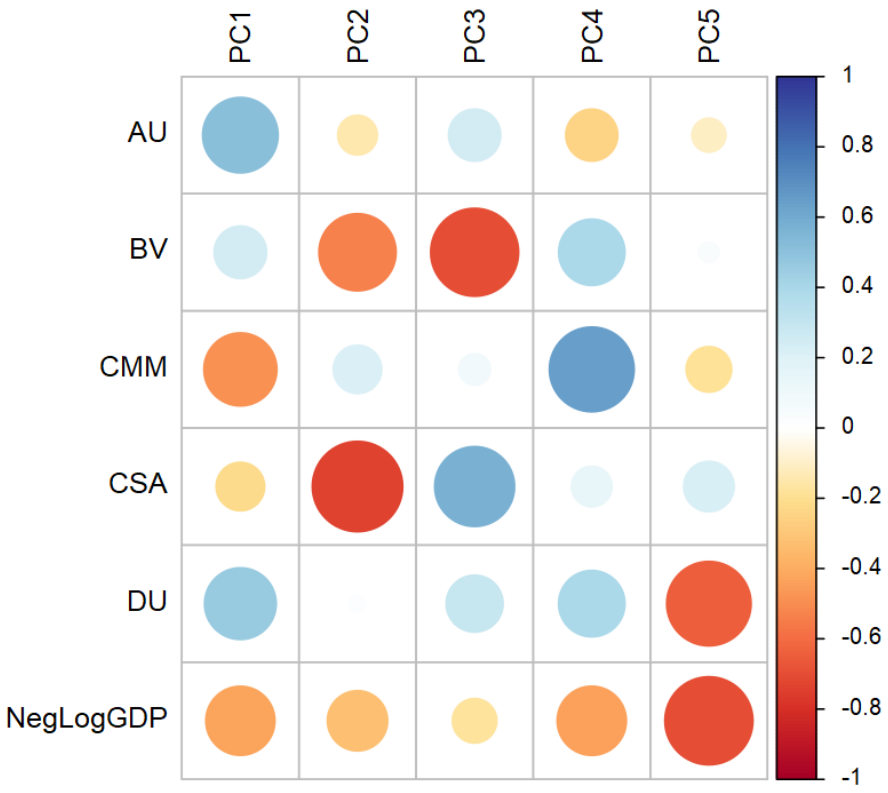

Figure 5. Correlation plot comparing the effects of each stress factor on each principal component. Strong positive correlations are represented by large blue circles, no correlation is represented by small white circles, and strong negative correlations are represented by large red circles.

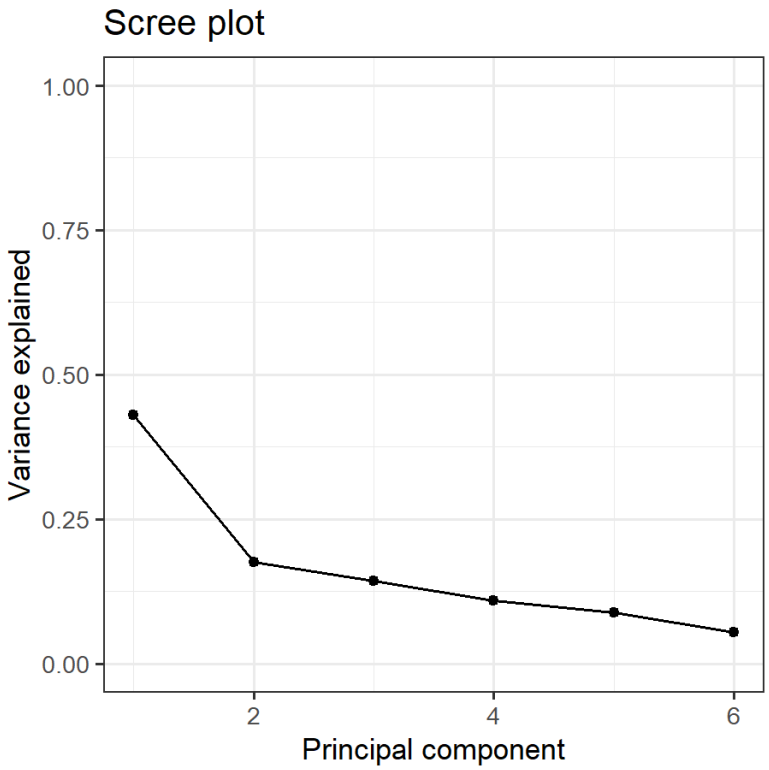

Figure 6. Data variance explained by each principal component in PCA.

Table 5. Attribution of principal components based on the stress factors that influence them the most.

Principal component	Our classification	Strongest stress factors
PC1	High income, high drug use	Alcohol use, drug use, -child and maternal mortality, -poverty
PC2	Low adverse childhood experiences	-Bullying victimization, -childhood sexual abuse
PC3	Adult-based adverse childhood experiences	Childhood sexual abuse, -bullying victimization
PC4	Healthcare inequality	Child and maternal mortality, -poverty
PC5	High income, low drug use	-Drug use, -poverty

PC1 showed a very interesting trend in the model with rheumatoid arthritis, our 'control' model. This component accounts for 43% of the variation of all our predictors and

demonstrated a very strong relationship with RA (Figure 7.A). As the value of PC1 (high income, high drug use) increased, the prevalence of arthritis also increased, but only in females. In males, the prevalence of disease did not increase or decrease with a change in stress. PC2 (low adverse childhood experiences) shows a very different trend. Both males and females showed very clear declines in slope with rheumatoid arthritis with both sexes slopes being approximately equal (Figure 7.B). PC3 (adult-caused adverse childhood experiences) showed equal slopes in both sexes that rise with increasing rheumatoid arthritis values (Figure 7.C). PC4 (healthcare inequality) is the only component (other than PC1) to show a stark difference in sexes. Females show a very strong decline in PC4 with an increase in disease but a small increase in disease with higher PC4 values in males (Figure 7.D). Finally, PC5 (high-income, low drug use) showed a slight positive relationship that looks approximately even between sexes (Figure 7.E).

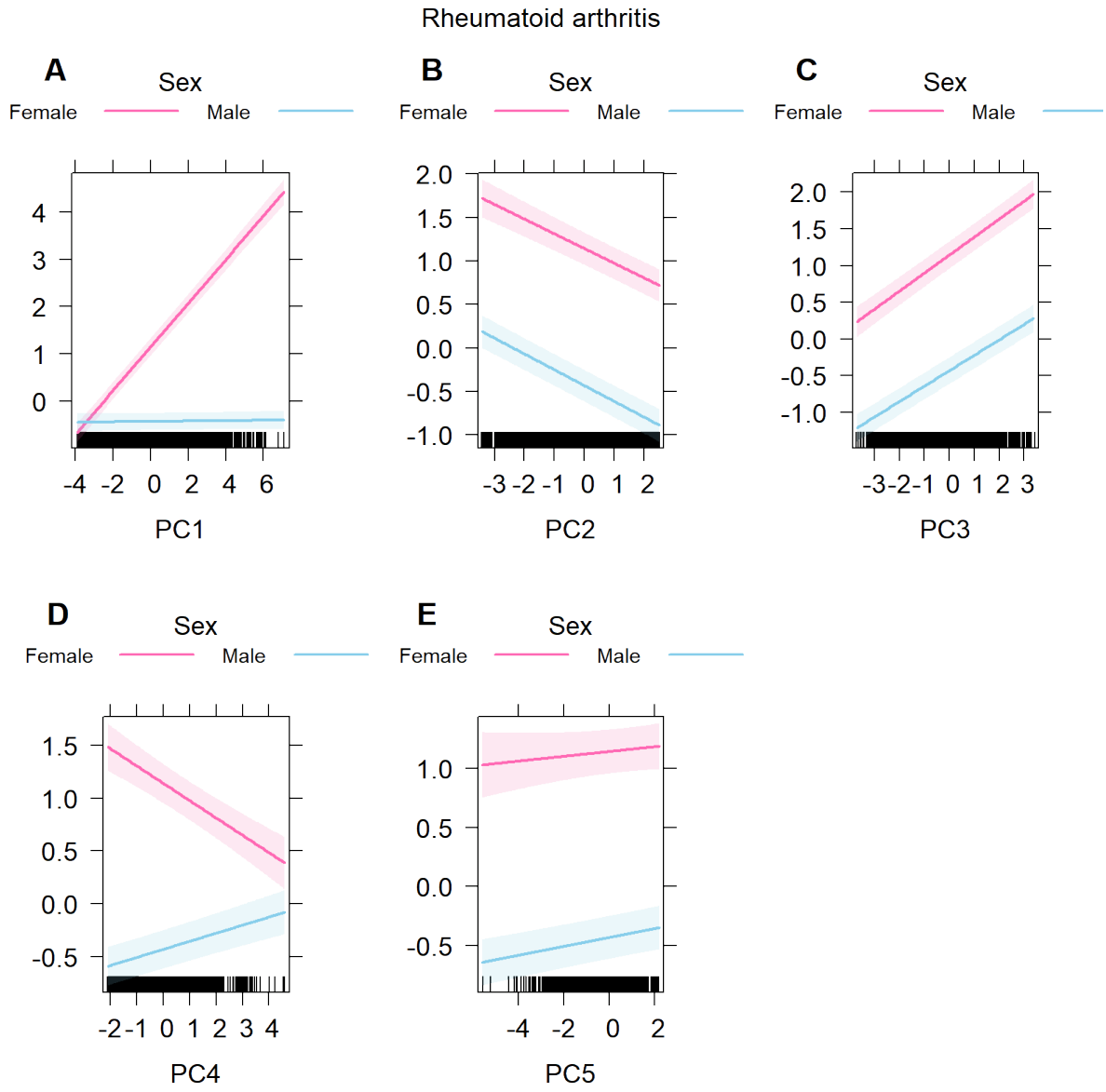

Figure 7. Effects of principal components 1 through 5 on rheumatoid arthritis. The pink colour indicates the female effects, and the blue line indicates the male effects.

Mental illnesses PCAs

Using the same principal components from the rheumatoid arthritis model, we created generalized linear mixed models for the four mental illnesses (Figure A. 5 - Figure A. 9). All the diseases showed a similar pattern with PC1 (high income, high drug use) where the female values increased dramatically while the male values either stayed relatively flat or even declined with added stress (Figure A. 5). All the male-biased illnesses showed a higher

y-intercept in males than females, but as PC1 increased, female rates quickly surpassed male rates.

PC2 (low adverse childhood experiences) showed a negative relationship between stress and disease for all the female-biased illnesses for both males and females, but a mixed relationship for both male-biased illnesses (Figure A. 6). Females showed a slight positive relationship between PC2 and bipolar disorder, while males showed a slight negative relationship. Schizophrenia showed a positive relationship for both males and females, with a higher rate of disease with increased PC2 values in males than females.

PC3 had a relatively positive relationship with all the diseases with slight exceptions to males with depression and anxiety (Figure A. 7). Rheumatoid arthritis showed a greater rate of disease with increased PC3 than the other diseases, but the rest all increased in a relatively consistent rate.

The relationships between PC4 and each disease varied widely (Figure A. 8). Rheumatoid arthritis had a strong negative relationship with females and a positive relationship with males and PC4. MDD showed a slight decline in rate of disease with increased PC4 in both males and females. Anxiety disorders also showed a slight decline in males, but a much steeper decline in females. Bipolar disorder in females was negatively correlated with PC4 but slightly positively correlated in males. Finally, both males and females with schizophrenia showed a positive relationship between PC4 and the disease, but the rate of disease increased faster in males than in females.

Finally, PC5 also varied widely for each disease (Figure A. 9). Males and females with rheumatoid arthritis showed a slight positive relationship with PC5 and both sexes with depression showed a slightly negative relationship with it. Females with anxiety had an unchanging rate of illness with increasing PC5 while males showed a decrease in disease

prevalence with higher PC5. Bipolar disorder showed positive relationships with PC5 for both sexes, but a much higher rate of increase in females than males. Lastly, males and females with schizophrenia both showed a strongly positive association between disease rate and PC5.

Chapter 4: Discussion

Each stress factor that we included in our study showed wide variability in male and female disease prevalence. Throughout this chapter, we will describe the influence of each stress factor, and the variables that may have led to this result. We will also explain the influence of estrogen on stress and psychosis to help explain the male-bias in a select few disorders. Next, we will explain the principal component analysis and how the stress factors interact together to influence disease rates in males and females. Finally, we will discuss the limitations to our project and what efforts we made to remedy these in our study.

