Risk factors and outcomes associated with generalised anxiety disorder: findings from a large, population study

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Summary

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Scientific interest in the clinical implications, public health importance, and risk factors of anxiety disorders has grown substantially in the past two decades. Despite this, the evidence base on anxiety is insufficient to inform health care planning and policy-making. Further research on the outcomes and risk factors associated with anxiety disorders, and ways of mitigating these risks is needed.

One of the aims of this thesis was to provide an overview of the existing literature on the prevalence of anxiety in adults living in countries across the globe, and to describe the prevalence in the context of various health states and life stages. Because generalised anxiety disorder is one of the most common psychiatric conditions in the population, the remainder of the thesis focused on this disorder and aimed to explore its links with health service use and mortality. Risk for this condition was also explored and area deprivation was studied as a possible determinant. Since depression is commonly studied alongside anxiety, the relationship between the residential environment and major depressive disorder was also assessed. Finally, to provide insight into the mitigation of risks of generalised anxiety disorder, a study of coping mechanisms was undertaken.

Primary study findings from this thesis are based on the European Prospective Investigation of Cancer in Norfolk, a large, population study of British people over the age of 40.

Results from the systematic review showed that anxiety is common in population sub-groups around the world, with women, younger people, and those suffering from chronic physical conditions, such as cancer and cardiovascular disease being particularly affected. Results from the primary studies of the thesis showed that generalised anxiety disorder is associated with increased risk for deaths, though it is not significantly associated with non-psychiatric

hospital admissions. Results from the risk factor analyses showed that living in a deprived area is associated with generalised anxiety disorder in women and major depressive disorder in men. The risk mitigation analysis indicated that sense of coherence is an important coping mechanism that can protect against generalised anxiety disorder among women living in disadvantaged circumstances.

My work has shown novel associations and attempted to provide a more complete picture of one of the most common psychiatric conditions in the population by focusing on several angles: health outcomes, risk factors, and ways of mitigating risks.

I dedicate this thesis to all the people affected by anxiety.

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List of Abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence Interval
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
EPIC	European Prospective Investigation of Cancer
FU	Follow-up
GAD	Generalised anxiety disorder
GEE	Generalised estimating equation
HADS	Hospital Anxiety and Depression Scale
HLEQ	Health and Life Experiences Questionnaire
HLQ	Health and Lifestyle Questionnaire
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard ratio
ICD	International Classification of Disease
IMD	Index of Multiple Deprivation
IRR	Incidence rate ratio
MCS	Mental component summary
MDD	Major depressive disorder
MS	Multiple sclerosis
NHS	National Health Service
OCD	Obsessive compulsive disorder
ONS	Office of National Statistics
OR	Odds ratio
PCS	Physical component summary
SD	Standard deviation
SES	Socio-economic status
SF-36	Medical Outcomes Study 36-Item Short Form
SOC	Sense of coherence

STAI	State-Trait Anxiety Inventory
PTSD	Post-traumatic stress disorder
WHO	World Health Organization
ZINB	Zero inflated negative binomial regression

List of Publications and Presentations from this Dissertation

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1 Introduction

Generalised anxiety disorder (GAD) is a prevalent mental health problem, which can lead to negative health consequences, such as disability and risk of suicide. [1, 2] Yet, despite these consequences, relatively little is known about its risk factors (particularly those at the area level), protective factors, and potential impact that this disorder can have on people and society. Further insight into this is needed to inform prevention and intervention efforts.

This thesis uses data from a British population-based cohort study to assess the impact that GAD has on the population in terms of risk of early death and non-psychiatric hospital admissions. To gain insight into possible risk factors, area deprivation as a determinant of anxiety is explored among women and men separately. Since depression is commonly studied alongside anxiety, further insight into area deprivation as a possible risk factor for major depressive disorder (MDD) among women and men is also provided. To determine whether risks of GAD can be mitigated, coping mechanisms among those exposed to adverse circumstances, such as living in disadvantage, are explored.

Thesis findings are presented in the context of previous literature, and my studies address some of the methodological limitations of current research. This chapter presents a brief introduction to anxiety and the rationale for studying this mental health problem.

1.1 Definition

Anxiety is "an abnormal and overwhelming sense of apprehension and fear often marked by physical signs (such as tension, sweating, and increased pulse rate), by doubt concerning the reality and nature of the threat, and by self-doubt about one's capacity to cope with it." [1] All animals experience what humans characterise as anxiety when faced with threatening or dangerous situations. In these circumstances, anxiety is beneficial because it helps us to overcome challenges and deal with obstacles, potentially saving our lives. When this anxiety emotion is taken to the extreme and becomes counterproductive, debilitating, and impairing, that is when an anxiety disorder may ensue. When it becomes difficult to sleep at night, concentrate on tasks, or form relationships with others because of symptoms, psychopathology may be present. [2,3]

Anxiety disorders have been classified by the International Classification of Diseases (ICD) [4] and the Diagnostic and Statistical Manual of Mental Disorders (DSM) [5], the more commonly-used classification system in epidemiology studies. While these conditions represent a separate nosological group in the DSM, they are part of the "neurotic, stress-related and somatoform disorders" in the ICD.

1.2 Brief overview of anxiety disorders

Anxiety disorders are the most common class of psychiatric conditions in the general population. [6, 7] Approximately 4 out of every 100 people around the world are affected by these disorders [8], with Euro-Anglo cultures showing the highest prevalence. [9] In 2010, the one-year prevalence of anxiety disorders for individuals living in North America was reported to be one of the highest and estimated to be 7.5% (uncertainty intervals: 6.6%-8.6%) for women and 4.0% (uncertainty intervals: 3.5%-4.5%) for men. [8] These conditions often start early in life, are unremitting, and have a persistent course. [6, 10, 11] Their annual cost has been estimated to be $ 42.3 billion in the US [12], and according to the Global Burden of Disease Study, anxiety disorders have been linked to approximately 26.8 million disability adjusted life years. The Global Burden of Disease study examined mental disorders across world regions, as detailed elsewhere. [13, 14]

Anxiety can increase the risk of health service use and related costs, the development of other psychiatric disorders, such as MDD, substance abuse, and personality disorders, and can lead to suicide. [2] Those affected are more likely to have decreased work productivity and lower educational achievement compared to people without anxiety. [15, 16]

To gain a deeper understanding of anxiety, a brief historical perspective is warranted.

1.3 Brief historical perspective of anxiety

Over a hundred years ago, anxiety was conceptualized by Freud as 'neurosis'. He described anxiety as falling into one of four syndromes: 1) general irritability, 2) chronic apprehension/anxious expectation, 3) anxiety attacks, and 4) secondary phobic avoidance. He believed that anxiety could either be "free-floating" and permanently present in consciousness, or could occur in short bursts as in an anxiety attack. He drew his theories on the aetiology of anxiety on psychoanalysis, which attempted to explain the links between internal human drives and societal expectations. Although psychiatrists had difficulty accepting psychoanalytic theories, they embraced this field after seeing soldiers returning home from World War I with 'traumatic neuroses'. This provided the impetus for the publication of the DSM-I. [2, 17]

Both the DSM-I and DSM-II referred to anxiety as 'neuroses', and diagnostic algorithms in these manuals were primarily driven by unproven psychoanalytic theories. When scepticism began to grow about Freud's theories, researchers started moving away from psychoanalysis and towards objectively-measured data to characterise disorders; researchers started examining factors, such as age of onset, patterns of chronicity and severity of symptoms to make diagnoses. [2, 17]

The DSM-III was the first manual to include more valid and reliable anxiety assessment methods. In the DSM-III, 'anxiety disorders' were first described and divided into panic disorder and GAD, and phobic disorder was divided into agoraphobia, social phobia, and simple or specific phobia. As agoraphobia seemed to frequently co-occur with panic disorder, these two were linked in the DSM-III-R. Further changes in the nomenclature of anxiety disorders occurred in the later iterations of the DSM; however, it is beyond the scope of this thesis to go into such detail. [2, 3, 17]

Although the evolution of the measurement and identification of anxiety disorders has improved substantially since the first edition of the DSM, it was not until the past two decades that research interest in this field really began to grow and further improvements to the classification of anxiety created more refined psychopathology categories. Increased interest in this field was driven by greater recognition of the burden of anxiety and implications associated with untreated illness. [17] However, in spite of increased research output on this topic, several methodological issues have been plaguing the field. A discussion of these is warranted to better understand study findings and place them into context. Several studies have been undertaken on the number of people affected by anxiety in countries around the world; however, differences in psychopathology measuring instruments and diagnostic criteria, changing case definitions, and variability in sampling and participant interview techniques have all contributed to heterogeneity in study findings. These will be discussed next.

1.4 Methodological issues plaguing the anxiety field

Research interest in a condition is partly driven by the number of people that it affects – if it affects a large proportion of the population, it is deemed to have potential public health significance. A number of studies have been carried out to determine the number of people affected by anxiety or its prevalence in regions around the world. However, many of these studies are limited for several reasons. The instruments used to measure anxiety in non-western parts of the world were largely developed for use on western populations and might not capture the mental illness that is experienced in non-western contexts. [9, 18-20] As such, differences in prevalence observed between cultures may be real or could represent a methodological artifact. [9] In addition to the challenge in capturing cultural presentations of psychiatric disorders, there are also different types of instruments used to identify anxiety, such as diagnostic interviews, medical records, administrative databases, and self-reported questionnaires. [21] The application of different diagnostic criteria to anxiety assessment tools further contributes to the heterogeneity in prevalence estimates between studies. [22] For example, older studies using DSM criteria relied on hierarchy rules, which prohibited the assignment of certain conditions in the presence of others, and this led to the underestimation of various mental disorders. [17]

Other methodological issues arise with changes in case definitions (what constitutes an anxiety disorder) and trends in participant sampling and interview techniques – these issues have been discussed by various systematic reviews on the burden of mental disorders. [8, 21] Various ways of sampling participants and interview techniques have become increasingly popular in recent times, such as multistage random sampling and the use of probe questions. [8, 23, 24] This too can determine who is identified as an anxiety case and recruited into studies. Further, when selecting samples for studies, changes in the methods of measurement of the conditions that actually give rise to anxiety (such as, the denominator in prevalence estimates or the 'cases' in case-control studies) could also pose issues. Case definitions and assessment instruments for identifying physical diseases or neurologic conditions linked to anxiety have changed over time, and this can impact numbers reported in studies. For example, detection of multiple sclerosis (MS) has improved with advances in magnetic resonance imaging (MRI), which means that more cases of MS are potentially now being detected than previously. [21, 25] If anxiety is frequently present in the context of MS, then higher comorbidity estimates for both conditions are now being reported.

Finally, the sampling framework also needs to be considered when comparing study estimates (community vs. clinic-based settings) on the prevalence of anxiety. These issues need to be taken into account when interpreting study findings.

1.5 Risk factors and outcomes linked to anxiety

A number of systematic reviews have been undertaken on the burden of anxiety. Although each review is informative in its own right, it is not possible to acquire a complete understanding of the overall burden of anxiety across populations, settings, and time by examining single reviews. To provide a complete picture of the state of knowledge on the prevalence of anxiety disorders in populations across the globe for this thesis, a review of reviews was indicated.

Once a clearer picture of the burden of anxiety is provided, it is important to determine the consequences associated with the mental illness. There is much less literature on the outcomes, risk factors, and ways of mitigating the risks of anxiety – at least in comparison with disorders, such as depression. If anxiety leads to deleterious health outcomes, such as early death and is found to place a strain on an already-overburdened health care system, then this will be important for clinicians, scientists, and policy-makers to know about so that measures can be taken. A disorder is judged to be 'important' for public health not only on its frequency but also the sequelae with which it is associated and its societal impact. [17] Research on this is limited. If anxiety is linked to serious health consequences such as health service use and early death, research can begin to uncover its risk factors so that prevention and intervention efforts can be appropriately targeted. Finally, information on ways of mitigating risks for anxiety is needed to inform prevention programmes.

The next section presents a detailed rationale on the need to conduct a review of reviews on the burden of anxiety, and the state of knowledge on important outcomes and risk factors. Since GAD is one of the most common anxiety disorders in the general population [26, 27] and will be the focus of this thesis, the literature reviewed in the next section will focus on GAD (with the exception of the review of reviews). Briefly, GAD is marked by excessive and pervasive worry occurring for at least six months in addition to symptoms, such as restlessness, muscle tension, insomnia, concentration difficulties, fatigue, and irritability. [3]

1.5.1 The burden of anxiety across the globe

Given that anxiety disorders are among the most common mental health problems in the general population and clinical settings, tend to have an early age of onset and persist across the lifecourse [6, 10, 11, 28], it is important to determine the burden of these conditions in populations across the globe to provide an evidence base for public health policy and service planning. Such information would be particularly relevant for resource-poor countries lacking mental health policies. [9] As mentioned previously, literature on the burden of anxiety is fragmented and heterogeneity in study methodology hampers comparability of findings across studies. Furthermore, a number of reviews are based on highly selected populations, further contributing to problems with generalisability. A synthesis of the literature on the burden of anxiety reveals the state of knowledge, gaps in research and areas where further studies are needed.

A global synthesis of prevalence studies can identify existing evidence on sub-groups with the highest burden of anxiety in regions across the world. Risk for anxiety has been shown to be higher in certain segments of the population, such as those who have experienced marital disruption [29], socioeconomic disadvantage [30], people living in urban environments [31], and those exposed to trauma [32]. A synthesis of the literature can provide a better understanding of those who are most affected.

A systematic review of reviews can also provide insight into time trends of anxiety. Research conducted in the United States (US) [24] suggested that anxiety increased between 1950 and 1990, and pointed to changes in family structure, environmental threats, sexual norms, and social bonds as possible driving factors. This research, however used symptom screening instruments to measure anxiety, rather than structured, reliable, and validated assessment methods, such as the DSM. Knowing whether anxiety has increased over time in regions around the world can be used to inform health care policy, health care funding allocation, and provide impetus to accelerate the deployment of health care services. [8]

To understand who is most affected by anxiety, an examination of this mental health problem in the context of other conditions, such as cancer or diabetes is warranted. This is important, because the presence of psychiatric comorbidity can lead to decreased quality of life and reduced compliance with medication [33, 34] – such findings have clinical implications. Furthermore, treatment for a psychiatric condition may aggravate a second health problem. Thus, adequate recognition of mental illness and knowing which patients are most likely to have anxiety is important to direct intervention efforts. [35, 36]

1.5.2 Risk factors, outcomes, and risk mitigation in relation to GAD

As previously mentioned, information on the outcomes, risk factors, and ways of mitigating risks of anxiety is important for public health efforts. A brief review of the state of knowledge on this will be presented – the focus will be GAD, because it is one of the most common anxiety disorders in the population [26, 27] and is the focus of this thesis.

GAD is characterised by symptoms, such as restlessness, insomnia, concentration difficulties, fatigue, irritability, and muscle tension. These symptoms can lead to physical health problems, such as backaches, headaches, heart palpitations and chest tightness. People with GAD overestimate the likelihood of negative events happening to them, they tend to perceive the future negatively, and tend to interpret ambiguous situations as threatening. They can worry about several aspects of life, such as career, finances, work, and relationships. [2, 3] The methods chapter contains a more detailed description of GAD according to the DSM-IV criteria.

1.5.2.1 Anxiety and early mortality

Several investigators have examined the possible link between anxiety and mortality, with some studies reporting positive associations [37-39], absent associations [40, 41], or even improved survival in those with anxiety [42]. A number of studies are longitudinal and population-based; however, most of these are limited by their small sample sizes, short follow-up periods, and use of generic measures, such as the State-Trait Anxiety Inventory (STAI) to assess psychopathology. Short follow-up periods can make it difficult to detect potentially chronic effects of anxiety on health. Further, using generic measures such as the STAI can fail to capture aspects of anxiety (such as, the excessive, uncontrollable worry in

GAD) that may be associated with increased mortality. [43] A meta-analysis [44] of 12 studies on the association of anxiety post-myocardial infarction with mortality indicated that only one of these studies measured individual disorder, namely GAD. Another limitation of previous research has been the predominant focus on either all-cause mortality or early death from cardiovascular disease (CVD); significantly fewer studies have investigated other major causes of death, such as cancer. Recent research, however, has begun turning that around and has started examining the link of individual psychiatric disorders with various outcomes. Before I present results from these studies, I will briefly synthesize the latest review on the association between anxiety and all-cause mortality.

A systematic review [45] of prospective cohort studies examined the link between anxiety and all-cause mortality. It showed that clinically anxious people had a 9% higher chance of dying early compared to controls. When studies based only on community samples were aggregated, the link with all-cause mortality disappeared. Studies that adjusted for depression also failed to find an association. There are several limitations associated with the community-based studies in this review. Some used old criteria (ex. DSM-III) with low reliability for case ascertainment, others did not assess individual anxiety disorders (which might be more clinically meaningful), and failed to adjust for important confounders such as medical history and disability [46, 47]. The HUNT study [47] of over 60,000 people living in Norway found that total anxiety had a U-shaped relationship with total mortality; however, the exposure was anxiety symptoms experienced in the past 2 weeks captured using the Hospital Anxiety and Depression-Anxiety (HADS-A) scale. The HADS has been found to differentiate poorly between anxiety and depression. [48] Other studies [49, 50] found that total anxiety symptoms were not linked to total mortality, however they examined anxiety symptoms experienced in the past 4 weeks using the Goldberg Depression and Anxiety scale. [49] Symptom scales might not capture anxiety conditions as well as structured, rigorous assessment methods, such as the DSM. Also, the items in symptoms scales or checklists might be less specific than those in clinical interviews. [43] A number of studies on mortality also had small sample sizes [49-51], making it difficult to find meaningful associations. Some studies examined individual anxiety disorders, such as GAD, however, these studies used old criteria with low reliability (ex. 'generalised anxiety' measure based on DSM-II [52]), had very small sample sizes [51, 53], and lacked generalisability because they were restricted to a segment of the population, such as very old people [54].

Studies on individual anxiety disorders

The most recent study on GAD [55] is a prospective, cohort study of over 3,000,000 people using Danish register data; it showed that people with anxiety had a 62% higher chance of dying prematurely compared to those without GAD over a 10-year follow-up period, after accounting for depression. The link between GAD and major causes of death, such as cancer mortality was not examined. When the authors examined the association between total anxiety disorders and mortality from specific causes, they failed to find a link with cancer mortality [55]; these findings, however, are unreliable because of clinical heterogeneity in anxiety diagnoses. If a particular anxiety disorder is related to early death, its effect is diluted if lumped together with other disorders that are not associated with mortality. Furthermore, the authors used treatment for anxiety (psychiatric inpatient or outpatient contact for anxiety disorders) as their exposure variable. Using register treatment data to define anxiety is problematic for several reasons. First, the accuracy of coding of psychiatric illnesses might be suboptimal if done by a non-clinical administrator rather than a clinician. Coding accuracy can also be an issue in a non-specialist centre: although mental health codes are rigorously defined, the vast majority of general practitioners who are not psychiatrists might not be familiar with subtle aspects to the coding definitions. Furthermore, single codes can make it difficult to capture a mixed picture, where there may be more than one relevant diagnosis. Second, recording bias might present another problem where only the most severe conditions are recorded, or because of incentives to record various conditions, only some illnesses are captured (because some other event influences likelihood of recording or because there is an incentive to record various problems). Potentially, recording of data may vary depending on the implications of subsequent data use. In sum, using register treatment data to define anxiety has limitations. Structured assessment methods using valid and reliable criteria, such as that stipulated by the DSM should be used to identify those with mental disorders.

Another register-based study [56] of over 3,000,000 Danish people showed that individuals with obsessive compulsive disorder (OCD), which was considered an anxiety disorder in DSM-

IV, had an increased risk of premature mortality compared with the general population. This study, however, suffers from the same limitations as the latter study.

Further population-based research using structured assessment methods for psychiatric disorders, and large samples is needed. Also, further research on GAD, one of the most common mental health problems in the population is needed.

1.5.2.2 Health service use among those with anxiety

Many studies examining the association between mental illness and non-psychiatric health service use have focused on depression, panic disorder, and post-traumatic stress disorder (PTSD), while significantly fewer have focused on disorders, such as GAD. The link between depression and health service use has been well-established in several clinical and community-based studies [57]. Much less research has been conducted on anxiety, although links with health service use have been found. Total anxiety disorders have been shown to increase the risk for primary care service use, and consultations in general medical, emergency and specialty settings, such as cardiology and dermatology [58, 59]. This research, however, has been based on patients from outpatient clinics, thus leading to possible selection bias. PTSD has also been associated with health service use, such as increased investigations and prescribed medications compared to those without this disorder, but much of the literature on this [60, 61] has been based on highly-selected samples with limited generalisability. Two of the more recent studies on GAD showed it to be associated with health care use. One Canadian study [62] suggested a higher rate of medical visits to primary care practitioners in those with GAD, while a US study [63] also found a higher frequency of specialty medical care visits in affected individuals. Both of these studies recruited clinical samples, with the potential for self-selection bias. None of these studies assessed whether the severity of anxiety, such as frequency of lifetime episodes, chronicity of the disorder, and age of onset, contributes to even higher health service use rates. A severe course of anxiety could lead to even worse outcomes, thus such information is important to know.

Further research using a population-based cohort and rigorous anxiety assessment tools is needed. Since GAD is one of the most common anxiety disorders in the general population, further research on its links with health service use is needed.

1.5.2.3 Area deprivation as a risk factor for GAD

Literature on the possible impact of the environment or living context on the mental health of women and men separately is scarce and findings are mixed. Of the paucity of studies available, most of the research is cross-sectional, population-based, and conducted in the US or Canada. Research from North America [64, 65] showed that state income inequality measured using the Gini coefficient, and disadvantage measured using the Census were linked to symptoms of depression in women, but not in men. This contradicted earlier North American research [66, 67], which found no gender differentials in relation to depression. In the UK, links between area deprivation and common mental disorders have been found for women only. [68]

Research on the possible influence of the environment on anxiety is even scarcer. Only one contextual study [69] has been conducted on the links between GAD and socioeconomic disadvantage among women and men, separately. No association with anxiety was found, however the area measure of socioeconomic disadvantage was based only on the local unemployment rate and the median area income. Other indexes, such as the Townsend index would have been preferable, because they capture several important aspects of the living context, such as non-home ownership, non-car ownership, and overcrowding. Also, the contextual study on GAD [69] measured generalised anxiety symptoms experienced in the past week using a symptom checklist, rather than psychiatric disorder identified using a structured instrument and validated criteria, such as the DSM. Further research on the influence of the places in which we live on risk of having anxiety is needed and using sound criteria for measuring psychopathology.

Anxiety disorders affect a substantial proportion of the population (around 4 out of every 100 people) [8], and are associated with disability and impairment [17]. Therefore, knowing whether the neighbourhoods we live in can increase risk of having these conditions is important for prevention and intervention efforts. It is equally important to assess possible relationships with the environment from a gendered perspective.

Women and men tend to experience the places in which they live differently, and this can lead to differential health outcomes. First, the genders tend to ascribe different levels of importance to neighbourhood factors. For example, women are much more fearful of living in an unsafe neighbourhood where assault is a possible. If they fear for their safety, they may restrict leisure activities such as walking, which can negatively impact their mental health. [70, 71] Second, women are exposed to different types of stressors because of differences in gender norms. Gender is a status position which has been linked to access to material and social resources. Women are more likely to be single parents, have lower incomes, have their educational attainment and career trajectories interrupted because of domestic duties, and are given different types of job roles (which can expose them to hazards) than men. [65-68, 72] As such, living in disadvantage may be particularly detrimental for women's mental health.

Previous studies have not examined whether living in a deprived area can increase the risk for GAD in women and men separately. Knowing whether one of the genders is particularly affected can be used to deploy mental health resources to those areas and population sub-groups needing them most.

1.5.2.4 Area deprivation as a risk factor for depression

A substantial proportion of those with anxiety have had depression at some point in their lives [2], and a number of the risk factors linked to anxiety are similar for depression. Comorbidity between these two disorders is also common; however, it might be more meaningful from a clinical standpoint to assess these two problems separately.

Depression is a leading cause of disability worldwide, and can increase the risk for impairment and suicide. [73] As with anxiety, many studies have examined individual-level risk factors of depression, such as, history of trauma and stressful life events. [74] However, the residential environment can have a profound influence on mental health, independent of individual-level factors. [75] Three recent systematic reviews [76-78] on the links between neighbourhood characteristics and depression have had mixed findings – although a number of primary studies within these reviews found statistically significant associations, others did not. The heterogeneity in findings was due to varying length of follow-up time of participants, variation in the definition of neighbourhood boundaries (administrative census tracts, buffers around participants' homes, self-reported delimitations of neighbourhoods), indices or single items used to define neighbourhood characteristics, study design (cross-sectional versus longitudinal studies), confounders that were adjusted for in analyses, sample characteristics, and ways of measuring psychopathology. A number of studies within these reviews failed to adjust for important confounders such as medical history, sampled old individuals or those from specific racial/ethnic groups thus lacking generalisability, and assessed symptoms of depression rather than disorders. Furthermore, some studies used place-based indicators which might not be relevant for depression (e.g., density of neighbourhood alcohol outlets). Therefore, additional studies using representative population-based samples with adequate adjustment for confounders and large sample sizes are needed. In addition, studies measuring neighbourhood characteristics using theoretically-sound indices capturing important aspects of the environment such as non-home ownership and non-car ownership are necessary.

Finally, research on the relationship with depression according to gender is lacking and needed. Some of the literature on this topic was reviewed in the previous section. Knowing that one gender is at greater risk of developing depression when exposed to neighbourhood characteristics, such as deprivation may help to target interventions and more effectively allocate scarce resources. This thesis will focus on MDD which is described as feeling sad or depressed, or losing interest in activities or work which once provided pleasure for a period of at least two weeks; the affected individual also experiences symptoms such as, gaining or losing weight, having trouble falling asleep or sleeping too much, feeling tired or low on energy, and feeling unable to sit still or feeling slowed down.

1.5.2.5 Coping mechanisms among those with anxiety

The residential environment, such as one characterised by deprivation can have harmful effects on mental health independent of personal circumstances. [75, 79] Thus, building on people's strengths and summoning their coping skills might be a way of overcoming the stress and adversity associated with living in deprived areas. [68, 80]

Personal dispositions and attitudes to life can be health-promoting resources; [81] studies [82, 83] showed that some people exposed to adversity have good coping skills and are able to maintain their well-being, while others with poor coping skills develop mental disorders, impairment, and are at increased risk for mortality. The question therefore is, what differentiates these two groups?

In 1987, Aaron Antonovsky coined the term "sense of coherence" (SOC), which describes the inner resources that an individual has to overcome stress and adversity, and a way of viewing life as predictable and meaningful. People with a strong SOC believe that the challenges encountered in life are worthy of investment and can be understood (comprehensibility); that internal and external resources are available to the individual to meet life demands (manageability); and that life has a purpose and enough meaning to devote these resources to overcoming life challenges (meaningfulness). [84] The concept of SOC stems from salutogenesis theory, which focuses on people's strengths as determinants of wellbeing, and coping resources to preserve health. People with a strong SOC tend to experience better health and show a higher quality of life than those with a weak SOC; this was reported by two systematic reviews. [80, 81] Both reviews included 458 scientific publications and 13 doctoral theses, and showed that a strong SOC promotes quality of life in people with a host of conditions, such as schizophrenia, coronary heart disease, ischemia, and elderly people with hip fractures. A strong SOC was related to good physical and self-perceived health, and was negatively associated with anxiety, depression, and post-traumatic stress disorder (PTSD). [80, 81]

SOC and health are correlated but independent constructs, and the presence of protective factors, such as coping resources, is not the same as the absence of risk factors. Also, the factors that are associated with SOC have been shown to be somewhat different from those that increase the risk for anxiety and depression. [80, 81]

Weak SOC has been studied as a risk factor for stress and subsequent mental disorders, and it has also been examined as a moderator of this association. Living in deprivation can give rise to stress [69]; therefore, it is important to determine whether a strong SOC can buffer the effects of area deprivation on mental health, particularly risk of having GAD.

The literature on SOC and mental health is highly fragmented, based on a number of cross-sectional studies, and sometimes using highly-selected samples such as those exposed to extreme circumstances or traumatic events. Studies are based on small sample sizes; use incomplete adjustment for covariates and fail to consider important confounders such as personal socioeconomic circumstances, medical history and behaviour risk factors; and assess coping in relation to stress or stressful life events, such as exposure to wars. For example, two studies examined SOC in people living in urban and rural communities in Israel that were exposed to missile attacks, making generalisability to the wider population difficult. Both studies examined SOC in small samples of 138 teenagers and 150 adults, and measured anxiety using the STAI [85, 86]. Measuring symptoms of anxiety rather than individuals disorders might not be clinically meaningful, and items from symptom scales often lack the specificity of clinical interviews. The studies [85, 86] on people exposed to missile attacks also failed to control for important confounders, such as demographic factors and medical history, which might lead to residual confounding. A third cross-sectional study [87] conducted in Norway examined whether SOC buffers stress and reduces anxiety in a sample of 1209 school children. It also used the STAI to assess anxiety, failed to adjust for important confounders, such as medical and psychiatric comorbidities, and used a cross-sectional design, making it difficult to establish temporality between exposure and outcome. [87]

There is a scarcity of research on coping in relation to the living context, and no study has examined whether SOC can buffer the effect of area deprivation on risk of having GAD. Further research on this issue using a large, population-based sample with adequate adjustment for covariates is needed. Also, further studies focusing on individual anxiety disorders, such as GAD are necessary.

However, before any research on coping mechanisms, risk factors and outcomes is undertaken, it is first necessary to gain an understanding of the burden of anxiety in the population. To do this, I conducted a systematic review of reviews on the prevalence of anxiety disorders in countries around the world. Results are presented next.

2 An umbrella review of the prevalence of anxiety disorders in adult populations

ABSTRACT

Introduction

A fragmented research field exists on the prevalence of anxiety disorders. Here I present the results of an umbrella review on this topic. I included the highest quality studies to inform practice and policy on this issue.

Methods

Using PRISMA methodology, extensive electronic and manual citation searches were performed to identify relevant reviews. I used PRISMA in accordance with previous research. Screening, data extraction, and quality assessment were undertaken by two reviewers. Inclusion criteria consisted of systematic reviews or meta-analyses on the prevalence of anxiety disorders that fulfilled at least half of the AMSTAR quality criteria.

Results

I identified a total of 48 reviews and described the prevalence of anxiety across population sub-groups and settings, as reported by these studies. Despite the high heterogeneity of prevalence estimates across primary studies, there was emerging and compelling evidence of substantial prevalence of anxiety disorders generally (3.8–25%), and particularly in women (5.2–8.7%); young adults (2.5–9.1%); people with chronic diseases (1.4–70%); and individuals from Euro/Anglo cultures (3.8–10.4%) versus individuals from Indo/Asian (2.8%), African (4.4%), Central/Eastern European (3.2%), North African/Middle Eastern (4.9%), and Ibero/Latin cultures (6.2%).

Conclusion

The prevalence of anxiety disorders is high in population sub-groups across the globe. Recent research has expanded its focus to Asian countries, an increasingly greater number of physical and psychiatric conditions, and traumatic events associated with anxiety. Further research on illness trajectories and anxiety levels pre- and post-treatment is needed. Few studies have been conducted in developing and under-developed parts of the world and have little representation in the global literature.

2.1 Introduction

Anxiety disorders–characterised by excessive worry, fear, hyperarousal, and avoidance-are some of the most common psychiatric conditions in the Western world. [2] The prevalence of anxiety disorders in the US is estimated to be 18% [29], and their annual cost in this region is reported to be $42.3 billion [12]. In the European Union (EU), 69 million people are affected by anxiety disorders in a given year, making them the most prevalent psychiatric conditions in the EU. [88] In 2010, they contributed to 26.8 million disability adjusted life years worldwide. [13] While a number of reviews have focused on the burden of depression and its economic, social, and health care policy implications, substantially fewer have assessed anxiety.

The past decade has seen increased research interest into anxiety disorders, in large part because of a greater recognition of their burden and the implications associated with untreated illness. Clinical reviews have shown that the presence of an anxiety disorder is a risk factor for the development of other anxiety and mood disorders and substance abuse. In clinical and population-based studies, the development of comorbidities makes the treatment of primary and secondary disorders difficult, contributes to low remission rates, poor prognosis and risk of suicide. [2, 89] Untreated anxiety has been associated with significant personal and societal costs, related to frequent primary and acute care visits, decreased work productivity, unemployment, and impaired social relationships. [2]

A number of primary studies on the prevalence of anxiety have been undertaken, but the variability in findings has made generalisability to the wider population difficult. This variability mainly results from differences in study setting (i.e., culture; clinical vs. population-based), age and sex composition of samples, length of follow-up, methods of anxiety assessment, and caseness criteria (i.e., types and number of disorders examined). Systematic reviews on the prevalence of these conditions in highly select, homogeneous population sub-groups have been undertaken, but the selective citation of such estimates presents a distorted view of the overall burden of anxiety and limits generalisability.