Chapter 4.1: Effects of stress factors on diseases

When we began this project, we hoped to find overall patterns of stress on disease and were not concerned with the specifics of each stressor on each disease. As we conducted our study, however, it became more and more clear that each stressor that we measured had a widely different relationship with each disease. We found that 1) Our RA model showed female heightened sensitivity to changes in alcohol use and drug use, 2) most of our mental disorder models followed suit, showing that drug and alcohol use had heightened relationships in females, but minimal relationships with males, 3) the RA model had a strong inverse relationship with poverty, where poorer countries had lower rates of disease, 4) with the exception of anxiety disorders, most of our other models also had a negative relationship between disease and poverty. If we had just combined each stress factor into one variable, we would have missed all the complexities that each stress factor presents. For this reason, we will first expand on each stress factor, it's relationship with each disease, and finally, the implications of these relationships.

Poverty

In many of our models, rates of poverty showed strong relationships with disease that often varied by sex. Unexpectedly, richer countries tended to have higher rates of rheumatoid arthritis and some mental illnesses. This differed from our hypothesis that stress, in this case from poverty, positively correlates with increased disease rates. We predicted that limited access to necessary resources for life and comfort, such as food, clean water, housing, education, etc. would increase rates of stress and therefore inflammatory diseases, but that did not match the results shown by our data. Before concluding that poverty either decreases stress, or even decreases rates of disease, we must consider possible confounding variables that would make the data appear this way. To begin, we will first explore the rheumatoid arthritis model that serves as our makeshift 'control', in order to investigate the relationships between poverty and disease without the two-way interactions that are so common within stressors and mental illnesses. Then, we will expand our exploration to consider the findings from the mental illness models and compare these with rheumatoid arthritis.

Rheumatoid arthritis and poverty

As mentioned above, our RA model showed much higher prevalence rates in wealthy countries than poorer countries, which aligns with current literature. Our findings with RA are not the only autoimmune diseases that share this pattern. In fact, most autoimmune disease rates are higher in wealthier countries (Bach, 2002), a phenomenon that has sparked a plethora of scientific debate. One of the most popular theories to describe this trend is the *hygiene hypothesis,* described in more detail in our introduction. The hygiene hypothesis would predict that countries with higher access to sanitation and more rigorous hygiene practices would have higher rates of RA. It is very possible that the influence of developmental exposure to diverse microbiota in poorer countries has a much more

prominent effect on inflammatory disease prevalence than an increase in stress that stems from higher rates of poverty. Importantly, this does not mean that the stress of poverty has no or very little effect on disease rates, but instead that the effect of the hygiene hypothesis is so strong that it masks any influence that the stress of poverty would have. Additionally, our results showed a steeper increase in disease rates with higher wealth in females than in males. We, again, attribute this to the hygiene hypothesis, as stronger immune systems may show a bigger change when primed during development than those with weaker immune systems. Given than females have a generally stronger immune system, we would predict that differences in wealth would show larger changes in disease prevalence for them, which aligns with our findings.

There are other influences that may also have led to lower rates of RA in poorer countries, including some confounding variables. There may be lower general access to testing for rheumatoid arthritis and mental illnesses in poorer countries which artificially deflate the rate of each disease. This could be a reason why wealthier countries showed a positive relationship with disease. That being said, the data from the GBD study used hospital and health clinic data while also using random surveys and self-reporting. The difference in testing likely does not account for the entire difference in disease rate between poorer and wealthier countries. Another interesting confounding factor could be the difference in the perceived impact of the disease versus an objective measure of disease severity. A study by Putrik et al. (2016) that investigated the impact of country wealth on rheumatoid arthritis severity found that poorer countries had significantly lower self-reported symptom severity and pain than wealthier countries even though physician-reported disease levels were actually slightly higher in poorer places. Another study investigating the relationship between disease burden in German patients with RA showed that wealthier patients tended to experience less severe symptoms than their poorer counterparts (Callhoff et al., 2017). This relationship

between wealth and RA is likely complicated with other confounds. Interestingly, Rudan et al. (2015) found that low and middle-income countries in North and South America had significantly higher rates of RA than countries of comparable income in other continents. It is possible that people in the Americas have some cultural, social, and/or genetic traits that increase susceptibility to the economic relationship with RA. This also could point to the importance of income inequality on the impact of wealth and disease risk in certain countries. This being said, although the poorer countries in both North and South America have relatively high-income inequality compared to the rest of the world, Southern Africa greatly exceeds both of these in wealth inequality (Figure 8).

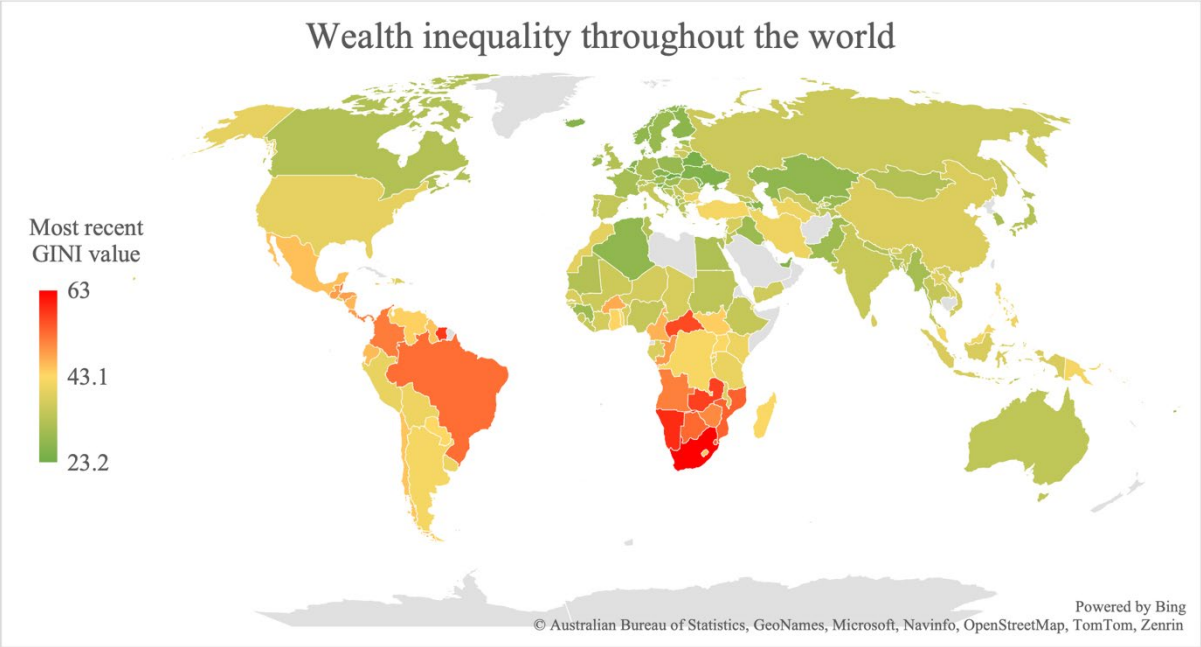

Figure 8. Wealth inequality in countries throughout the world measured by their most recent GINI value between 1989 to 2021 from The World Bank.

Notably, not all income differences respond the same way. Studies of RA patients in Columbia and Germany noted that patients with lower household incomes had a worse disease presentation than people with higher incomes (Callhoff et al., 2017; Santos-Moreno et al., 2019). Importantly, although these trends were present across almost all the wealth brackets studied, in the Columbia study, the only significant difference was between the

wealthiest 15% compared to the rest of the population (Santos-Moreno et al., 2019). Another study investigating the impact of wealth on inflammatory bowel disease, another female-biased autoimmune disease, found only the people with income in the top quartile showed significant differences in disease presentation compared with other income levels (Ahsan et al., 2020). International data shows similar patterns to within-country studies, where wealthier countries had lower severity of RA symptoms compared to poorer countries (Putrik et al., 2016). It's important to consider the effects of access to medication for patients of different incomes. It is very possible that a large part of the lower disease severity in wealthier patients is attributable to their access to medication that lowers the severity of their symptoms (Putrik et al., 2016). This does not act to decrease the overall prevalence rate, though. Patients must be diagnosed with rheumatoid arthritis to take many of the medications used to lessen their symptoms. The data from our study uses prevalence rates of disease, not necessarily the impact of the disease. Although it appears that findings from this data and other studies are contradictory, they may not be, as prevalence rates can be high while disease severity is low and vice versa.

Wealth and mental disorders

The mental disorders that we studied did not all show an increase in prevalence rate with wealth, like we saw with RA. Combined anxiety disorders and bipolar disorder rates slightly increased with country wealth, but there was very little differences between sexes, unlike RA. Other studies have also found higher rates of anxiety disorders in wealthier countries (Ruscio et al., 2017). Notably, this only seems to be true on a population-wide scale because within countries, individuals with lower household income have higher rates of anxiety disorders than higher income individuals (Hudson, 2005). It is possible that some of the symptoms that are highlighted in the current diagnostic criteria are less applicable to individuals in lower or

middle-income countries due to differences in culture and stigma surrounding anxiety disorders. For a long time, people have speculated a relationship between bipolar rates and socioeconomic status. In the past, some studies found higher rates of bipolar disorder in higher income individuals (Verdoux & Bourgeois, 1995). More recently, though, studies find no relationship, or even a slight inverse between bipolar rates and wealth (Schoeyen et al., 2011). It is possible that bipolar disorder rates are less sensitive to the various differences between countries than other mental illnesses. It is also possible that this may share a cause with the lack of female-bias in bipolar disorder. Perhaps if bipolar disorder were a female-biased disease, it would show a higher susceptibility to differences in wealth between countries.

Major depressive disorder had slightly lower prevalence rates in wealthier countries with females showing a steeper decline with wealth than males. Interestingly, some studies investigating how socio-economic status effects depressive symptoms on an individual level have demonstrated the relationship between higher rates of MDD and higher income. Other studies have found a slightly protective effect of income on depression (C. Li et al., 2022; Sareen et al., 2011). A review investigating the effects of the multi-faceted components of socio-economic status found that the specifics differed, and that measuring income as a whole was not sufficient to find a clear pattern (Lund et al., 2010). Even with the complications of all the components of socio-economic status, our study still found higher country income to be protective for MDD prevalence rate. This could indicate that the effects of stress that are experienced generally by people in lower-income countries may outweigh all the effects that increase MDD rates in wealthier countries. We would predict that any effect of wealth on MDD would be more drastic in females given their stronger immune systems and general predisposition to depressive disorders.

Wealth showed the largest effect on schizophrenia rates than any other mental disorder. The rates of schizophrenia were much higher in wealthier countries with a steeper rate of change in males than females. While there is no simple definite reasoning for this stark relationship, there are some possible explanations that could help describe it. Firstly, migrating people have been found to experience higher rates of schizophrenia than people who remain in one country (McGrath et al., 2004). Considering that people are more likely to immigrate to wealthier countries, this could explain some of the heightened rates of schizophrenia in high income countries. Schizophrenia rates also have been found to be higher in countries with bigger gaps in income equality; the larger the wealth gap, the higher the rates of schizophrenia (Burns et al., 2014). In general, wealthier countries tend to have slightly higher rates of income inequality, although the variation is very high, so this could also explain some of the increased schizophrenia rates in richer countries. Additionally, symptoms of schizophrenia may differ by culture. For example, one study showed that a schizophrenia symptom, called catatonia, is present in 10% of schizophrenia patients in developing countries but is only present in 1% of patients in developed countries (Jablensky et al., 1992). Other symptoms showed the opposite pattern, being much higher in developed countries than developing ones. The development of the most widely used diagnostic criteria for most mental disorders were created in western, high-income countries (Alarcón, 2009). Considering that symptoms of various diseases may differ substantially in other countries, it's likely that there is a general pattern of underdiagnosis, or perhaps misdiagnosis in poorer, developing countries. There is also a confound of access to diagnosis at all in low-income countries. With reduced access to healthcare, it's possible that people who experience psychotic symptoms may never receive a diagnosis and/or treatment for their disease. This would also underinflate the estimates of schizophrenia prevalence in these regions. Some of the primary data used in the GBD database does have this problem by using treatment centre

data, health insurance data, or other means that rely on some present treatment and/or diagnostic opportunities to work. Other studies in the dataset don't follow this pattern and randomly sample individuals from low-income regions and conduct surveys with people to determine more accurate community prevalence rates. Even so, these studies are still vulnerable to the bias of western-centred diagnostic criteria. Considering all the confounds that result in lower prevalence rates found in low-income countries, it is very difficult to say how much of the schizophrenia rate variation is true, and how much results from biased data collection and disease definitions.

Alcohol and drug use

Substance use, like drugs and alcohol, have been frequently found to show strong relationships with many diseases, especially mental disorders (Rehm et al., 2009). Interestingly, our data showed higher rates of female-biased illnesses in countries with higher drug and alcohol use, but particularly in females. The male-biased and neutral diseases (schizophrenia and bipolar disorder) both showed a less substantial relationship with substance use irrespective of sex. The exact reasoning behind this trend is still unknown, but there are many direct and indirect effects of substance use that could play a role here. It's important to note that males tend to have higher rates of substance use than females, meaning the increase in the effects of substance use in females is not solely attributable to increased exposure. Firstly, alcohol and drugs have complex relationships with chronic vs. acute use, and the immune system. Sometimes alcohol consumption and certain drugs act as anti-inflammatory agents, while others are pro-inflammatory.

Rheumatoid arthritis, major depressive disorder, and combined anxiety disorders all showed similar patterns of the effects of alcohol use. There is a non-existent or very minimal relationship between the diseases and alcohol use for males, and a substantial relationship for

females. This indicates that females in countries with higher alcohol use are more sensitive to the effects of this stressor on the development of these diseases, while it seems that males have almost no effect. Importantly, substance use is not just a predictor of stress, but additionally a result of it. Unfortunately, this makes any assumptions of causality difficult, especially when dealing with mental illnesses where alcohol use disorders are often comorbid. Because of the inclusion of rheumatoid arthritis in the data, we can compare the effects of alcohol use on RA first for a less confounded model before drawing any conclusions from the mental illness models. When considering drug use, RA and MDD stayed similar to one another, with positive associations between the stress factor and disease in females, but seemingly no effect in males. Anxiety disorders responded differently, though, with females showing a slight decrease in the relationship between drugs and the disease, but again, males had seemingly no effect. In the case of drug use, it is possible that the excessive worrying characteristic of many anxiety disorders would prevent the use of illicit and/or recreational drugs in fears of having a negative reaction. This may indicate a reverse relationship, where lower drug use does not cause higher rates of anxiety, but instead that people who have anxiety are less likely to use drugs. RA and MDD show positive associations with drug use in females, but not in males.

Bipolar disorder and schizophrenia both showed very little sex differences in the effects of alcohol use. Bipolar showed a slightly negative relationship between alcohol and disease while schizophrenia showed a slightly positive one. Similar patterns are observed for males and females with drug use and bipolar disorder, but not with drug use and schizophrenia. In our data, females show a positive relationship between schizophrenia and drug use, while males show a negative relationship. In the literature, sex differences in drug use are multifaceted in schizophrenia patients. Women use drugs later in life (Caton et al., 2014) but show higher risk of substance use relapse than men (Mendrek & Fattore, 2017). Additionally,

many studies show male heightened rates of drug use in schizophrenia patients (Nesvåg et al., 2014; Opler et al., 2001), while this would logically lead to a positive relationship between drug use and schizophrenia in males more than females, the opposite is true. Clearly, there are more factors in these populations than the direct cause of drug use on schizophrenia.

Based on the intricate connections between drugs, alcohol, inflammation, social norms, culture, and the disparities in substance use disorders between males and females, as well as the higher rates of female-biased diseases in countries with elevated substance use, it is our belief that females may be more vulnerable to the adverse consequences of drug and alcohol consumption on the risk of developing inflammatory diseases.

Bullying victimization

Our data showed a minimal relationship between bullying and rates of diseases. Out of all our stress factors, bullying had the lowest prediction of disease. But even so, there are many factors that contribute to these relationships that could explain a low correlation between this stress factors and the diseases.

Although the literature has demonstrated a relationship of sex differences between bullying and illness (S. Kim et al., 2018; Klomek et al., 2009; Williams et al., 2017), our data showed mixed, inconclusive results. RA and anxiety disorders showed similar patterns to one another with slightly higher male relationship with bullying and disease than in females. While MDD and schizophrenia showed slightly higher associations with bullying in females than in males. Bullying showed minimal effects on bipolar disorder in both males and females. These discrepancies between the effects of bullying on disease could be due to the different effects of various types of bullying. Physical bullying, emotional bullying, and cyberbullying all likely have different effects on an individual and may act separately when predicting exposure to stress differently in males and females. It also seems as though each disease may

respond slightly differently to the effects of bullying. One study found that people who were genetically susceptible to schizophrenia were more likely to develop symptoms if they had a history of bullying victimization (Pergola et al., 2019). Another possibility is that bullying experiences are relatively consistent between countries, so any effect that it has on these diseases would not be found by measuring these on a country-wide scale. Although, studies have found that, even between European countries, rates of bullying vary country-to-country by as much as 36% (Craig et al., 2009). There could also be a discrepancy between the amount of reported bullying and the actual level of bullying experienced by children, where some behaviours are seen as so common that students don't consider them as bullying in some countries, where others would. With all of these factors considered, the relationship between bullying and our diseases is still unclear, and we would strongly recommend further study on a smaller scale to investigate these relationships more thoroughly.

Childhood sexual assault

The relationships between childhood sexual assault (CSA) and our diseases that we found were not straightforward and did not necessarily reflect previous data collected on this topic. We found that rates of CSA are positively linked to RA in males, but slightly negatively in females. This is seemingly counter-intuitive as multiple studies have found a positive association between a history of childhood sexual assault and experiencing rheumatoid arthritis (Baiden et al., 2021; Spitzer et al., 2013). That being said, these effects are on a country-wide level, and it is possible that individual-level effects of CSA are very different than population-level effects. Male and female MDD rates both had very little change in disease with differences in childhood sexual assault levels. Anxiety rates in females were negatively associated with CSA, and males had seemingly no correlation. These findings for both MDD and anxiety disorders also contradict the current literature, as studies have found a

positive relationship between depressive and anxiety disorders with experiences of childhood sexual assault (Bellis et al., 2019). Our data showed very little relationship between bipolar disorder and CSA in females and a slightly negative effect in males. But in the literature, female bipolar patients have found to have higher risks of having experienced childhood trauma (including CSA) than male bipolar patients, contradicting our findings (Etain et al., 2013; Guillen-Burgos et al., 2023). Finally, both males and females showed positive associations between schizophrenia and childhood sexual assault. But other studies have shown that childhood sexual abuse is associated with psychosis in females, but not in males (Fisher et al., 2009). In general, because psychotic disorders are higher in males, perhaps the similar effects of childhood sexual assault are a result of the female sensitivity to the effects of CSA and male sensitivity for schizophrenia.

Finally, it's important to consider that rates of CSA are much higher in females than in males. This means that an increase in the exact same number of cases in both males and females would drastically change the male rates of CSA, while barely affecting the rates in females. This could also explain some of the counter-intuitive findings surrounding CSA and disease. Like with all of our other stress factors, we believe that investigations on an individual-level are very important to provide necessary context to country-wide population data and encourage such research to take place.

Child and maternal mortality

Our data showed a slightly negative relationship between RA and CMM in females and a very large decline in males. This pattern is very similar to the relationship between RA and poverty. Child and maternal mortality rates are highly correlated with income, and it is possible that many of the effects that influence the rates of disease in countries with varying wealth are the same as those with varying child and maternal mortality rates. It is likely that

the ‘hygiene hypothesis’ also plays a role here, where areas that have lower standards for healthcare and sanitation practices (and subsequently lower autoimmune diseases) have higher rates of maternal and childhood mortality rates. In our data, the relationships between CMM with MDD and schizophrenia rates differed from RA. Female MDD and schizophrenia rates slightly declined with CMM, while there was a large increase in males. It is possible that the effect of losing a partner directly contributes to the rates of depression and schizophrenia in males and that male-specific effect is enough to cause such a large difference between sexes. Additionally, some research indicates that physical stress that mothers undergo positively contributes to development of schizophrenia in offspring, but specifically in male children, not females (Malaspina et al., 2008). The stress of famine, lack of access to healthcare, and discrimination in countries that experience higher child and maternal mortality that pregnant mothers experience may directly lead to increased rates of schizophrenia development in males, explaining the strong positive relationship for them, but not for females. Anxiety rates did not show a strong relationship with CMM but females did show a slightly inverse relationship between the two. This is seemingly counter intuitive, but also possibly a random chance given how minimal the effect size is. The relationship between bipolar disorder rates and CMM were not very strong in males or females, but both showed a slight positive effect.

Much of the same confounding variables that are necessary in the conversation surrounding poverty are relevant when considering CMM. We would suggest future investigations directly considering the death of a spouse or mother rather than CMM rates on a population level. We additionally recommend stratifying rates of CMM by country wealth to try and limit the confound of poverty influencing the risk of CMM.

Overall, the relationships of each individual stress factor with each disease show interesting differences between sexes. Given the immense complexity of the interactions between stress factors, disease, and populations, we recommend further investigation of each disease and each stress factor on an individual basis to determine more direct connections, rather than general patterns across the world.

Estrogen and psychosis

A common thread in the male-biased mental illnesses that were included in this study is the presence of psychosis. A common symptom of both schizophrenia and bipolar disorder is psychosis but this is also a much more common symptom in males than in females. Previous links have found a connection between higher levels of estrogen and lower rates of psychosis (Maric et al., 2005). One possible mode for this relationship is through estrogen modulation of Dopamine2 (D2)-receptor sensitivity in the brain (Sárvári et al., 2014). The D2 receptors are involved in psychosis and act as the primary active site for almost all antipsychotic medications (Seeman et al., 1976). Even though females have a stronger immune system and both schizophrenia and bipolar disorder are linked to increases in inflammation, estrogen presence could be protective against a large part of both of these diseases: experiencing psychosis. This would be the factor that contributes to the male bias in the diseases the include psychotic symptoms. Additionally, of the females that do experience bipolar disorder and schizophrenia, some research has found that males generally have more prominent psychotic symptoms, while females experience more depressive symptoms within the diagnostic criteria (Grossman et al., 2008; Wozniak et al., 2013). *Females seem to be vulnerable to depressive and anxiety traits, while protected against some psychotic traits which may balance out to the approximately equal prevalence of bipolar disorder between sexes.* This would explain much of the variation that we see between our diseases.

Particularly, if different stress factors, like childhood sexual assault, were especially linked to the development of psychosis, this could explain why certain stressors increase schizophrenia and bipolar, while influencing depression, anxiety, and RA less.

Chapter 4.2: Perspective from principal component analyses

Our investigation involved conducting a PCA to investigate the interactions between stress factors, and how these groupings impacted diseases differently. We found very strong evidence that relationships between some stress factors interact to influence diseases in predictable and notable ways. Particularly, our first principal component consistently showed a strong, positive relationship with each disease in females, and very little relationship at all in males. The factors that combined to make PC1 were of interest in understanding this trend. PC1 represented the majority of the data from the stress factors, particularly through high associations with alcohol and drug use, a very small positive relationship with bullying, a very slight inverse relationship with childhood sexual assault, and strong inverse relationships with both poverty rates and child and maternal mortality. This component could represent some overreaching pattern that spans across all these factors either positively or negatively.

One important consideration here is differences in the relationships between drug and alcohol use with wealth between sexes. Alcohol and drug use rates are consistently higher in males and females, but this gap is much smaller in wealthier countries (Rehm et al., 2009). This could be due to societal norms, cultural expectations, the discrimination of women, access to money, or religion. In general, richer countries also report higher consumption of alcohol. But there is a lot of variability in the wealth of countries with high and low alcohol consumption. Poor countries where alcohol use is high have many more health impacts of alcohol consumption than poor countries where alcohol is low or in rich countries where

alcohol use is high (Dawson et al., 2005). This is likely somewhat attributable to higher rates of treatment for alcohol use disorders and higher access to healthcare interventions when experiencing health consequences of alcohol use. When we look at the same patterns on an individual level instead of a country level, we see that people with higher incomes are more likely to drink alcohol, but of everyone that does drink, people with lower socioeconomic statuses drink higher volumes and are more negatively impacted by the social and health consequences (Huckle et al., 2010). It is also vital to recognize the effects of religious customs on the consumption of alcohol throughout the world to help explain the patterns of alcohol use in countries. In the Islamic faith, alcohol is usually considered to be 'haram' or forbidden, so alcohol use is generally much lower in countries with high Muslim populations (Luczak et al., 2014). Countries in the Middle-East, Northern Africa, and Oceania generally have high Muslim populations and have some of the lowest alcohol consumption rates in the world. Importantly, countries with a high Muslim population tend to have more legal discrimination against women than countries with other faith majorities (Morrisson & Jütting, 2005). Given that female rates of disease are so strongly related to PC1 for all diseases, while male rates are not, even male-biased diseases, this component cannot explain the male-bias in some inflammatory illnesses. That being said, the relationship between PC1 and each disease is still very notable, especially considering that it represents the majority of the variation in our original data.