To overcome these limitations, I conducted a systematic review of reviews or an 'umbrella review', which is a document synthesizing findings from other systematic reviews (umbrella review link) focusing on specific topics. An umbrella review "focuses on a broad condition or problem for which there are two or more potential interventions and highlights reviews that address these potential interventions". [90, 91] The broad condition that I focused on was anxiety, specifically the prevalence of anxiety. Although I did not focus on interventions, I examined population sub-groups that may be affected by this condition and highlighted the reviews reporting the prevalence of anxiety in those population sub-groups. A strength of an umbrella review is that it gives the reader an overview about the state of knowledge in a particular area and combines relevant reviews together. [90, 91] The anxiety field is made up of a high number of narrow component reviews – synthesizing findings from these reviews is informative and provides a basis for decisions regarding resource deployment towards population sub-groups that are most affected by anxiety. [90, 91]

The aim of my umbrella review (systematic review of reviews) was to provide a comprehensive synthesis and description of the prevalence of anxiety disorders in the general population, as well as in clinical outpatient and inpatient groups affected by a range of chronic physical diseases and psychiatric disorders, as reported by individual reviews. Individuals recruited from the community can have different risk factor profiles than those sampled from clinical settings, potentially giving rise to different rates of mental health problems amongst these groups. [2, 89] As a result, the burden needs to be assessed across different settings and segments of the population. To provide insight into the demographic groups that are most affected, I reported on estimates for men and women and different age groups, if this information was available. Since a number of studies [2, 92, 93] have identified the need to better understand the geographical variation of mental health problems, I included reviews that captured studies conducted across the globe at national and sub-national levels. To provide insight into the chronicity of anxiety disorders, I provided period (i.e., 12-month) and lifetime prevalence estimates. If the duration criterion was not clearly stated or the 'point' or 'current' prevalence was indicated, I simply referred to these estimates as 'prevalence'.

Findings from this umbrella review will shed light on the groups that are most affected by anxiety disorders, and can be used to inform targeted screening and treatment efforts. This will be important in the planning of health services and the development of evidence-based policy. Finally, results from this review can be used to identify areas where further research is needed.

This is the first study to provide a comprehensive synthesis of the disparate findings from systematic reviews undertaken on the burden of anxiety across the globe and using a systematic approach.

2.2 Methods

2.2.1 Search strategy

I defined a systematic review in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [94] (appendix 1). I included high-quality reviews that reported the prevalence of anxiety disorders in the general population or clinic-based settings. I searched for reviews on young, middle-aged, and older adults with risk behaviours (i.e., drug abuse), chronic or infectious diseases, psychiatric conditions, who are vulnerable, and living in countries across the globe. Reviews on the treatment of anxiety were not included, as I consider this to be a separate review topic that would merit an in-depth analysis.

To identify reviews meeting the inclusion criteria, I searched Medline (inception-May, 2015), PsycInfo (1987-May, 2015), and Embase (inception-May, 2015) using combinations of keywords relating to anxiety and prevalence (appendix 2). Reference lists were hand-searched for additional reviews. Titles and abstracts of Non-English language articles were translated to assess relevance. I excluded unpublished data. The review protocol is registered on PROSPERO [95].

2.2.2 Inclusion criteria

I searched for reviews that reported the lifetime, period, or point prevalence (or simply 'prevalence') of GAD, obsessive-compulsive disorder (OCD), social anxiety disorder or social phobia, agoraphobia, panic disorder with or without agoraphobia, and simple or specific phobia, and anxiety not otherwise specified (NOS). Studies that reported the prevalence of aggregated anxiety disorders, sub-threshold disorders, or anxiety symptoms were also included. Reviews were included regardless of the sampling framework used in primary studies.

Reviews were included regardless of the method of anxiety assessment. Specifically, reviews capturing primary studies on threshold and subthreshold disorders that were assessed through fully, semi-, or unstructured interviews administered by clinicians or trained professionals, symptom checklists, clinician diagnoses, and self-report were accepted. Interviews or self-reported questionnaires that mapped to standard classificatory systems, such as the DSM [5] or the ICD [4], were also included.

I screened titles and abstracts with Louise Lafortune, and disagreements were resolved through discussion. Dissertations, case reports, letters, and commentaries were excluded. I then retrieved full-text articles for further assessment.

2.2.3 Quality assessment

Systematic reviews can vary in their methodological quality and may therefore produce different results with respect to the same objectives. To address this problem and help readers in assessing the quality of systematic reviews, several tools have been developed. Some of these, however, have been lengthy or have had other limitations, making their use difficult. The AMSTAR tool, a validated measurement tool for assessing the quality of systematic reviews, overcomes a number of previous limitations. [96] It is also the instrument that I used to determine the quality of my reviews meeting the inclusion criteria – I undertook this process with Rianne Van Der Linde. If reviews met at least five of the AMSTAR criteria [96], they were included. A detailed description of AMSTAR and each of its criteria for assessing quality can be found elsewhere. [96]

For example, some of the AMSTAR quality criteria assess whether an "a priori" design was established (e.g., whether the research question and inclusion criteria were determined prior to the commencement of the review), whether there was duplicate study selection and data extraction (e.g., whether two people undertook data extraction and a procedure was in place should disagreements arise), if the literature search was comprehensive (e.g., whether at least two databases were searched and additional searches, such as those done by hand were conducted), whether the quality of primary studies was examined (e.g., a priori methods of examining study quality should be established), etc. [96]

2.4. Data extraction and analysis

Data extraction was performed by Rianne Van Der Linde and I using a standardized form capturing: the dates of publication and literature search; objectives; number of studies reviewed; prevalence of anxiety; sample characteristics; sample size range of primary studies; recommendations for future research, and limitations of primary studies and review. Disagreements were resolved through discussion.

Studies were grouped according to five common themes and prevalence was described in the context of: 1) addiction, 2) other mental and neurological disorders, 3) chronic physical diseases, 4) trauma, and 5) vulnerable population sub-groups. If there were fewer than three reviews on a chronic physical disease, it was grouped under: 'other chronic physical diseases' or 'other chronic physical diseases in end-stage'. Vulnerable population sub-groups refers to individuals at high risk for poor health, who may experience stigma, marginalization, or health service access barriers.

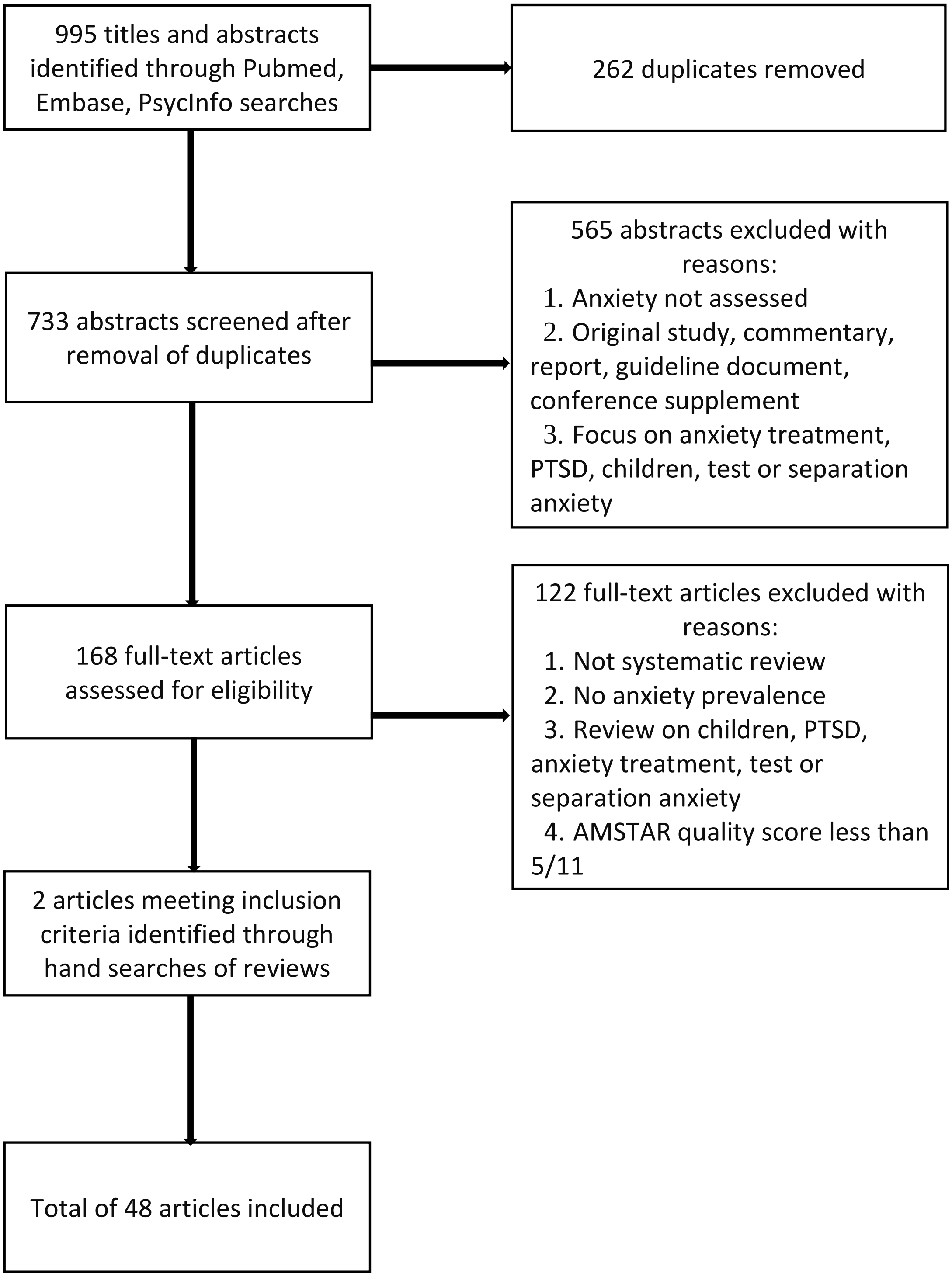
I did not perform a meta-analysis because of the heterogeneity in study methodology. Quantitative measurement of heterogeneity was not undertaken. Finally, a meta-analysis of primary studies included in 48 systematic reviews would not have been feasible. I described the prevalence of individual and aggregate anxiety disorders, subthreshold disorders, or symptoms of anxiety, as reported by the systematic reviews. If reviews provided clear prevalence estimates for men and women and different age groups, I also included this information.

2.3 Results

The search identified 1,232 reviews on anxiety. After 338 duplicates were removed, titles and abstracts were screened, and the full text of 198 articles was retrieved. In total, 46 systematic reviews met the inclusion criteria (figure 2.1). Reference searches identified two additional reviews as relevant, yielding a total of 48 reviews in this umbrella review (appendix 3).

Of the 48 reviews, seven focused on the descriptive epidemiology of anxiety disorders, while five reviewed anxiety in relation to addiction. Four focused on mental and neurological disorders. A total of 19 reviews assessed anxiety in the context of chronic physical diseases: most of these focused on CVD (n=6) and cancer (n=7), followed by respiratory disease (n=3) and diabetes (n=3); the rest examined end-stage physical disease (n=4), and conditions that have been less commonly studied in the anxiety field (n=4). Three reviews examined anxiety in the context of trauma, and ten focused on vulnerable population sub-groups. Most of the reviews included international studies.

Figure 2.1 Flowchart of main search strategy and article selection for umbrella review



2.3.1 The global distribution of anxiety disorders

Seven reviews focused on the descriptive epidemiology of anxiety disorders, presenting age-, sex-, and time trends. In one international review [22], the pooled one-year and lifetime prevalence of total anxiety disorders was estimated to be 10.6% (95% CI: 7.5%, 14.3%) and 16.6% (95% CI: 12.7%, 21.1%), respectively. Given the health care policy and service planning implications of high estimates, a high-quality meta-analysis [8] investigated whether the age-standardized point prevalence of anxiety increased over the last decade. Studies on cultures across the globe were reviewed and findings showed that the prevalence in 1990 (3.8% [95% CI: 3.6%, 4.1%] was very similar to that in 2005 and 2010 (4.0% [95% CI: 3.7%, 4.2%]). A sharp rise in younger people over time was noted, but changing age and population structures were hypothesized to be the drivers of this. Prevalence was found to be lowest in East Asia (2.8% [95% CI: 2.2%, 3.4%]) and highest in North America (7.7% [95% CI: 6.8%, 8.8%]) and the North African/Middle Eastern region (7.7% [95% CI: 6.0%, 10%]). [8] A less rigorous review [22] estimated the highest lifetime prevalence of anxiety disorders in Swiss and US populations (23%-28.7%), and the lowest in studies on Korea (9.2%). In Pakistan [97], the prevalence of total anxiety ranged from 1.76% to 25%, while a meta-analysis on Germany [98] reported it to be 13.5% (95% CI: 7.1%, 24.3%).

Women are almost twice as likely to be affected as men (female:male ratio of 1.9:1), with sex differences persisting over time and across high and low resource settings. [22, 9, 99] Irrespective of culture, individuals under the age of 35 years are disproportionately affected by anxiety disorders [8, 9] with the exception of Pakistan, where midlife represents a period of high burden [97].

Globally, specific phobia (4.9% [95% CI: 3.4%, 6.8%] and GAD (6.2% (95% CI: 4.0%, 9.2%) appear to have the highest lifetime prevalence, and panic disorder the lowest (1.2% [95% CI: 95% CI: 0.7%, 1.9%]). [22] In Germany, however, specific phobia (5.2%, [95%CI: 3.3%, 8.2%]) and GAD (3.7%, [95% CI: 2.3%, 6.0%]) are reported to be the most prevalent anxiety disorders. [98] In addition to geographical variation, caseness criteria is an important consideration when comparing estimates. One review reported an almost two-fold higher prevalence of subthreshold GAD when the duration criterion was relaxed from 3 months to 1 month (3.6%

vs 6.1%). In this review, older age groups showed the lowest estimates of past-year subthreshold GAD (3%). [100]

2.3.2 Addiction

Five reviews focused on anxiety experienced in relation to addictive behaviours, including substance misuse, pathological gambling, and compulsive internet use. A global review on non-medical prescription opioid use (NMPOU) reported the overall lifetime anxiety prevalence in patients at admissions or in treatment for substance abuse problems to range from 2% to 67%. [101] While the prevalence of anxiety diagnoses is reportedly high at 29% (95% CI: 14%, 44%), that of subthreshold anxiety is higher still, with half of NMPOU populations enrolled in substance abuse treatment in North America reporting symptoms (50% [95% CI: 16%, 84%]). [102] In contrast, general population samples of NMPOU in North America show a substantially lower prevalence of anxiety (16% [95% CI: 1%, 30%]). [103] No significant age or sex-effects were found in NMPOU groups enrolled in substance use treatment. [102]

Two other risk behaviours that have received attention in the addiction field include problem and pathological gambling, and more recently, internet addiction. When a global meta-analysis assessed 11 community samples of pathological gamblers, the prevalence of anxiety disorders was reported to be 37.4%. [104] The prevalence of anxiety in the context of internet addiction is lower and comes mostly from studies conducted in Asian countries. A meta-analysis found the prevalence of anxiety to be over two times higher in community samples of people with internet addiction compared to control subjects (23.3% [95% CI: 14.8, 34.8%] vs 10.3% [95% CI: 5.0, 19.9%]), with those under the age of 39 being most affected. [105]

2.3.3 Other mental and neurological disorders

In Europe, approximately 13%-28% of people with bipolar disorder recruited from clinical and community settings have comorbid anxiety, with GAD and panic disorder being frequently experienced by this population. [106] In US and Italian samples with bipolar disorder [35], OCD is also common. The prevalence of this anxiety disorder in those who are bipolar has been shown to range from 11.1% to 21% in population-based studies, and 1.8% to 35.1% in clinical samples.

OCD is also highly comorbid with schizophrenia. A global review [36] estimated the prevalence of this disorder in people diagnosed with schizophrenia to be 12.3% (95% CI: 9.7%, 15.4%). The prevalence of obsessive compulsive symptoms (OCS) not meeting full caseness criteria was over twice that of OCD (30.7% [95% CI: 23%, 39.6%]). Lower anxiety prevalence was linked to Sub-Saharan African origin. Age and sex did not influence OCD or OCS rates. [36] These estimates were mainly based on groups from clinical settings.

One of the highest prevalence figures of psychopathology was found by a review on MS [21], which reported that almost 32% of people with MS have an anxiety disorder and over half experience symptoms. Some of the primary studies included in this review were based on participants recruited from the general population, suggesting that men and women with MS are at high risk for psychopathology. Health anxiety may be an important issue in this population sub-group, given that 26.4% of those with MS are affected. Study methodology made a significant contribution to the figures reported. Estimates of anxiety prevalence were substantially higher if they were derived through self-reported questionnaires (25.5% [95% CI: 16.7%, 34.3%]) compared to administrative databases or medical records (15.4%, [95% CI: 0%, 39.0%]). [21]

2.3.4 Chronic physical diseases

2.3.4.1 CVD

Six reviews reported the prevalence of anxiety in the context of CVD. Approximately a tenth of patients with CVD and living in Western countries are affected by GAD (10.94% [95% CI: 7.8%, 14.0%] [107], with women showing higher anxiety levels than men. [108] Anxiety symptom prevalence among patients with congestive heart failure is 2%-49% [109], and in end-stage patients suffering from heart disease, it is 49%. [110] Further, panic disorder is a common diagnosis in patients with coronary artery disease, with the prevalence ranging from 10% to 50% in this sub-group. [108]

Individuals with non-cardiac or non-specific chest pain presenting to emergency departments, particularly women and those who are younger, appear to be disproportionately affected by anxiety. Compared to those with a determined cause of chest pain, anxiety prevalence was found to be higher in those with unknown aetiology (21%-53.5% of non-cardiac chest pain patients have probable anxiety). [111]

A high-quality, global meta-analysis of population-, hospital-, and rehabilitation-based studies found the prevalence of anxiety disorders in stroke patients to vary between 18% (95% CI: 8%, 29%) and 25% (95% CI: 21%, 28%) when measured by clinical interview and rating scales, respectively. [112] Age and sex did not influence the probability of having anxiety after stroke in most of the included studies. GAD and phobic disorders were the commonest anxiety disorders post-stroke.

2.3.4.2 Cancer

Seven reviews assessed anxiety among individuals diagnosed with or receiving treatment for cancer and in spouses of cancer patients. The prevalence of anxiety among cancer patients varies between 15% and 23%, with symptoms rising to 69%-79% in the later stages of disease. There was no reported evidence with respect to age and sex. [108, 110]

A meta-analysis [113] on working-age and older adults living in Mainland China showed that the overall prevalence of anxiety in individuals with a cancer diagnosis was higher than that in non-cancer controls (49.7% [95%CI: 20.0%, 89.1%] and 17.5%, respectively). Among German patients with breast cancer, the prevalence of anxiety was comparatively lower than in Chinese patients, ranging from 28.0% to 33.0%. [98]

Randomized controlled trials (RCT) and non-RCT studies conducted across the globe showed that approximately a fourth to over half of individuals undergoing or who had undergone breast cancer treatment experienced anxiety. [114] Lower levels of anxiety were observed in patients undergoing radiotherapy rather than chemotherapy. During chemotherapy, young age and high trait anxiety measured before infusions were correlated with the intensity of anxiety experienced. [114] Among ovarian cancer patients, younger age groups were also disproportionately affected by anxiety. Following treatment for ovarian cancer, psychopathology tended to persist, with almost half (47%) of individuals experiencing anxiety symptoms at three months post-treatment. [115]

Long-term cancer survivors and their spouses also experience elevated levels of anxiety. In a global meta-analysis of outpatient clinic, hospital, and population-based samples [116], the prevalence of anxiety in individuals who had been diagnosed with cancer at least 2 years previously was found to be much higher than in healthy controls (17.9% [95% CI: 12.8%, 23.6%] and 13.9% [95% CI: 9.8%, 18.5%], respectively). Further, almost half (40.1% [95% CI: 25.4%, 55.9%]) of spouses of long-term cancer survivors developed anxiety. No age or sex effects were reported.

2.3.4.3 Respiratory disease

Three reviews focusing on anxiety in the context of respiratory disease indicated that the prevalence of anxiety was high among adults with COPD (32%-57%) [109], and higher still among those with far-advanced, end-stage respiratory disease (51%-75%). [110] Among acute lung injury/acute respiratory distress syndrome (ALI/ARDS) survivors discharged from intensive care units in the US and Germany, anxiety levels ranged from 23% to 48%. [117] No age or sex effects were reported.

2.3.4.4 Diabetes

Three systematic reviews assessed anxiety in adults with diabetes. One high-quality global review of mostly North American and European studies [118] showed that the prevalence is significantly elevated in those with diabetes compared to other groups, but is also dependant on caseness criteria. Approximately 15% to 73% of people with diabetes have anxiety symptoms not meeting threshold criteria (vs. 19.9% to 43.1% of non-diabetic individuals), while 1.4% to 15.6% of people with diabetes meet threshold criteria for an anxiety disorder (vs. 1.6% to 8.8% of non-diabetic individuals). In another review capturing studies predominantly conducted in primary care or clinical settings, women with diabetes were found to have an almost two-fold higher prevalence of anxiety than men with diabetes (55.3% and 32.9%). [119] Age effects were not reported. The anxiety disorders that are most common in the context of diabetes are anxiety not otherwise specified, specific phobia, GAD, and social phobia. [108, 119]

2.3.4.5 Other chronic physical diseases

Four reviews assessed anxiety in population sub-groups with polycystic ovary syndrome (PCOS), benign joint hypermobility syndrome, musculoskeletal pain, and age-related macular degeneration. Clinical, mostly Western samples of women with polycystic ovary syndrome (PCOS) had a much higher prevalence of generalised anxiety symptoms than control groups (20.4% and 3.9%, respectively). [120] There is some evidence that social phobia and OCD are comorbid with PCOS. Differences in anxiety levels according to age were not found. [120]

Widely varying anxiety prevalence figures have been reported for Mediterranean populations with benign joint hypermobility syndrome (BJHS) (5%-68%) [121], as well as for Western populations with musculoskeletal pain (0%-20.9%) [122]. In relation to the latter group, the link between fibromyalgia and anxiety appears to be particularly strong. In people with BJHS, commonly occurring comorbidities are agoraphobia and panic disorder. [121] The only chronic condition that has failed to show a link with anxiety is age-related macular degeneration; while this review recruited patients from clinics, it was largely based on US studies. [123]

2.3.4.6 Other chronic physical diseases in end-stage

Four reviews assessed anxiety in end-stage conditions. A global meta-analysis of mostly Western studies [124] estimated the pooled prevalence of anxiety disorders in palliative cancer patients to be 9.8% (95% CI: 6.8%, 13.2%). Estimates appear to vary widely by condition. Among patients with chronic renal failure, the prevalence of anxiety symptoms was found to be 25% in the terminal stage [109], whereas another review found a prevalence of 38% in patients with end-stage renal disease. [124] Although patients suffering from end-stage AIDS showed a high symptom prevalence of 8%-34%, the highest estimates were found for end-stage COPD (51%-75%) and cancer patients (13%-79%). [110] No associations between age or sex and anxiety were found in palliative-care settings. [124]

2.3.5 Trauma

Three reviews tackled the issue of anxiety in the context of trauma. The first was primarily based on findings from UK and US studies and focused on traumatic limb amputees, and included veterans that had served in Vietnam, Iraq and Afghanistan. [125] Very high prevalence figures were found, with anxiety affecting a fourth of traumatic limb amputees in some studies to over half in others. The second review was global in scope and assessed the frequency of lifetime anxiety among individuals with a history of sexual abuse. [126] Widely varying anxiety estimates were reported by this review, ranging from 2% to 82%. Finally, a third review focused on GAD in refugees residing in high-income western countries; over half of the refugees were from southeast Asia. This meta-analysis estimated that 4% of refugees experience GAD. [127] No age or sex effects in relation to anxiety disorders were reported.

2.3.6 Vulnerable population sub-groups

2.3.6.1 Older people and their caregivers

Five reviews assessed anxiety in older people and their caregivers. The prevalence of anxiety disorders in old age varies widely in community (1.2%-14%) and clinical (1%-28%) studies conducted mostly in European and North American settings. Estimates are even higher when anxiety symptoms are accounted for. GAD is the commonest anxiety disorder in old age, with the prevalence ranging from 1.3% to 4.7%. [128] A random-effects model [129] showed that specific phobia also occurs frequently in older samples living in the community, while agoraphobia is the rarest anxiety disorder. [128] Women are at higher risk for psychopathology than men. [128]

Older population sub-groups with cognitive dysfunction and their caregivers are disproportionately affected by anxiety. [130] In older people with mild cognitive impairment (MCI), the prevalence of anxiety symptoms varies from 11% to 75%. [130, 131] Caregivers of older people with cognitive impairment are also affected by anxiety (prevalence estimates of 3.7%-76.5%), with women and younger caregivers showing elevated levels. [128, 132]

2.3.6.2 Pregnant women

Three reviews focused on pregnant women. A meta-analysis of international studies [133] reported higher OCD prevalence in pregnant (2.07%, [95% CI: 1.26%, 3.37%]) and postpartum (up to 12 months) (2.43%, [95% CI: 1.46%, 4.00%]) women compared to the general population (1.08%, [95%: 0.80%, 1.46%]). Asia and Europe had the lowest prevalence of OCD across conditions, while the Middle East and Africa had the highest. In Ethiopian and Nigerian samples recruited from health clinics and the community [134], the prevalence of anxiety was found to be high during both the pre- and post-natal periods (14.8% [95% CI: 12.3%, 17.4%] and 14.0% [95% CI: 12.9%, 15.2%], respectively), with younger women showing elevated anxiety compared to older women. [134] There is also some evidence from UK and US studies that a high BMI may contribute to anxiety symptoms during pregnancy. [135]

2.3.6.3 Individuals identifying as lesbian, gay or bisexual (LGB), and self-harm patients

Two reviews focused on 1) predominantly Western individuals living in the community and identifying as LGB, and 2) self-harm patients presenting to general hospitals in countries across the globe. In LBG men, anxiety prevalence was estimated to be 3%-20%, while LGB women showed somewhat higher estimates, at 3%-39%. [136] In a global meta-analysis of self-harm patients presenting to hospitals, the prevalence of anxiety disorders was found to be 35% (95% CI: 21.9%, 48.6%). Age- and sex-based differences were small, while rates of anxiety were highest in young and old age groups of self-harm adults. [137] All non-Western studies of self-harm patients were based in Asia, while most of the Western studies were conducted in the UK.

2.4 Discussion

I have synthesized 48 reviews on prevalence studies conducted across the globe. This is the first review to undertake a comprehensive synthesis of the systematic reviews conducted to date on the prevalence of anxiety disorders. It provides a comprehensive, up-to-date summary of the state of knowledge in this area.

A number of studies within the reviews were conducted in North America (predominantly the US) and Europe, included clinical and general population samples, and used mainly DSM or ICD criteria to ascertain diagnoses. Younger age groups, women, and people from North America and North Africa/Middle East showed the highest prevalence of anxiety. Estimates remained stable or declined with age, and secular trends were not observed in relation to the prevalence of total anxiety.

Compared to healthy populations or control groups, prevalence was higher in individuals with chronic physical diseases, and the burden was particularly high in the end stage. Anxiety symptoms tended to persist post-disease if present before disease onset, reflecting a chronic, unremitting pattern of psychopathology. Individuals exposed to trauma or who were vulnerable and at risk for stigma, such as older people with cognitive impairment, were also more likely to experience anxiety. Prevalence figures were heterogeneous, and this made comparison between studies difficult. Heterogeneity was driven by differences in caseness criteria and sampling methods. For example, a meta-regression [36] that assessed the influence of instrument differences on OCD prevalence in the context of schizophrenia showed that the prevalence was higher with the use of the Yale-Brown Obsessive Compulsive Scale (YBOCS)/Obsessive Compulsive Inventory (OCI) [138, 139] compared to other instruments. Also, the lower the threshold of the YBOCS, the higher the estimated prevalence. A range of methods was used to measure anxiety, such as, standardized, structured interviews administered by trained professionals, clinician diagnoses, symptom checklists, and self-report. Some reviews attempted to handle the assessment of anxiety in alternative ways. For example, one review [9] mapped estimates onto ICD or DSM diagnostic criteria and conducted a meta-analysis to provide an aggregate measure of anxiety. Other reviews either did not attempt a meta-analysis, or because of very large differences in sampling methods within primary studies, reported disaggregated estimates and ranges found in primary studies. Across reviews, higher prevalence figures were found when subthreshold disorders or symptoms were assessed and when lifetime rather than past-year or current prevalence was estimated. With the exception of one review [130], authors did not account for the use of psychoactive prescription medicines, such as anxiolytics, which could influence the reporting of anxiety symptoms.

Reviews produced inflated prevalence estimates with the use of less robust methodologies. Within reviews, low and variable response rates across primary studies were identified as another limitation. In one review, response rates across studies ranged from 45.9% to 99.5%. [99]

The areas that received the most attention in the anxiety field include addiction and chronic physical diseases (mainly cancer, CVD, and respiratory diseases), while anxiety disorders other than PTSD in the context of 1) trauma and 2) psychiatric or neurological conditions, such as internet addiction and MS, are relatively new and underresearched areas. Surprisingly, only one review [136] examined LGB groups, despite this population being at high risk for poor health [140]. Authors of this review [136] called for further research to produce more refined and consistent definitions of LGB and the recruitment of more representative samples.

Although most of the reviews included in this systematic review were conducted in the last few years, the field of anxiety is rapidly gaining research interest. Some differences in findings and methodologies between older and more recent reviews were noted. For example, recent reviews are increasingly recognizing that early adulthood is the period with the highest peak in anxiety, and the contexts within which psychopathology is assessed are expanding to a greater number of physical diseases and newly emergent disorders (e.g., internet addiction). Also, newer research is starting to expand its scope to Asian countries, a previously identified limitation. More recent reviews are of higher quality, and have started considering instrument differences and their effects on prevalence estimates, another previously identified limitation.

Limitations of review of reviews

This review has some limitations. Despite extensive database searches, it is possible that some reviews have been missed. Also, the high heterogeneity in anxiety assessment methods and sampling frameworks within primary studies contributed to large differences in prevalence estimates within and across reviews, making it difficult to draw conclusions about the burden of anxiety. Also, a number of the reviews were based on English-language studies conducted in predominantly Western settings, making generalisability to other parts of the world difficult.

2.5 Conclusions

Anxiety disorders are increasingly being recognized as important determinants of poor health and major contributors to health service use across the globe. [2, 89] Despite epidemiologic advances in this field, important areas of research remain under- or unexplored. There is a need for further studies on the prevalence of anxiety disorders in the context of: personality disorders; Indigenous cultures in Canada, the US, New Zealand, and Australia; African, Middle Eastern, Eastern European, Asian and South American countries; and marginalized populations, such as injection drug users, street youth, and sex workers. These recommendations can serve to guide the research agenda, and most importantly, help develop tailored and timely interventions.

This chapter showed that anxiety disorders are prevalent across the globe, and can affect young healthy populations, as well as people living with serious, chronic conditions, though knowledge gaps regarding these conditions remain. Given the high burden of anxiety, it is important to determine whether it has societal impact and leads to negative health outcomes, and subsequently explore its risk factors.

The next chapter presents my objectives and general scientific argument for my thesis using the WHO Commission on Social Determinants of Health framework. [72] It shows how the context influences health inequities, such as risk of having GAD among women and men separately. It also shows how GAD can potentially have an influence on society.