PC2 (low adverse childhood experiences) also shows interesting relationships with each disease. Each of the 3 female-biased illnesses (RA, MDD, and anxiety) all show similar patterns where both males and females show a moderate decline in disease with increasing PC2. The sex-neutral disease, bipolar disorder, shows a slight positive relationship in females and slight negative relationship in males. Schizophrenia shows a moderately positive relationship with PC2 in females and a very strong positive relationship in males. This

principal component is particularly notable because the pattern that it shows directly mimics the groupings of each sex-bias of our diseases. Interestingly, this principal component is made up almost entirely of negative influences from all stress factors with the exception of CMM, which only slightly positively contributes to PC2. This grouping of stress factors is remarkable because the underlaying pattern that it represents in the populations could possibly be an important link in the female-bias of some inflammatory illnesses. We categorised this component as representing “low adverse childhood experiences” due to it’s main driving stress factors being lower rates of childhood sexual abuse and bullying victimization. For our three female-biased diseases, MDD, RA, and anxiety, less exposure to adverse childhood experiences correlates with lower rates of diseases. This aligns with our prior expectations. But bipolar disorder and schizophrenia do not share the same trend. Female bipolar rates and schizophrenia rates for both sexes increase with exposure to lower adverse childhood experiences, with male schizophrenia rates showing the most drastic incline. These results oppose much of the current literature that links schizophrenia and many other inflammatory illnesses to childhood trauma (Bellis et al., 2019; Mersky et al., 2013; Zietz et al., 2020). We believe other factors influencing this principal component, such as sex differences in rates of childhood adverse experiences in each country or differences in perception of these various experiences, may be influencing the results with this component.

PC3, PC4, and PC5 represent less and less of the variation in the stress factor data but are still worth considering in their relationships with each disease. PC3 (adult-caused adverse childhood experiences) showed positive relationships with all diseases in females, and a mixed relationship with males, potentially demonstrating a female-specific sensitivity to abuse in the hands of adults, but not peers, especially in regards to the development of MDD and anxiety disorders. PC4 (healthcare inequality) had positive correlations with all female disease prevalence rates with the exception of schizophrenia, while males had positive

relationships in RA, bipolar disorder, and schizophrenia but negative relationships with MDD and anxiety. Finally, PC5 had widely variable relationships between each disease in both sexes. Although these principal components may not be as significant in their effects on disease, they are still important to consider as a piece of the puzzle.

Our investigation utilizing PCA has revealed significant associations between stress factors and diseases, particularly in relation to sex differences. PC1 represents a comprehensive pattern of stress factors that consistently influences diseases in females but has minimal impact in males. PC2 mimics the grouping of sex-biased diseases and highlights the potential link to inflammatory illnesses in females. PC3, PC4, and PC5 all contribute to the understanding of sex-biased diseases, emphasizing the importance of considering specific stress factor interactions. These findings provide valuable insights into the complex relationship between stress, sex, and disease outcomes.

Chapter 4.3: Joint consideration of individual stress factors and PCs

Across both analyses, we have established substantial sex differences in disease prevalence in response to stress. While the specific effects of each stress factor and principal component differ on disease rates, some general trends emerge. Firstly, the effects of the hygiene hypothesis are strong, and must be addressed in utilizing data both within and across populations. Secondly, both drug and alcohol use rates change in similar, but still unique ways across sexes and disease. We believe that a focus on the most impactful stress factors tells the clearest story of our disease data.

As PC1 represents the most variation in our data, we consider it of prime importance and see it as a combination of our most impactful stress factors. Across all of our diseases, PC1 had a strong positive relationship with females, and minimal relationship with males. We believe

this represents the combined effects of drug and alcohol use with the impacts of immune system priming with commensal microbiota during development as seen in impoverished countries. We believe the relationship that we see with PC1 explains part of the female-bias in inflammatory disorders. Importantly, both bipolar disorder and schizophrenia also show the exact same relationship with PC1 as the female-biased disorders we study. If there were no other factors at play, then we would expect to see a female-bias in both bipolar and schizophrenia just like rheumatoid arthritis, MDD, and anxiety. We believe the missing factor here may be the protective effects of estrogen against psychosis. Both bipolar and schizophrenia patients often experience psychosis, with this experience being much more common in schizophrenia. As estrogen has been noted to protect against psychosis, we believe that females are more susceptible to the inflammatory components of mental illnesses (including schizophrenia and bipolar) due to stress, but because of their estrogen levels, rates of schizophrenia and bipolar disorder are dampened so much that bipolar is equal in sex prevalence and schizophrenia has a male-bias.

Chapter 4.4: Limitations

Our study was conducted with more than 100,000 points of data. Using such a robust dataset when conducting population-level, complex studies is necessary as more available data allows subtle effects to still be visualized. It also prevents some complexities with data assumptions that render some statistical modelling techniques invalid. That being said, when conducting any research involving mental illnesses, there are many confounding variables that may influence the data. It is important to recognize that causal relationships cannot be determined with so many unaccounted variables, but instead patterns can be identified to lead towards future areas for research and discovery. *We chose to study rheumatoid arthritis as a baseline model as we believed this disease would have less two-way effects between the stress*

factors than many mental illnesses. By doing this, we have attempted to add a 'control' disease that showed female bias but had less direct interactions with our stress factors. In the future, including male-biased 'control' diseases in addition to the female-biased 'control' diseases could help provide more context for the impacts of stressors on each of the mental illnesses.

We also recognize the societal stigma of mental health concerns in many cultures around the world. This could lead to falsely deflated rates of mental illness and could create even more extreme bias if that societal stigma was sex-biased, as it often is. In many cultures, men are expected to be stoic and logical, and may experience shame about experiencing emotion-centric disorders like depression or anxiety. As difficult as this confound is, we hope that the influence of it is minimal in our data given that much of our sources come from individual surveys and treatment centres focused on the presence or absence of particular symptoms rather than the presence or absence of a diagnosis itself. Even so, the lists of symptoms themselves may contribute to bias in the data. Current diagnostic criteria were built upon centuries of research in Western countries, meaning that cultural differences in mental illness expression may not be well recognized in a diagnosis. For example, some communities may consider sharing one's feelings outwardly to be a sign of maturity and strength, while other communities may consider it a sign of weakness. A person may be able to share their feelings and connect with their community well in the first group, while unable to do so within the second group. This is not because of a difference in the person's illness, but because of a difference in their cultural context. Having a Western-centric cultural context for measuring mental illness prevalence throughout the whole world could both inflate or deflate the actual rates of disease. This issue must be dealt with from the very definition of each illness in order to reflect the widely variable experiences of cultures. This problem is also likely exacerbated by a lack of access to diagnostic practices and healthcare in general. People living in poorer

countries likely have reduced access to healthcare which would lead to deflated prevalence rates of diseases and lowered access to treatment in these places. In addition to this, the diagnostic criteria for the mental illnesses in this study have changed over the course of the 26 years included in this study. This change in criteria has likely led to higher rates of incorrect diagnoses, especially in earlier years of the data we collected. Additionally, due to the data available in the GHDx, we included anxiety disorders combined, instead of separately. Each anxiety disorder is a remarkably different illness, including different symptoms, onset, and demographics. Combining these diseases together decreases the clarity of the effects of stress on anxiety as a whole.

Additionally, data on a population-wide scale can differ dramatically from data on an individual level. A country may have generally high rates of wealth but if that wealth is exceptionally uneven, an average of GDP does not accurately represent the majority of the population. The differences in modes of data collection used in each country may also bias the data. Countries that have higher overall wealth are likely able to support a higher budget for funding research. This creates a bias of much more data available in richer countries. Poorer countries may primarily use data that is already easily accessible, such as hospital patient records, but this also creates bias. Low-income populations generally have lower access to healthcare treatment than higher-income populations, so many people from poor countries go undiagnosed, untreated, and uncounted in their records.

In future research, it's vital that some of these limitations are addressed to further investigate the relationship between stress, sex, and disease. Conducting models to assess further modes of stress, such as domestic abuse, unemployment rates, divorce rates, prison rates, and others could shed more light on the relationship between stress and disease. In addition,

incorporating further diseases, both mental illnesses and autoimmune diseases, would provide more insight into how the relationships between different diseases, sexes, and stress differ.

Chapter 5: Conclusion

In this study, we investigated role of social stress factors on the relative prevalence of diseases and mental disorders in males and females. We demonstrated a series of complex relationships between inflammatory illnesses and stress factors through the use of GLMMs and PCA. We showed that males and females may respond differently to stress, affecting rates of disease prevalence. We showed (1) that some stress factors, like drug and alcohol use, showed particularly strong relationships with female-biased diseases in females, while other stress factors, like bullying victimization and childhood sexual abuse, had minimal relationships to rates of each disease; and (2) that poverty has an inverse relationship with rates of inflammatory diseases, possibly through the mechanisms described in the hygiene hypothesis. The relationships between sex, stress, inflammation, and disease are still hazy, but we have demonstrated significant sex differences in disease rates predicted by stress.

The model we used as a control, rheumatoid arthritis, showed a sex-biased relationship with all stress factors included in our study. Female alcohol and drug use were strongly correlated with RA, while poverty and child and maternal mortality both showed a strong male relationship with the disease. MDD and combined anxiety disorders both showed similar relationships with stress factors to rheumatoid arthritis, while schizophrenia and bipolar disorder tended not to. These similarities follow sex-biased grouping of the diseases, where the female-biased diseases shared similar patterns with one another. *This may demonstrate a similar relationship between stress and disease for female-biased illnesses, while differing relationships with male-biased illnesses.* In addition, when conducting our PCA, our primary component was strongly positively represented by drug and alcohol use and strongly negatively represented by child and maternal mortality and wealth. The relationships with these stress factors may highlight an important influence of immune system priming (or the

hygiene hypothesis) during development on the sex-specific effects of stress on disease around the world.

Overall, it has already been established that experiencing stress can act to increase inflammation throughout the body. When that inflammation increases, it can lead to higher levels of inflammatory disorders, such as rheumatoid arthritis and many mental illnesses. Since females generally have a stronger immune system, they may be more susceptible to the effects of stress on their inflammation. *From our data, we believe that higher levels of perceived stress results in even higher levels of inflammation in females than males, resulting in a female-biased of rheumatoid arthritis, major depressive disorders, and anxiety disorders.* Although bipolar disorder and schizophrenia are associated with inflammation, it is possible that estrogen acts as a protective factor against psychotic symptoms, reducing the risk of females acquired disorders with psychotic symptoms, like bipolar disorder and schizophrenia.

We strongly encourage the continued research into sex differences in mental illness, stress, and inflammation as these disorders are common in almost every country throughout the world. Investigating the causes of some of the most prevalent diseases is vital to repairing the damage formed by the systemic neglect of women in healthcare research for centuries.

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Appendix

Table A. 1. Locations of Outliers for each disease and each sex. + or – outlier refers to the outlier being above the center of the data (+), or below the center of the data (-).