3 Conceptual framework

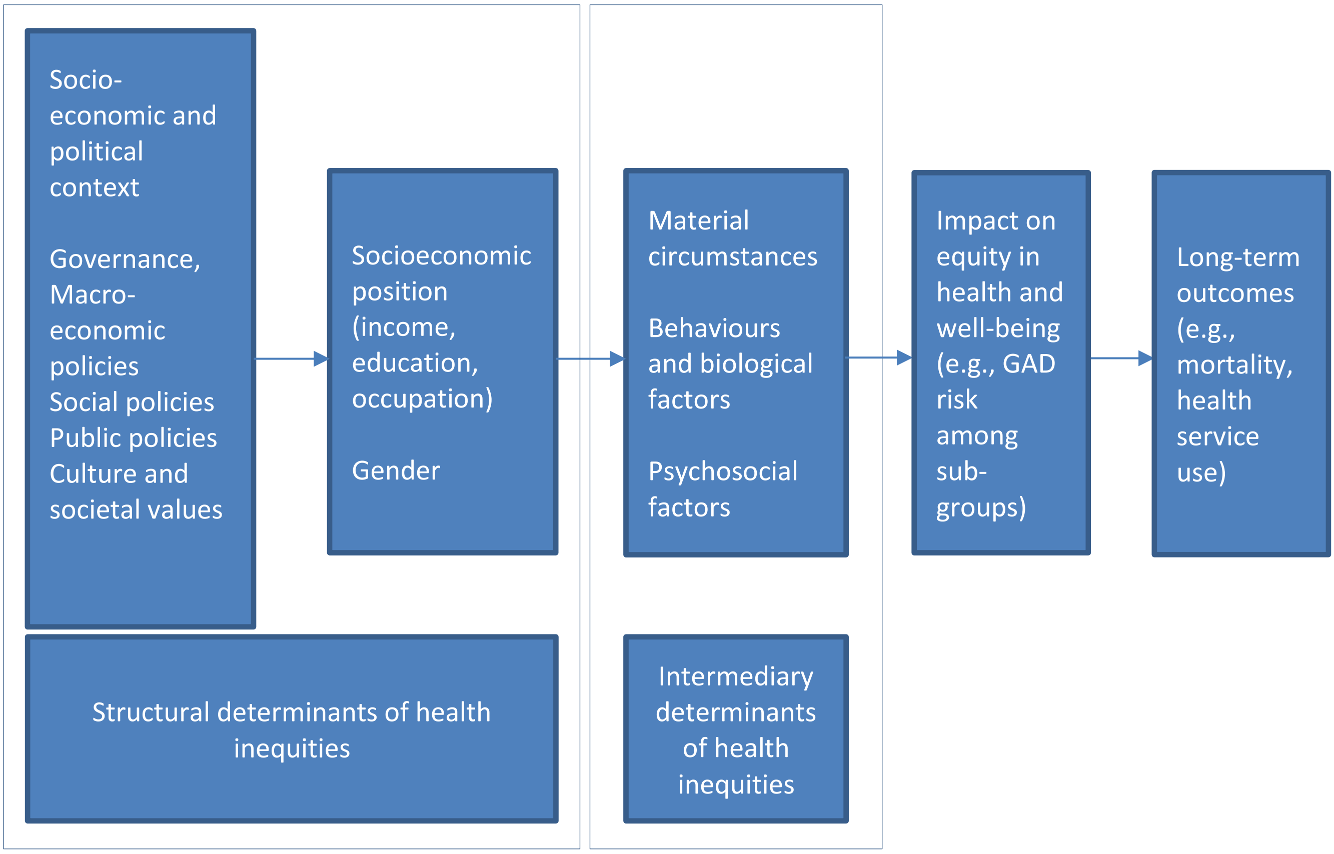
3.1 Introduction

This thesis explores whether GAD is associated with serious health consequences such as health service use and mortality, risk factors for GAD (area deprivation), and possible ways of mitigating its risks through coping mechanisms.

The World Health Organization (WHO) Commission on Social Determinants of Health [72] created a framework that shows how risk factors including structural determinants can influence our health and lead to health inequities. This framework is the theoretical basis for the chapters on risk factors for anxiety (area deprivation) and coping mechanisms, and guides outcomes linked to GAD – health service use and mortality.

The WHO Commission on Social Determinants of Health framework is described next. It shows how society influences our health and leads to health inequities. It describes how the wider context acts on socioeconomic position and gender, which are structural determinants of health, to generate and reinforce inequality in society. Structural determinants then give rise to intermediary determinants of health: material, behaviour, and psychosocial factors, and social capital. [72] These intermediary determinants ultimately have an impact on health and health inequities, as shown in the diagram below.

3.2 Conceptual framework: structural and intermediary determinants of GAD and long-term outcomes



3.3 The WHO Commission on Social Determinants of Health framework

The WHO Commission on Social Determinants of Health states that health is rooted in social and economic contexts. The way that society is organized, the policies that it stipulates, and the way that it distributes social and material resources among population sub-groups leads to social stratification. Social stratification then leads to unequal distribution of social determinants of health, such as housing, nutrition, and sanitation across sub-groups. When some people enjoy better health than others because of unfair social processes and unequal distribution of social determinants, this is when health inequities arise. [72, 141] To combat health inequities, one must look at and target the wider context, the governance patterns, and the economic, public and social policies in order to ensure fair access to goods and opportunities for all people. [72, 141]

The WHO Commission on Social Determinants of Health states that social position is a product of social stratification. Social and economic contexts influence individual social positions, which then determine access to power, prestige, resources, and ultimately health. [142, 143] People of low social positions are low on the social hierarchy, and tend to experience feelings of shame, exclusion from society, and reduced well-being compared to those who are more affluent. [144] Those who are disadvantaged also tend to have different lifestyles and patterns of risk behaviours than wealthier people [143, 145] - poorer people tend to eat less healthily, exercise less, and smoke and drink more than those who are richer, which leads to health differentials among groups of various social strata. People of low social status are also more likely to experience poorer health because of differential vulnerability and exposure to health-damaging conditions at work, at home, or in the neighbourhood. [72]

3.3.1 How does socioeconomic position influence health?

As mentioned previously, socioeconomic position is an important factor influencing health. It is called a structural determinant, because it can generate and reinforce inequality in society, and is influenced by the wider context.

The WHO describes socioeconomic position as a composite of resource- and prestige-based measures. Resource-based measures refer to material resources and assets, such as wealth, while prestige-based measures refer to social ranking and access to services, knowledge and goods. [142, 143] Prestige-based measures include occupation, education, and income. [142] These are indicators of socioeconomic status. Occupation can facilitate exposure to contaminants and hazards at work which can affect health, and is linked to decision latitude during employment (the degree of control over one's job has been linked to mortality and disease). [146, 147] Education provides access to information and facilitates receptivity to health messages and access to health services, while income provides access to material resources to buy health goods. [72]

Socioeconomic position can be measured at three levels: the individual, household, and area or neighbourhood level. [142] If indicators of socioeconomic status, such as income, education, and occupation are not available, then proxies such as living standard (non-home ownership, non-car ownership) can be used. [72]

3.3.2 Gender as a structural determinant of health inequities

In addition to socioeconomic status, there are other structural determinants which can influence health and health inequities, including gender and ethnicity. Gender will be briefly discussed, because it pertains to this thesis. First, however, a distinction needs to be made between sex and gender. Sex refers to biological characteristics, while gender is a social construct referring to the relations between men and women or boys and girls that are subject to norms. [148, 149]

Gender is an important structural determinant that is shaped by the wider context, including culture and governance. Women have historically been the victims of discrimination, and because of this have had limited opportunities for education, and well-remunerated and respected forms of employment. [150] Women have taken on different job roles and tasks than men, which has exposed them to different hazards and contaminants affecting their health. Women have traditionally been seen as ‘care-takers’ in society and involved in domestic work, which might have led to an interruption in their education or career paths. As such, they have derived fewer resources with which they could maintain or improve their health. [72, 150]

Because gender is tied to the material and social resources that one derives from the environment and is an important contributor to health, it is necessary to take this variable into account in analyses.

3.4 Intermediary determinants

Structural determinants, such as socioeconomic position and gender give rise to intermediary determinants affecting health. These intermediary determinants include material, psychosocial, and behavioural factors, and social capital.

1. Material resources

Material resources refer to financial resources, housing, and the surrounding environment. People with financial resources have enough money with which to buy necessary items for daily living, such as food and clothing, which are important for health. Housing refers to the indoor quality of homes, such as having central heating, a washing machine, as well as conditions inside the home such as dampness and overcrowding. [151] People living in homes that do not meet certain standards of living are at risk for poor outcomes – such as individuals living in overcrowded spaces who are at risk for infection. [72] The surrounding environment or the neighbourhood in which one lives can also affect health. [142] This has been shown by studies using the 'broken windows index' – neighbourhoods characterised by dilapidated housing, and litter and graffiti have higher rates of sexually transmitted infections, such as gonorrhea. [152]

2. Psychosocial factors

Regarding psychosocial factors, people of lower socioeconomic positions are more likely to be exposed to stressors, poor working conditions, situations which are frightening and difficult to cope with, and lack of social support compared to those of higher social standing. [143] Stress and being exposed to situations which overwhelm coping capacities can be detrimental for health. Having small social networks with which to buffer the effects of stress can also be harmful for the individual. [72]

3. Behavioural factors

Behavioural factors refer to lifestyle or risk behaviours, such as diet, physical activity, alcohol intake, and smoking. People of lower social classes are more likely to be exposed to stress, and in an effort to cope with it, turn to unhealthy means of coping, such as eating unhealthy food and drinking alcohol. [153] Those of lower social classes are also more likely to smoke and exercise less than those of higher social standing. [72, 154, 155]

4. Social capital

Social capital refers to social relationships and resources that flow from social networks. [156, 157, 158] Risk behaviors and decisions that people make regarding lifestyle choices may be traced back to the social networks that they are part of. [72] It is beyond the scope of this chapter to define the various types of social capital and different theories on this concept. However, those who lack social capital and have little social support tend to show poorer health.

In summary, social determinants, such as socio-economic position and gender are important factors influencing health. However, as mentioned in the beginning of this chapter, these social determinants cannot be studied in isolation and often need to be traced back to the broader context out of which they arise.

The policies of a society affect educational and employment opportunities, material resources and the social protection that is offered to the poorest members of society – such factors can buffer the effect of social determinants, including individual socio-economic status on health. It is possible to act on and modify structural and intermediary determinants of health by acting on contextual features of the environment through policy. [72]

3.5 Conclusion

The broader social context, defined by policies, governance, and culture provides some groups with power and prestige, thus leading to the social stratification of people. [143] This stratification has an influence on the social determinants of health inequities, such as socioeconomic position and gender. These underlying social determinants of health inequities then shape health outcomes through intermediary determinants, including material and psychosocial circumstances, and behavioural factors. A number of studies have shown that social class is an important contributor to mortality and morbidity inequalities. [145, 159] Children growing up in deprived households are at higher risk for development delays, poor cognitive functioning, and disability compared to their more affluent peers. [160-163] Children growing up in disadvantage have fewer educational opportunities [164], and thus potentially poorer health down the road. While socioeconomic position is a powerful determinant of health outcomes, health, in turn, can have an influence on the underlying social determinants. Poor health can lead to downward mobility in socioeconomic position through health selection effects. [72, 165]

The only way to address the link between structural determinants of health inequities and poor outcomes is through the socioeconomic political context – through programs and policies aiming to address inequities so that the most deprived members of society can enjoy good health and well-being as more affluent individuals do. [72]

When choosing conceptual frameworks to explain the findings of this thesis, I found the WHO framework particularly well suited for the reasons mentioned above and below. However, it is possibly a limitation that there were other models out there that might have helped in different ways. Also, the WHO framework did not cover all the activities I examined in my thesis, such as influence of mental disorders on society (health service use, mortality).

3.6 Thesis

In this thesis, I have examined area deprivation as a risk factor for GAD and MDD from a gendered perspective. My premise was that people living in the most deprived areas are at high risk for poor mental health, and I examined this for women and men separately, in accordance with earlier literature. In the WHO framework, socioeconomic position and gender have been shown to be important structural determinants of health inequities. [72] While I measure individual social class, I control for this variable as a confounder. My interest lies in broader community-level effects of area deprivation on health over and above personal circumstances (the WHO framework also stipulates that socioeconomic position can be measured at the area level and proxies for this measure, such as non-home ownership and non-car ownership can be used – the Townsend index I used in my analyses was composed of these proxies). I want to know whether living in affluence or deprivation contributes to differences in risk of having GAD or MDD – this is akin to the health inequities resulting from socioeconomic position described by the WHO framework. I also wanted to examine this question from a gendered perspective, because gender has been shown to be a structural determinant affecting health.

If living in a deprived area leads to GAD in a particular gender, then it would it would be interesting to determine whether GAD also leads to deleterious health outcomes, such as mortality in that gender group – this would be further evidence of health inequities stemming from possible discrimination. It would also be useful to determine if GAD also results in high health care use in one of the genders (potentially because of poor underlying health or risk behaviours) and places a strain on an overburdened health care system. However, in my thesis, I examined the overall impact of GAD on health service use and mortality without stratifying by sex. Although health inequities according to gender are an important topic, my primary interest was anxiety's influence on society and risk factors tied to anxiety so that prevention and intervention efforts can be informed. Perhaps future work can take this research further and examine these links with GAD from a gendered perspective.

Finally, I wanted to determine whether risks of anxiety can be mitigated through coping mechanisms – in the WHO framework, coping is shown to be an intermediary determinant linking underlying structural determinants, such as socioeconomic position (in my case, area deprivation) to health outcomes (in my case, GAD).

3.7 Thesis objectives

- To determine the impact that anxiety has on the health service system within a population study with record linkage.
- To determine the impact that anxiety has on mortality within a population study with record linkage.
- Exploration of risk for GAD within a large population derived population cohort.
- Exploration of risk for MDD within a large population derived population cohort.
- Synthesis of the evidence generated to consider potential for mitigation of impact of GAD.

4 Methods

For the core chapters looking at the relationship between GAD and mortality, health service use, area deprivation, and coping, I used data from the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk). [166] The EPIC-Norfolk study was also used for the chapter on area deprivation as a possible risk factor of depression. I used survival analysis to understand the relationship with mortality, zero-inflated negative binomial regression to explore links with health service use, and generalised estimating equations and logistic regression to determine associations with area deprivation and coping. I conducted multiple imputations for missing data for the chapter on mortality. All my analyses accounted for potential confounders linked to the exposure and outcome.

4.1 Brief overview of settings, population, and study methods

The European Prospective Investigation of Cancer (EPIC) study began in 1989 with the objective of studying the relationship between diet and cancer. It started as a prospective, large-scale study aiming to recruit people from populations with wide variation in diet and cancer incidence. The EPIC study includes cohorts in countries around the world: France, Germany, Greece, Italy, the Netherlands, Spain, the UK, Denmark, Norway, and Sweden. Over the years, it widened its aims to include exposures other than diet, such as physical activity and psychosocial factors, and endpoints other than incident cancer, including determinants of disability and mortality at mid-life and beyond. [166]

When the EPIC-Norfolk study was started, the intention was to recruit 25,000 people from the general population living in Norwich and the surrounding towns and rural areas. This location was chosen, because it had little outward migration and was mainly served by one District General Hospital – the Norfolk and Norwich University Hospital. This target sample size was chosen, because of the need to include a large enough number of participants for detailed analyses to be undertaken, but also to allow measurement of exposures to be conducted with sufficient precision. The sample size thus represented a compromise between having enough cases to allow for powered analyses and the need to include more discriminating instruments for measuring exposures. All 35 general practices located in the study site were approached and 77,630 patients from those practices invited to participate. If consent to participate was received, respondents were invited to complete a Health and

Lifestyle Questionnaire (HLQ) and undergo a health check; over the years, subsequent waves of data collection occurred during which participants had the opportunity to complete follow-up HLQs and undergo health checks – these will be described below. The EPIC-Norfolk cohort has also been record linked to administrative databases to examine health endpoints, which will also be discussed in this section.

The EPIC-Norfolk study received ethics approval from the Norwich District Health Authority ethics committee. [166]

4.1.1 Health and Lifestyle Questionnaire (HLQ) and baseline health check

Recruitment of participants occurred between 1993 and 1997. [166] Of the 77,630 invitations that were sent out to the patients on the general practice registers, 30,445 people consented to take part in the study and filled in the HLQ, and of these, 25,639 attended the baseline health check. The HLQ gathered information on sociodemographics, risk behaviours, and medical history including social class, occupational history, marital status, smoking, alcohol intake, physical activity, reproductive history (for women), and previous diagnoses of physical health problems. The health check was performed by trained nurses, and examined participants' height and weight, body circumference; measures related to chest, waist, hip, as well as urinalysis, spirometry, and blood pressure were taken.

4.1.2 Health and Life Experiences Questionnaire (HLEQ)

Eighteen months after the baseline HLQ was rolled out, the psychosocial HLEQ was administered to participants. The HLEQ is a structured, self-assessment instrument designed to capture primarily social and psychological factors, including symptoms of depression and anxiety according to core criteria stipulated by the DSM-IV. Because GAD and MDD were considered prevalent conditions in the population, these were the only psychiatric disorders examined by the HLEQ. Measurement of GAD and MDD was based on the short-form scales of the formal structured assessment methods derived from the National Comorbidity Survey. [167] The symptom criteria included in the HLEQ was designed to identify those likely meeting putative diagnoses for GAD or MDD at any point in their lives, and to provide a description of the course of the disorders based on frequency, chronicity, and age of onset measures.

4.1.3 Record linkage with administrative databases

The EPIC-Norfolk cohort was also linked to administrative health databases (National Health Service [NHS] Central Register) to ascertain health endpoints, such as deaths and admissions to hospital. Deaths were flagged through death certification, and vital status was established for the cohort through record linkage with the UK Office of National Statistics (ONS). Prevalent cancer cases were identified using record linkage with the ONS and the East Anglian Cancer Registry, and hospital admissions data were captured by merging the cohort with the East Norfolk Primary Health Care Trust hospitalisation databases. The hospitalisation databases captured information on hospital activity for study participants treated anywhere in England and Wales. [166]

4.1.4 Other health checks and questionnaires not used in this thesis

The HLQ, HLEQ, ONS, East Anglian Cancer Registry, and the East Norfolk Primary Health Care Trust hospitalisation databases were used in this thesis. There were other data sources, however, which were not included as part of this dissertation - some of these will be briefly described to provide a brief overview of the EPIC-Norfolk study.

4.1.4.1 Health checks

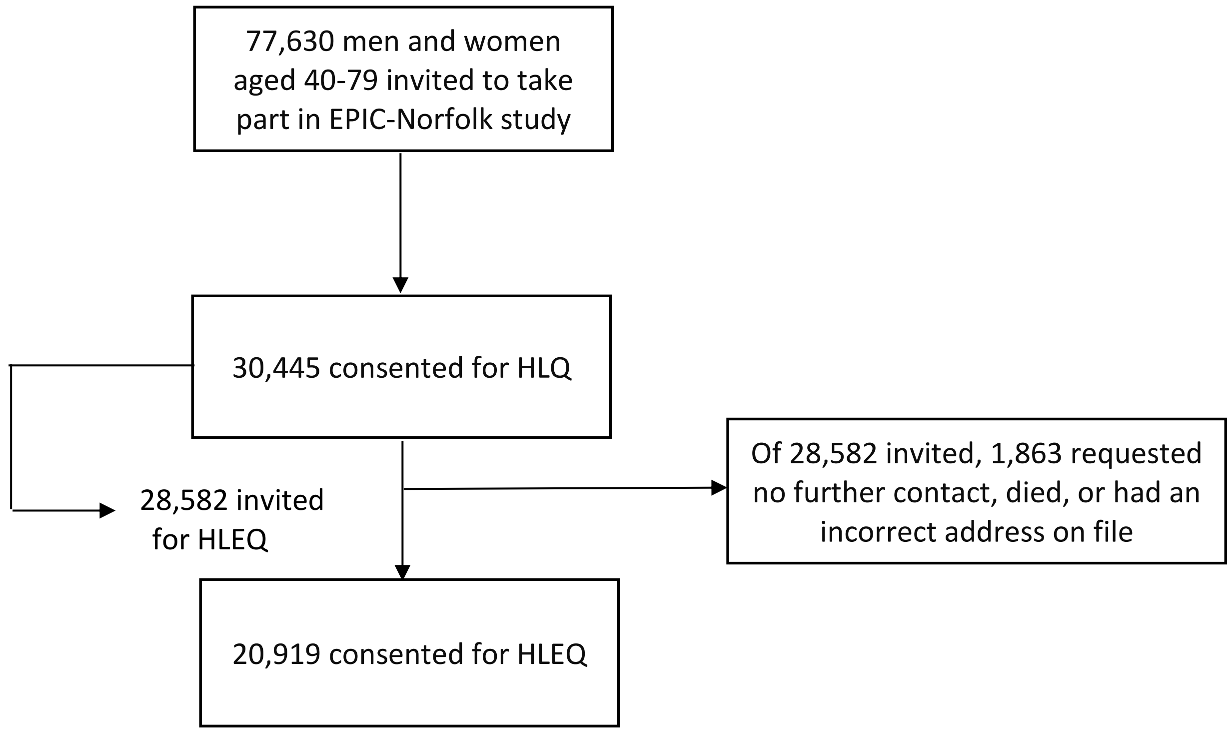
Following the baseline health check, a second health examination was conducted on 15,786 participants in 1997-2000, and measures from the first check were repeated, with the addition of heel bone ultrasound and impedance for body fat percentage. [168] The third health examination was conducted on 8623 participants in 2006-11 and previous measures were repeated, with the addition of skin ageing measures, cognitive assessment, physical capability measures, objective measures of physical activity, and eye examinations. The first two health checks took approximately 30 minutes to complete, while the third took from 2 hours 30 minutes to 3 hours. Participants were sent invitations and took part in these health checks unless they had died, requested no further contact from the research team, or could not be traced.

4.1.4.2 HLQs

In addition to the health checks, participants were sent self-assessment, postal HLQs to complete on a regular basis. They were permitted to complete the HLQs at any wave of data collection, regardless of whether or not they had completed previous versions of the questionnaire or had failed to undertake health checks. The follow-up HLQs had a common format across waves of data collection and examined sociodemographics; medical history; risk behaviours such as alcohol intake, smoking, and physical activity; and menstrual history and hormone replacement therapy use (for women). Participants could return these questionnaires by post or during one of the clinic visits. The first follow-up to the baseline HLQ occurred in 1995-2000 (follow-up [FU]1 HLQ), the second in 1998-2000 (FU2 HLQ), the third in 2002-2004 (FU3 HLQ), and the fourth in 2004-2011 (FU4 HLQ). Participants were sent invitations to fill out the HLQs unless they had died, requested no further contact from the research team, or could not be traced.

There were other postal questionnaires that participants received during follow-up, such as ones focusing on diet or physical activity; however, these will not be described further. The flowchart of the EPIC-Norfolk study as related to this thesis is shown in figure 4.1. The characteristics of those who responded to this study versus those who did not are compared in appendix 4.

Figure 4.1 Flowchart showing number of EPIC-Norfolk participants at each study stage



4.2 Measurements

4.2.1 HLQ

The HLQ was designed to provide insight into the sociodemographic factors, medical history, and risk behaviors of EPIC-Norfolk participants. It was posted to participants and was sent back to the research team either by mail or in person during one of the clinic visits. It contains sections on medical history; risk behaviours, including smoking, alcohol intake, and physical activity; and sociodemographics, including sex, marital status, education, occupational history, and social class. The sections and questions from the HLQ used in this thesis will be described below.

4.2.1.1 Medical history

To determine prevalent disease, participants were asked, ‘Has the doctor ever told you that you have any of the following?’, followed by a list of diseases, such as diabetes, asthma, thyroid disease, and cancer.

4.2.1.2 Risk behaviors

4.2.1.2.1 Smoking

The following questions were used to ascertain smoking status: ‘Have you ever smoked as much as one cigarette a day for as long as a year?’, with options to tick yes or no in the boxes provided. If participants ticked ‘no’, they were classified as a ‘never smoker’. Those who ticked ‘yes’ to the following question, ‘Do you smoke cigarettes now?’ were classified as a ‘current smoker’. Former smokers checked ‘yes’ for the first question and ‘no’ for the second.

4.2.1.2.2 Alcohol intake

Participants were asked, ‘At present, how many alcoholic drinks do you have each week?’, with options to include numbers for each of four categories of drinks (and to write ‘0 units’ if none consumed): 1) beer, cider or lager, 2) wine, 3) sherry or fortified wine, and 4) spirits – whisky, gin, brandy, liqueurs etc. A unit of alcohol was defined as half pint of beer, cider, or lager; a glass of wine; a single unit of spirits (whisky, gin, brandy, or vodka); or a glass of sherry, port, vermouth, or liqueurs. The measure of total alcohol consumption included the total units of alcohol consumed in a week. [169]

4.2.1.2.3 Physical activity

Participants were asked about the amount of physical activity involved in their work. They were asked to tick the best representation of their present activities from the following four possibilities: 1) sedentary occupation (spends most of the time sitting, such as in an office), 2) standing occupation (spends most time standing or walking, such as those working as shop assistants or hair dressers), 3) physical work (involves some physical effort including handling of heavy objects and use of tools, such as those in carpentry or nursing professions), 4) heavy manual work (involves very vigorous physical activity including handling of very heavy objects, such as in bricklaying).

Participants were then asked to list recreational activity in hours per week. They were required to complete the following question: ‘In a typical week during the past 12 months, how many hours did you spend on each of the following activities? (Put ‘0’ if none.)’, with options, such as walking, cycling, gardening, and housework. They were required to list the average amount of time spent, in hours per week, in winter and summer for each of the options listed.

Using responses from these two questions, an index was created and allocated participants to the following four categories: inactive (sedentary job and no recreational activity); moderately inactive (sedentary job with <0.5 h recreational activity per day, or standing job with no recreational activity); moderately active (sedentary job with 0.5-1 h recreational activity per day, or standing job with <0.5 h recreational activity per day, or physical job with no recreational activity); and active (sedentary job with >1 h recreational activity per day, or standing job with >1 h recreational activity per day, or physical job with at least some recreational activity, or heavy manual job). [169] This index was validated against energy expenditure calculated from heart-rate monitoring with individual calibration. [170] A study using this validated index/questionnaire further showed that both work and recreational physical activity were independently associated with reduced risk of mortality and CVD incident events. [171]

4.2.1.3 Sociodemographics

4.2.1.3.1 Sex

Participants were instructed to indicate their sex.

4.2.1.3.2 Marital status

Participants were asked their marital status and were instructed to tick boxes as appropriate: married, single (or never married), widowed, divorced, or separated.

4.2.1.3.3 Education

Participants were asked about their highest educational attainment, including: <O-level or no qualifications; O-level or equivalent; A-level or equivalent; and degree or equivalent. O-level indicates educational attainment equivalent to the completion of schooling up to 15 years, while A-level indicates education equivalent to the completion of schooling up to 17 years. Degree or equivalent refers to post-school qualifications after completion of A-levels or equivalent. [172, 173]

4.2.1.3.4 Occupation

Participants were asked whether they had a paid job.

4.2.2 Baseline health check

4.2.2.1 Anthropometry

At baseline, a health check was undertaken on 25,639 participants in 1993-1997 to acquire data on respiratory function, undertake anthropometry as well as blood pressure measurements and urine samples.

A standard protocol was used by trained nurses to take anthropometric measures. [174] Height to the nearest millimeter and weight to the nearest 0.2 kilograms were measured without shoes and in light clothing using a free-standing stadiometer and digital scales. [166, 175] Body mass index (BMI) was calculated as the weight in kilograms divided by the height in metres squared.

4.2.3 HLEQ

The main variables in this thesis were derived from the HLEQ, which was administered to participants in 1996-2000; therefore, this questionnaire will be described in greater detail than previous questionnaires/health checks.

As mentioned previously, the EPIC-Norfolk study was originally designed to examine the relationship between diet and cancer. Over the years, it expanded to include other endpoints and measure exposures other than diet, such as social and psychological factors. Because of mounting evidence showing a potential link between psychosocial factors and chronic disease outcomes [176], the decision was made to include an assessment of affective health in the EPIC-Norfolk study. As this was a very large study based on a sample size of over 20,000 people (to allow for detailed examination of incident chronic disease), it was not possible to use trained personnel to undertake clinical diagnoses of psychiatric disorders on participants. The specialist skills needed and the time participants would have had to devote to diagnostic interviews over and above the completion of extensive self-assessment questionnaires would not have been feasible. As such, it was determined that structured, retrospective questionnaires would be posted to participants for self-completion. [177]

After extensive literature reviews on the links between psychosocial factors and chronic disease, personal communications with the principal investigator of the National Comorbidity Survey, and pilot testing, the HLEQ was developed. [177]

Regarding the pilot testing: in 1995, two studies were undertaken on 50 participants recruited from two East Anglian Community general practices that were not participating in EPIC-Norfolk. The aim of the piloting was to test procedures, determine participant willingness to answer questions, and detect ambiguities in the wording of the questionnaire so that it could be refined. Of those approached to participate, 78% returned a completed HLEQ. [177]

The final form of the HLEQ consisted of 36 pages and measured 7 areas: health and daily activities, work, social life, mood, lifetime events, childhood experiences and personal beliefs. Among other factors, it included the SF-36 instrument developed by the Rand Corporation for the Health Insurance Experiment in the US [178], a three-item SOC scale based on Aaron Antonovsky's work [84], and a structured self-assessment approach for the identification of people thought likely to have met putative diagnoses for GAD and MDD at any time in their lives. The development of the mood section measuring GAD and MDD was based on the design of the short-form symptom scales from the National Comorbidity Survey [167], discussions with the principal investigator of the NCS, and pilot testing. Measures of GAD and MDD were representative of core diagnostic criteria stipulated by the DSM-IV. As it was beyond the scope of the HLEQ to check for all exclusion criteria in the DSM, only criteria A (symptoms) and C (clinically significant distress or impairment) were used. [177, 179]

The HLEQ assessed GAD and MDD episode onset and offset timings. Information on the age of onset of the earliest episode was collected, as well as any episodes that may have occurred between the first and most recently reported episode. [177]

Although the HLEQ was carefully designed, the use of self-reported questionnaires might be called into question in regards to their ability to provide valid psychiatric diagnoses.

To provide answers to this, the prevalence of MDD in EPIC-Norfolk as measured by the HLEQ was compared with the prevalence derived through interviewer-based assessment methods in the UK – comparable findings were reported. [177] Furthermore, in accordance with previous studies, data based on the HLEQ instrument showed that the prevalence of MDD was higher in women and differences in genders became less pronounced with age. [177] Although no such studies were undertaken on GAD, there is no reason to expect that findings for the latter disorder would be any different than for MDD.

The next section includes a description of the SF-36 measure, the SOC scale, and GAD and MDD variables. The age of participants was determined using this questionnaire. These measures will be described next.

4.2.3.1 Disability

Disability was examined using the Medical Outcomes Study 36-Item (SF-36) questionnaire. The SF-36 was originally developed as a generic measure of subjective health status as part of the Medical Outcomes Study (MOS) in the US. [180] It is a 36-item measure capturing 8 health dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, energy/vitality, bodily pain, and general health perception. Each dimension is composed of several questions. This measure has been used by researchers worldwide and has been translated into over 40 languages. The SF-36 has been frequently used in health services research to determine whether interventions contribute to an improvement in patient quality of life.

The eight dimensions of the SF-36 were used to create two higher order scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS) according to algorithms specified by the original developers. Lower scores on these measures represent worse health. Further details on the construction of this measure are provided in Surtees et al. 2004. [181] This thesis only used the PCS score, because MCS components might be part of the expression of psychiatric illness. [181]

4.2.3.2 Sense of coherence (SOC)

The HLEQ included a three-item SOC questionnaire [182] that assessed each of the SOC constructs. The questions and algorithm used to create the SOC measure are provided in detail, because this was one of the main variables in one of the chapter analyses. The following questions were used to assess each SOC construct:

Comprehensibility:

Do you usually feel that the things that happen to you in your daily life are hard to understand?

Manageability:

Do you usually see a solution to problems and difficulties that other people find hopeless?

Meaningfulness:

Do you usually feel that your daily life is a source of personal satisfaction?

Participants were given the choice of responding to these questions with yes, usually; yes, sometimes; and no. Comprehensibility was reverse scored, and all items were then summed to provide a total SOC scale ranging from 0 to 6. Higher scores represent weaker SOC.

4.2.3.3 Generalised anxiety disorder (GAD)

The HLEQ questionnaire captured the onset and offset timings of episodes of past-year GAD, which was the main variable used in this thesis. [119] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was diagnosed if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge. The box below details the criteria that were used to determine whether participants were likely to have met putative diagnoses of DSM-IV past-year GAD.

The following questions were used to create the DSM-IV past-year GAD variable:

D11. People differ in how much they worry. Thinking back over your life, do you worry more than most people, less than most people, or about the same as most people in your situation?

More Less About the same

D12. Have you ever had a time in your life when you have been particularly nervous or anxious, worrying more than you needed to about things for six months or longer?

Yes No

For the next few questions, please think of the most recent time in your life when you worried a lot more than most people who were in your situation, for six months or longer.

D13. During this time did you worry every day, just about every day, most days, about half the days or less than half the days?

Every day **Just about every day** **Most days**

About half the days Less than half the days

D14. During this time, did you have different worries on your mind at the same time?

Yes No

D. 15 During this time, how often did you find it difficult to control your worry?

Often **Sometimes** Rarely Never

D. 16 During this time, how often was your worry so strong that you couldn't put it out of your mind no matter how hard you tried?

Often **Sometimes** Rarely Never

The participant must fulfill criteria A:

Question D11 – circle one of the bolded options AND
Question D12 – circle one of the bolded options AND
Question D13 – circle one of the bolded options AND
Question D14 – circle yes

The participant must fulfill criteria B:

Question D15 – circle one of the bolded options AND
Question D16 – circle one of the bolded options

Symptoms

D. 17 Some people experience other feelings associated with their worry.
At these times when you were worried or anxious, were you also bothered by:

D17a being restless	yes	no
D17b being keyed up or on edge	yes	no
D17c being easily tired	yes	no
D17d having trouble concentrating because of worry	yes	no
D17e your mind going blank	yes	no
D17f being particularly irritable	yes	no
D17g your muscles often being tense	yes	no
D17h trouble falling asleep	yes	no
D17i trouble staying asleep	yes	no

Symptom 1 = D17a OR D17b
Symptom 2 = D17c
Symptom 3 = D17d OR D17e
Symptom 4 = D17f
Symptom 5 = D17g
Symptom 6 = D17h or D17i

The participant must fulfill criteria C:

Having 3 or more of the above 6 symptoms

D18. During these six months or more, how much did these worries interfere with your life (so much so that it kept you from working, including such things as housework, childcare, and other activities or from seeing friends or relatives?)

Often **Sometimes** Rarely Never

D19. During this time did you tell a doctor about these feelings or take any medication?

Yes No

D20. During this time did you seek help from anyone else, like a minister, or a friend, or did anyone suggest that you seek help?

Yes No

The participant must fulfill criteria E:

Question D18 – circle one of the bolded options AND
(Question D19 – circle yes) OR (Question D20 – circle yes)

Participant must have criteria A and B and C and E to be considered a GAD case

4.2.3.4 Major depressive disorder (MDD)

The HLEQ was also used to assess presence of MDD.

First, to meet criteria for MDD, respondents needed to answer positively to one of these two questions:

a. 'Have there ever been times in your life when you felt sad or depressed for 2 weeks or more in a row?'

b. 'Have there ever been times in your life when you lost interest in most things like your work or activities that usually give you pleasure, for 2 weeks or more in a row?'

To meet criteria for current MDD, cases were to additionally have met at least five of the following symptoms that resulted in help-seeking: gaining or losing weight without trying, trouble falling asleep or sleeping too much, feeling tired, unable to sit still or feeling slowed down, feeling guilty or ashamed, feeling inferior or worthless, having trouble concentrating, and thinking about death. Participants were asked to estimate the onset and (if appropriate) offset timings and to describe the history of the problem. They were asked about the age when symptoms first developed and subsequent episode recurrence. Current MDD was defined as an episode that had offset within 12 months of the HLEQ assessment.

Since MDD was the outcome variable in one of the chapters, the questions and algorithm used to identify an MDD case will be provided:

The following questions were used to create the current MDD variable:

D1. Have there ever been times in your life when you felt sad or depressed for two weeks or more in a row?

Yes No

D2. Have there ever been times in your life when you lost interest in most things like your work or activities that usually give you pleasure, for two weeks or more in a row?

Yes No

For the next few questions, please think of the most recent two-week episode during your life when these feelings of sadness, depression or loss of interest were worst.

D3. During that time did the feelings of being sad or depressed, or loss of interest usually last all day long, most of the day, about half the day or less than this?

All day long **Most of the day** About half the day

Less than half the day

D4. During those two weeks, did you feel this way every day, almost every day or less often?

Every day **Almost every day** Less often

Symptoms

D5. During those two or more weeks did you:

D5a gain or lose weight without trying?	**yes**	no
D5b have more trouble falling asleep than you	**yes**	no
usually do, or sleeping too much?	**yes**	no
D5c feel tired out or low on energy all the time	**yes**	no
D5d feel unable to sit still and had to keep moving or the opposite – feeling slowed down and having trouble moving?	**yes**	no
D5e* feel guilty or ashamed of yourself for something you did or thought?	**yes**	no
D5f* feel inferior or even worthless?	**yes**	no
D5h have trouble concentrating, thinking, or making decisions?	**yes**	no
D5i think a lot about death, either your own, someone else's, or suicide?	**yes**	no

*D5e and D5f count as 1 symptom; if either present.

D6. People differ in how much their day to day activities are affected when they feel sad or depressed or lose interest in the things that they normally enjoy. The next few questions are about how you were affected by these feelings and experiences during this same time that you have just described.

D6a. During those two weeks (or more), how much did these feelings and experiences interfere with your life (so much that it kept you from working, including such things as housework, children, and other activities or from seeing friends or relatives).

Often **Sometimes** Rarely Never

D6b. During this time did you tell a doctor about these feelings or take any medication?

Yes No

D6c. During this time did you seek help from anyone else, like a minister, or a friend, or did anyone suggest that you seek help?

Yes No

D7b. Is it still going on?

Yes No

The participant must fulfill criteria A:

At least 5 bolded symptoms from above. At least one of the symptoms must be: (D1=yes & D3=all day or most of the day & D4=every day or almost every day) or (D2=yes & D3=all day or most of the day & D4=every day or almost every day)

The participant must fulfill criteria C:

D6a=often or sometimes & (D6b=yes or D6c=yes)

Participant must have criteria A and C and D7b=yes to be considered an MDD case

4.2.3.5 Age

The age the participant was at the time the HLEQ questionnaires were returned to the researchers was the age used in analyses in this thesis.

4.2.3.6 Marital status

Participants were asked their marital status and were instructed to tick boxes as appropriate: married, single (or never married), widowed, divorced, or separated.

4.2.4 1991 Census

4.2.4.1 Social class

Individual-level social class was coded according to the Registrar General's occupation-based classification scheme and information from the 1991 Census was used to do this. [183] Social class I represented professionals, social class II managerial and technical occupations, social class III subdivided into nonmanual and manual skilled workers, social class IV partly skilled workers, and social class V unskilled manual workers. For men, their own occupation at the time of the survey was used to code social class unless they were unemployed, in which case their partner's was used. Social class for men without employment and without partners was unclassified. For retired men, their last occupation was used. Women's social class was based on their partner's unless the partner's social class was unclassified, missing, or they had no partner, in which case social class was based on the women's own occupation. The social class of women who were unemployed and without a partner was unclassified. [172]

4.2.4.2 Area deprivation

To examine area deprivation, one of the most commonly-used measures of area deprivation in the UK was used: the Townsend Index [184, 185]. This index is a composite measure of four variables obtained from the 1991 Census: 1) percentage of economically active residents over age 16 who are unemployed, 2) percentage of households that do not own a car, 3) percentage of private households that are not owner occupied, and 4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district. Each variable was standardized by obtaining Z scores (dividing the mean by the standard deviation across enumeration districts in England and Wales). The Z values of the four variables were added together to produce a Townsend index score for each enumeration district. Positive values of the index indicated enumeration districts that were more deprived, while negative values indicated those that were less deprived; 0 represented the national mean. The postal codes of participants were record linked to enumeration districts, and participants were considered to live in deprived areas depending on the Townsend index score assigned to their enumeration district. [184]

4.3 Follow-up of cohort

The EPIC-Norfolk cohort was flagged for hospital admissions and deaths through the NHS Central Register. [166] Death certification was used to identify participants who died, and vital status until 2015 was established for the whole cohort through record linkage with the UK ONS. Nosologists coded underlying cause of death according to the ICD-9 and ICD-10. Underlying cause of deaths was coded as follows - CVD: ICD-9 codes 401-448, ICD-10 codes I10-I79; cancer: ICD-9 codes 140-208, ICD-10 codes C00-C97; respiratory diseases: ICD-9 codes 460-496, ICD-10 codes J00-J99.

The EPIC-Norfolk cohort was also record linked to databases maintained by the East Norfolk Primary Health Care Trust using participants' unique NHS numbers to provide information on hospital admissions until 2009. These databases captured all hospital activity of study residents treated anywhere in England and Wales. About 95% of the admissions were to the Norwich University Hospitals NHS Foundation Trust. Each admission within these databases was typically characterised by several episodes; the start and end dates of episodes, as well as admission and discharge dates were used to determine the number of hospital admissions for participants. [186]

4.4 Statistical Methods

4.4.1 Statistical analysis

In this section, a brief overview of the statistical methods used in each chapter will be provided; however, detailed explanations of the analytical methods are included within the chapters.

Each chapter is based on slightly different samples with adjustment for slightly different covariates, depending on the research question. In accordance with the literature, potential confounders that were associated with the exposure and outcome were selected for each analysis.

The chapters typically begin with a description of the prevalence of past-year GAD broken down by sociodemographic and health status categories, such as, marital status, social class, education, disability, psychiatric history, and behavior risk factors, including alcohol intake, physical activity, and smoking. Next, progressive adjustment for covariates is undertaken to examine the way that the effect estimate of the exposure changed as confounders were introduced in the models.

Two chapters on the influence of the residential environment on risk of having GAD or MDD used generalised estimating equations to account for the potential correlation introduced by the clustering of individuals within residential areas. The chapter on the link between anxiety and mortality used survival analysis, while the chapter on the influence of GAD on health service use was based on zero-inflated negative binomial regression. The chapter on coping as a moderator of the association between area deprivation and GAD used logistic regression. In accordance with the WHO framework [72] and previous literature on the influence of the living context on mental health, the chapters on the residential environment and its link with GAD and MDD examined associations from a gendered perspective.

4.4.2 Handling of missing data

Most of the missing data in this thesis arose from covariates, such as, the SF-36 and the BMI; there was also some missing data for GAD. Nevertheless, there is no strong reason to believe that those who completed the questions on these variables differed systematically with respect to important characteristics from those who did not. In line with other EPIC-Norfolk studies, all chapters were based on a complete case analysis, with the exception of one chapter that investigated missing data through multiple imputations. The effect estimates based on imputed data were similar to those obtained though complete case analysis. Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC) was used for all analyses.

The next chapter presents my first analysis, the link between GAD and mortality.

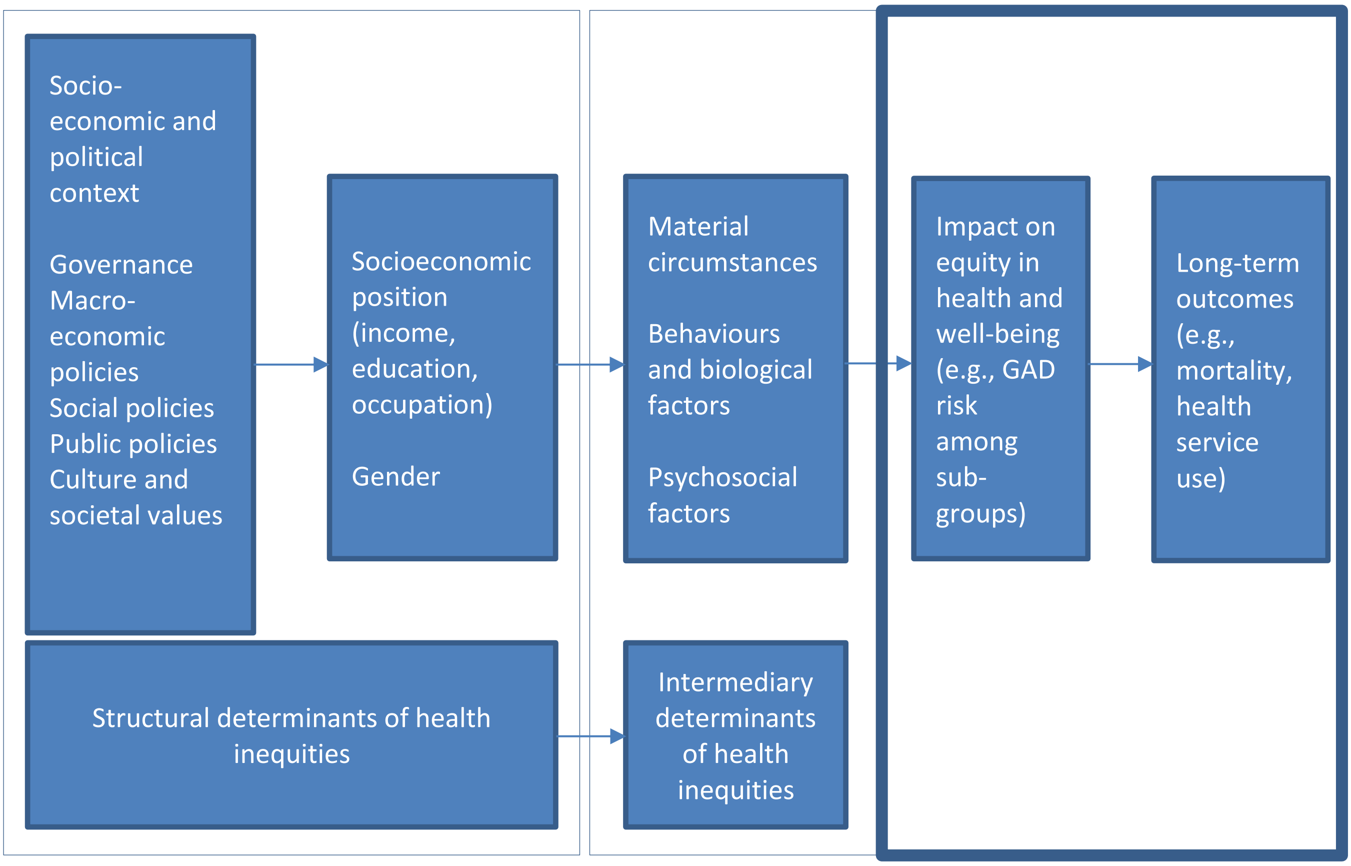
5 Generalised anxiety disorder (GAD) and early mortality: a longitudinal, population study

Preface to chapter

The conceptual framework showed that the context can give rise to health inequities, which can be manifested as differential risks of having GAD among population sub-groups. People with GAD may then be at increased risk for deleterious health outcomes; however, further work is needed to clarify this.

Whether GAD can lead to negative health consequences, such as early death from major causes of disease remains to be elucidated. This chapter will assess the possible link between GAD, measured according to the Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV), and mortality in the EPIC-Norfolk study.

The part of the conceptual model with the bolded outline refers to those who have anxiety, which may subsequently give rise to sequelae.



ABSTRACT

Introduction

It remains unclear whether GAD contributes to excess deaths from major causes of disease, because of limitations of previous studies.

Methods

I determined whether GAD is associated with cause-specific mortality in 16,110 people over the age of 40, living in England, and who took part in EPIC-Norfolk. I used a structured health questionnaire to capture DSM-IV GAD in 1996-2000. I ascertained death from all causes and all cancers in participants until 2015. This is a longitudinal, cohort study.

Results

During a 19-year follow-up period, 4169 participants died. GAD was statistically significantly associated with increased risk of mortality from all causes (adjusted mortality hazard ratio 1.38, 95% CI: 1.11, 1.72), as well as with cancer mortality (adjusted mortality hazard ratio 1.62, 95% CI: 1.15, 2.28). The associations persisted after accounting for demographic characteristics, social class, somatic and psychiatric comorbidity, and behaviour risk factors.

Conclusion

I show, for the first time that people with GAD are at a significantly increased risk of all-cause mortality and cancer deaths. These findings are highly important and have policy and clinical implications. GAD could be a warning signal for future poor health and general practitioners should be vigilant for this. Additional studies are needed to determine why anxiety is linked to cancer processes.

5.1 Introduction

Anxiety disorders [5] are the most common class of psychiatric disorders in the general population. [6, 7] They are associated with high impairment and disability, risk of suicide and suicidal ideation, and high health service use rates. [17, 89, 187, 188] The Global Burden of Disease study estimated their annual direct cost to be $42.3 billion [12], and on a global scale, anxiety disorders have been linked to approximately 26.8 million disability adjusted life years.[13]

Epidemiological evidence has been accumulating on the association between anxiety and major causes of death, yet findings have been mixed. Anxiety symptoms have been associated with mortality from all causes [38, 39, 51, 189, 190] and CVD [38, 191, 192], while other studies have found absent [40, 41, 193, 194] or even negative [42] associations with these outcomes. One study even linked anxiety to survival and improved cardiovascular outcomes. [42] This confusion with respect to mortality extends to other common causes of death, such as respiratory diseases and cancers, and findings on these outcomes have also been mixed after adjustment for behavioural and clinical factors. [38, 195]

The inconsistency in findings relates to the fact that much of the work on mortality has been based on small sample sizes, short follow-up periods, different anxiety assessment methods, and clinical populations. Small studies have insufficient power to detect associations and can result in unreliable effect estimates. A small sample size also makes it difficult to assess reverse causality, and the anxiety that is measured may be the worry or fear experienced because of the development of a severe disease rather than the presence of an independent psychiatric disorder. A number of studies have followed participants for less than five years, which might not be enough time for the development of enough outcome events, particularly in community populations. A healthier sample recruited from the general population will need to be followed for a longer time than a high-risk, clinical group, because it may be chronic, rather than acute anxiety that is more predictive of poor health outcomes in healthier people. Finally, many previous studies have assessed broad feelings of anxiety-whose clinical relevance might be limited- and in hospitalized samples that are in poorer health than general population cohorts. In view of these limitations, the objective of this study was to examine the longitudinal association between GAD, one of the most common anxiety disorders in the general population [26, 27], and principal causes of death relating to CVD, respiratory disease, cancer, and other conditions in a longitudinal, population-based cohort of over 15,000 British people. This is one of the largest and most comprehensive studies to examine these associations.

5.2 Methods

5.2.1 Study design and participants

The study design for this particular research examining anxiety and mortality is a longitudinal, cohort study design.

Although the methods were described in a previous chapter, they will be briefly presented again. Data were drawn from the longitudinal, population-based EPIC-Norfolk, described in detail elsewhere. [166, 196]

Between 1993 and 1997, 30,445 participants over the age of 40 years living in Norwich and the surrounding towns and rural areas were identified through general practice age-sex registers. During this time, 25,639 participants attended a baseline health check during which anthropometric measures, such as height and weight, were taken. Participants completed questionnaires over the follow-up period which assessed psychiatric disorders, demographic characteristics, social class, medical conditions, and behavioural risk factors.

5.2.2 Assessment of GAD

In 1996-2000, 20,919 men and women completed a postal HLEQ, which was used to identify those meeting criteria for DSM-IV GAD. [179] The exposure in this study was past-year GAD. The onset and offset timings of episodes of GAD measured in the past year were identified using the HLEQ. [179] Past-year GAD consisted of having at least one episode that had offset within 12 months of administration of the HLEQ.

To fulfill DSM-IV criteria for this disorder, participants needed to have had uncontrollable, excessive worry for six months or longer on most days than not that resulted in life interference and help-seeking. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge.

5.2.3 Assessment of covariates

Potential confounders were chosen a priori based on previous literature, [45, 55, 56] and were selected based on their association with the exposure and outcome. For example, age is related to both anxiety and mortality. As age increases, the risk of anxiety diminishes [197, 198, 199] but the risk of mortality rises [200]. In terms of gender, women have been shown to be more affected by anxiety [201], but tend to have lower death rates at all ages compared to men. [202] Education has also been found to play a role, with those of lower educational attainment or early termination of education having both poorer mental health and higher mortality rates. [203, 204, 205] Single and separated/divorced/widowed marital status has also been linked to anxiety and early mortality. [206, 207] Social class has similarly been linked to anxiety and mortality, with manual social class being particularly deleterious for health (although the link between anxiety and socioeconomic status is not always clear [208]). [199, 209] In addition, the following groups of people may be more likely to have anxiety: those suffering from medical conditions [119, 201], disability [206, 210], and depression [206], and who are overweight [211]. People who are affected by physical comorbidities [212], disability [213], and depression [214] are also more likely to die prematurely. In regards to risk behaviours, individuals who smoke [215, 216], drink [217], and are inactive [218, 219] are more likely to have anxiety and vice versa in bidirectional relationships. These same groups (smokers [220], heavy drinkers [221], and inactive people [222]) are also more likely to die early.

The baseline HLQ was used to ascertain sex (male, female), marital status (single, married, widowed, separated, divorced), education (highest level of education attained: no qualifications, educated to age 16 years, educated to age 18 years, or educated to degree level), and self-reported physician diagnoses of major medical conditions diseases (self-reported stroke, myocardial infarction, and cancer).

Behaviour risk factor measures included alcohol intake (units of alcohol/week), smoking status (current, former, non-smoker), and physical activity (inactive, moderately inactive, moderately active, active). Using information from the baseline health check, BMI was calculated (weight in kilograms divided by height in metres squared).

The 1991 Census was used to ascertain social class (professionals, managerial and technical occupations, skilled workers divided into non-manual and manual, partly skilled workers and unskilled manual workers), and the HLEQ was used to identify age, marital status, lifetime MDD defined according to the DSM-IV, and disability.

To determine disability levels, I used the PCS of the SF-36, a widely-used, validated self-assessment tool. Higher scores indicate better health. [178]

Categorization of variables

Variables were categorized as per the literature and in order to ensure sufficient cell size. Age was assessed per 10 year age bands [177]; education was categorized into low (no qualifications) vs. high (educated to age 16 years, educated to age 18 years, or educated to degree level) [223]; marital status into single, married, and others (widowed, separated divorced) [223]; social class into nonmanual (professionals, managerial and technical occupations, skilled workers) vs. manual (partly skilled and unskilled manual workers) [223]; self-reported physician diagnoses into yes (any of the diseases) vs. no (none of the diseases) [223]; physical activity was categorized into inactive vs. active (moderately inactive, moderately active, active) [224]; alcohol intake into <7 units, 7-14 units, 14-21 units, and >=21 units [225]; smoking status was left in its original form (current, former, never smoker) as was originally entered in the EPIC-Norfolk database [223]; and BMI and PCS (disability) scores were dichotomized. MDD was left as a dichotomous variable as originally created based on the DSM-IV classification.

5.2.4 Ascertainment of deaths

Linkage with the UK ONS allowed me to establish vital status for participants. Underlying cause of death was coded according to the Ninth and Tenth Revisions of the ICD (CVD: ICD-9 codes 401-448, ICD-10 codes I10-I79; cancer: ICD-9 codes 140-208, ICD-10 codes C00-C97; respiratory diseases: ICD-9 codes 460-496, ICD-10 codes J00-J99). The follow-up period over which vital status was ascertained included the time between the administration of the HLEQ in 1996-2000 and January 31, 2015.

5.2.5 Statistical analysis

Characteristics of the participants were compared by GAD status – Pearson's chi-square test was used to determine whether differences were statistically significant for categorical variables. To determine the association between past-year GAD and mortality, Cox proportional hazards regression was conducted. The endpoints were death from all causes, as well as mortality from CVD, all cancers, respiratory diseases, and all other causes. Because the number of cases of death from CVD and respiratory disease were too small, I did not conduct analyses on these endpoints (as such, the 'other causes' category was left out as an outcome, as well) – these will not be discussed further. Analyses relating to all-cause and cancer mortality were undertaken. The proportional hazards assumption was assessed using Kaplan-Meier plots and Schoenfeld's residual test. There was a slight indication from Schoenfeld's residual test that the pre-existing health conditions variable may have violated the proportional hazards assumption and therefore, was included the strata statement in the Statistical Analysis Software (SAS) Version 9.3 program (hence, an effect estimate was not derived for this variable). The Kaplan-Meier plots also show that there is very little difference in survival between those with and without anxiety (this changes, however, when age [a negative confounder] is introduced in the models, as explained later [appendix 5]). Models were constructed for GAD as the exposure with progressive adjustment of covariates to show the influence of potential confounders on the association with mortality: unadjusted; A. adjusted for age, sex, education, marital status, social class, pre-existing health conditions, and disability; B. further adjusted for MDD; C. with additional adjustment for physical activity level, smoking status, alcohol intake, an BMI. Participants with complete data on all covariates were retained for analysis.

Hazard ratios (HR) with 95% CI were calculated with 'no GAD' as the reference category. Two-sided statistical tests were implemented with a p-value of <0.05 considered to be statistically significant. Analyses were implemented in Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC).

5.3 Results

77,630 people from general practices in Norfolk were invited to take part in the study. Of the 30,445 people who consented at baseline, 20,919 completed the HLEQ during follow-up. I had limited data on non-responders. [166, 196] Of those who completed the HLEQ, 16,110 were available for analysis in this study, because they had data on all covariates. The number of missing observations for each covariate was: 1 for age, 9 for education, 47 for marital status, 458 for social class, 1,386 for disability, 468 for MDD, 479 for GAD, 169 for smoking, 213 for alcohol, and 2,698 for BMI. Participants were followed between 1996 and 2015 (19 years). Notable findings from the missing data analysis show that people with missing GAD more often had high disability, MDD, and low alcohol consumption (appendix 6).

During 1996-2000, GAD was identified in 347 out of 16110 (2.2%) people. Table 5.1 shows sociodemographic, medical history, and lifestyle characteristics by GAD status. Participants who were younger than 65 years, female, single and of 'other' marital status, with high disability levels, lifetime depression, and current smokers had higher prevalence of GAD.

Table 5.1 Baseline characteristics by past-year GAD among 16,110 participants who completed the HLEQ in 1996–2000, European Prospective Investigation into Cancer-Norfolk, United Kingdom

Characteristic	Number with characteristic	Percentage and no. with past-year GAD
Socio-demographics		
Age (years)		
<50	2059	3.3 (67)[a]
50-60	5595	2.8 (158)
60-70	5216	1.6 (86)
>=70	3240	1.1 (36)
Sex		
Female	8914	2.5 (220)
Male	7196	1.8 (127)[b]
Education[‡]		
Low	5313	1.9 (103)
High	10797	2.3 (244)
Marital status		
Single	583	3.1 (18)[a]
Married	13130	2.0 (256)
Other[*]	2397	3.1 (73)
Social class		
Manual	5961	1.9 (114)
Non-manual	10149	2.3 (233)
Health status		
Physical conditions		
Yes[+]	1475	2.4 (36)
No	14635	2.1 (311)
Disability level		
High[¶]	8056	2.9 (232)[a]
Low	8054	1.4 (115)
Lifetime MDD		
Yes	2524	8.8 (221)[a]
No	13586	0.9 (126)
Lifestyle		
Category of body mass index		
Higher (>=26)	7612	2.2 (168)
Lower (<26)	8498	2.1 (179)
Physical activity level		
Inactive	4448	2.3 (102)
Active[¥]	11662	2.1 (245)
Smoking status		
Current	1641	4.5 (73)[a]
Former	6759	1.9 (130)
Never	7710	1.9 (144)
Alcohol intake		

<7[α]	10270	231 (2.2)
7-14	3166	67 (2.1)
14-21	1375	24 (1.7)
>=21	1299	25 (1.9)

[+] Prevalent physical disease: stroke, heart attack, cancer
[¥] Moderately inactive, moderately active, active
[‡] High education: O-level, A-level, degree; low education: refers to no education
[*] Other: divorced, separated, widowed
[¶] Above the PCS value of 50.6
[α] 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit
[a] $P < 0.001$
[b] $P < 0.05$

Over the 19-year follow-up period, there were a total of 4169 all-cause deaths and 1508 cancer deaths. Table 5.2 shows the unadjusted and adjusted HR for associations between GAD and sociodemographic and health risk factors, and all-cause mortality (Models A-C).

Table 5.2 Associations between past-year GAD reported in 1996-2000 and all-cause mortality in 16,110 participants, European Prospective Investigation into Cancer-Norfolk, United Kingdom, 2000–2015

	Hazard Ratios and 95% CI				
Characteristic	**Crude IRR**	**A[1]**	**B[2]**	**C[3]**	**p-value for model C**
Past-year GAD					
Yes	0.95 (0.76, 1.18)	1.41 (1.13, 1.75)	1.44 (1.15, 1.79)	1.38 (1.11, 1.72)	0.0043
No	1.00	1.00	1.00	1.00	
Socio-demographics					
Age					
Per 10 years	3.52 (3.37, 3.67)	3.22 (3.08, 3.36)	3.21 (3.07, 3.36)	3.25 (3.10, 3.40)	<0.0001
Sex					
Women	0.59 (0.56, 0.63)	0.58 (0.55, 0.62)	0.58 (0.55, 0.62)	0.63 (0.59, 0.67)	<0.0001
Men	1.00	1.00	1.00	1.00	
Education‡					
Low	1.51 (1.42, 1.61)	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.05 (0.98, 1.12)	0.1790
High	1.00	1.00	1.00	1.00	
Marital status					
Single	1.35 (1.16, 1.57)	1.34 (1.15, 1.56)	1.34 (1.15, 1.56)	1.31 (1.13, 1.53)	0.0177
Married	1.00	1.00	1.00	1.00	
Other*	1.63 (1.51, 1.75)	1.27 (1.17, 1.37)	1.27 (1.17, 1.38)	1.21 (1.12, 1.32)	
Social class					
Manual	1.05 (0.98, 1.12)	1.09 (1.02, 1.16)	1.08 (1.01, 1.16)	1.06 (0.99, 1.13)	0.0900
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Physical conditions					
Yes⁺	--	--	--	--	
No	1.00	1.00	1.00	1.00	
Disability level					
High¶	2.26 (2.12, 2.41)	1.40 (1.31, 1.50)	1.40 (1.31, 1.50)	1.35 (1.26, 1.45)	<0.0001
Low	1.00	1.00	1.00	1.00	
Psychiatric conditions					
Lifetime MDD					

Yes	0.74 (0.68, 0.82)			0.94 (0.85, 1.03)	0.1961
No	1.00		1.00	1.00	
Lifestyle					
Physical activity					
Active[¥]	1.00			1.00	
Inactive	1.95 (1.83, 2.08)			1.19 (1.11, 1.27)	<0.0001
Smoking status					
Current smoker	1.79 (1.62, 1.98)			2.12 (1.92, 2.35)	<0.0001
Former smoker	1.73 (1.62, 1.85)			1.20 (1.12, 1.29)	
Never smoker	1.00			1.00	
Alcohol intake					
<7[α]				1.00	
7-14	0.90 (0.83, 0.97)			0.88 (0.81, 0.95)	
14-21	0.95 (0.84, 1.06)			0.99 (0.88, 1.11)	
>=21	1.19 (1.07, 1.33)			1.13 (1.01, 1.27)	<0.0001
BMI					
High	1.30 (1.23, 1.39)			1.06 (1.00, 1.13)	0.0710
Low	1.00			1.00	

[1] Model A: adjusted for sociodemographics (age, sex, education, marital status, social class), physical conditions, disability

[2] Model B: adjusted for sociodemographics, physical conditions, disability, MDD

[3] Model C: adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol, BMI

ǂ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

⁺ Physical conditions: stroke, heart attack, cancer

¶ Below the PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

Main finding: GAD and all-cause mortality

Analyses adjusted for sociodemographic factors, pre-existing health conditions and disability showed that GAD was significantly associated with risk of all-cause mortality (HR=1.41, 95% CI: 1.13, 1.75). The effect estimate changed somewhat when MDD was added to the model (HR=1.44, 95% CI, 95% CI: 1.15, 1.79). Compared to the previous analysis, the association became slightly attenuated when smoking, physical activity, alcohol intake, and BMI were included as covariates (HR=1.38, 95% CI: 1.11, 1.72). The findings remained unchanged when those with a history of cancer were excluded.

In a sensitivity analysis based on a fully-adjusted model, a time-dependent covariate was introduced and the effect estimate for all-cause mortality remained highly significant in the long-term (>4 years follow-up: HR=1.40, 95% CI: 1.11, 1.76).

Other findings: covariates related to all-cause mortality

The final multivariable model of the main analysis which adjusted for all covariates showed that other variables were significantly associated with mortality. Namely, people of single and 'other' marital status (HR=1.31, 95% CI: 1.13, 1.53 and HR=1.21, 95% CI: 1.12, 1.32, respectively), with high disability levels (HR=1.35, 95% CI: 1.26, 1.45), who were inactive (HR=1.19, 95% CI: 1.11, 1.27), and current and former smokers (HR=2.12, 95% CI: 1.92, 2.35 and HR=1.20, 95% CI: 1.12, 1.29, respectively) had a somewhat high risk of dying early. Also, participants who were older (HR=3.25, 95% CI: 3.10, 3.40), drank 21 units of alcohol or more (HR=1.13, 95% CI: 1.01, 1.27), and were overweight (HR=1.06, 95% CI: 1.00, 1.13) had a higher risk of dying early (HR=3.25, 95% CI: 3.10, 3.40). In contrast, participants who were women (HR=0.63, 95% CI: 0.59, 0.67) and drank between 7 and 14 units of alcohol (HR=0.88, 95% CI: 0.81, 0.95) had improved survival compared to other participants.

Table 5.3 shows the unadjusted and adjusted HR for associations between GAD and sociodemographic and health risk factors, and cancer mortality (Models A-C).