Disease	Location	Sex	+ or - outlier
MDD	Gambia	Female	+
MDD	Greece	Female	+
MDD	Greenland	Female	+
MDD	Portugal	Female	+
MDD	Uganda	Female	+
MDD	Angola	Male	+
MDD	Central African Republic	Male	+
MDD	Congo	Male	+
MDD	Equatorial Guinea	Male	+
MDD	Gabon	Male	+
MDD	Greenland	Male	+
MDD	Palestine	Male	+
MDD	Uganda	Male	+
Anxiety	Brazil	Female	+
Anxiety	Cyprus	Female	+
Anxiety	France	Female	+
Anxiety	Germany	Female	+
Anxiety	Iran	Female	+
Anxiety	Ireland	Female	+
Anxiety	Lebanon	Female	+
Anxiety	Netherlands	Female	+
Anxiety	New Zealand	Female	+

Anxiety	Norway	Female	+
Anxiety	Portugal	Female	+
Anxiety	Switzerland	Female	+
Anxiety	United States of America	Female	+
Anxiety	Australia	Male	+
Anxiety	Brazil	Male	+
Anxiety	Cyprus	Male	+
Anxiety	Iran	Male	+
Anxiety	Ireland	Male	+
Anxiety	United States of America	Male	+
Anxiety	Lebanon	Male	+
Anxiety	Switzerland	Male	+
Anxiety	Netherlands	Male	+
Anxiety	New Zealand	Male	+
Anxiety	Norway	Male	+
Anxiety	Portugal	Male	+
Anxiety	Mongolia	Male	-
Anxiety	Kyrgyzstan	Male	-
Anxiety	Uzbekistan	Male	-
Anxiety	Viet Nam	Male	-
Bipolar	New Zealand	Female	+
Bipolar	New Zealand	Male	+
Schizophrenia	Australia	Male	+
Schizophrenia	Greenland	Male	+
Schizophrenia	New Zealand	Male	+
Schizophrenia	United States of America	Male	+

Schizophrenia	Netherlands	Male	+
Schizophrenia	Ireland	Male	+
Schizophrenia	Greenland	Female	+
Schizophrenia	Ireland	Female	+
Schizophrenia	Netherlands	Female	+
Schizophrenia	United States of America	Female	+
Rheumatoid Arthritis	Finland	Female	+
Rheumatoid Arthritis	Honduras	Female	+
Rheumatoid Arthritis	Ireland	Female	+
Rheumatoid Arthritis	Mexico	Female	+
Rheumatoid Arthritis	Comoros	Male	+
Rheumatoid Arthritis	Djibouti	Male	+
Rheumatoid Arthritis	Eritrea	Male	+
Rheumatoid Arthritis	Kenya	Male	+
Rheumatoid Arthritis	Malawi	Male	+
Rheumatoid Arthritis	Mozambique	Male	+
Rheumatoid Arthritis	Rwanda	Male	+
Rheumatoid Arthritis	Somalia	Male	+
Rheumatoid Arthritis	South Africa	Male	+
Rheumatoid Arthritis	Uganda	Male	+
Rheumatoid Arthritis	Tanzania	Male	+
Rheumatoid Arthritis	Zambia	Male	+

Stress factor effects on disease grouped by disease

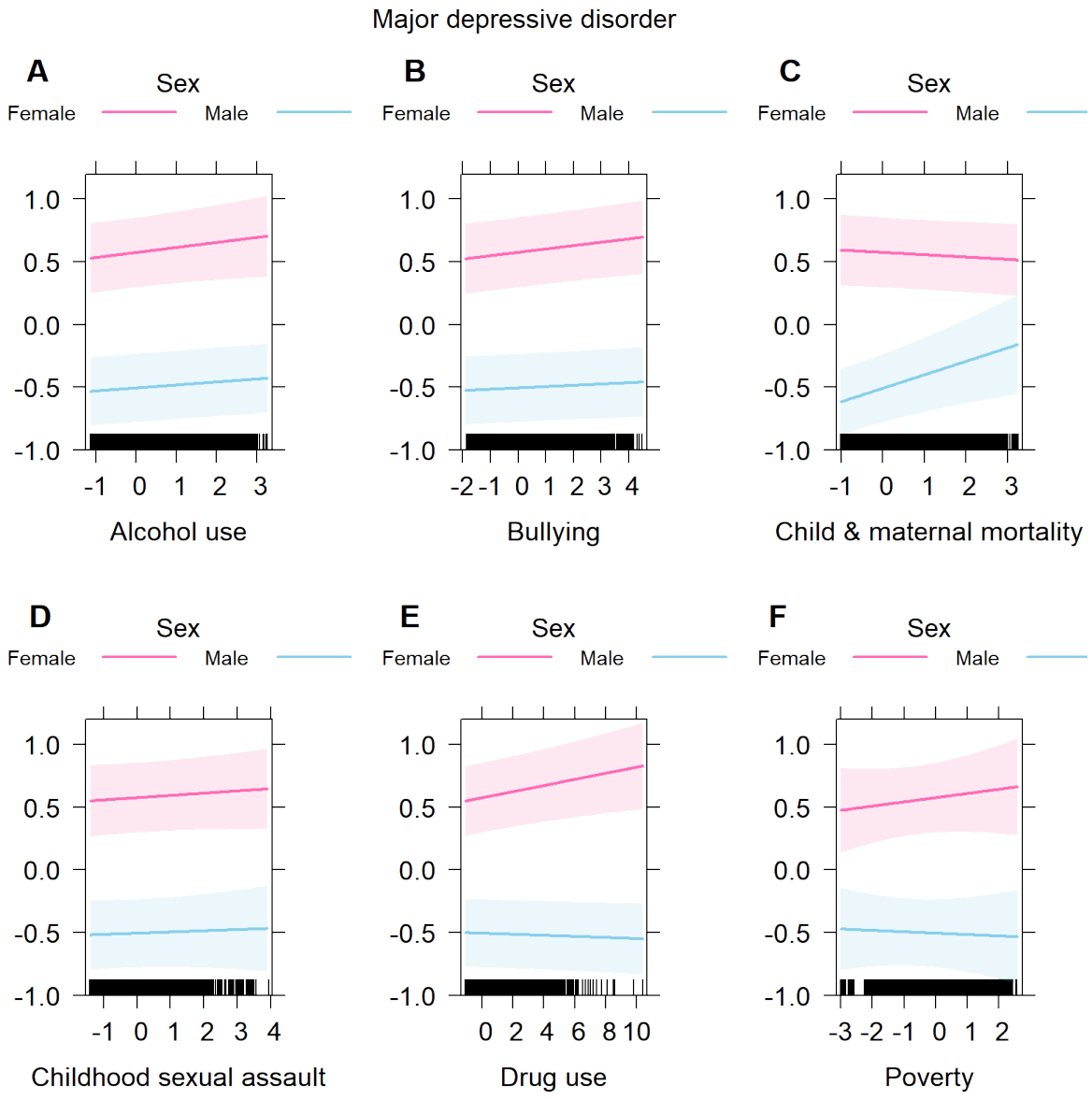

Figure A. 1. The effects of stress factors on the prevalence rate of major depressive disorder in males (blue) and females (pink). Shaded regions represent 95% confidence intervals.

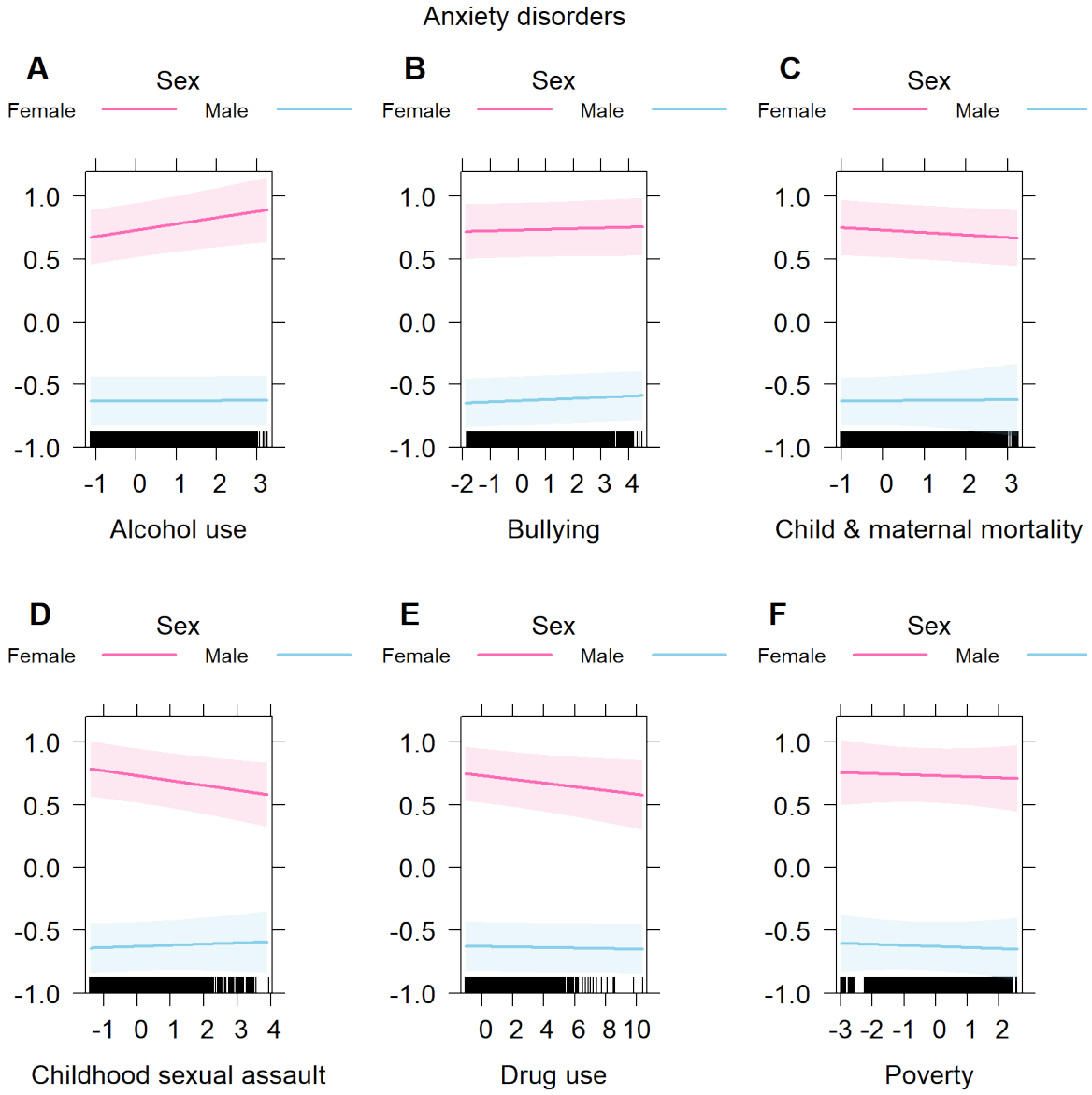

Figure A. 2. The effects of stress factors on the prevalence rate of anxiety disorders in males (blue) and females (pink). Shaded regions represent 95% confidence intervals.