Table 5.3 Associations between past-year GAD reported in 1996-2000 and cancer mortality in 16,110 participants, European Prospective Investigation into Cancer-Norfolk, United Kingdom, 2000–2015

	Hazard Ratios and 95% CI				
Characteristic	**Crude IRR**	**A[1]**	**B[2]**	**C[3]**	**p-value for C**
Past-year GAD					
Yes	1.12 (0.81, 1.56)	1.50 (1.08, 2.10)	1.70 (1.21, 2.39)	1.62 (1.15, 2.28)	0.0058
No	1.00	1.00	1.00	1.00	
Socio-demographics					
Age					
Per 10 years	2.33 (2.19, 2.47)	2.19 (2.04, 2.34)	2.16 (2.02, 2.31)	2.22 (2.07, 2.38)	<0.0001
Sex					
Women	0.60 (0.55, 0.67)	0.62 (0.56, 0.69)	0.62 (0.56, 0.69)	0.68 (0.60, 0.76)	<0.0001
Men	1.00	1.00	1.00	1.00	
Education[‡]					
Low	1.35 (1.22, 1.50)	1.04 (0.93, 1.17)	1.04 (0.93, 1.16)	1.01 (0.91, 1.13)	0.7408
High	1.00	1.00	1.00	1.00	
Marital status					
Single	1.01 (0.77, 1.34)	1.02 (0.77, 1.34)	1.01 (0.77, 1.34)	1.01 (0.76, 1.34)	0.4011
Married	1.00	1.00	1.00	1.00	
Other[*]	1.30 (1.14, 1.49)	1.13 (0.98, 1.30)	1.15 (1.00, 1.33)	1.10 (0.96, 1.27)	
Social class					
Manual	1.13 (1.02, 1.25)	1.15 (1.03, 1.28)	1.14 (1.02, 1.27)	1.11 (1.00, 1.24)	0.0602
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Physical conditions					
Yes[+]	--	--	--	--	
No	1.00	1.00	1.00	1.00	
Disability level					
High[¶]	1.73 (1.56, 1.92)	1.20 (1.08, 1.34)	1.21 (1.09, 1.35)	1.18 (1.06, 1.31)	0.0032
Low	1.00	1.00	1.00	1.00	
Psychiatric conditions					
Lifetime MDD					
Yes	0.64 (0.55, 0.76)		0.76 (0.65, 0.90)	0.74 (0.63, 0.88)	0.0005
No	1.00		1.00	1.00	

Lifestyle				
Physical activity				
Active[¥]	1.00		1.00	
Inactive	1.51 (1.36, 1.68)		1.04 (0.93, 1.16)	0.495
Smoking status				
Current smoker	2.05 (1.75, 2.39)		2.27 (1.93, 2.67)	<0.0001
Former smoker	1.63 (1.46, 1.83)		1.22 (1.08, 1.37)	
Never smoker	1.00		1.00	
Alcohol intake				
<7[α]	1.00		1.00	0.243
7-14	0.95 (0.83, 1.09)		0.91 (0.80, 1.04)	
14-21	0.97 (0.80, 1.17)		0.96 (0.79, 1.16)	
>=21	1.26 (1.05, 1.50)		1.12 (0.93, 1.35)	
BMI				
High	1.26 (1.14, 1.39)		1.07 (0.97, 1.19)	0.1855
Low	1.00		1.00	

[1] Model A: adjusted for sociodemographics (age, sex, education, marital status, social class), physical conditions, disability

[2] Model B: adjusted for sociodemographics, physical conditions, disability, MDD

[3] Model C: adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol, BMI

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: stroke, heart attack, cancer

¶ Below the PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

Main finding: GAD and cancer mortality

Anxiety was associated with increased risk for cancer mortality, after adjustment for sociodemographic factors, pre-existing health conditions and disability (HR=1.50, 95% CI: 1.08, 2.10). Further adjustment for MDD did not attenuate the relationship with cancer mortality and it remained statistically significant (HR=1.70, 95% CI: 1.21, 2.39). GAD remained significantly associated with cancer mortality after additional adjustment for physical activity level, smoking status, alcohol intake, and BMI (HR=1.62, 95% CI: 1.15, 2.28). The findings remained unchanged when those with a history of cancer were excluded.

In a sensitivity analysis based on a fully-adjusted model, a time-dependent covariate was introduced and the effect estimate for cancer mortality remained highly significant in the long-term (>4 years follow-up: HR= 1.66, 95% CI: 1.16, 2.36).

Other findings: covariates related to cancer mortality

When other covariates were considered in relation to cancer mortality in the final multivariable model, the following emerged as increasing risk of death: people with high disability levels (HR=1.18, 95% CI: 1.06, 1.31), and current and former smokers (HR=2.27, 95% CI: 1.93, 2.67 and HR=1.22, 95% CI: 1.08, 1.37, respectively). Increasing age (HR=2.22, 95% CI: 2.07, 2.38) and manual social class (HR=1.11, 95% CI: 1.00, 1.24) were also associated with increased risk of dying early, though the last variable was borderline significant. Variables which were associated with decreased risk of premature mortality included being a woman (HR=0.68, 95% CI: 0.60, 0.76), and having MDD (HR=0.74, 95% CI: 0.63, 0.88).

Multiple imputations for main findings relating GAD to all-cause and cancer-mortality

When I conducted multiple imputations for missing data (appendix 7), the effect estimates were similar to those obtained through complete case analysis (all-cause mortality: HR=1.34, 95% CI: 1.09, 1.65; cancer mortality: HR=1.53, 95% CI: 1.14, 2.06).

5.4 Discussion

Main findings

In this large, longitudinal study, I found that GAD was associated with all-cause mortality and death from cancer (in the complete case analysis), after controlling for potential confounders. When I conducted multiple imputations for missing data, the effect estimates remained similar.

GAD was associated with a 38% chance of premature mortality from all causes. When I examined cause of death related to anxiety, I found that GAD was positively associated with cancer mortality. People with anxiety had a 45% higher chance of dying from cancer than those without anxiety. The associations with all-cause and cancer mortality persisted after adjustment for age, sex, marital status, education level, social class, chronic physical diseases, disability, MDD, smoking, alcohol intake, physical activity, and BMI. The effect estimates for excess deaths from all causes and cancer specifically remained high after four years of follow-up, suggesting that reverse causality is not an issue.

Secondary findings

When I examined covariates in relation to all-cause mortality, the following increased risk of death: being older, single and of divorced/separated/widowed marital status, inactive, overweight, current and former smokers, having high disability levels, and consuming 21 units or more of alcohol. In contrast, women and people who drank 7-14 units of alcohol had a decreased risk of all-cause mortality.

When I examined the covariates related to cancer deaths, I found that people of older age, manual social class, with high disability levels, and who were current and former smokers had an increased risk of premature cancer mortality. On the other hand, women and those with MDD were at a lower risk of early death from cancer.

Strengths and limitations

This is one of the largest population-based studies to examine the association between GAD and mortality. I had access to a large sample of 16110 participants living in the community, and there were over 4000 deaths during follow-up. This provided enough power to analyse in detail all-cause mortality and deaths related to cancer, and investigate reverse causality; nonetheless, other causes of death could not be explored because of small case numbers. I had complete data on mortality, participants were followed for a long period of time, and a structured questionnaire was used to derive a clinically relevant measure of anxiety. I had access to detailed health and lifestyle information, enabling me to adjust for a range of relevant confounders. I had a large list of self-reported physician diagnoses of chronic physical diseases that I used to ascertain medical histories. Despite this, the residual effect of diseases not captured by this study, but that are associated with GAD and mortality may be present. Unmeasured confounders, such as other illnesses linked to anxiety and mortality that were not captured by the HLEQ may pose a problem; if these confounders were not included in the analysis, then the effect estimates reported for GAD may be overestimated. Nevertheless, the medical histories ascertained from participants were extensive and allowed for adequate adjustment of covariates. Second, past illness may have been underreported, because participants may have forgotten or omitted disclosing information about conditions they were diagnosed with. If the illness was diagnosed a long time before EPIC-Norfolk began and participants failed to recall it, then this could have introduced measurement error and affected the hazard ratio of the medical history variable. Since the error in recall of past medical conditions was independent of the outcome status, non-differential misclassification may have biased the effect estimates of the medical history variable towards the null.

Past risk behaviours, such as smoking and drinking may also have been underreported, because of social desirability bias. This type of bias occurs when people give socially acceptable answers and omit reporting information that might be viewed in a negative light [233]. As such, the hazard ratios for risk behaviours may be underestimated in this study.

Residual confounding may be another issue – if there is error in measuring a confounder or it is not accurately measured, then it is still not completely accounted for in the analysis. For example, the confounding effect of smoking in the anxiety-mortality association might not be completely removed with the use of 'ever', 'never', and 'former' smoking categories. Additional variables, such as length of time smoking might need to be considered and included in the models.

In regards to the categorization of the covariates, there could have been different ways of performing this procedure. For example, instead of creating dichotomous social class and disability variables, these covariates could have been left in their original form. This might have resulted in potentially less information being lost in analyses. [234]

Non-participation and selection out of the study

Finally, non-participation in this study could be another problem if the findings from this research are not generalizable to the wider UK population. Results from this study are applicable to the types of people taking part in it. People that enrolled in EPIC-Norfolk tended to be healthier and more affluent than those living in other parts of England. As such, results may not generalize well to those residing in extremely deprived areas. Another problem is that this research was based on volunteers taking part, thus leading to possible volunteer bias (the inclusion of motivated participants which might have a better health and risk factor profile than non-participants). To determine the extent that volunteer bias is an issue, it would have been useful to compare respondents and non-respondents on several sociodemographic factors, risk behaviours, and medical history variables. However, it is not possible to acquire such detailed information from individuals not willing to participate. EPIC-Norfolk has, nevertheless, been shown to be representative of the general resident population of England in terms of anthropometric measures. [166]

Non-participation could also bias effect estimates; this would be an issue if the people who select into the study have characteristics that are different from the ones who refuse to participate, and if these characteristics are linked to the likelihood of surviving (outcome). If, however, respondents differ from non-respondents only in their likelihood of having GAD (exposure), then the hazard ratios remain unaffected. In a prospective cohort study, such as EPIC-Norfolk, it is more the case that respondents and non-respondents differ in terms of their likelihood of having the exposure rather than the outcome (participants are unaware of future mortality) – in this instance, different exposure probabilities do not bias the effect estimates.

The biggest issue for cohort studies, however, is selection out of the study or loss to follow-up – especially if the people lost have different probabilities of the exposure-outcome relationship than the ones who remain in the study. For example, if the people lost to follow-up are more likely to have GAD and to die of cancer, then this could bias the findings. This is not an issue in the EPIC-Norfolk study, because migration in this population is negligible and tracking of respondents over the years has been excellent.

Comparison with other studies

GAD and all-cause/cancer mortality

This is one of the largest population-based studies to consider the association between GAD and mortality. In this study, I was able to include the risk factors that I wanted to. I included more potential confounders than a number of other studies [45], and similar covariates as the most recent population-based research on anxiety and mortality [55].

My findings relating to all-cause mortality are in line with a recent, large population study showing that people GAD had a 62% higher chance of dying early than people without this condition in Denmark. [55] Another recent Danish study showed that people with another anxiety disorder had a significantly increased risk of premature mortality compared to others. [56] Both of these studies, however, used registers to define cases based on psychiatric treatment data. Most of the previous studies that have examined the link between anxiety and all-cause mortality have indeed reported positive associations. This could be attributed to the use of clinical populations [45] and symptom checklists assessing a general proneness to anxiety rather than specific psychiatric disorders. This is why population-based research using a valid measure of individual anxiety disorders, such as the study I carried out was needed.

My findings are in contrast to three previous population-based studies. [40, 43, 193] The Health 2000 Study and the Rotterdam Study measured anxiety according to DSM-IV criteria, and found no association with total mortality in adults that were followed for over four years. [43, 193] The first study, however, used a much smaller sample size than mine (making it potentially difficult to determine significant associations), and the second had a relatively short follow-up period (which might not allow enough outcome events to develop).

In addition to the null or positive findings reported in the literature, three other studies found negative and U-shaped associations. A small clinical study suggested that anxiety symptoms contributed to improved survival. [42] Another sampled patients with cardiac problems and suggested that anxiety improved survival in healthier populations, but was associated with excess deaths in those who were in poorer health. [235] The population-based Nord-Trøndelag Health Study reported a U-shaped relationship, such that increased mortality risk was related to low and high anxiety symptom burden. [47] These three studies all used the HADS to measure general feelings of anxiety. It may be that moderate levels of anxiety are beneficial for health as they prompt people to seek help in the early stages of disease and comply with medical treatment, whereas high anxiety levels might represent a reaction to serious somatic illness. When I investigated reverse causality for all-cause and cancer mortality, the effect estimates in the later follow-up time remained highly significant. When I controlled for major physical diseases, GAD remained associated with excess deaths from all causes and cancer over the entire follow-up period.

Few studies have examined the link between anxiety and deaths from specific causes. This study is the first to show an association between GAD and cancer mortality. A population, register-based Dutch study examined total anxiety disorders and found no association with cancer mortality. [55] Although it is useful to have insight into whether mental disorders are linked to worse health overall (e.g, total mortality), there might be issues with combining several conditions into one category (e.g., all causes of death), because the effect of individual disorders is diluted. My results are mostly in line with two population-based studies on incident cancer in Taiwan, which showed that anxiety disorders were associated with an increased risk (in men, but not in women). [236, 237] In one of these studies, men with GAD had a 30% higher risk for incident cancer compared to men without GAD (SIR=1.30, 95% CI:

1.15-1.46). [237] These studies are on cancer incidence, however, and the evidence base relating to death from principal causes is lacking.

Other covariates in relation to all-cause/cancer mortality

- *Factors that increase risk of death*

Most of the findings that I obtained in relation to all-cause and cancer mortality were to be expected, based on the literature. Other research has shown that having any disability, smoking, and physical inactivity is associated with all-cause mortality. [238, 239, 240] People with disability are at an increased risk for early death because of clinical or sub-clinical disease leading to a downward spiral in health. [241] Smoking, physical inactivity, HIGH alcohol intake, and being overweight may be tied to lifestyle factors (such as, poor diet) which can also increase the risk of death. [242, 243, 244] Other factors linked to all-cause mortality include being never married, divorced or widowed. [245] The literature has documented the protective effects that marriage can have, such as increased social support, improved access to health information, greater quality of life, and compliance with medical treatment. [246, 247, 248] In relation to age, older people tend to have worse health than their younger counterparts, and poor health can increase risk for mortality. [249, 250]

Similar arguments can be made as to why older people, as well as those who are disabled and current and former smokers are at increased risk for cancer death. Those of manual social class also had an increased risk of dying early from cancer, although this finding was borderline statistically significant. It could be that social class confers social status (linked to material and social resources and access to health care) [72]; social status also contributes to cognitive development and makes people more informed about health and options for seeking treatment if experiencing early symptoms of illness. [238, 251] Thus, if people have low social status, they could be at higher risk for poor prognosis and subsequent mortality.

- *Factors that decrease risk of death*

In relation to the factors that decrease risk of all-cause mortality, being a woman and consuming moderate amounts of alcohol are important. Women might be less likely to engage in risk behaviours linked to mortality, such as smoking in comparison with men. [252] The finding linking moderate alcohol intake and decreased mortality is not surprising and in line with the literature; moderate consumption of alcohol may actually be beneficial for health. [253] The same findings emerged with respect to cancer mortality with the exception of alcohol intake; although moderate levels of alcohol were associated with improved survival, this variable did not reach statistical significance. It could be that alcohol is beneficial for certain health endpoints (ex. mortality from causes other than cancer).

The result, however, on the link between depression and decreased risk of premature cancer mortality is in contrast to the previous literature. [254] I verified the code and analysis, and when progressively-adjusted models (including the full multivariable model) were re-run, the results remained the same. Since this study investigated whether participants "ever had an episode of depression" using a questionnaire, there could be alternative explanations for the unexpected association with mortality, such as recall error. Participants, especially those at older ages (respondents in EPIC-Norfolk were at midlife and beyond when they completed the HLEQ) may not accurately remember whether they ever had an episode of depression) and this could have had an impact on the effect estimate. Also, it could be that people who remembered past depression episodes had better health on average than the ones who did not remember past depressive symptoms – the latter group could thus have been incorrectly classified as 'not depressed' in this study. This explanation is in line with research showing that depression has been linked to emotional and cognitive deficits, including memory problems. [255] The more severe the depression is, the greater the memory impairment. [256] If people who were severely depressed tended to forget about past episodes and were also in poorer health, then it follows that those remembering their depression are in slightly better health and more likely to survive. To determine whether this is really the case, medical charts should be compared to participant information or MDD cases identified through the HLEQ (the only drawback is that some depressed participants may not have consulted a doctor for their symptoms and received a medical diagnosis). In this study, MDD was linked to improved survival with regards to both all-cause mortality and death from cancer, although only the link with the latter outcome was statistically significant. Recall error may vary according to people's health conditions, thus, when lumping all causes of death into one variable, associations with specific endpoints may become diluted.

In contrast to MDD, GAD was measured "in the past year", the period immediately before the administration of the HLEQ questionnaire. As such, it might have been much easier for respondents to remember whether they had experienced symptoms of GAD and not be misclassified.

Furthermore, it could also be that the number of cases meeting full diagnostic criteria for MDD in this study might be insufficient to draw firm conclusions regarding this variable. A larger study using a higher number of MDD cases might be needed to re-assess this association.

Mechanism of effect relating GAD and mortality

Possible mechanisms underlying anxiety, pathogenesis, and mortality include biological-, behavioural risk-, and coping-related factors. Direct mechanisms of anxiety include overactivation of the stress system and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, impaired immunity, and the release of pro-inflammatory cytokines, which can lead to a downward spiral in health. [257] Anxiety symptoms have also been linked to the overexpression of tumour necrosis factor-alpha and interleukin-6, both of which have been implicated in inflammation-associated carcinogenesis. [257, 258] Indirect mechanisms refer to anxiety giving rise to risk behaviours, such as, smoking, physical inactivity, and alcohol use, which in turn, increase the risk for premature death. Anxiety may also be associated with avoidant coping strategies affecting adherence to medical treatment. I was able to control for important risk behaviours in my analyses, including smoking, physical activity, and alcohol intake; however, the associations between anxiety and mortality remained highly significant. Although I could not control for medical compliance in this study (if I would have done so, I suspect that the effect estimates for anxiety might have diminished slightly), I controlled for important somatic diseases that are associated with anxiety and mortality. This suggests that indirect mechanisms do not fully explain the increased risk of mortality in people with GAD.

Some studies suggest that the presence of GAD may be a protective health factor, leading to more frequent medical consultations and earlier detection of disease. [40] A study on prostate cancer in Taiwan indicated that individuals with anxiety may be more likely to undergo PSA testing and rectal examinations. [237] However, when the authors excluded the first year of follow-up, the incidence rate of prostate cancer was still higher in those with GAD, suggesting that factors other than increased medical help-seeking are accounting for this association. When I included a time-dependent covariate in the model, the effect estimate for cancer mortality remained high after four years of follow-up.

5.5 Conclusion

GAD is common in the population, debilitating and impairing [2]. Previous studies that assessed its link with mortality were mostly based on small samples, used generic measures of anxiety, and short follow-up periods. Many focused on mortality from all causes or CVD, while few examined other principal causes of disease, such as cancer. My study overcomes a number of limitations of previous research and shows for the first time, that GAD is associated with increased risk of early death from cancer. In line with previous research, I also show that GAD is linked to all-cause mortality.

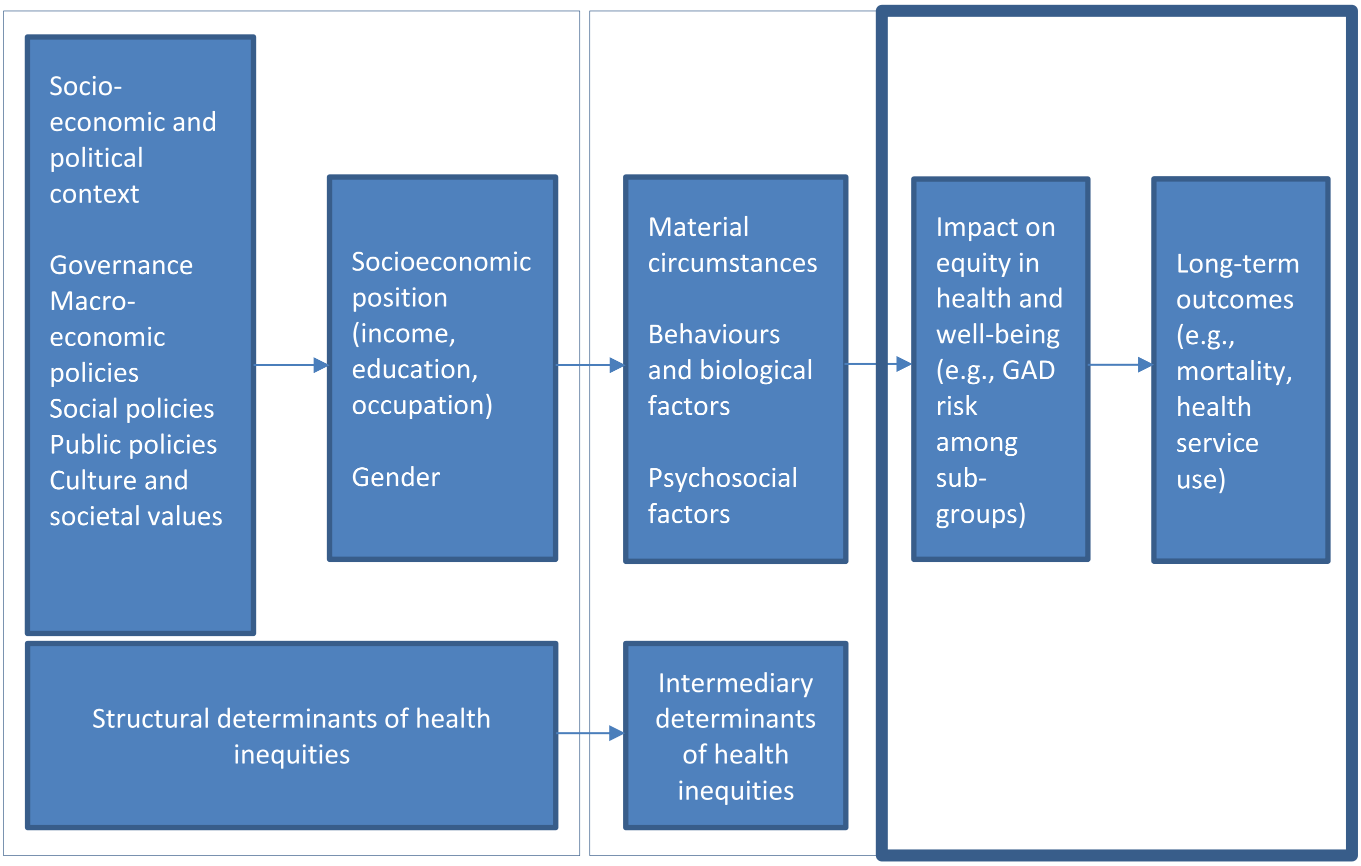
Results from this chapter clearly show that anxiety is associated with deleterious health outcomes. To further inform prevention and intervention efforts, it is important to determine whether GAD is also related to high consumption of health care resources. The next chapter investigates this.

6 Generalised anxiety disorder (GAD) and non-psychiatric hospital admissions: findings from a large, population cohort study

Preface to chapter

The conceptual framework shows that the context can give rise to health inequities. The context can refer to residential environments characterised by disadvantage, while health inequities are the differential risks of having GAD among population sub-groups because of unequal distribution of resources across settings (i.e. fewer resources among those living in disadvantage compared to their more affluent peers). People who develop GAD may then be at increased risk for subsequent deleterious health outcomes, such as morbidity and health service use.

To determine whether a condition has societal significance, its links with health service use, among other factors, needs to be determined. This chapter will examine the association of GAD, measured according to the Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV), with non-psychiatric hospital admissions in a large, population-based British cohort.



ABSTRACT

Introduction

GAD is the most common anxiety disorder in the general population, and has been associated with high economic and human burden. However, it has been neglected in the health services literature. The objective of this study is to assess whether GAD leads to non-psychiatric hospital admissions using data from EPIC-Norfolk. Other aims include determining whether early or late onset forms of the disorder, episode chronicity and frequency, and comorbidity with MDD contribute to non-psychiatric hospital admissions.

Methods

30,445 people over the age of 40 were recruited through general practice registers in England. Of these, 20,919 completed a structured HLEQ used to assess past-year GAD according to the DSM-IV. Anxiety was examined in 1996-2000, and health service use was captured between 2000 and 2009 through record linkage with large, administrative health databases. 17,939 participants had complete data on covariates. The study design for this particular research is a cohort study design.

Results

2.2% (393/17,939) of respondents had GAD. Anxiety was not independently associated with non-psychiatric hospital admissions (IRR=1.04, 95% CI: 0.90, 1.20) over nine years. However, those whose anxiety was comorbid with DSM-IV MDD showed a statistically significantly increased risk for non-psychiatric hospital admissions (IRR=1.23, 95% CI: 1.02, 1.49).

Conclusion

People with GAD and MDD comorbidity were at an increased risk for hospital admissions. Clinicians should consider that meeting criteria for a pure or individual disorder at one point in time, such as past-year GAD does not necessarily predict deleterious health outcomes; rather different forms of the disorder, such as comorbid cases might be of greater importance.

6.1 Introduction

Anxiety disorders are the most common class of psychiatric disorders in the general population. The Global Burden of Disease study [13] estimated that anxiety disorders contribute to 26.8 million disability adjusted life years, and their annual direct cost is $42.3 billion [12]. GAD is characterised by excessive, pervasive worry, and a number of additional symptoms, such as restlessness and muscle tension. It is a prevalent and disabling condition in adults, and can lead to serious impairment in social and occupational functioning. [259] GAD is associated with poor quality of life, impaired functioning and risk of suicide. [188, 260-262] Across the anxiety disorders, this condition has been found to be the most debilitating. [2, 260] Although there is effective treatment for GAD, only a third of those affected receive any treatment. [262] This is because anxiety disorders are frequently under-recognized and mismanaged by clinicians in primary care, which is often the first point of contact for those with mental health problems. [263]

Although detection of anxiety in clinical settings is poor [264, 265] and the presence of undiagnosed mental health problems can contribute to further emotional distress in patients down the line [265], it could be that disorders such as GAD represent more than just psychological or worry-related symptoms. It may be that anxiety symptoms are masking underlying poor physical health or could be an early warning signal for future health problems that are not yet detectable by standard medical tests. Such problems cannot be simply resolved through psychological therapies or psychotropic medication.

Anxiety has been linked to HPA axis dysregulation and inflammation, and this can lead to poor health. [2] A recent study of hospitalized patients [266] also showed that people with anxiety disorders had more co-morbid physical conditions, including CVD and its risk factors, compared to people without anxiety disorders. Conversely, anxiety could also represent a response to underlying medical illness, and physical illness can exacerbate anxiety; the possibility of a bidirectional relationship between anxiety and physical health should not be excluded. [267, 268] Compelling evidence from prospective studies, however, has shown that anxiety can indeed increase the risk of serious chronic conditions, such as cancer [237] and coronary heart disease (CHD) [269].

When investigating the links between mental disorders and health outcomes, early or late-onset forms of anxiety disorders, as well as psychiatric comorbidity should be also considered. A study [269, 270] of over one million Swedish men followed for over 20 years showed that early-onset forms of mental disorders in particular led to increased risk of incident CHD. Anxiety disorders, such as, GAD are also frequently comorbid with MDD [271], and psychiatric comorbidity has been associated with poorer quality of life, worse prognosis, and higher use of health services for mental health problems than pure forms of the disorder. [272, 273, 274] Therefore, identifying clinical aspects, such as, early or late onset forms of the condition, episode chronicity and frequency, and comorbidity with MDD can lead to better clinical management and more accurate prediction of future disability and health service use. [275]

GAD is one of the most common anxiety disorders in the general population [276] and the primary care setting [2, 277], and has been associated with high economic and human burden. However, it has been neglected in the health services literature, with the exception of some studies showing GAD to contribute to higher use of primary care services in primary care samples. [62, 63, 278, 279] Clinical samples, however, have the potential for self-selection bias. Whether GAD leads to non-psychiatric hospital admissions is unknown.

The objective of this study will be to assess the association between GAD and non-psychiatric hospital admissions in a longitudinal, population cohort of over 18,000 British individuals followed for 9 years. The aim is also to determine whether early or late onset forms of the disorder, episode frequency and chronicity, and comorbidity with MDD contribute to non-psychiatric hospital admissions.

6.2 Methods

Study design and population

The study design for this particular research examining anxiety and health service use is a cohort study design.

The study population was drawn from the EPIC-Norfolk longitudinal, cohort study, described in detail elsewhere. [166] Briefly, a total of 30,445 participants over the age of 40 living in Norwich and the surrounding towns and rural areas were recruited between 1993 and 1997 using general practice registers. At baseline, they completed a health questionnaire capturing sociodemographics and medical history. During follow-up, between 1993 and 2000, participants completed self-reported postal questionnaires provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address. Between 1996 and 2000, respondents completed an HLEQ [166] used to capture information on psychiatric disorders, other psychosocial factors, and risk behaviours. The HLEQ was also used to identify the age of participants and marital status. Record linkage with administrative health databases using a unique identifier was used to determine hospitalisation admissions data until 2009.

All participants recruited through general-practice registers and who completed a baseline health questionnaire were eligible to be included in my study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in my analysis.

Assessment of GAD

The HLEQ was used to derive a measure of GAD according to the DSM-IV. The HLEQ captured the onset and offset timings of episodes of past-year GAD. [179] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was diagnosed if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge.

Assessment of covariates

Potential confounders (based on the literature) included sociodemographics (age, sex, education, marital status, social class, employment), risk behaviours (alcohol use, smoking, physical activity), MDD, prevalent physical diseases, and disability. Potential confounders were chosen based on their links to the exposure, which was anxiety, and the outcome, health service use. The following variables were associated with health service use in the literature and thus chosen as potential confounders: age, sex, educational level, marital status, social class, employment, ill health and disability, depression, physical activity, smoking and alcohol intake.

Some studies showed that people at older ages [280], women [281, 282], those of low educational status, who are divorced/separated/widowed [282], and with mental and physical comorbidity [282] have higher health service use in comparison with others. Other variables linked to health service use were activities of daily living and alcohol dependence [282, 283]; these may be linked to poor health and thus translating into health care utilisation. Smoking has also been linked to poorer physical health [284], and a decline in health or the presence of comorbidities have been related to increased use of health services [282]. People with disabilities have been shown to use emergency department services more frequently than others [285]. Lower education or income have also been linked to hospital and emergency department service use (if people do not have general practitioners, they might visit the emergency department instead) [286]. Finally, physical activity has been linked to health care use in that those who are more active have shorter hospital stays [287]. Unemployment has additionally been related to use of health care services [288]. Unemployed people might be lacking the social contact provided by the workplace; as per the literature, lonely or isolated people might make more frequent trips to the clinic to fulfill their socialization needs. [289]

These same variables are related to anxiety. For example, younger people [197, 198, 199], women [201], people who are single or separated/divorced/widowed [206], with mental and physical comorbidity [119, 201, 206], and disability [206, 210] tend to have higher levels of anxiety than others. In regards to risk behaviours, people who smoke [215, 216], drink [217], and are inactive [218, 219] may be at higher risk for anxiety and vice versa in bidirectional relationships (e.g., tobacco can increase the risk for poor health and anxiety [215], but anxious people can also take up smoking to cope with feelings of uneasiness [216]). People with anxiety are also less likely to complete their education [16] and as a result, may have diminished employment prospects. People who are unemployed have also been shown to have high levels of anxiety. [290] Further, anxiety might take a heavier toll on those from manual social classes compared to those who are non-manual. [291]

The final categorization of the variables took cell size into account and was also done in accordance with previous literature. [179, 183, 223, 292-295] Age was first assessed as a categorical variable, and subsequently divided into 10-year bands. [177] Sex was categorized into male vs. female; marital status was categorized into: married, single (or never married), and others (widowed, divorced, separated) [223]; educational attainment into high (vocational or formal qualifications at the A- or O-level or degree-level qualifications) vs. low (no formal qualifications) [223]. Social class was derived using the Computer-Assisted Standard Occupational Coding [183] and categorized as follows: I (professionals), II (managerial and technical occupations), III non-manual and III manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). To assign social class to men and women, the male partner's current or past occupation was used. If this information was not available, the female partner's occupation was used. If the social class from either partner was unavailable, then it was coded as missing. The final categorization of social class included manual: skilled manual, partly skilled, and unskilled; and non-manual: professionals, managerial and technical, and skilled non-manual [223]. Employment was divided into yes vs. no [223].

Behaviour risk factor measures included alcohol intake (units of alcohol/week), smoking status (current, former, non-smoker), and physical activity (inactive, moderately inactive, moderately active, active). Presence of past-year DSM-IV MDD (yes/no) was also assessed.

[177] Alcohol intake was divided into <7 units, 7-14 units, 14-21 units, and >=21 units [225]; smoking status was left in its original form (current, former, never smoker) as was originally entered in the EPIC-Norfolk database [223]; and physical activity was categorized into inactive vs. active (moderately inactive, moderately active, active) [224]. MDD was also left as dichotomous as originally created based on the DSM-IV classification.

Individual-level health status was examined through the construction of a variable capturing major prevalent physical diseases associated with anxiety. [201] This was based on HLQ questions asking participants: “Has the doctor ever told you that you have any of the following?”, followed by a list of options, such as stroke, myocardial infarction, and cancer. The final prevalent physical disease variable was divided into yes (having any of the diseases) vs no [223]. To determine disability levels, I used the PCS of the SF-36, a widely-used, validated self-assessment tool. Higher scores indicate better health. [178]

All of these individual-level variables were regarded as potential confounders and selected based on the literature and their association with anxiety and health service use. [296, 297, 201]

Hospital service use

All analyses are based on non-psychiatric hospitalisations and the outcome in this study is number of hospital admissions. Primary care service use was not captured in this study.

Frequency of hospitalisation between 2000 and 2009 was determined using administrative health databases maintained by the NHS. The East Norfolk Primary Health Care trust databases were used, and these are updated on an ongoing basis and provide information on clinical and administrative data from participating facilities, such as, hospitals.

England is under a publicly-funded health care system (the NHS), free at the point of delivery; therefore, I expect factors, such as access to health insurance or personal income, to have minimal impact on the care that is obtained by study participants. The databases used in this study are maintained by the NHS, which is likely to capture most hospital admissions from the population, as private sector provision is minimal. This means that admissions data in my study can be considered complete for the ascertainment of hospital/health service use, and the likelihood of bias minimal. To access hospital services in the UK, a referral is needed from the primary care practitioner, who acts as a gate-keeper to secondary care.

The East Norfolk Primary Health Care databases were linked to the EPIC-Norfolk cohort using participants' unique NHS number, which allows complete record linkage across settings and calendar time.

Vital status for participants was determined through record linkage with the UK ONS. Vital status was available for all participants. This allowed me to exclude those who died before their health service use was ascertained.

Statistical Analysis

First, demographics, social class, medical and psychiatric conditions, and risk behaviours were compared by GAD status – Pearson's chi-square test was used to determine whether differences were statistically significant for categorical variables. Second, the mean number of hospital admissions was determined for each characteristic/covariate - the Kruskal Wallis test was used to determine statistical significance for categorical covariates with three or more categories, while the Wilcoxon rank-sum test was used for dichotomous covariates.

Since the number of hospital admissions was skewed and the variance was much larger than the mean, zero-inflated negative binomial regression was used for frequency of hospital utilisation (number of hospital admissions). The log-likelihood test showed that this model was superior to Poisson regression. Three models were fitted for hospital admissions with progressive adjustment of covariates: model A adjusted for sociodemographics (age, sex, education, marital status, social class, employment), physical conditions and disability; model B further accounted for past-year MDD (assessed at the same questionnaire point as past-year GAD); and model C further controlled for physical activity, alcohol, and smoking.

Finally, I determined whether the risk for hospitalisation was higher among those with: 1) 3 or more episodes of lifetime GAD (versus those with fewer than 3 episodes or no GAD), 2) episodes that lasted on average 6 months or more (versus those with fewer than 6 months or no GAD), 3) age of onset at 30 years or younger (versus people with age at onset over 30 years or no GAD), and 4) psychiatric comorbidity with MDD (versus no GAD-MDD comorbidity). Two-sided statistical tests for the maximum likelihood zero inflation parameter estimates were conducted and a p-value of <0.05 was used for statistical significance. Analyses were implemented in Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC).

To arrive at the study size, I went through the following steps: of the 30,445 who completed the baseline HLQ, I retained those participants who completed the HLEQ (20,919), and of these, I kept those people with complete data on all covariates (17,939).

6.3 Results

Of the 30,445 people recruited at baseline, 20,919 participants completed the HLEQ; most of the missing observations were from past-year GAD (479), past-year MDD (700), and disability (1,386); the rest of the missing observations were generated from the other covariates. Notable findings from the missing data analysis show that people with missing GAD more often had pre-existing health conditions, high disability, MDD, low alcohol consumption, and were without employment (appendix 8).

The final sample included a total of 17,939 participants. Participants were assessed between 2000 and 2009 (followed for 9 years).

In 1996-2000, GAD was present in 393 out of 17,939 (2.2%) people. Table 6.1 shows the baseline characteristics of participants by GAD status.

Table 6.1 Percentage and number of people with past-year GAD reported in 1996-2000 according to sociodemographic factors, health status, and behaviour risk factors for the EPIC-Norfolk cohort (n=17,939)

Characteristic	Number with characteristic	Percentage and number with past-year GAD
Socio-demographics		
Age (years)		
<50	2359	3.4 (79)[a]
50-60	6209	2.9 (179)
60-70	5733	1.6 (94)
70+	3638	1.1 (41)
Sex		
Women	9937	2.5 (249)[b]
Men	8002	1.8 (144)
Education[‡]		
Low	6106	2.0 (120)[b]
High	11833	2.3 (273)
Marital status		
Single	686	3.6 (25)[a]
Married	14538	2.0 (284)
Other[*]	2715	3.1 (84)
Social class		
Manual	6836	2.0 (137)
Non-manual	11103	2.3 (256)
Employment		
Yes	7712	2.0 (155)
No	10227	2.3 (238)
Health status		
Physical conditions[+]		
Yes	9166	2.7 (251)[a]
No	8773	1.6 (142)
Disability level		
High[¶]	8900	3.0 (266)[a]
Low	9039	1.4 (127)
Psychiatric conditions		
Past-year MDD		
Yes	934	21.4 (200)[a]
No	17005	1.1 (193)
Behaviour risk factors		
Physical activity		
Active[¥]	12822	2.1 (272)
Inactive	5117	2.4 (121)
Smoking status		
Current smoker	1893	4.7 (89)[a]
Former smoker	7470	1.9 (141)
Never smoker	8576	1.9 (163)
Alcohol intake		
>=21[α]	1410	2.1 (30)
14-21	1515	1.7 (25)

7-14	3491	2.0 (70)
<7	11523	2.3 (268)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

[a] $P < 0.001$

[b] $P < 0.05$

Those with GAD were more likely to be younger than 50 years of age, women, current smokers, of higher educational attainment, single, with physical conditions, high levels of disability, and MDD. Table 6.2 summarizes the means and standard deviations of the number of hospital admissions by participant characteristics.

Table 6.2 Non-psychiatric hospital admissions (mean, SD) by participant characteristics in 17,939 British people between 2000 and 2009

Characteristic	Total number with characteristic	Number of admissions Mean (SD)
Past-year GAD		
Yes	393	4.0 (6.3)[a]
No	17546	3.4 (13.0)
Socio-demographics		
Age (years)		
<50	2359	1.9 (9.8)[a]
50-60	6209	3.0 (16.5)
60-70	5733	3.8 (11.2)
70+	3638	4.6 (9.6)
Sex		
Women	9937	3.1 (14.0)[a]
Men	8002	3.9 (11.3)
Education[‡]		
Low	6106	4.1 (17.1)[a]
High	11833	3.1 (10.1)
Marital status		
Single	686	3.0 (8.9)[a]
Married	14538	3.3 (10.9)
Other[*]	2715	4.0 (21.0)
Social class		
Manual	6836	4.0 (18.3)[a]
Non-manual	11103	3.1 (7.8)
Employment		
Yes	7712	2.5 (9.1)[a]
No	10227	4.1 (15.1)
Health status		
Physical conditions[+]		
Yes	9166	3.9 (10.4)[a]
No	8773	3.0 (15.1)
Disability level		
High[¶]	8900	4.4 (16.5)[a]
Low	9039	2.5 (7.8)
Psychiatric conditions		
Past-year MDD		
Yes	934	4.5 (13.6)[a]
No	17005	3.4 (12.9)
Behaviour risk factors		
Physical activity		
Active[¥]	12822	3.2 (13.3)[a]
Inactive	5117	4.1 (11.7)
Smoking status		
Current smoker	1893	4.6 (26.8)[a]
Former smoker	7470	3.8 (11.4)

Never smoker	8576	2.9 (8.6)
Alcohol intake		
>=21[α]	11523	3.5 (11.8)[a]
14-21	3491	3.3 (18.0)
7-14	1515	3.0 (7.9)
<7	1410	3.3 (9.9)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

[a] $P < 0.001$

[b] $P < 0.05$

Participants with GAD had a higher frequency of hospitalisation compared to those without GAD. Some of the findings show that frequency of hospitalisation was markedly higher among older age groups, men, those with low educational attainment, unemployed participants, those with high levels of disability, and with past-year MDD.

Main findings: GAD and hospital admissions

Table 6.3 shows the unadjusted and adjusted incidence rate ratios (IRR) of hospital admissions by GAD status.

Table 6.3 Associations between past-year GAD reported in 1996-2000 and non-psychiatric hospital admissions in 2000-2009 in 17,939 British people over the age of 40

	IRR and 95% CI			
Characteristic	**Crude IRR**	**A**[1]	**B**[2]	**C**[3]
Past-year GAD				
Yes	1.18 (1.02, 1.36)	1.25 (1.09, 1.43)	1.10 (0.96, 1.27)	1.03 (0.89, 1.19)
No	1.00	1.00	1.00	1.00
Socio-demographics				
Age				
Per 10 years	1.36 (1.33, 1.40)	1.19 (1.16, 1.23)	1.20 (1.17, 1.24)	1.22 (1.18, 1.25)
Sex				
Women	0.80 (0.76, 0.83)	0.76 (0.73, 0.79)	0.76 (0.72, 0.79)	0.78 (0.74, 0.81)
Men	1.00	1.00	1.00	1.00
Education‡				
Low	1.30 (1.24, 1.36)	1.13 (1.08, 1.18)	1.13 (1.08, 1.19)	1.11 (1.06, 1.16)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.88 (0.79, 0.99)	0.85 (0.77, 0.95)	0.85 (0.76, 0.95)	0.84 (0.76, 0.94)
Married	1.00	1.00	1.00	1.00
Other*	1.21 (1.14, 1.28)	1.17 (1.11, 1.24)	1.14 (1.07, 1.21)	1.09 (1.03, 1.16)
Social class				
Manual	1.29 (1.23, 1.34)	1.24 (1.19, 1.30)	1.24 (1.19, 1.30)	1.21 (1.16, 1.26)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.64 (1.57, 1.71)	1.18 (1.12, 1.25)	1.18 (1.12, 1.24)	1.15 (1.09, 1.21)
Health status				
Physical conditions+				
Yes	1.32 (1.26, 1.37)	1.18 (1.13, 1.23)	1.17 (1.12, 1.22)	1.18 (1.13, 1.23)
No	1.00	1.00	1.00	1.00
Disability level				
High¶	1.78 (1.71, 1.86)	1.52 (1.45, 1.59)	1.51 (1.44, 1.57)	1.48 (1.42, 1.55)
Low	1.00	1.00	1.00	1.00
Psychiatric conditions				
Past-year MDD				
Yes	1.34 (1.22, 1.48)		1.34 (1.22, 1.48)	1.34 (1.21, 1.47)
No	1.00		1.00	1.00
Lifestyle				
Physical activity				
Active¥	1.00			1.00
Inactive	1.27 (1.21, 1.33)			1.04 (1.00, 1.09)
Smoking status				
Current smoker	1.60 (1.49, 1.72)			1.51 (1.41, 1.62)
Former smoker	1.33 (1.27, 1.39)			1.13 (1.08, 1.19)

Never smoker	1.00		1.00
Alcohol intake			
>=21[α]	0.88 (0.84, 0.93)		0.93 (0.88, 0.98)
14-21	0.93 (0.85, 1.01)		0.92 (0.85, 1.00)
7-14	1.03 (0.97, 1.10)		1.01 (0.95, 1.08)
<7	1.00		1.00

[1] Model A: adjusted for sociodemographics (age, sex, education, marital status, social class, employment), physical conditions, disability

[2] Model B: adjusted for sociodemographics, physical conditions, disability, MDD

[3] Model C: adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

After adjustment for sociodemographic variables, physical conditions, and disability, GAD was associated with a 25% higher incidence rate of hospitalisation (IRR=1.25, 95% CI: 1.09, 1.43). The incidence rate ratio was somewhat attenuated and became statistically non-significant after further adjustment for MDD (IRR=1.10, 95% CI 0.96, 1.27). The effect estimate approached the null after additional adjustment for behaviour risk factors (IRR=1.03, 95% CI: 0.89, 1.19).

Secondary findings – other covariates and hospitalizations

A number of covariates were associated with increased risk of hospital admissions in the final multivariable model; namely: increasing age (IRR=1.22, 95% CI: 1.18, 1.25), low education (IRR=1.11, 95% CI: 1.06, 1.16), people who are separated/divorced/widowed (IRR=1.09, 95% CI: 1.03, 1.16), manual social class (IRR=1.21, 95% CI: 1.16, 1.26), with no employment (IRR=1.15, 95% CI: 1.09, 1.21), who have physical conditions (IRR=1.18, 95% CI: 1.13, 1.23), high disability (IRR=1.48, 95% CI: 1.42, 1.55), MDD (IRR=1.34, 95% CI: 1.21, 1.47), and are current and former smokers (IRR=1.51, 95% CI: 1.41, 1.62 and IRR=1.13, 95% CI: 1.08, 1.19, respectively). Physical inactivity was associated with a borderline increased risk of hospital admissions (IRR=1.04, 95% CI: 1.00, 1.09).

A few variables were associated with decreased risk of non-psychiatric hospitalizations; namely: women (IRR=0.78, 95% CI: 0.74, 0.81), single marital status (IRR=0.84, 95% CI: 0.76, 0.94), and drinking 21+ units of alcohol as well as 14-21 units (IRR=0.93, 95% CI: 0.88, 0.98 and IRR=0.92, 95% CI: 0.85, 1.00).

Main findings – different forms of GAD and hospitalizations

Next, I assessed whether risk for hospital admissions varied by frequency of GAD lifetime episodes, anxiety episode chronicity, GAD age of onset, and whether the hospitalisation risk was higher in those with psychiatric comorbidity (with MDD) (table 6.4). Results are based on fully-adjusted models.

Secondary findings – other covariates and hospitalizations

Regarding the other covariates, similar findings as above emerged (e.g., increased risk of hospitalizations in those with higher age, low education, manual social class, etc.).

Table 6.4 Associations between different forms of GAD reported in 1996-2000 and non-psychiatric hospital admissions in 2000-2009 in 17,939 British people ages 40+

Characteristic	IRR and 95% CI			
GAD type				
Frequent GAD				
Yes[a]	1.07 (0.91, 1.26)[e]			
No	1.00			
Chronic GAD				
Yes[b]		1.07 (0.85, 1.35)[e]		
No		1.00		
Early age GAD onset				
Yes[c]			1.15 (0.95, 1.40)[e]	
No			1.00	
Comorbid GAD				1.23 (1.02, 1.49)[e]
Yes[d]				1.00
No				
Socio-demographics				
Age				
Per 10 years	1.22 (1.18, 1.25)	1.22 (1.18, 1.25)	1.22 (1.18, 1.25)	1.21 (1.17, 1.25)
Sex				
Women	0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.74, 0.81)	0.78 (0.74, 0.82)
Men	1.00	1.00	1.00	1.00
Education‡				
Low	1.11 (1.06, 1.16)	1.11 (1.06, 1.16)	1.11 (1.06, 1.16)	1.13 (1.07, 1.18)
High	1.00	1.00	1.00	1.00
Marital status				
Single	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.84 (0.76, 0.94)	0.83 (0.74, 0.93)
Married	1.00	1.00	1.00	1.00
Other*	1.09 (1.03, 1.16)	1.09 (1.03, 1.16)	1.10 (1.03, 1.16)	1.03 (0.97, 1.10)
Social class				
Manual	1.21 (1.16, 1.26)	1.21 (1.16, 1.26)	1.21 (1.16, 1.26)	1.21 (1.15, 1.26)
Non-manual	1.00	1.00	1.00	1.00
Employment				
Yes	1.00	1.00	1.00	1.00
No	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)	1.17 (1.11, 1.24)
Health status				
Physical conditions+				
Yes	1.18 (1.13, 1.23)	1.18 (1.13, 1.23)	1.17 (1.13, 1.23)	1.17 (1.12, 1.22)
No	1.00	1.00	1.00	1.00
Disability level				
High¶	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)	1.48 (1.42, 1.55)	1.48 (1.41, 1.55)
Low	1.00	1.00	1.00	1.00
Psychiatric conditions				
Past-year MDD				
Yes	1.33 (1.21, 1.46)	1.34 (1.22, 1.47)	1.32 (1.21, 1.46)	--

No	1.00	1.00	1.00	
Lifestyle				
Physical activity				
Active[¥]	1.00	1.00	1.00	1.00
Inactive	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.04 (1.00, 1.09)	1.02 (0.97, 1.07)
Smoking status				
Current smoker	1.51 (1.41, 1.62)	1.51 (1.41, 1.62)	1.51 (1.40, 1.62)	1.56 (1.45, 1.68)
Former smoker	1.13 (1.08, 1.19)	1.13 (1.08, 1.19)	1.13 (1.08, 1.19)	1.14 (1.09, 1.20)
Never smoker	1.00	1.00	1.00	1.00
Alcohol intake				
>=21[α]	0.93 (0.88, 0.98)	0.93 (0.88, 0.98)	0.93 (0.88, 0.98)	0.95 (0.90, 1.00)
14-21	0.92 (0.85, 1.00)	0.92 (0.85, 1.00)	0.92 (0.85, 1.00)	0.89 (0.82, 0.97)
7-14	1.01 (0.95, 1.08)	1.01 (0.95, 1.08)	1.01 (0.95, 1.08)	1.01 (0.95, 1.08)
<7	1.00	1.00	1.00	1.00

[a] 3+ episodes of lifetime GAD
[b] GAD episodes lasted at least 6 months
[c] GAD developed before 30 years of age
[d] GAD-MDD comorbidity
[e] Adjusted for sociodemographics, physical conditions, disability, MDD, physical activity, smoking, alcohol
‡ High education: O-level, A-level, degree; low education: refers to no education
* Other: divorced, separated, widowed
+ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis
¶ Below the PCS value of 50.6
¥ Moderately inactive, moderately active, active
α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

People with more than 3 lifetime episodes had a somewhat higher risk of hospitalisation (IRR=1.07, 95% CI: 0.91, 1.26). Those whose episodes lasted, on average, 6 months or longer also had a slight increased risk for admissions compared to those with shorter episodes (IRR=1.07, 95% CI: 0.85, 1.35). People who developed GAD before 30 years of age were 16% more likely to be admitted to the hospital than those who developed it later in life (IRR=1.15, 95% CI: 0.95, 1.40), although this finding was not statistically significant. Finally, I determined whether GAD comorbid with MDD is associated with non-psychiatric hospital admissions. Results showed that people with GAD-MDD comorbidity had a 23% higher chance of being admitted to hospital than people without comorbidity – this association was statistically significant (IRR: 1.23 ,95% CI: 1.02, 1.49).

6.4 Discussion

Main findings – GAD and hospital service use

This is the first study to assess the association between GAD and hospital service use in a population-based cohort. This longitudinal study showed that having an episode of GAD in the past year was not independently associated with hospital admissions during the subsequent nine years. Chronic GAD (at least 6 months), frequent GAD (at least 3 lifetime episodes), and anxiety with an early age of onset (before 30 years) did not show statistically significant associations with non-psychiatric hospitalisations. In contrast, people with GAD and MDD comorbidity were at an increased risk of being admitted to hospital than those without MDD comorbidity. The association between GAD-MDD comorbidity and non-psychiatric hospital admissions was statistically significant.

People with past-year GAD were more likely to have medical conditions; nonetheless, including these covariates in the model left the association between past-year GAD and hospital admissions statistically significant. It was only when MDD was introduced in the model as a potential confounder that any remaining association with hospital service utilisation was explained away.

Secondary findings – covariates and hospital service use

When covariates were considered in relation to non-psychiatric hospitalization, the following emerged as increasing hospital service use: increasing age, low education, people who are separated/divorced/widowed, those of manual social class, with physical conditions, high disability, MDD, who are current or former smokers, and physically inactive. Because physical inactivity was borderline non-significant, this result will not be discussed further. The variables which were associated with decreased risk of hospitalizations included being a woman, single, and drinking 14-21 units as well as >=21 units of alcohol.

Strengths and limitations

There are several strengths associated with this study. I had a large, population-based sample of middle- and older-aged adults and adequately adjusted for a range of possible confounders. I used a structured questionnaire to assess past-year GAD according to DSM-IV criteria, used large administrative health databases to examine hospital service use (avoiding the self-reporting bias found in questionnaire studies), and participants were followed for a long time. I had a large list of self-reported physician diagnoses of chronic diseases that I used to ascertain medical histories. Despite this, the residual effect of diseases not captured by my study, but that are associated with GAD may be present. There may be illnesses that are associated with anxiety and health service use that have not been captured by my medical history variable. If unmeasured confounders (a confounder is associated with both the exposure and the outcome and does not lie on the causal pathway between the two) are unaccounted for in the analysis, then the effect estimate I report in this study for GAD may be inflated. When I controlled for medical history in my analyses, the effect estimate became attenuated; therefore, I suspect that adjusting for further medical conditions would lead to further attenuation of the incidence rate ratio. Past illness may also have been underreported, either because participants failed to recall past conditions or failed to disclose such information when filling in the HLQ. This would also lead to incomplete adjustment of the confounding variable, medical history.

Another issue related to residual confounding could be measurement error in the risk behaviour covariates. For example, categorizing smoking status into current, former, or never may not completely remove the confounding effects of this variable; additional variables, such as length of time smoking might need to be included in the analysis.

In regards to the completeness of my adjustments, my models thoroughly adjusted for potential confounders, and more so than most of the literature assessing the association between anxiety and health service use. It may have been beneficial, however, to adjust for additional psychiatric comorbidities, such as other anxiety disorders, and physical diseases. This might have attenuated effect estimates even further. Information on additional psychiatric comorbidities was not collected by EPIC-Norfolk.

In regards to the categorization of my variables, information may have been lost when covariates were re-classified (for example, dichotomizing the continuous disability variable). This is discussed in chapter 5.

Another limitation is that a negligible proportion of participants may have obtained care at private facilities. This would bias the findings and present a problem, however, if people with the exposure (GAD) were mostly treated at private facilities rather than publicly-funded hospitals and, as such their outcome (hospital admissions) would not be captured by this study. This scenario seems implausible. Another issue is that the databases used in this study did not capture admissions to hospitals outside the UK. Migration in the EPIC-Norfolk cohort, however, is minimal and may be disregarded.

I may have overadjusted models with the inclusion of self-evaluated impairment, as this may be part of the expression of psychiatric illness. This can lead to attenuation of effect estimates. If participants chose not to answer certain questions in the HLEQ, this contributed to missing data and loss of information; to accommodate this, I retained participants for whom I had complete data on all covariates.

Non-participation may be another limitation if the results from this study do not generalize to the UK population; also, non-participation can bias the findings. In terms of non-participation biasing the findings, this is less of an issue for prospective cohort studies. The reasoning for this and further discussion on non-participation was included in the chapter on mortality.

A further limitation is that I did not have data on primary care service use. Merging population cohorts, such as EPIC-Norfolk, with primary care service administrative databases and hospitalisation databases would have provided a more complete picture of the burden of GAD on the health care system.

This study was conducted on people ages 40 years and older and may not be generalisable to younger age groups. I suspect that the strength of the association between GAD-MDD comorbidity and non-psychiatric hospital admissions is weaker for younger populations who are typically healthier than older people. Although young people have a high burden of mental health problems [201, 298], they (especially adolescents) are less likely to have non-psychiatric hospitalisations than older people [280]. It could take many years until the effects of anxiety comorbid with depression accumulate and manifest as poor physical health, thus translating into higher use of non-psychiatric hospital services. As such, I would expect the strength of the association between GAD-MDD comorbidity and hospitalisations to be weaker in young people, however, future studies should investigate this.

Participants were required to complete detailed dietary and lifestyle questionnaires and undergo periodic health assessments. Because those who participated in EPIC-Norfolk were more affluent and healthier than individuals living in other parts of England, my results may not generalise to people living in extremely deprived areas. This is an example of volunteer bias, whereby people choosing to take part in studies tend to be healthier, have fewer risk behaviours, and higher socioeconomic status than those refusing. [299] As such, the findings from research based on volunteers may not be applicable to the wider population (threat to external validity). However, EPIC-Norfolk has been shown to be representative of the general resident population of England, but only in terms of anthropometric measures. [166]

Comparison with other studies

Main findings – GAD and hospital service use

Most of the studies assessing the link between psychiatric disorders and non-psychiatric health service utilisation have focused on depression and, to a lesser extent, panic disorder and PTSD, while other anxiety disorders have been significantly underresearched. Most of the studies on depression as a stand alone measure have shown an association with health service use in both clinical and community samples. [57] There are substantially fewer studies on anxiety, and a number of these have shown positive associations with health service use. A US study [59] that recruited patients from an outpatient clinic showed that anxiety disorders were linked to higher utilisation of primary care services compared to depressive or addictive disorders. Patients, however, were recruited from an outpatient clinic located in a predominantly rural area, which might have affected generalisability. Another study showed anxiety disorders to be associated with a higher number of consultations in general medical, emergency and specialty settings, such as cardiology and dermatology. [58] In this study, people were sampled from an anxiety clinic, thereby leading to possible selection bias. Other studies showed PTSD and GAD to be associated with health care use; however, this research was based on highly-select samples that have limited generalisability. [60-63] In contrast to the literature, a major strength of my study was that it was population-based. There is also a lack of research assessing whether different forms of the disorder contribute to even higher health service use rates (comorbid cases are typically the most severe, hardest to treat and with the poorest prognosis [2]).

Secondary findings – covariates and health service use

When covariates were considered in relation to non-psychiatric hospitalization, most of the findings were to be expected, such as increased health service use in those who are older, of low education, manual social class, who are separated/divorced/widowed, in poor health (physical conditions) and disability, MDD, and who are current or former smokers. Older people are more likely to have undiagnosed comorbidities, thus leading to potentially higher health care use. People of low socioeconomic status tend to have poor mental health and may present to their GP with unexplained physical symptoms. The consulting physician may not recognize the presence of a psychiatric condition, and may ask the patient to undergo extensive medical work-ups and even possible hospitalization. [2] Disadvantaged people also have lower mental health literacy and higher unmet needs for mental health care [300]. If individuals do not recognise symptoms of mental illness (such as panic disorder, often tied to health care use [301]) in themselves, they cannot help guide the physician to an accurate diagnosis. People of lower social classes may also have poorer health and higher rates of subclinical disease than those on the higher rungs of the social hierarchy. This could also translate into higher rates of hospital service use.

People who are separated/divorced/widowed may use health services more often, because of unmet psychological needs. It may be that they are contacting the health care system to fulfill socialization needs. People who are in these marital status categories, however, have also been shown to have poorer health than others, which could also be contributing to higher use of health care resources. [302]

Individuals with physical conditions, who are disabled, and with MDD might have greater comorbidities than others, thus translating into higher rates of hospitalisations. Current and former smokers may have lifestyles, such as poor diet, contributing to ill health.

The variables which were associated with decreased risk of hospitalizations included being a woman, single, and an alcohol drinker. Findings on gender differences with respect to hospital service use are mixed [303, 304, 305]. There is some evidence that people who never marry tend to have lower rates of hospitalisations than others [302], and the results on moderate alcohol consumption are in line with prior research – it could be that moderate alcohol drinking is beneficial for health [225].

Mechanisms

A more severe course of GAD can lead to higher rates of health services because of unhealthy behaviours, such as smoking and alcohol (which I controlled for in my analyses). It could also be that a more severe form of anxiety, such as GAD-MDD comorbidity is associated with poorer underlying health, which then leads to higher health service use rates. Although I controlled for several chronic diseases, I might have missed some conditions that are associated with GAD-MDD comorbidity and hospitalisations. A third explanation for higher health service use in those with comorbid anxiety and depression could relate to inflammatory pathways. If clinically apparent signs of disease have not yet developed in those with psychiatric comorbidity or are at an early, undetectable stage, it will not be possible to measure these factors and adjust for them in analyses.

Interpretation

GAD is a debilitating and impairing condition. [2] The evidence base on its association with health services is small and confined to clinical settings with the potential for self-selection bias. My study overcomes many limitations of previous studies, and clarifies that individual episodes of GAD measured at a single point in time (ex. in the past year) are not associated with health service use. Instead, it shows that cases that are comorbid with depression can lead to increased use of hospital services, after controlling for a range of important confounders. In this study, GAD-MDD comorbidity was associated with a statistically significantly increased risk of hospital admissions.

6.5 Conclusion

This chapter showed that people whose GAD was comorbid with MDD had a higher risk for hospital admissions over 9 years between 1996-2000 and 2009 in the EPIC-Norfolk study.

Despite the findings on pure GAD from this chapter, the previous analysis showed anxiety to be independently associated with deleterious health outcomes: all-cause and cancer mortality. Therefore, to inform prevention and intervention efforts, it is necessary to explore possible determinants that give rise to this condition.

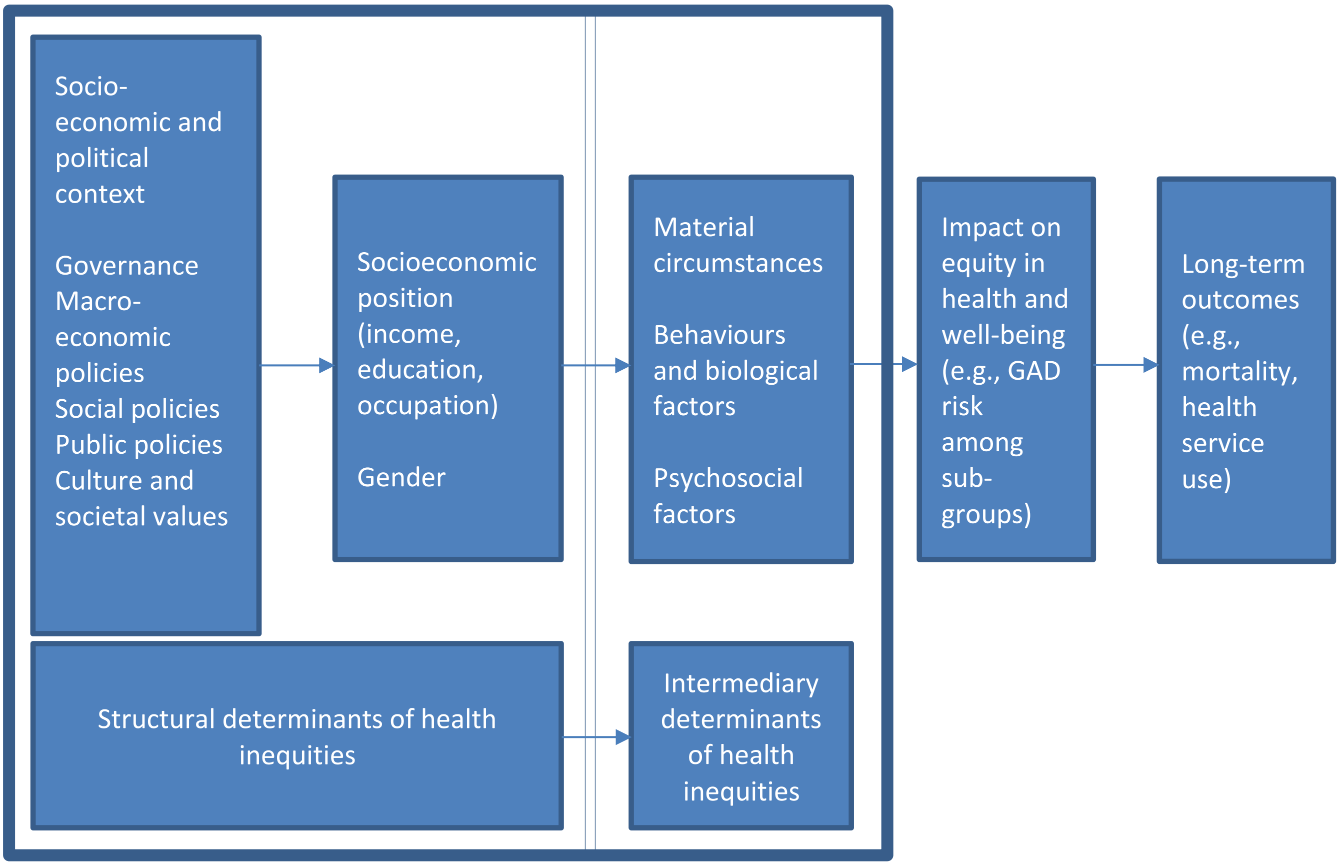
The next chapter will examine a risk factor for poor mental health – a residential environment characterised by disadvantage. The association between area deprivation and GAD is explored among women and men separately using data from the EPIC-Norfolk study.

7 Sex differences in the association between area deprivation and generalised anxiety disorder (GAD): British population study

Preface to chapter

According to the conceptual framework, the socioeconomic context can give rise to health inequities, which are unfair and socially produced. If people living in disadvantage compare their status and resources with those living in more affluent communities, then feelings of shame, worthlessness, and stress can arise in the former. [72] Stress can then increase the risk for poor mental health.

Area-level disadvantage can be regarded as a structural determinant, because it generates inequality in society. Compared to residents living in more affluent communities, those residing in areas of lower socioeconomic circumstances likely have less access to resources and suffer from a poorer health profile, which may negatively affect their mental health. Gender is also a structural determinant, which can lead to health inequities. As a result of social norms and culture, women have historically had lower status positions and resources compared to men. Differential access to resources can then contribute to health differences among the genders. This chapter investigates whether living in a disadvantaged context increases the risk of having GAD among women and men separately using data from the EPIC-Norfolk study. GAD is measured according to the DSM-IV.



ABSTRACT

Introduction

Studies have shown that area-level deprivation measured by factors, such as non-home ownership, non-car ownership and household overcrowding, can increase the risk for mental disorders over and above individual-level circumstances, such as education and social class. Whether area-level deprivation is associated with generalised anxiety disorder (GAD) independent of personal circumstances, and whether this association is different between British women and men is unknown.

Methods

30 445 people from the general population aged 40 years and older and living in England consented to participate at study baseline, and of these, over 20,000 participants completed a structured HLEQ used to capture GAD. Area deprivation was measured in 1991 using Census data, and past-year GAD was assessed according to DSM-IV criteria in 1996–2000. 10 275 women and 8219 men had complete data on all covariates.