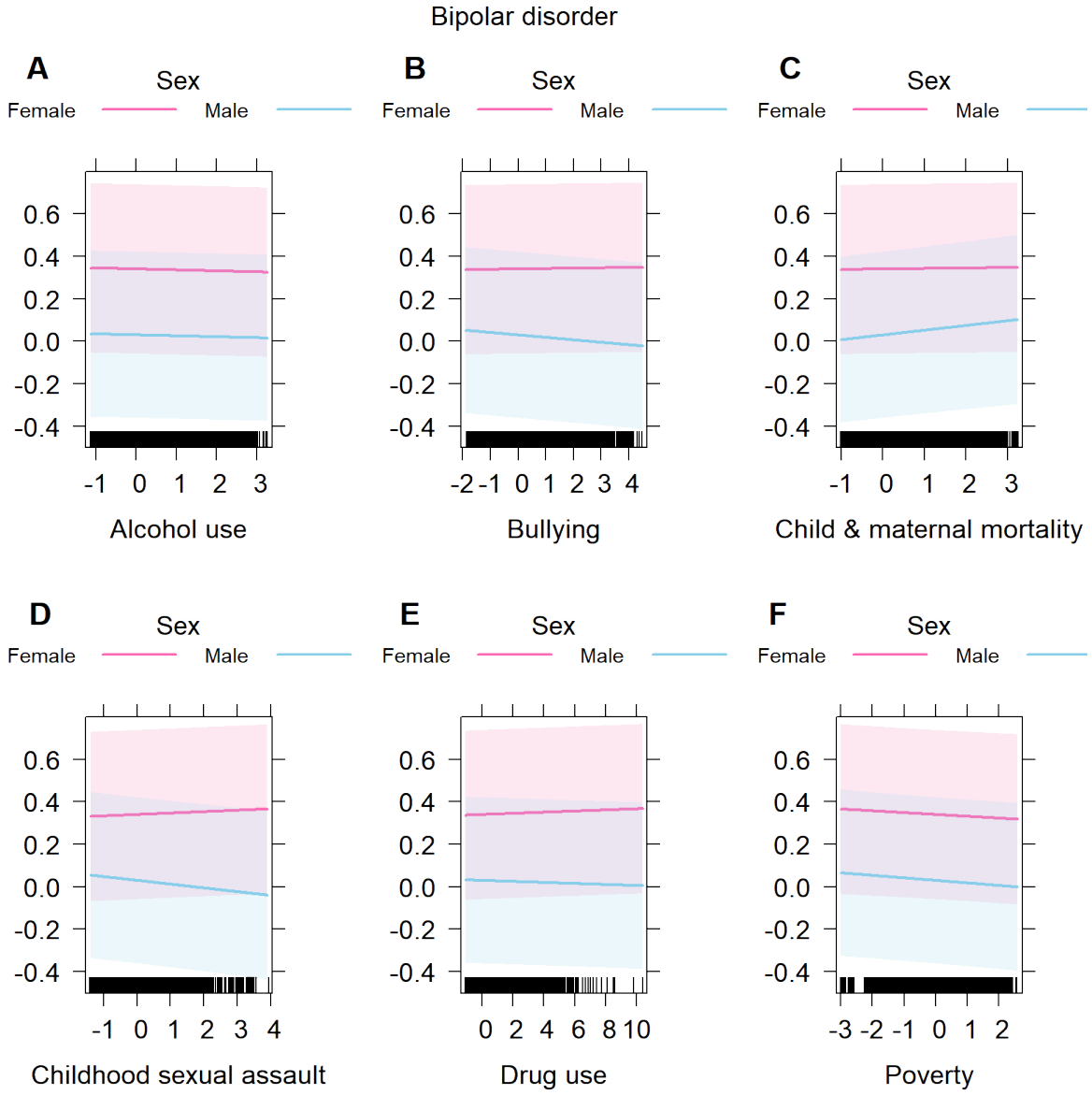

Figure A. 3. The effects of stress factors on the prevalence rate of bipolar disorder in males (blue) and females (pink). Shaded regions represent 95% confidence intervals.

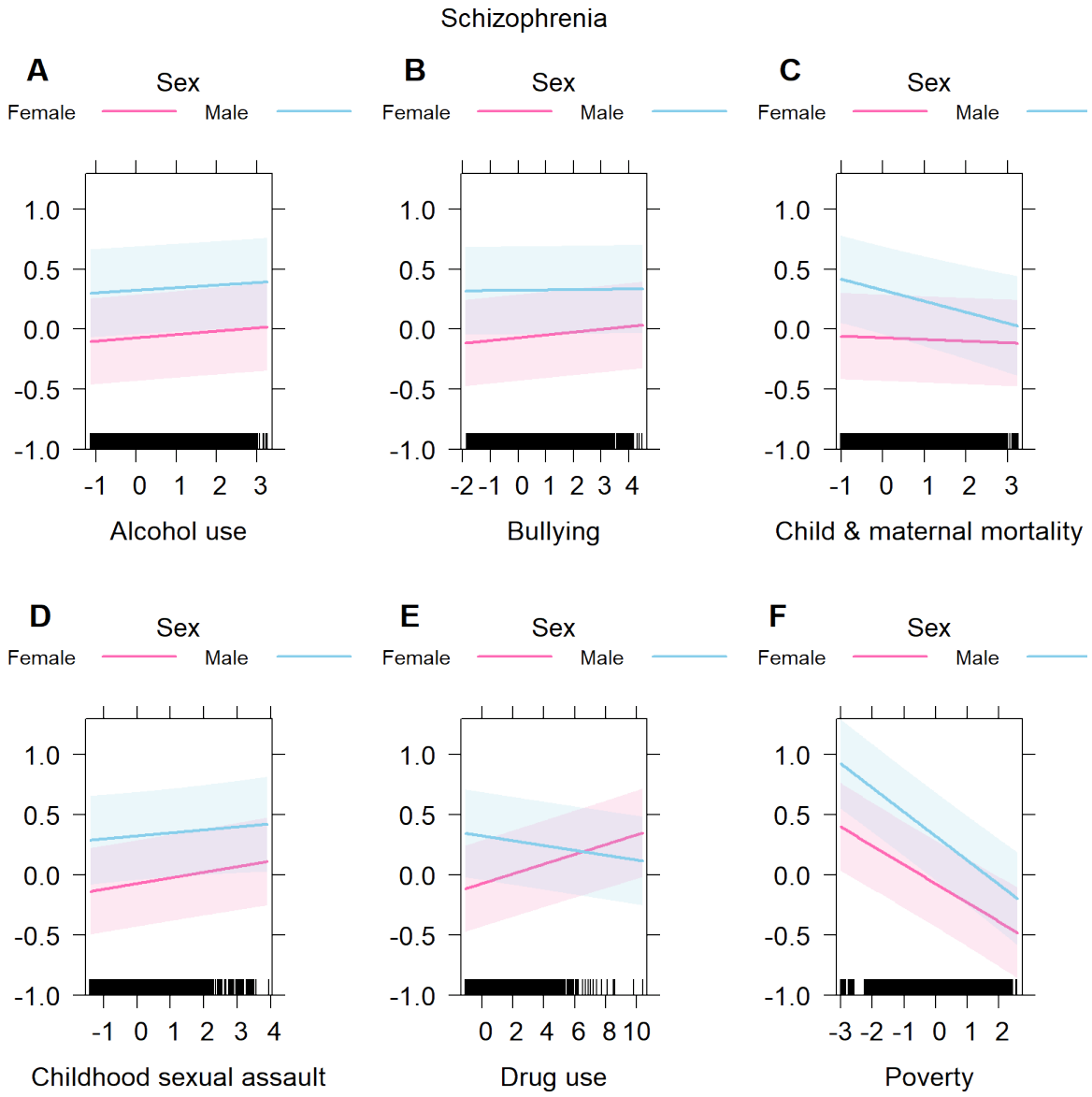

Figure A. 4. The effects of stress factors on the prevalence rate of schizophrenia in males (blue) and females (pink). Shaded regions represent 95% confidence intervals.

Principle component effects on disease grouped by principle component

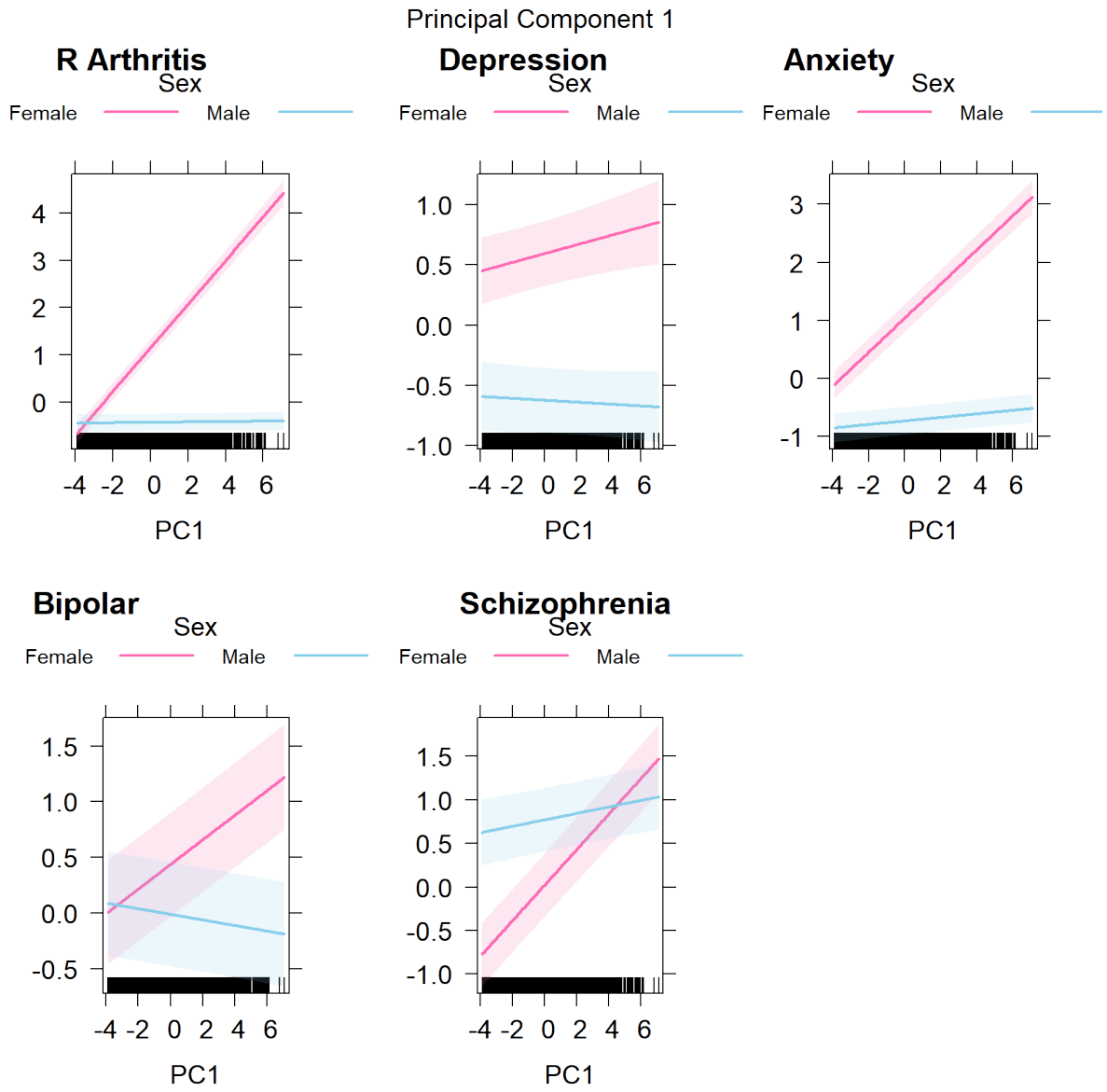

Figure A. 5. Effects of principal component 1 on rheumatoid arthritis, major depressive disorder, anxiety disorders, bipolar disorder, and schizophrenia prevalence rates on males (blue) and females (pink). Shaded regions surrounding the lines represent 95% confidence intervals.

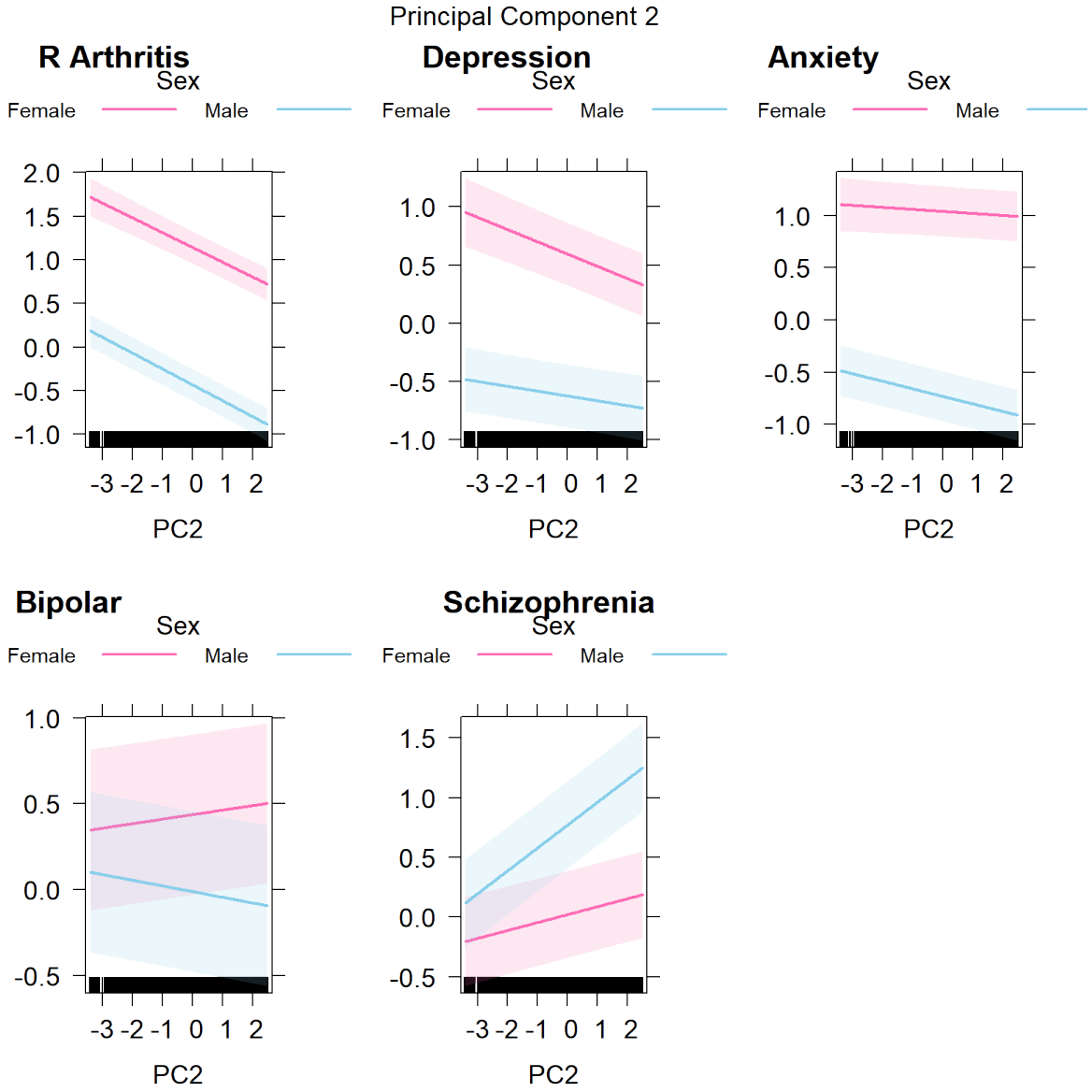

Figure A. 6. Effects of principal component 2 on rheumatoid arthritis, major depressive disorder, anxiety disorders, bipolar disorder, and schizophrenia prevalence rates on males (blue) and females (pink). Shaded regions surrounding the lines represent 95% confidence intervals.