Although area deprivation was measured before anxiety in EPIC-Norfolk, this study should be considered cross-sectional, because participants may have had GAD at the time that the Census was carried out. EPIC-Norfolk did not measure incident GAD in this research.

Results

In this study, 2.5% (261/10 275) of women and 1.8% (145/8219) of men had GAD. Women living in the most deprived areas were over 60% more likely to develop anxiety than those living in areas that were not deprived (OR=1.63, 95% CI 1.21 to 2.21; p=0.001), but this association between deprivation and GAD was not apparent in men (OR=1.13, 95% CI 0.72 to 1.77; p=0.598).

Conclusion

There is evidence that women and men’s mental health is differentially affected by the living context. This may need to be considered by policy-makers and public health authorities, and efforts to reduce anxiety in women living in deprivation should be encouraged.

7.1 Introduction

GAD is a common and persistent disorder, and is associated with increased risk for disability and suicide. [2, 11, 187, 261, 306] GAD can lead to serious impairment in social and occupational functioning, and once it develops, it increases the risk for major depression, substance misuse and serious physical medical conditions. [237, 261, 307, 308] This disorder has a chronic course and is difficult to treat. [261] Consequently, it is important that its risk factors are identified for prevention and targeted intervention.

Few studies have assessed the risk factors of GAD; therefore, information is scarce. The studies that have been undertaken have focused on characteristics measured at the level of the individual, such as personal income and education, [309, 310, 311] demographics [312, 313] and family history of psychopathology. [313] However, research has shown that the living context, such as area deprivation, can have profound effects on health, independent of personal characteristics. [75, 79, 314] Area deprivation refers to residential environments or living contexts characterised by factors, such as high levels of unemployment, non-home ownership, non-car ownership and low income. [314]

Many studies conducted in western countries have shown that living in areas characterised by high-income inequality can lead to significantly increased risks for serious medical conditions and mortality. [75, 79] A meta-analysis of cohort studies showed that people living in areas of high-income inequality, as measured by the GINI index, had an increased risk for mortality. [315] Population-based studies further showed that living in disadvantaged neighbourhoods or places where there is high chronic stress can increase the risk for mental disorders, such as depression. [67, 68, 316] Whether area deprivation can be used to predict GAD is unknown.

In this population-based, cohort study, I examine the association between area deprivation and GAD, while controlling for a number of confounders, including previous medical conditions, major depressive disorder and sociodemographic factors. Results are presented separately for women and men, and this is performed for several reasons. Research has shown that women are more likely to develop anxiety compared with men, mainly due to genetic and hormonal factors, social roles or gender norms and environmental factors. [65, 69, 317] Gender has been linked to resources derived from the environment. [65, 317] Compared with men, women have been shown to have less access to material resources and social status positions, and this can influence mental health. Women also seem to interact with their environment differently. For example, women are exposed to different stressors compared with men, because of gender differences with respect to social roles. [65, 68]

Despite these differences, research examining the link between the living context, such as area deprivation, and mental health among women and men, separately is scarce. It remains unclear whether there are sex differences in the association between area deprivation and risk of GAD—and the objective in this study is to assess this. Knowing that one sex is at risk of developing anxiety when exposed to deprived circumstances helps to tailor interventions and allocate scarce resources according to need. [318]

7.2 Methods

Although the methods were described in detail in a previous chapter, they will briefly be presented again here. Data were drawn from EPIC-Norfolk, whose design and study methods have been described in detail elsewhere. [166] In brief, a prospective population-based cohort of 30 445 participants aged 40–74 years were recruited by post between 1993 and 1997 through general practice age–sex registers in the city of Norwich and the surrounding small towns and rural areas (77 630 people were initially invited to join EPIC-Norfolk). At baseline (1993–1997), 30 445 participants consented to join the study and completed a postal HLQ that captured information on sociodemographics, including sex, marital status, highest educational attainment and self-reported physician diagnoses of physical diseases. Using participants' postal codes, a measure of area deprivation was derived based on the 1991 Census. Social class was also obtained from the Census. Between 1993 and 2000, participants completed self-reported postal questionnaires, provided they: (1) were still alive, (2) did not ask to be removed from the study's mailing list and (3) had a valid mailing address.

During 1996–2000, 20 921 participants completed a structured, psychosocial HLEQ questionnaire. During this time, an assessment of GAD and MDD was made according to the DSM-IV. [5, 179] Using the HLEQ questionnaire, age, marital status, and then disability measures based on the SF-36 were also derived. [178]

All participants recruited through general practice registers and who completed a baseline health questionnaire were eligible to be included in this study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in the analysis.

Dependent variable

The primary outcome in this study was past-year GAD. The self-reported HLEQ questionnaire captured the onset and offset timings of episodes of past-year GAD. [179] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was present if participants reported having uncontrollable, excessive worry for 6 months or longer on most days than not that resulted in disability or impairment.

In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep and feeling keyed up or on edge.

Individual-level measures (potential confounders)

Individual-level measures included sex, social class, marital status, and educational level, health status, disability, MDD, and age. These potential confounders were selected based on their association with anxiety and area deprivation; sex was not adjusted as a confounder in analyses, because men and women were examined separately in this study. Chapter 6 elaborates on the links between each of these covariates and anxiety. In regards to area deprivation: people of lower social classes [319, 320], who are not married (especially those divorced) [321], with low education [322], disabled [323], and with physical and mental comorbidities are more likely to live in disadvantage [72, 78, 324]. Although it is beyond the scope of this chapter to go into further detail, there are bidirectional relationships between some of these variables. For example, it could be that living in disadvantage means access to fewer health resources (thus, leading to poor mental health and anxiety), but it could also be that poor mental health leads to downward social mobility and relocation of people to deprived areas. [72, 78]

There are trends in deprivation rates in relation to various age groups [325]; age is also significantly related to anxiety [201]. As such, this variable is included in the models, in line with the literature. [274]

The final categorisation of the variables took cell size into account and was also performed in accordance with previous literature. [179, 223, 292-295, 326] Social class was derived using the Computer-Assisted Standard Occupational Coding [183] and categorised as follows: (1) professionals, (2) managerial and technical occupations, (3) non-manual and manual (skilled workers), (4) partly skilled workers and (5) unskilled manual workers. To assign social class to men and women, the male partner's current or past occupation was used. If this information was not available, the female partner's occupation was used. If the social class from either partner was unavailable, then it was coded as missing. The final categorisation of social class included manual: skilled manual, partly skilled and unskilled; and non-manual: professionals, managerial and technical, and skilled non-manual. [223] Marital status was categorised into three groups: married, single (or never married) and others (widowed, divorced, separated). [223] Educational attainment was categorised into high (vocational or formal qualifications at the A-level or O-level or degree-level qualifications) versus low (no formal qualifications). [223]

Individual-level health status was assessed through the construction of a variable capturing major prevalent physical diseases associated with anxiety. [201] This was based on HLQ questions asking participants: 'Has the doctor ever told you that you have any of the following?', followed by a list of options, such as allergies, asthma, cancer, stroke, heart attack, diabetes, thyroid conditions, etc. The final prevalent physical diseases variable was divided into yes (any of the diseases) vs. no. [223] To determine disability levels, I used the PCS of the SF-36, a widely used, validated self-assessment tool. Higher scores indicate better health. Lifetime MDD was assessed using the HLEQ, and DSM-IV criteria were applied. [179]

Age was first assessed as a categorical variable and subsequently divided into 10-year bands. [177]

All of these individual-level variables were regarded as potential confounders and selected based on the literature and their association with anxiety [28, 201, 327, 328] and deprivation. [329, 330]

Area-level measure (exposure variable)

To examine area deprivation, I used one of the most commonly used measures of area deprivation in the UK: the Townsend index. [184, 185] This index is a composite measure of four variables obtained from the 1991 Census: (1) percentage of economically active residents over age 16 who are unemployed, (2) percentage of households that do not possess a car, (3) percentage of private households that are not owner-occupied, and (4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district. These four factors were then standardised by deriving Z scores (dividing the mean by the SD across enumeration districts in England and Wales). The Z values of the four variables were added together to produce a Townsend index score for each enumeration district. Positive values of the index indicate enumeration districts that are more deprived, while negative values indicate those that are less deprived; 0 represents the national mean. The postal codes of participants were record linked to enumeration districts, and participants were considered to live in deprived areas depending on the Townsend index score assigned to their enumeration district. [184]

The Townsend deprivation index was also disaggregated into its four constituent components to determine whether any one of these four is associated with GAD or if it is the combined components that matter.

Study design

Although area deprivation was measured before anxiety in EPIC-Norfolk, this study should be considered cross-sectional, because participants may have had GAD at the time that the Census was carried out. EPIC-Norfolk did not measure incident GAD in this research.

Statistical analysis

Characteristics of the participants were compared by GAD status - Pearson's chi-square test was used to determine whether differences were statistically significant for categorical variables. I used correlated data analysis to assess the association between individual-level and area-level risk factors of GAD. A population-average model was constructed, which accounted for the potential correlation introduced by the clustering of individuals within enumeration districts. To estimate the population-average effect of the risk factors of interest on past-year GAD, I used generalised estimating equations. As past-year GAD represents a binary outcome (yes/no) and the intracluster correlation is assumed to be equal, GEE with a logit link and an exchangeable correlation structure was used. Adjusted ORs and 95% CIs based on robust SEs were estimated. Standard multivariate logistic regression was also conducted and compared with the findings based on GEE.

Individual-level measures consisted of sociodemographic and health-related variables, whereas the area-level measure comprised the Townsend index. Townsend index scores were used to create a dichotomous variable, with 0 as the cut-point (representing the national average). Similarly, when the Townsend index was disaggregated into its four consistent components, each variable was dichotomised using 0 (the national average) as the cut-point.

Analyses were conducted separately for men and women. First, unadjusted effect estimates were determined. Next, models were constructed to adjust for (1) age, social class, educational attainment; then for (2) age, social class, educational attainment, lifetime history of MDD; and finally for (3) age, social class, educational attainment, lifetime history of MDD, physical diseases and disability level. Age was first assessed as a categorical variable, and subsequently divided into 10-year bands. Models were constructed for participants with complete measurements on all covariates. It was not possible to group the GAD variable otherwise since it was created and categorised according to the DSM-IV, [177, 179] and area deprivation was analysed in accordance with the literature. [294, 331] In a subsequent analysis, a fully adjusted model was built in which the Townsend index was replaced by its four constituent components to determine whether any one of these four variables is significantly associated with GAD.

Finally, analyses were run with GAD without MDD as the outcome, in which past-year MDD was excluded. All models used two-sided statistical tests and a p value of <0.05 was considered statistically significant. Analyses were implemented in Statistical Analysis Software (SAS) V.9.3 (SAS Institute, Cary, North Carolina, USA).

To arrive at the study size, I went through the following steps: of the 30,445 who completed the baseline HLQ, I retained those participants who completed the HLEQ (20,921), and of these, I kept those people with complete data on all covariates (18,494).

7.3 Results

77,630 people from general practices in Norfolk were invited to take part in the study, and of these, 30,445 consented. The characteristics of responders versus non-responders are compared in appendix 4; compared to non-responders, those who took part consisted of slightly more women and slightly more participants younger than 50 years. Of the 30,445 people recruited at baseline, 20,921 completed the HLEQ during follow-up. Of those who completed the HLEQ, 18,494 (88.4%) were available for analysis in this study, because they had data on all covariates. The number of missing observations for each covariate were: 9 for education, 47 for marital status, 497 for GAD, 468 for MDD, 458 for social class, 75 for the Townsend index, and 1,386 for the SF-36. Participants were followed between 1993 and 2000 (7 years).

The study sample consisted of a total of 10,275 women and 8,219 men over the age of 40. Table 7.1 shows the distribution of individual- and area-level characteristics by past-year GAD.

Table 7.1 Distribution of characteristics for women (n=10,275) and men (n=8,219) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Women		Men	
Characteristic	**Number with characteristic**	**Percentage and number with past-year GAD**	**Number with characteristic**	**Percentage and number with past-year GAD**
Individual-level variables				
Socio-demographics				
Age (years)				
<50	1444	3.7 (54)	961	3.2 (31)[a]
50-60	3693	3.2 (119)	2645	2.4 (63)
60-70	3167	1.9 (61)	2739	1.2 (33)
>70	1971	1.4 (27)	1874	1.0 (18)
Education[‡]				
Low	4030	2.1 (83)	2363	1.7 (39)
High	6245	2.9 (178)	5856	1.8 (106)
Marital status				
Single	414	3.1 (13)	302	4.0 (12)[a]
Married	7714	2.4 (183)	7221	1.5 (111)
Other[*]	2147	3.0 (65)	696	3.2 (22)
Social class[¥]				
Manual	3820	2.3 (89)	3281	1.7 (55)
Non-manual	6455	2.7 (172)	4938	1.8 (90)
Health status				
Prevalent physical disease[+]				
Yes	5660	3.1 (174)	3836	2.2 (86)[b]
No	4615	1.9 (87)	4383	1.4 (59)
Disability level				
High[¶]	5258	3.3 (172)	4009	2.6 (104)[a]
Low	5017	1.8 (89)	4210	0.97 (41)
Lifetime MDD				
Yes	1926	8.7 (167)	934	10.0 (93)[a]
No	8349	1.1 (94)	7285	0.7 (52)
Area-level variable				
Townsend index				
Deprivation				
Yes (>0)	1636	3.9 (64)	1237	2.3 (28)
No (<=0)	8639	2.3 (197)	6982	1.7 (117)

[+] Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies (allergies and hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

[¥] Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

[‡] High education: O-level, A-level, degree; low education: refers to no education

[*] Other: divorced, separated, widowed
[¶] Below the PCS value of 50.6
[a] $P < 0.001$
[b] $P < 0.05$

The overall prevalence of past-year GAD was 2.5% (261/10275) for women and 1.8% (145/8219) for men. Women and men with GAD were younger than 50 years of age, of higher educational attainment, single, in non-manual occupations, with prevalent physical diseases, higher levels of disability, and MDD (table 7.1).

Main findings: area deprivation and GAD

Findings from the correlated data analysis showed that the risk of GAD in women living in the most deprived areas was over 70% higher than in those living in the least deprived areas, even after adjusting for age and socio-economic status (OR=1.77, 95% CI: 1.33– 2.36) (table 7.2).

Table 7.2 Odds ratios for past-year GAD according to individual- and area-level characteristics for women (n=10,275) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Odds ratios and 95% CI				
Characteristic	**Unadjusted**	**Model A[1]**	**Model B[2]**	**Model C[3]**	**P-value for Model C**
Individual-level variables					
Socio-demographics					
Age					
(per 10 years)	0.65 (0.56–0.74)	0.63 (0.54–0.73)	0.73 (0.62–0.85)	0.66 (0.56–0.77)	<0.0001
Education[‡]					
Low	0.72 (0.55–0.93)	0.85 (0.64–1.12)	0.90 (0.68–1.20)	0.90 (0.68–1.20)	0.475
High	1.00	1.00	1.00	1.00	
Marital status					
Single	1.33 (0.75–2.36)	1.31 (0.73–2.36)	1.36 (0.74–2.50)	1.34 (0.73–2.47)	0.618
Married	1.00	1.00	1.00	1.00	
Other[*]	1.28 (0.96–1.71)	1.48 (1.09–2.00)	1.09 (0.80–1.48)	1.07 (0.79–1.46)	
Social class[¥]					
Manual	0.87 (0.67–1.13)	0.89 (0.68–1.17)	0.89 (0.68–1.18)	0.85 (0.64–1.13)	0.271
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Lifetime MDD					
Yes	8.34 (6.44–10.79)		7.55 (5.78–9.86)	7.00 (5.34–9.17)	<0.0001
No	1.00		1.00	1.00	
Prevalent physical disease[+]					
Yes	1.65 (1.27–2.14)			1.43 (1.09–1.88)	0.011
No	1.00			1.00	
Disability level					
High[¶]	1.87 (1.45–2.43)			1.88 (1.42–2.49)	<0.0001
Low	1.00			1.00	
Area-level variable					
Townsend index					
Deprivation					
Yes (>0)	1.74 (1.31–2.32)	1.77 (1.33–2.36)	1.65 (1.23–2.22)	1.63 (1.21–2.21)	0.001
No (<=0)	1.00	1.00	1.00	1.00	

1. Adjusted for age, socioeconomic status (education, marital status, social class)
2. Adjusted for age, socioeconomic status, lifetime MDD
3. Adjusted for age, socioeconomic status, lifetime MDD, physical disease and disability
[+] Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis
[¥] Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
[‡] High education: O-level, A-level, degree; low education: refers to no education
[*] Other: divorced, separated, widowed
[¶] Below the PCS value of 50.6

The OR reduced slightly after additionally controlling for MDD (OR=1.65, 95% CI: 1.23–2.22, p=0.001), but remained significant. A strong association was present after further adjusting for prevalent physical diseases and disability (OR=1.63, 95% CI: 1.21–2.21; p=0.001). To further determine the aspect of deprivation that is specifically related to GAD in women, the four separate components of the Townsend index were included in a fully-adjusted model. Results showed that the effect estimates were highest for non-car ownership (OR=1.46, 95% CI: 0.96, 2.23; p=0.080), followed by non-home ownership (OR=1.27, 95% CI: 0.86, 1.88; p=0.237), and were lowest for unemployment (OR=1.07, 95% CI: 0.73, 1.58; p=0.720) and overcrowding (OR=0.75, 95% CI: 0.53, 1.08; p=0.120); these variables did not reach statistical significance.

In men, no association existed between anxiety and area deprivation in both unadjusted and adjusted analyses (model C OR=1.13, 95% CI: 0.72–1.77; p=0.598) (table 7.3).

Table 7.3 Odds ratios for past-year GAD according to individual- and area-level characteristics for men (n=8,219) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Odds ratios and 95% CI				
Characteristic	**Unadjusted**	**Model A[1]**	**Model B[2]**	**Model C[3]**	**P-value for Model C**
Individual-level variables					
Socio-demographics					
Age					
(per 10 years)	0.59 (0.49–0.71)	0.58 (0.48–0.71)	0.63 (0.51–0.77)	0.52 (0.41–0.64)	<0.0001
Education[‡]					
Low	0.91 (0.63–1.32)	1.13 (0.75–1.70)	1.16 (0.78–1.74)	1.09 (0.73–1.63)	0.670
High	1.00	1.00	1.00	1.00	
Marital status					
Single	2.65 (1.44–4.86)	2.34 (1.26–4.36)	2.67 (1.39–5.10)	2.57 (1.32–5.01)	0.0144
Married	1.00	1.00	1.00	1.00	
Other[*]	2.09 (1.31–3.33)	2.21 (1.39–3.52)	1.48 (0.90–2.44)	1.51 (0.91–2.51)	
Social class[¥]					
Manual	0.92 (0.65–1.29)	0.83 (0.58–1.20)	0.84 (0.58–1.23)	0.74 (0.50–1.09)	0.125
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Life-time MDD					
Yes	15.38 (10.87–21.76)		14.25 (9.97–20.37)	12.88 (8.99–18.46)	<0.0001
No	1.00		1.00	1.00	
Prevalent physical disease[+]					
Yes	1.68 (1.20–2.35)			1.53 (1.07–2.20)	0.021
No	1.00			1.00	
Disability level					
High[¶]	2.71 (1.88–3.90)			3.10 (2.13–4.51)	<0.0001
Low	1.00			1.00	
Area-level variable					
Townsend index					
Deprivation					
Yes (>0)	1.36 (0.90–2.06)	1.26 (0.82–1.94)	1.19 (0.76–1.85)	1.13 (0.72–1.77)	0.598
No (<=0)	1.00	1.00	1.00	1.00	

1. Adjusted for age, socioeconomic status (education, marital status, social class)
2. Adjusted for age, socioeconomic status, lifetime MDD
3. Adjusted for age, socioeconomic status, lifetime MDD, physical diseases and disability
⁺ Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis
¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
‡ High education: O-level, A-level, degree; low education: refers to no education
* Other: divorced, separated, widowed
¶ Below the PCS value of 50.6

I had similar findings when logistic regression was used in these models instead of generalised estimating equations, suggesting that the intra-class correlation is negligible (findings not shown).

To assess whether deprivation was associated with past-year GAD without MDD in women, I excluded participants reporting past-year MDD (while controlling for all covariates in a fully-adjusted model). Deprivation continued to be strongly associated with past-year GAD (OR= 1.61, 95% CI: 1.06–2.43) (findings not shown). In men, the association was still statistically non-significant (OR=1.34, 95% CI: 0.73–2.47).

Secondary findings: covariates and GAD

When I examined the influence of covariates on GAD in women (table 7.2 model C), the following emerged as increasing risk of anxiety: lifetime MDD (OR=7.00, 95% CI: 5.34, 9.17), prevalent physical disease (OR=1.43, 95% CI: 1.09, 1.88), and high disability level (OR=1.88, 95% CI: 1.42, 2.49). In contrast, increasing age was associated with decreased risk of anxiety (OR=0.66, 95% CI: 0.56, 0.77). Similar findings emerged in men (table 7.3, model C), with the exception of marital status. Men who were single were more likely to develop anxiety than those who were married (OR=2.57, 95% CI: 1.32, 5.01) (this finding was not statistically significant in women (OR=1.34, 95% CI: 0.73–2.47).

7.4 Discussion

In this analysis of data from a population-based, cohort study, I show, for the first time, that area deprivation is significantly associated with increased risk for GAD in women, but not in men. The association in women was independent of characteristics measured at the level of the individual, including sociodemographics and major medical conditions. When I assessed the specific aspects of deprivation associated with anxiety in women, I found that those living in areas characterised by a high level of non-car ownership and non-home ownership were at increased risk of GAD, although the associations were not statistically significant. It appears that it is the overall effect of living in deprivation rather than a particular aspect of the living context that is associated with a statistically significantly increased risk of anxiety in women. It is difficult to show causality between area deprivation and GAD; however, a rigorous analysis based on cohort data is an acceptable method of examining this relationship. The analysis was rigorous, because I used a common, theory-based measure of area deprivation and a valid measure of GAD, controlled for covariates that are associated with the exposure (area deprivation) and outcome (GAD), had access to a large sample size of over 18 000 people and followed participants for a long period (7 years).

When I assessed the covariates that were associated with GAD, the following emerged as increasing risk of anxiety in both men and women: lifetime MDD, prevalent physical disease, and disability. The only additional finding in men was that those who were single were also at a higher risk of GAD than those who were married. Increasing age, on the other hand, was linked to a lower chance of having anxiety in both men and women.

Potential mechanisms

The context as measured by Census composite deprivation indices appears to have a different relationship with the mental health of women and men, even after adjusting for individual socioeconomic status, demographics and other psychiatric and major medical conditions. Several mechanisms can account for this. Women perceive, relate to and engage differently from men. [332, 333] Women are more exposed to the living context perhaps due to their greater uptake of part-time work and domestic or childrearing duties. [334] Since they are more embedded in their neighbourhoods, they are also more likely to be exposed to the stress that comes with living in deprived circumstances. [69, 70, 335] Exposure to stress has been associated with central nervous system dysfunction and hypothalamic–pituitary–adrenal axis dysregulation, which have been implicated in the aetiology of GAD. [336, 337] Women may also perceive the environment differently compared with men. Neighbourhood safety and fear of being sexually assaulted appear to be much more of a concern for women. [70, 71] If women perceive their neighbourhood to be unsafe, they are less likely to engage in activities, such as walking, and this can negatively impact their mental health. [70, 338] Perceiving neighbourhoods as unsafe can also erode social cohesion and can make women more hesitant to create social ties with others. [65] This can increase their risk of depression and related mental disorders, because women derive health benefits from being embedded in social networks. [65] Living in deprivation can also make individuals feel excluded from society and ashamed, [64] and these feelings of exclusion are particularly harmful for women's mental health. [64, 65]

Men and women may also perceive and exhibit the effects of stress in different ways. [339] Women who are highly distressed tend to develop internalising disorders, while men are more prone to substance abuse and antisocial personality. [340] The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study [341] showed that total number of stressors experienced in life had a significantly stronger association with heavy drinking in men than in women. Therefore, men living in deprivation might be more likely to develop negative outcomes, such as heavy drinking, rather than anxiety.

Secondary findings: covariates and GAD

Men and women with poor mental and physical health are at high risk for anxiety, and the literature supports these findings. Depression is highly comorbid with anxiety, and many people with the former develop or have the latter disorder. [2] Often, having one mental disorder predisposes to a second, and then a third, and so on. Disability has also been linked to anxiety. Impairment can increase the risk for poor mental health, and the reverse is also true. Studies have shown people with GAD are more disabled than those without anxiety, and the impairment is a result of the anxiety symptoms rather than any comorbid psychiatric disorder, such as depression. [63, 342] Poor health can also increase the likelihood of having GAD. Physical diseases, such as cancer, heart disease, and diabetes have been linked to anxiety. [107, 110, 114, 119] The link between anxiety and physical diseases could be a result of inflammatory mechanisms or health behaviours, such as poor diet and medication adherence. [2, 257, 343, 344]

One of the findings that emerged in this study was that single men had an increased risk of GAD, while this association was not statistically significant in women. Again, this is in line with the literature, which shows that single men tend to have poorer health and feel more lonely (loneliness is linked to psychiatric disorders [345]) than single women. [346]

As expected, increasing age was associated with decreased risk of GAD, and this is also supported by research. It could be that older people learn how to cope better with feelings of anxiety throughout the lifespan, or because they are retired, they may be less exposed to situations which are anxiety-inducing, such as social interactions at work. [128, 198] Another factor could be that those who survive to older ages are healthier than people dying younger – those who die earlier in life might have more health conditions, unhealthy lifestyle behaviours (which can increase the risk for poor mental health), and comorbidities, including anxiety. [347]

Strengths and weaknesses

This study reveals that anxiety in women is strongly linked with area disadvantage. It has several strengths. I had a large, population-based sample of middle-aged and older-aged adults and adequately adjusted for a range of possible confounders. I used a structured, self-reported questionnaire to assess the presence of past-year GAD, and participants were followed for a long period of time. I overcome methodological limitations of previous studies by employing a commonly used, theoretically sound measure of area deprivation capturing important features of the environment, such as unemployment and non-home ownership. I also had a large list of self-reported physician diagnoses of chronic physical diseases that I used to establish medical histories. Despite this, the residual effect of diseases not captured by the HLEQ, but that are associated with GAD and area deprivation may be present. Past illness may have been under-reported, which may have introduced measurement error. An additional point that I would like to raise is that any error in misclassifying people with respect to their exposure or outcome was non-differential and likely biased the effect estimates towards the null. Any measurement error for GAD was non-differential with respect to area deprivation and vice versa. These limitations and the associated biases have been discussed in detail in chapter 5.

Although I controlled for important confounders in my analyses, I would have liked to additionally adjust for covariates that frequently co-occur with GAD, such as other anxiety and personality disorders. However, this information was not captured by EPIC-Norfolk. If I would have had data on further psychiatric comorbidities, I suspect that the main effect estimates would have attenuated further in progressively adjusted models.

With respect to the categorization of confounders, it is possible that the use of a greater number of categories or the use of the variable in its original form (ex., disability as continuous instead of dichotomous) might have resulted in slightly less loss of information. This is discussed in chapter 5.

Participants were required to complete detailed dietary and lifestyle questionnaires and undergo periodic health assessments. Since those who participated in EPIC-Norfolk were somewhat less deprived and healthier than individuals living in other parts of England [166, 294] my results may not generalise to people living in extremely deprived circumstances. It could be that the association between anxiety and deprivation is even stronger in the most deprived areas. However, to confirm this assertion, this research needs to be replicated and using participants sampled from all parts of England – this would increase generalizability to the wider English population.

Also, when comparing the demographic characteristics of responders versus non-responders (appendix 4), I found that participants were slightly younger (than 50 years) and slightly more women than men consented – this, again, might have affected generalizability of the findings to the wider population. With respect to bias, it is unlikely that the association found within my cohort is explained by selection bias. It is unlikely that the association in non-responders would be in the opposite direction to that which I obtained in my study.

The biggest issue for cohort studies, however, is not selection into the study, but rather selection out of the study or loss to follow-up. Since migration in the Norfolk population is minimal and tracking of participants has been excellent, loss of participants does not present a problem.

Another limitation is that some of the areas classified as deprived in 1991 might have shown an improvement in socioeconomic circumstances over time and become more affluent, and vice versa. Although this might present an issue for samples drawn from busy, urban environments, I expect changes in area-level circumstances for the EPIC-Norfolk cohort to have been small. Many EPIC-Norfolk participants come from rural areas, where significant urban development and change in the residential environment are unlikely to have occurred during the study period. [294] Nonetheless, to account for potential changes in GAD rates and area-level circumstances, future studies should assess the association between anxiety and area deprivation at multiple time points.

Although area deprivation was measured in 1991 and GAD in 1996–2000, I expect the association between anxiety and area deprivation in women to be even stronger with more recent data. First, older, as well as, more recent literature has shown that poor women or those living in disadvantage are more likely to develop negative health outcomes, while men less so. [69, 333, 348] Second, women are increasingly taking on multiple roles in society, such as income-earner, childbearer and carer, which is adding to their burden (especially if they are living in deprivation). [318] Third, research has also shown that anxiety rates have been increasing in women in recent times. [298] For these reasons, I expect the association between area deprivation and GAD to be even stronger in women at the present time.

Finally, this research should be considered as having a cross-sectional design. Although area deprivation was measured before anxiety, prevalent rather than incident cases of GAD were ascertained. As such, some people might have had anxiety at the time that area deprivation was measured (or immediately before and afterwards too). In cross-sectional research, the exposure and outcome are measured at the same point in time, making it difficult to establish temporality. A longitudinal design would be needed to determine whether living in a deprived area leads to incident cases of GAD.

An issue with cross-sectional research is reverse causality, and not knowing whether the anxiety/poor mental health determines people to move to more deprived areas or whether living in a deprived area truly increases the risk for anxiety. Nevertheless, reverse causality seems a rather implausible explanation for the findings.

Placing my research in context

Although other studies have shown that the places where people live have a substantial impact on health [75, 79], studies on the links between area deprivation and mental disorders among men and women, separately are limited. A recent, large, population-based study [68] of over 21 000 people living in Ireland showed that area deprivation was associated with a significantly increased risk for common mental disorders in women, but not in men, after controlling for demographic and socioeconomic factors. In line with this, a study [65] of over 2700 adults living in Canada showed that greater neighbourhood disadvantage also was associated with increased risk of depressive symptoms in women, but not in men. Research conducted in the USA had similar findings. [64] This indicates that characteristics of the living context seem to influence women's health in particular. Very few studies have assessed the association between deprivation and mental health among women and men, separately and research specifically focusing on anxiety disorders is scarcer still.