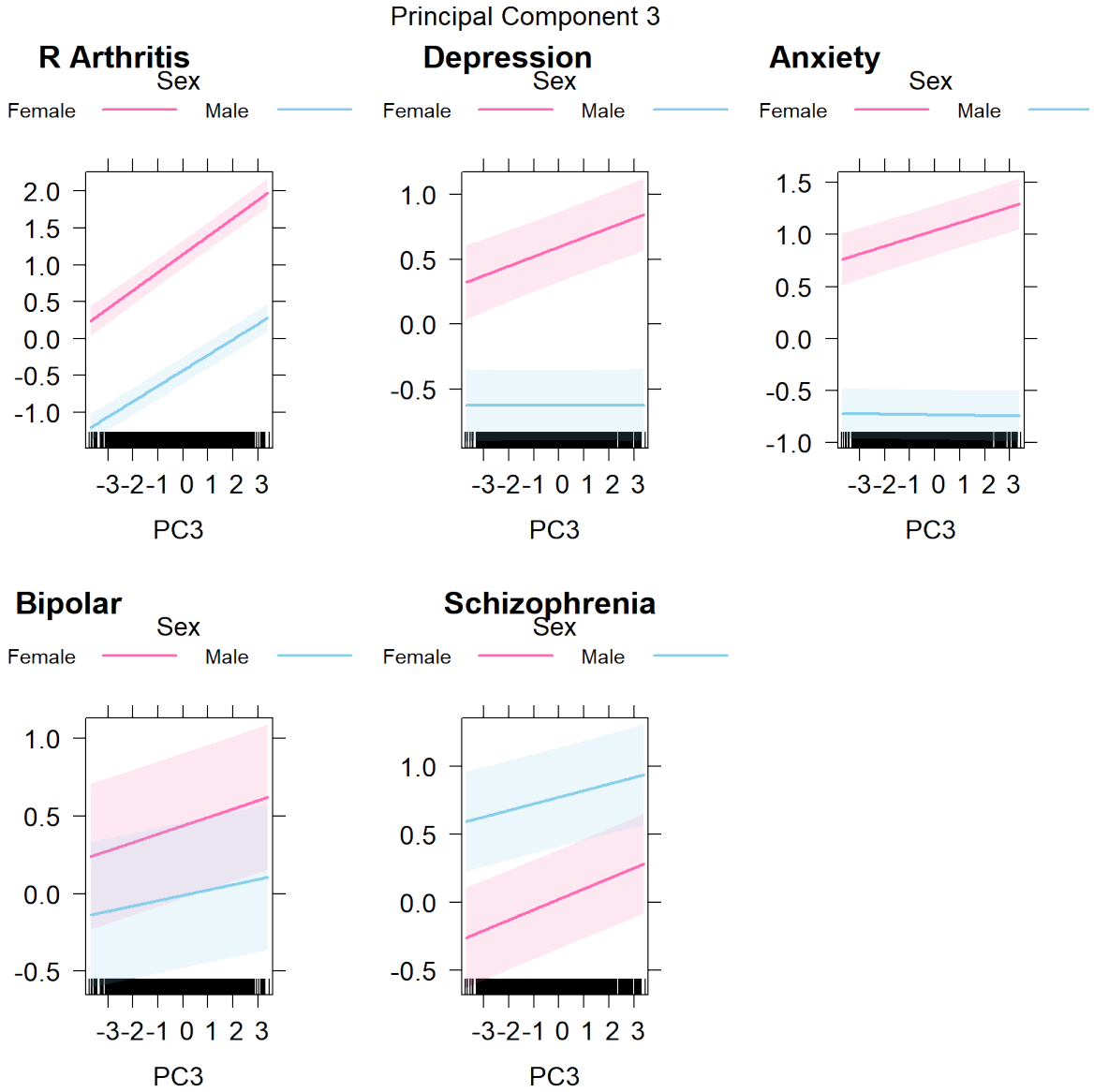

Figure A. 7. Effects of principal component 3 on rheumatoid arthritis, major depressive disorder, anxiety disorders, bipolar disorder, and schizophrenia prevalence rates on males (blue) and females (pink). Shaded regions surrounding the lines represent 95% confidence intervals.

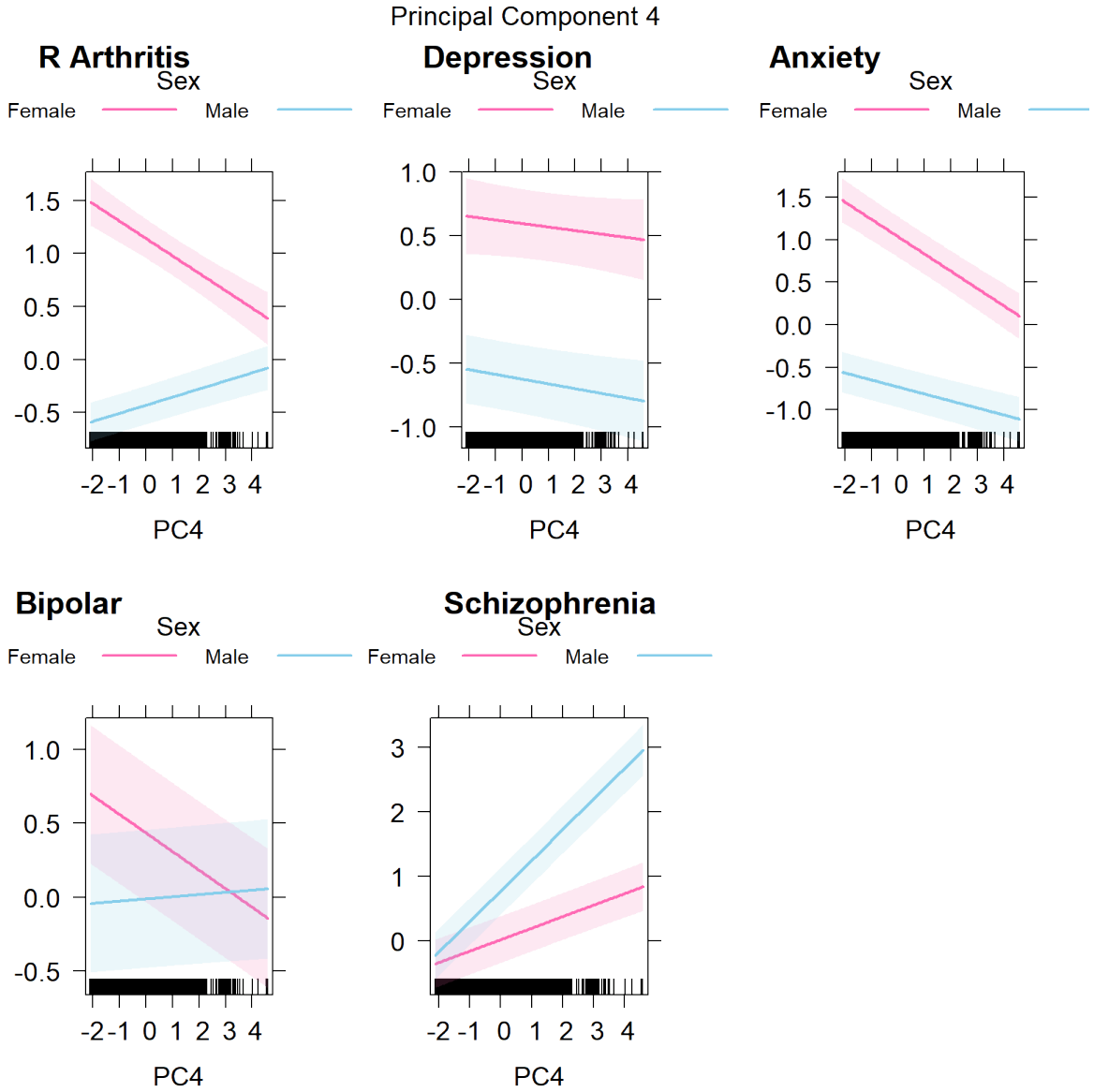

Figure A. 8. Effects of principal component on rheumatoid arthritis, major depressive disorder, anxiety disorders, bipolar disorder, and schizophrenia prevalence rates on males (blue) and females (pink). Shaded regions surrounding the lines represent 95% confidence intervals.

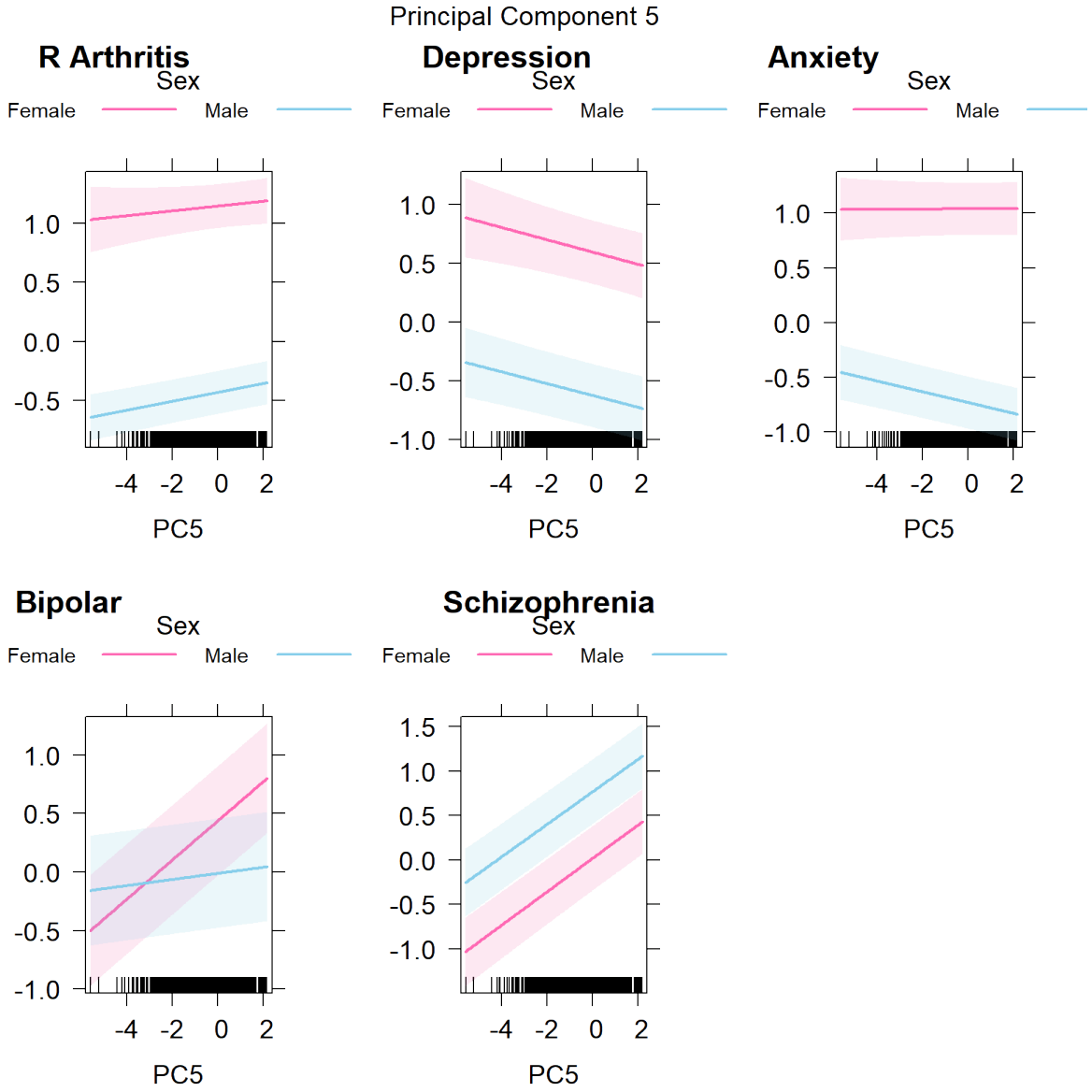

Figure A. 9. Effects of principal component on rheumatoid arthritis, major depressive disorder, anxiety disorders, bipolar disorder, and schizophrenia prevalence rates on males (blue) and females (pink). Shaded regions surrounding the lines represent 95% confidence intervals.

Coefficients from stress factor models

*Table A. 2. Model effects of stress factors on scaled prevalence rate of **major depressive disorder**. '*' indicates a significant p-value with $\alpha<0.05$.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	0.653	0.143	4.576	4.75E-06 *

Sex (male)	-1.146	0.054	-21.215	< 2 E-16 *
Alcohol use	0.040	0.023	1.761	7.82E-02
Bullying	0.027	0.010	2.592	9.55E-03 *
Mat. mort.	-0.019	0.015	-1.255	2.10E-01
Child. Assault	0.018	0.021	0.863	3.88E-01
Drug use	0.024	0.010	2.503	1.23E-02 *
Year	-0.006	0.001	-7.747	9.45E-15 *
Poverty	0.034	0.043	0.784	4.33E-01
Sex(m) x alcohol	-0.016	0.022	-0.729	4.66E-01
Sex(m) x bullying	-0.016	0.011	-1.493	1.35E-01
Sex(m) x mat. mort.	0.126	0.038	3.322	8.92E-04 *
Sex(m) x child. assault	-0.008	0.030	-0.278	7.81E-01
Sex(m) x drug use	-0.029	0.010	-2.974	2.94E-03 *
Sex(m) x year	0.005	0.000	13.630	< 2 E-16 *
Sex(m) x poverty	-0.045	0.013	-3.339	8.41E-04 *

*Table A. 3. Model effects of stress factors on scaled prevalence rate of **combined anxiety disorders**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	0.709	0.111	6.378	1.79E-10 *
Sex (male)	-1.349	0.049	-27.337	< 2 E-16 *
Alcohol use	0.050	0.020	2.544	1.10E-02 *
Bullying	0.006	0.009	0.649	5.16E-01
Mat. mort.	-0.020	0.013	-1.532	1.25E-01
Child. Assault	-0.039	0.018	-2.162	3.06E-02 *

Drug use	-0.015	0.008	-1.771	7.66E-02
Year	0.002	0.001	2.236	2.53E-02 *
Poverty	-0.009	0.028	-0.314	7.54E-01
Sex(m) x alcohol	-0.049	0.019	-2.570	1.02E-02 *
Sex(m) x bullying	0.003	0.009	0.366	7.14E-01
Sex(m) x mat. mort.	0.023	0.029	0.785	4.33E-01
Sex(m) x child. assault	0.048	0.024	2.009	4.46E-02 *
Sex(m) x drug use	0.013	0.008	1.533	1.25E-01
Sex(m) x year	-0.001	0.000	-3.161	1.57E-03 *
Sex(m) x poverty	0.000	0.011	0.006	9.95E-01

*Table A. 4. Model effects of stress factors on scaled prevalence rate **bipolar disorder**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	0.337	0.203	1.660	9.68E-02
Sex (male)	-0.316	0.026	-12.094	< 2 E-16 *
Alcohol use	-0.005	0.002	-2.427	1.52E-02 *
Bullying	0.002	0.001	2.182	2.91E-02 *
Mat. mort.	0.002	0.001	1.995	4.61E-02 *
Child. Assault	0.007	0.002	3.511	4.47E-04 *
Drug use	0.003	0.001	3.383	7.16E-04 *
Year	2.0E-04	4.9E-05	4.070	4.69E-05 *
Poverty	-0.009	0.008	-1.059	2.90E-01
Sex(m) x alcohol	1.1E-04	0.002	0.047	9.62E-01
Sex(m) x bullying	-0.013	0.002	-7.156	8.32E-13 *

Sex(m) x mat. mort.	0.020	0.010	2.007	4.47E-02 *
Sex(m) x child. assault	-0.024	0.009	-2.845	4.44E-03 *
Sex(m) x drug use	-0.005	0.001	-4.207	2.58E-05 *
Sex(m) x year	4.3E-04	6.0E-05	7.198	6.13E-13 *
Sex(m) x poverty	-0.003	0.002	-1.493	1.35E-01

*Table A. 5. Model effects of stress factors on scaled prevalence rate of **schizophrenia**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	-0.060	0.183	-0.328	7.43E-01
Sex (male)	0.399	0.037	10.719	< 2 E-16 *
Alcohol use	0.028	0.009	2.983	2.85E-03 *
Bullying	0.023	0.004	5.762	8.31E-09 *
Mat. mort.	-0.014	0.006	-2.397	1.65E-02 *
Child. Assault	0.047	0.009	5.137	2.79E-07 *
Drug use	0.041	0.004	10.269	< 2 E-16 *
Year	-0.001	2.2E-04	-4.441	8.94E-06 *
Poverty	-0.158	0.019	-8.487	< 2 E-16 *
Sex(m) x alcohol	-0.006	0.009	-0.689	4.91E-01
Sex(m) x bullying	-0.021	0.005	-3.814	1.37E-04 *
Sex(m) x mat. mort.	-0.078	0.025	-3.097	1.95E-03 *
Sex(m) x child. assault	-0.022	0.020	-1.067	2.86E-01
Sex(m) x drug use	-0.061	0.004	-14.353	< 2 E-16 *
Sex(m) x year	-1.2E-04	1.8E-04	-0.689	4.91E-01
Sex(m) x poverty	-0.043	0.007	-6.595	4.24E-11 *

Coefficients from principal component models

*Table A. 6. Model effects of principal components on scaled prevalence rate of **rheumatoid arthritis**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	1.068	0.097	11.060	< 2 E-16 *
Sex (male)	-1.562	0.033	-46.960	< 2 E-16 *
PC1	0.462	0.012	38.300	< 2 E-16 *
PC2	-0.169	0.014	-12.400	< 2 E-16 *
PC3	0.245	0.012	20.130	< 2 E-16 *
PC4	-0.164	0.023	-7.240	4.39E-13 *
PC5	0.020	0.017	1.170	2.42E-01
Year	0.006	0.001	4.360	1.27E-05 *
Sex(m) x PC1	-0.458	0.011	-40.350	< 2 E-16 *
Sex(m) x PC2	-0.013	0.014	-0.880	3.78E-01
Sex(m) x PC3	-0.035	0.013	-2.700	7.04E-03 *
Sex(m) x PC4	0.240	0.023	10.250	< 2 E-16 *
Sex(m) x PC5	0.017	0.018	0.990	3.20E-01
Sex(m) x year	-0.001	0.001	-0.630	5.27E-01

*Table A. 7. Model effects of principal components on scaled prevalence rate of **major depressive disorde**r. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value

Intercept	0.687	0.139	4.930	8.12E-07 *
Sex (male)	-1.294	0.039	-33.330	< 2 E-16 *
PC1	0.037	0.014	2.670	7.52E-03 *
PC2	-0.105	0.014	-7.480	7.45E-14 *
PC3	0.073	0.012	6.010	1.80E-09 *
PC4	-0.028	0.023	-1.220	2.21E-01
PC5	-0.052	0.018	-2.980	2.87E-03 *
Year	-0.007	0.001	-5.710	1.14E-08 *
Sex(m) x PC1	-0.044	0.013	-3.480	5.09E-04 *
Sex(m) x PC2	0.064	0.016	4.050	5.16E-05 *
Sex(m) x PC3	-0.073	0.014	-5.170	2.40E-07 *
Sex(m) x PC4	-0.010	0.025	-0.380	7.04E-01
Sex(m) x PC5	0.002	0.018	0.110	9.12E-01
Sex(m) x year	0.006	0.002	3.980	6.85E-05 *

*Table A. 8. Model effects of principal components on scaled prevalence rate of **combined anxiety disorders**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	1.051	0.123	8.510	< 2 E-16 *
Sex (male)	-1.811	0.028	-64.940	< 2 E-16 *
PC1	0.294	0.010	29.370	< 2 E-16 *
PC2	-0.019	0.011	-1.800	7.15E-02
PC3	0.075	0.009	8.000	1.20E-15 *
PC4	-0.204	0.017	-11.680	< 2 E-16 *
PC5	0.001	0.013	0.040	9.70E-01
Year	-0.001	0.001	-0.920	3.55E-01
Sex(m) x PC1	-0.264	0.009	-28.300	< 2 E-16 *

Sex(m) x PC2	-0.053	0.012	-4.570	4.96E-06 *
Sex(m) x PC3	-0.079	0.010	-7.530	5.06E-14 *
Sex(m) x PC4	0.121	0.019	6.470	9.55E-11 *
Sex(m) x PC5	-0.050	0.014	-3.610	3.11E-04 *
Sex(m) x year	0.003	0.001	2.740	6.10E-03 *

*Table A. 9. Model effects of principal components on scaled prevalence rate of **bipolar disorder**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	0.462	0.238	1.939	5.25E-02
Sex (male)	-0.482	0.016	-30.260	< 2 E-16 *
PC1	0.111	0.006	19.728	< 2 E-16 *
PC2	0.026	0.006	4.591	4.40E-06 *
PC3	0.054	0.005	10.884	< 2 E-16 *
PC4	-0.126	0.009	-13.737	< 2 E-16 *
PC5	0.167	0.007	23.506	< 2 E-16 *
Year	-0.002	0.001	-4.022	5.77E-05 *
Sex(m) x PC1	-0.136	0.005	-25.861	< 2 E-16 *
Sex(m) x PC2	-0.059	0.006	-9.202	< 2 E-16 *
Sex(m) x PC3	-0.020	0.006	-3.392	6.93E-04 *
Sex(m) x PC4	0.140	0.010	13.651	< 2 E-16 *
Sex(m) x PC5	-0.141	0.007	-18.942	< 2 E-16 *
Sex(m) x year	0.003	0.001	4.474	7.67E-06 *

*Table A. 10. Model effects of principal components on scaled prevalence rate of **schizophrenia**. '*' indicates a significant p-value with α<0.05.*

Coefficient	Coefficient estimate	Standard error	Z value	P-value
Intercept	0.070	0.186	0.376	7.07E-01
Sex (male)	0.754	0.030	24.834	< 2 E-16 *
PC1	0.204	0.010	20.320	< 2 E-16 *
PC2	0.066	0.010	6.913	4.74E-12 *
PC3	0.076	0.008	9.471	< 2 E-16 *
PC4	0.178	0.015	12.130	< 2 E-16 *
PC5	0.188	0.012	16.246	< 2 E-16 *
Year	-0.004	0.001	-4.870	1.11E-06 *
Sex(m) x PC1	-0.167	0.010	-16.538	< 2 E-16 *
Sex(m) x PC2	0.125	0.012	10.298	< 2 E-16 *
Sex(m) x PC3	-0.028	0.011	-2.619	8.82E-03 *
Sex(m) x PC4	0.297	0.019	15.622	< 2 E-16 *
Sex(m) x PC5	-0.005	0.013	-0.382	7.02E-01
Sex(m) x year	-3.3E-04	0.001	-0.288	7.73E-01