My findings differ from the only other population-based, contextual study of generalised anxiety among men and women living in areas of low socioeconomic circumstances. [69] In this cross-sectional study, no association with anxiety was found; however, the measure of deprivation was based only on the local unemployment rate and median area income. Thus, the results are not directly comparable to mine. Further, the previous study used the Symptoms Checklist-90-Revised scale to measure symptoms of generalised anxiety, yielding different estimates than mine. In contrast to the DSM-IV, the Symptoms Checklist-90-Revised scale did not base the definition of generalised anxiety around excessive, uncontrollable worry, which is the central, defining feature of GAD, and used a much shorter time frame to assess symptoms. I used a thorough assessment of DSM-IV GAD, which was measured in the past year. In contrast to the previous study, I also examined area deprivation using a common, theoretically-sound index, covering a wide range of key domains relating to socioeconomic disadvantage, such as non-home ownership and non-car ownership. Studies assessing other health outcomes have suggested that the residential environment has a larger effect on women's health [69, 333], while individual-level factors relating to social status, such as employment, have the greatest impact on men's health. [332] Among disadvantaged women, it is not lack of money per se that leads to poorer health, but rather the inability to derive the necessary resources from the environment to make ends meet; this can translate into stress and anxiety. [349] Women are becoming financially independent as they enter the labour force, which means that economic hardship now impacts them, as well. Women perceive economic hardship as a barrier to managing daily life and making ends meet, which can increase their anxiety. In contrast, men link joss loss to a decline in social status. [332, 341, 349] When men experience job-related stresses, they tend to externalise the effects of such stress and develop substance abuse. [341, 298]

7.5 Conclusion

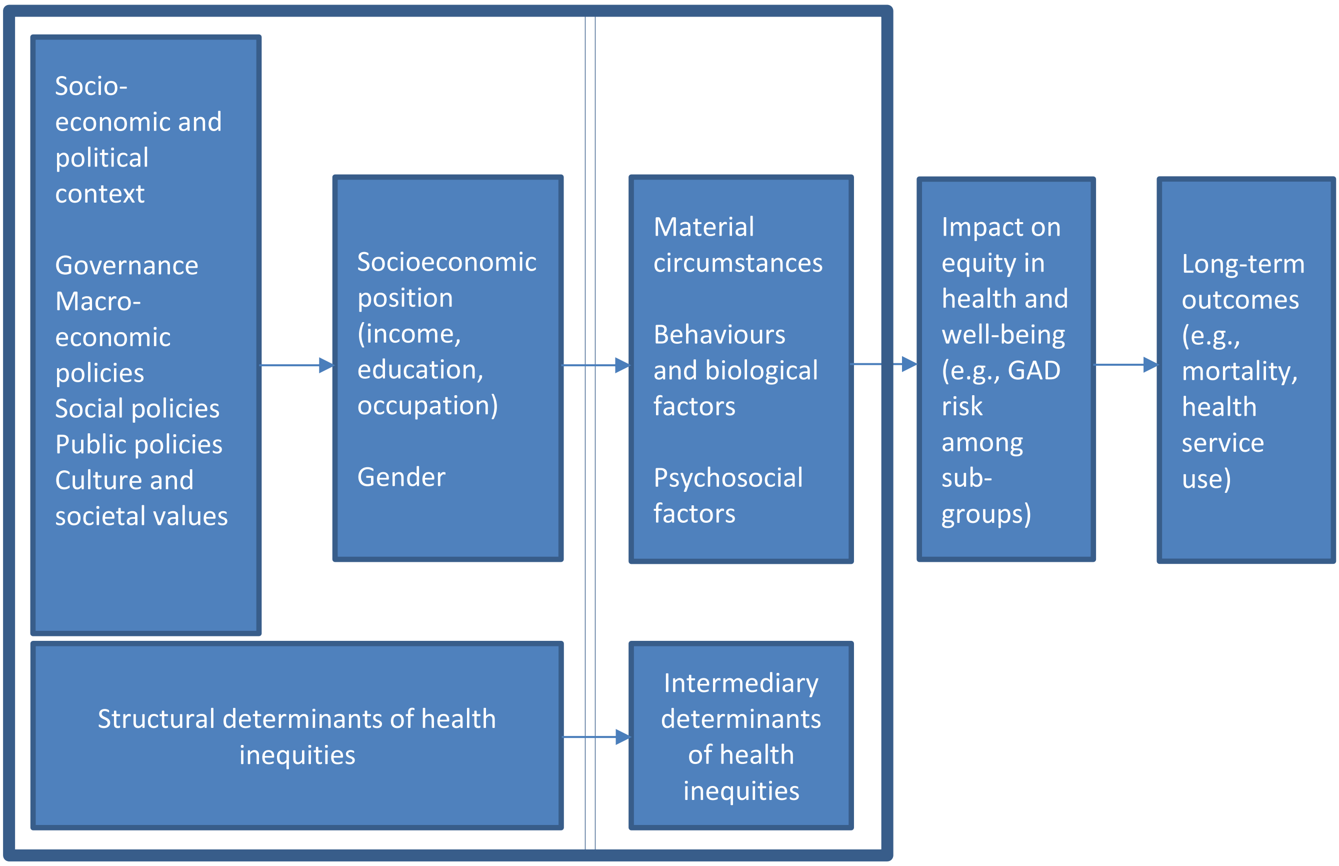
For the first time I show that living in a deprived area is associated with increased risk of GAD in women, while this is not observed in men after controlling for a range of confounders.

The next chapter focuses on MDD, which is commonly studied alongside GAD. Living in a deprived area has been shown to increase the risk of depression [76], and common mental disorders (anxiety comorbid with depression [68]). Research on pure MDD, however, in relation to area deprivation from a gendered perspective is lacking. The next chapter explores whether living in disadvantage is associated with increased risk of MDD in women and men separately using data from EPIC-Norfolk.

8 Sex differences in the association between area deprivation and major depressive disorder (MDD): British population study

Preface to chapter

In line with the conceptual framework, the previous chapter showed that living in a context characterised by disadvantage can lead to health inequities – women living in deprived areas had an increased risk of GAD, while this was not observed in men. GAD was measured according to the Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV). This chapter will investigate whether living in an area of low socioeconomic circumstances is associated with differential risk of having DSM-IV MDD in women and men using data from EPIC-Norfolk. As area-level disadvantage and gender are both structural determinants of health inequities, both of these factors deserve further research and need to be considered.



ABSTRACT

Introduction

Studies have shown that area-level deprivation measured by factors, such as, non-home ownership, non-car ownership, and household overcrowding, can increase the risk for mental disorders over and above individual-level circumstances, such as, education and social class. The objective of this study is to determine whether area-level deprivation is associated with MDD in British women and men separately while adjusting for individual-level factors such as social class.

Methods

30,445 people from the general population aged 40 years and older and living in England consented to participate at study baseline, and of these, over 21,000 participants completed a structured HLEQ used to capture MDD. Area deprivation was measured in 1991 using Census data, and current MDD was assessed according to DSM-IV criteria in 1996-2000. 8,239 men and 10,343 women had complete data on all covariates.

Results

In this study, 3.3% (339/10,343) of women and 2.1% (177/8,239) of men had MDD. Men living in the most deprived areas were 60% more likely to have depression than those living in areas that were not deprived (OR=1.60, 95%CI: 1.09, 2.35; p=0.018), but this association between deprivation and MDD was not apparent in women (OR=1.25, 95% CI: 0.94, 1.66; p=0.123).

Conclusion

The residential environment needs to be taken into account when developing mental health policy. Also, gender is clearly an important factor when it comes to assessing the impacts of the environment, and promoting good mental health.

8.1 Introduction

Depression is a common psychiatric disorder affecting more than 300 million people around the world. [73] According to the Global Burden of Disease Study [13], MDD contributed to 689.9 per 100,000 disability-adjusted life years in men and 1161.2 per 100,000 disability-adjusted life years in women in 2010. Depression can increase the risk for impairment, disability and suicide. [350, 351, 352] It has also been linked to decreased work productivity, poor quality of life, and high health service use. [350, 353, 354]

A number of studies have examined the individual-level risk factors of depression, such as, personal and parental history of psychopathology [355], genetics [356], history of trauma and stressful life events [357, 358], and socioeconomic status [359]. However, the residential environment or living context can have a profound influence on mental health, over and above individual-level factors [75, 79, 314]. In a systematic review [76] of 14 studies, about half found an association between neighbourhood socioeconomic conditions and depression. Living in an area of low socioeconomic status can expose people to a higher number of stressors, such as, violence, disorder, and noise pollution, and this can have deleterious effects on mental health. [360]

There is a wealth of literature on the effect of the places where people live on mental health. Findings from systematic reviews [77, 78, 361] assessing neighbourhood characteristics and depression show that there is large heterogeneity in findings, because of differences in study populations, the confounders that are adjusted for in analyses, and the measures and definitions used to delineate neighbourhoods. [78] Although there is much evidence on the influence of area-level disadvantage or deprivation on depression, research on this relationship from a gendered perspective is lacking.

In this large, population-based, cohort study, I examine the association between area deprivation and MDD in men and women separately, while controlling for a range of important confounders, including social class, previous medical conditions, psychiatric co-morbidity, and disability. Area deprivation refers to residential environments or living contexts characterised by factors, such as, high levels of unemployment, non-home ownership, non-car ownership, and low income. [314] Findings are disaggregated by sex, and this is done for several reasons. Gender frames access to resources derived from the environment. [65, 317] Compared to men, women have been shown to have less access to material and social conditions, and this can influence mental health.

However, there are additional reasons why findings are disaggregated by sex. Women and men tend to react to different kinds of stressors. Recent research has shown that men are more susceptible to work- and finance-related stressors, while women are more affected by deficiencies in their social networks and interpersonal relationships. [362, 363] Hence, living in a deprived area with high levels of unemployment might be particularly detrimental for men's mental health. This was evident when the economy shifted in the UK from a manufacturing- to a service-based one, and many men lost their jobs. [364] Prior to the shift, the local economy had relied on skilled and semi-skilled jobs, typically performed by men. When the economy changed, an increasing number of women entered employment (occupying mainly service industry jobs), and this had implications for traditional sex-defined social roles. Men who experienced reduced economic opportunities may have suffered from loss of role identify and self-esteem, and this had consequences for their physical and mental health. [364] A recent study [362] showed that men's mental health is particularly affected if they fail at key instrumental tasks, such as, work achievements and ability to provide for the family. In contrast, women are more likely to be depressed if they fail to meet their needs for relationship. [362] To this end, it appears that men and women are susceptible to different kinds of stressors.

It remains unclear whether men and women living in deprived areas are differentially susceptible to MDD. Knowing that one sex is at risk of developing depression when exposed to deprived circumstances helps to tailor interventions and allocate scarce resources according to need. This is particularly important at a time of scarce economic and health-related resources.

8.2 Methods

Although the methods of the thesis were described in a previous chapter, a short summary will be presented again with variables relevant to this chapter.

Data were drawn from EPIC-Norfolk, whose design and study methods have been described in detail elsewhere. [166] In brief, a prospective population-based cohort of 30,445 participants ages 40 to 74 years were recruited by post between 1993 and 1997 through general practice age-sex registers in the city of Norwich and the surrounding small towns and rural areas. At baseline (1993-97), participants completed a postal HLQ questionnaire that captured sociodemographics, including sex, highest educational attainment, marital status, and provided information on self-reported physician diagnoses of physical diseases. Using participants' postal codes, a measure of area deprivation was derived based on the 1991 Census. Social class was also obtained using the Census. Between 1993 and 2000, participants completed self-reported postal questionnaires provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address.

During 1996-2000, 20,919 participants completed a structured, psychosocial HLEQ questionnaire. During this time, an assessment of lifetime GAD and current MDD was made according to the DSM-IV [5]. Using the HLEQ questionnaire, age, marital status, and then disability measures based on the SF-36 were also derived. [178]

All participants recruited through general-practice registers and who completed a baseline health questionnaire were eligible to be included in my study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in my analysis.

Dependent variable

The primary outcome in this study was current MDD, which was measured using the HLEQ, a structured self-assessment instrument designed to provide a measure of depression for inclusion in a large-scale epidemiology project [177, 179]. DSM-IV criteria were applied to the psychiatric symptoms to determine whether participants had an episode of MDD that was ongoing at the time of the completion of the HLEQ questionnaire. Participants who reported a psychiatric episode were asked to estimate the onset and offset timings of the episode, and then to report an outline of the history of the problem. Participants were also asked about age at first symptom onset and subsequent episode recurrence.

The dependent variable in this study is current MDD, defined as an episode of MDD reported as ongoing at the time of the completion of the HLEQ.

The following two core criteria of MDD were first evaluated:

1. Have there ever been times in your life when you felt sad or depressed for two weeks or more in a row?
2. Have there ever been times in your life when you lost interest in most things like your work or activities that usually give you pleasure, for two weeks or more in a row?

If participants answered yes to one of these questions, they were then asked to think of the most recent two-week episode during their lives when these feelings of sadness, depression or loss of interest were the worst. They then had to report that these feelings of being sad, depressed, or loss of interest lasted all day or most of the day, and that during these two weeks of their most recent episode, they felt this way every day or almost every day.

In addition, at least five of the following symptoms had to be present: gaining or losing weight, having trouble falling asleep or sleeping too much, feeling tired or low on energy, feeling unable to sit still or feeling slowed down, experiencing guilt or shame or feeling worthless, losing confidence, having trouble concentrating, and thinking a lot about death or suicide.

Finally, it was evaluated whether these symptoms interfered with participants' lives and resulted in impairment.

Individual-level measures (potential confounders)

Individual-level measures included age, education, marital status, social class, and prevalent physical disease, health status, and MDD. These potential confounders were selected based on their links with depression and disadvantage. The links between each of the covariates and deprivation have been described in chapter 7. In regards to MDD, as age increases, the probability of depression also tends to increase [199]. Also, people with low socioeconomic status [366], those who are not married [365], and in poor mental and physical health [367, 368] may show higher levels of depression in comparison with other segments of the population.

The final categorization of the variables took cell size into account and was also done in accordance with previous literature. Educational attainment was categorized into high (vocational or formal qualifications at the A- or O-level or degree-level qualifications) vs. low (no formal qualifications) [223]. Marital status was categorized into three groups: married, single (or never married), and others (widowed, divorced, separated) [223]. Social class was derived using the Computer-Assisted Standard Occupational Coding [183] and categorized as follows: I (professionals), II (managerial and technical occupations), III non-manual and III manual (skilled workers), IV (partly skilled workers), and V (unskilled manual workers). To assign social class to men and women, the male partner's current or past occupation was used. If this information was not available, the female partner's occupation was used. If the social class from either partner was unavailable, then it was coded as missing. The final categorization of social class included manual: skilled manual, partly skilled, and unskilled; and non-manual: professionals, managerial and technical, and skilled non-manual [223]. Individual-level health status was assessed through the construction of a variable capturing major prevalent physical diseases. This was based on HLQ questions asking participants: "Has the doctor ever told you that you have any of the following?", followed by a list of options, such as allergies, asthma, cancer, stroke, heart attack, diabetes, thyroid conditions, etc. The prevalent physical diseases variable was categorized into yes vs. no [223].

Lifetime history of GAD was also assessed using the self-reported HLEQ questionnaire. [179] Lifetime GAD consisted of having ever had at least one episode that met core criteria stipulated by the DSM-IV. Anxiety was identified if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present: restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge.

To determine disability levels, I used the PCS derived from the HLEQ. The PCS is part of the SF-36, a widely-used, validated self-assessment tool. Higher scores indicate better health. [178]

Age was first assessed as a categorical variable and subsequently divided into 10-year bands [177].

All of these individual-level variables were regarded as potential confounders and selected based on the literature and their association with depression and area-level socioeconomic circumstances.

Area-level measure (exposure variable)

To examine area deprivation, I used one of the most commonly-used measures of area deprivation in the UK: the Townsend Index [184, 185]. This index is a composite measure of four variables obtained from the 1991 Census: 1) percentage of economically active residents over age 16 who are unemployed, 2) percentage of households that do not possess a car, 3) percentage of private households that are not owner occupied, and 4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district. Each variable was standardized by obtaining Z scores (dividing the mean by the standard deviation across enumeration districts in England). The Z values of the four variables were added together to produce a Townsend index score for each enumeration district. Positive values of the index indicate enumeration districts that are more deprived, while negative values indicate those that are less deprived; 0 represents the national mean. The postal codes of participants were record linked to enumeration districts, and participants were considered to live in deprived areas depending on the Townsend index score assigned to their enumeration district. [184]

The Townsend deprivation index was also disaggregated into its four constituent components to determine whether any one of these is associated with MDD or if it is the effect of the combined components that is important.

Statistical analysis

Characteristics of the participants were compared by MDD status – Pearson's chi-square test was used to determine whether differences were statistically significant for categorical variables. I used correlated data analysis to assess the association between individual- and area-level risk factors of MDD. A population-average model was constructed, which accounted for the potential correlation introduced by the clustering of individuals within enumeration districts. To estimate the population-average effect of the risk factors of interest on current MDD, I used generalised estimating equations. As current MDD represents a binary outcome (yes/no) and the intra-cluster correlation is assumed to be equal, generalised estimating equations with a logit link and an exchangeable correlation structure was used. Adjusted OR and 95% confidence intervals based on robust standard errors were estimated. Standard multivariate logistic regression was also conducted and compared to the findings based on generalised estimating equations.

Individual-level measures consisted of sociodemographic and health status variables, whereas the area-level measure comprised the Townsend index. Townsend index scores were used to create a dichotomous variable, with 0 as the cut-point (representing the national average). Similarly, when the Townsend index was disaggregated into its four consistent components, each variable was dichotomized using 0 (the national average) as the cut-point.

Analyses were conducted separately for men and women. First, unadjusted effect estimates were determined. Next, models were constructed that adjusted for 1) age, educational attainment, marital status, and social class; then for 2) age, educational attainment, marital status, social class, and GAD; and finally for 3) age, educational attainment, marital status, social class, GAD, physical diseases and disability level. Age was first assessed as a categorical variable, and subsequently divided into 10-year bands. Models were constructed for participants with complete measurements on all covariates.

In a subsequent analysis, a fully-adjusted model was built in which the Townsend index was replaced by its four constituent components to determine whether any one of these four variables is significantly associated with MDD.

Finally, analyses were run with pure MDD as the outcome in which past-year GAD was excluded. All models used two-sided statistical tests and a p-value of <0.05 was considered statistically significant. Analyses were implemented in Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC).

To arrive at the study size, I went through the following steps: of the 30,445 who completed the baseline HLQ, I retained those participants who completed the HLEQ (20,919), and of these, I kept those people with complete data on all covariates (18,582).

8.3 Results

At baseline, 30,445 participants were recruited from general practices in the city of Norwich and the surrounding towns and rural areas. Of these, 20,919 people completed the HLEQ during the follow-up period. In total, 18,582 out of 20,919 (88.8%) people were available for analysis, because they had complete data on all covariates. The number of missing observations for each covariate were: 9 for education, 47 for marital status, 417 for MDD, 434 for GAD, 458 for social class, 75 for the Townsend index, and 1,386 for the SF-36. Participants in this study were followed between 1993 and 2000 for a total of 7 years.

In this sample, there were 8,239 men and 10,343 women over the age of 40 years. Table 8.1 shows the distribution of individual- and area-level characteristics by current MDD.

Table 8.1 Distribution of characteristics for women (n=10,343) and men (n=8,239) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Women		Men	
Characteristic	**Number with characteristic**	**Percentage and number with MDD**	**Number with characteristic**	**Percentage and number with MDD**
Individual-level variables				
Socio-demographics				
Age (years)				
<50	1452	5.0 (72)[a]	964	3.4 (33)[a]
50-60	3719	3.9 (145)	2653	3.0 (80)
60-70	3182	2.1 (68)	2744	1.5 (40)
>70	1990	2.7 (54)	1878	1.3 (24)
Education[‡]				
Low	4056	3.5 (141)	2365	2.2 (51)
High	6287	3.2 (198)	5874	2.2 (126)
Marital status				
Single	417	2.4 (10)[a]	303	3.6 (11)[a]
Married	7757	2.7 (207)	7240	1.7 (122)
Other[*]	2169	5.6 (122)	696	6.3 (44)
Social class[¥]				
Manual	3833	3.3 (127)	3288	2.3 (76)
Non-manual	6510	3.3 (212)	4951	2.0 (101)
Health status				
Prevalent physical disease				
Yes[+]	5702	3.8 (214)[b]	3844	2.6 (100)[b]
No	4641	2.7 (125)	4395	1.8 (77)
Disability level				
High[¶]	5299	3.9 (208)[a]	4022	3.0 (119)[a]
Low	5044	2.6 (131)	4217	1.4 (58)
Lifetime GAD				
Yes	448	19.4 (87)[a]	255	22.4 (57)[a]
No	9895	2.6 (252)	7984	1.5 (120)
Area-level variable				
Townsend index				
Deprivation				
Yes (>0)	1646	4.6 (76)[a]	1242	3.6 (45)[a]
No (<=0)	8697	3.0 (263)	6997	1.9 (132)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

⁺ Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies (allergies and hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis
¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
¶ Below the PCS value of 50.6
[a] $P < 0.001$
[b] $P < 0.05$

The prevalence of (current) MDD was 2.1% (177/8,239) for men and 3.3% (339/10,343) for women. Women with MDD were younger than 50 years of age, more likely to be single, have prevalent physical disease, high disability, GAD, and live in deprived areas. Among men, similar patterns emerged (table 8.1).

After performing correlated data analysis, findings showed that the risk of depression in men living in the most deprived areas was 68% higher than in those living in the least deprived areas, even after accounting for age and socio-economic status (OR=1.68, 95% CI: 1.18, 2.40; p=0.004) (table 8.2).

Table 8.2 Odds ratios for MDD according to individual- and area-level characteristics for men (n=8,239) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Odds ratios and 95% CI				
Characteristic	**Unadjusted**	**Model A[1]**	**Model B[2]**	**Model C[3]**	**P-value for Model C**
Individual-level variables					
Socio-demographics					
Age					
(per 10 years)	0.65 (0.55, 0.77)	0.63 (0.53, 0.74)	0.69 (0.58, 0.82)	0.61 (0.51, 0.73)	<0.0001
Education[‡]					
Low	1.01 (0.72, 1.40)	1.11 (0.76, 1.60)	1.07 (0.73, 1.55)	1.00 (0.69, 1.46)	0.996
High	1.00	1.00	1.00	1.00	
Marital status					
Single	2.20 (1.17, 4.12)	1.87 (0.99, 3.55)	1.64 (0.86, 3.12)	1.62 (0.84, 3.14)	<0.0001
Married	1.00	1.00	1.00	1.00	
Other[*]	3.94 (2.76, 5.61)	3.97 (2.77, 5.71)	3.69 (2.47, 5.51)	3.82 (2.58, 5.66)	
Social class[¥]					
Manual	1.14 (0.84, 1.54)	0.99 (0.71, 1.36)	1.12 (0.80, 1.56)	1.04 (0.75, 1.45)	0.799
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Lifetime GAD					
Yes	18.87 (13.36, 26.65)		16.80 (11.64, 24.25)	14.08 (9.72, 20.39)	<0.0001
No	1.00		1.00	1.00	
Prevalent physical disease					
Yes[+]	1.50 (1.11, 2.02)			1.30 (0.94, 1.81)	0.117
No	1.00			1.00	
Disability level					
High[¶]	2.19 (1.59, 3.00)			2.20 (1.55, 3.12)	<0.0001
Low	1.00			1.00	
Area-level variable					
Townsend index					
Deprivation					
Yes (>0)	1.96 (1.39, 2.76)	1.68 (1.18, 2.40)	1.66 (1.13, 2.44)	1.60 (1.09, 2.35)	0.018
No (<=0)	1.00	1.00	1.00	1.00	

1. Adjusted for age, socioeconomic status (education, marital status, social class)
2. Adjusted for age, socioeconomic status, lifetime GAD
3. Adjusted for age, socioeconomic status, lifetime GAD, physical diseases and disability

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

+ Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

The OR reduced slightly after controlling for lifetime GAD (OR=1.66, 95% CI: 1.13, 2.44; p=0.009), but remained highly significant. After additionally adjusting for prevalent physical diseases and disability, the effect estimate became somewhat attenuated (OR=1.60, 95% CI: 1.09, 2.35; p=0.018), however, a strong association between area derivation and depression remained. (table 8.2) To determine the aspect of deprivation that is specifically associated with depression, the Townsend index was disaggregated into its four constituent components. Results showed that the OR was highest for unemployment (OR=1.82, 95% CI: 1.19-2.77; p=0.005), followed by non-car ownership (OR=1.23, 95% CI: 0.72, 2.09; p=0.450), and lowest for overcrowding (OR=0.94, 95% CI: 0.62, 1.44; p=0.777) and non-home ownership (OR=0.82, 95% CI: 0.50, 1.35; p=0.439). Of these, only the effect estimate for unemployment was statistically significant. Men living in area characterised by high levels of unemployment were over 80% more likely to have depression than those living in areas with low levels of unemployment. Next, I wanted to determine whether deprivation is associated with pure MDD, and thus I excluded past-year GAD; the association with depression remained statistically significant (OR=1.69, 95% CI: 1.10-2.58; p=0.016).

In women, while there was a statistically significant association in the model adjusting for age, education, marital status, and social class (OR=1.41, 95% CI: 1.08, 1.84; p=0.012), the association lost its significance in the fully-adjusted model (OR=1.25, 95%CI: 0.94, 1.66; p=0.123) (table 8.3).

I had similar findings when the models were run with logistic regression instead of generalised estimating equations. This suggests that the intra-class correlation is negligible (findings not shown).

Table 8.3 Odds ratios for MDD according to individual- and area-level characteristics for women (n=10,343) who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Odds ratios and 95% CI				
Characteristic	**Unadjusted**	**Model A[1]**	**Model B[2]**	**Model C[3]**	**P-value for Model C**
Individual-level variables					
Socio-demographics					
Age					
(per 10 years)	0.75 (0.66,0.85)	0.66 (0.58, 0.76)	0.72 (0.63, 0.83)	0.68 (0.58, 0.78)	<0.0001
Education[‡]					
Low	1.11 (0.89, 1.38)	1.26 (0.99, 1.60)	1.32 (1.03, 1.69)	1.33 (1.04, 1.70)	0.023
High	1.00	1.00	1.00	1.00	
Marital status					
Single	0.90 (0.47, 1.70)	0.96 (0.50, 1.83)	0.92 (0.48, 1.78)	0.92 (0.48, 1.77)	<0.0001
Married	1.00	1.00	1.00	1.00	
Other[*]	2.17 (1.73, 2.73)	2.51 (1.96, 3.21)	2.38 (1.85, 3.07)	2.34 (1.82, 3.01)	
Social class[¥]					
Manual	1.02 (0.81, 1.27)	0.96 (0.75, 1.21)	0.99 (0.77, 1.27)	0.97 (0.76, 1.24)	0.805
Non-manual	1.00	1.00	1.00	1.00	
Health status					
Lifetime GAD					
Yes	9.22 (7.07, 12.03)		8.37 (6.31, 11.09)	7.67 (5.76, 10.20)	<0.0001
No	1.00		1.00	1.00	
Prevalent physical disease[+]					
Yes	1.41 (1.13, 1.76)			1.27 (1.00, 1.61)	0.051
No	1.00			1.00	
Disability level					
High[¶]	1.53 (1.23, 1.91)			1.45 (1.14, 1.84)	0.003
Low	1.00			1.00	
Area-level variable					
Townsend index					
Deprivation					
Yes (>0)	1.55 (1.20, 2.02)	1.41 (1.08, 1.84)	1.28 (0.96, 1.69)	1.25 (0.94, 1.66)	0.123
No (<=0)	1.00	1.00	1.00	1.00	

1. Adjusted for age, socioeconomic status (education, marital status, social class)
2. Adjusted for age, socioeconomic status, lifetime GAD
3. Adjusted for age, socioeconomic status, lifetime GAD, physical diseases and disability

‡ High education: O-level, A-level, degree; low education: refers to no education
* Other: divorced, separated, widowed
¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual
+ Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis
¶ Below the PCS value of 50.6

Secondary findings – covariates and MDD

When I examined the covariates that were associated with increased risk of depression in men, the following emerged as statistically significant: being separated/divorced/widowed (OR=3.82, 95% CI: 2.58, 5.66), having lifetime GAD (OR=14.08, 95% CI: 9.72, 20.39), and disability (OR=2.20, 95% CI: 1.55, 3.12). Increasing age, on the other hand, was associated with decreased risk of MDD (OR=0.61, 95% CI: 0.51, 0.73).

Women showed the same pattern of findings, with the exception of education and physical health conditions. Low educational attainment was significantly associated with depression in women (OR=1.33, 95% CI: 1.04, 1.70), but less so in men (OR=1.00, 95% CI: 0.69, 1.46). Also, the link between physical health conditions and depression was borderline significant in women (OR=1.27, 95% CI: 1.00, 1.61), but not in men (OR=1.30, 95% CI: 0.94, 1.81) – the effect estimates, however, were very similar for both sexes.

8.4 Discussion

In this analysis of data from a population-based, cohort study I show, for the first time that area deprivation is significantly associated with increased risk for MDD in men, but not in women. The association in men persisted after accounting for characteristics measured at the level of the individual, including sociodemographics and major medical conditions. When I assessed the specific aspects of deprivation associated with depression in men, I found that living in areas characterised by a high level of unemployment contributed to a high risk of having depression. It is difficult to confirm causality between area deprivation and depression; however, a rigorous analysis based on observational data is a reasonable method of examining this relationship. The analysis was rigorous, because I used reliable and commonly-used measures of area deprivation and depression, controlled for important covariates that are associated with the exposure (area deprivation) and outcome (MDD), such as, medical history and disability, I had access to a large sample size of over 18,000 people, and followed participants for a long period (7 years).

Potential mechanisms

The living context, as measured by a Census deprivation index, appears to have a different relationship with the mental health of men and women after adjusting for a number of potential confounders. Several reasons can account for this. First, men appear to respond to stress occurring in their environment differently from women, especially if the stress is relating to financial and work-related problems. [362] The reason for this is that occupational and financial success is particularly important for men's mental health. Second, when living in disadvantaged regions, the possibility of hearing about job loss from others increases and this can promote anticipatory stress in those who are still working, which can increase their risk of depression. [369] This is particularly problematic for men who are perceived by their families as the main provider and head of household. In contrast, women's risk of depression seems to be influenced more by the social networks they are embedded in, the quality and continuity of relationships, the social support derived from neighbours and communities, and marital satisfaction. [362, 363] Women are more likely to experience depression as a result of unmet needs in relationships. Deficiencies in interpersonal relationships in women can lead to a perception that the self is unable to meet needs for self-worth and achievements, and this can increase their risk of poor mental health. [362] Men, on the other hand, have been shown to be more prone to depression as a result of failure in key instrumental tasks, including achievements at work and inability to provide for the family. [362]

Unemployment, often accompanied by low social ranking, can lead to loss of self-esteem and role identity in men. This was seen in the United Kingdom after the 1970's, when the economy shifted from a manufacturing to a service-based one. [364] The shift was accompanied by a loss of skilled and semi-skilled jobs among men, while women had to enter the workforce and partake in jobs that were primarily service-based. The loss of employment opportunities among men might have contributed to a loss of role identity and self-esteem in this group. [364] However, even more than a decade later after this shift in economy, men who lost their employment and were in low social class groups showed poorer self-rated health compared to women. [370] This is also mirrored by recent research. [362] This again supports the notion that men are affected by failure at key instrumental tasks. [362] The same phenomenon occurred in rural areas of Midwestern United States after the farm crisis and related events occurred in the 1980s. [371] Rural areas held agrarian values, characterised by male provider norms and 'rugged independence' [371]. After the farm crisis hit, men were no longer able to fulfil their economic provider role, and both sexes had to take on multiple jobs to make ends meet. This shook the traditional system, and created stress and contributed to high rates of depression in men. During this time, men also showed susceptibility to a wider range of stressors compared to women. [371]

Men and women also tend to experience and manifest the effect of stress in different ways. Women living in deprived areas have been shown to be more prone to anxiety (as indicated in the previous chapter), while men living in disadvantage are more likely to have depression. This could be a result of evolutionary, survival functions. Women have traditionally had the responsibility of childcare and ensuring the successful survival of future generations. [372] Therefore, living in deprived circumstances can trigger the fight or flight reaction, which can increase stress in findings ways to make ends meet so that they can raise their children. In this context, anxiety might be seen as protective, ensuring the survival of future generations. This is why women also tend to be more concerned about community features that can disrupt their caregiving role and negatively impact their family, such as, lack of safe play areas for children. [372, 373] Men have traditionally had the responsibility of being the provider, and if they are not able to fulfil this role, they are more likely to become depressed and potentially commit suicide. [362, 364] This is a problem in India, where suicide rates are high among male farmers whose crops have failed. [374, 375] In the UK, men with depression are also more likely than women to commit suicide. [376] Taken together, these findings suggest that women may actually be more resilient than men when encountering adversity. However, very little research has examined this, and previous studies in the mental health literature have typically described women as vulnerable. Further research on health from a gendered perspective is needed.

When exposed to the stresses and strains of deprivation, men are also more likely to develop substance abuse and this, in turn, can increase the risk for depression. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) study [341] showed that total number of stressors experienced in life had a significantly stronger association with heavy drinking in men than in women. Finally, when men experience mental health issues, they are less likely to seek help than women [371].

Secondary findings – covariates and MDD

The fact that men and women who were separated/divorced/widowed, had lifetime GAD, and disability had increased risk of depression is unsurprising. The literature has shown that people who are separated, divorced, or widowed tend to have higher depression rates than those who are married. [377] A reason for this could be that married people are less stressed and prone to risk behaviours, such as smoking and drinking, among other factors. [247] Engaging in risk behaviours can increase the risk of illness through physiological pathways, as well as injury. [247, 378] Also, the social network that marriage provides can be a buffer against stress and poor mental health. [247]

It is unsurprising that anxiety was related to increased risk of having depression in men and women. Anxiety is frequently comorbid with depression and one disorder always predisposes or increases the risk of having the other. [2]

Disability has also been linked to depression in the literature. Disabled people may experience discrimination, denied opportunities in life such as education, and barriers to accessing health services; they are also at risk for serious illness [379, 380] – all of these factors can increase their chance of having depression. In my study, ill health was indeed linked to depression, but only in women – and this finding was borderline significant; as such, it will not be discussed further. (The variable I created capturing ill health was composed of a range of conditions, including asthma, cancer, and diabetes, among others. It could be that most the conditions captured by my 'prevalent physical diseases' variable are particularly related to depression in women, while other conditions are more relevant for men's mental health. However, an in-depth examination of this is beyond the scope of this thesis.)

In my study, low education was associated with a small increased risk of depression in women, while less so in men. Other research has shown that education affects women's depression levels more strongly than men's. Women are less likely to have adequate income and positions of power compared to men – the lack of these resources, however, is less harmful for their mental health if they are able to substitute them with other resources. This is why education is particularly important for women's mental health. [381, 382]

Finally, I found that increasing age was associated with a decreased risk of depression, and this results is in line with the literature. Research has shown that depression rates tend to drop in older age groups, which could be due to better emotional control in older people. [198, 383] Some studies, however, have reported contradictory findings, with young and old people showing the highest rates. This could be due to the tools used to measure depression. Studies based on diagnostic criteria such as the DSM exclude those whose symptoms are due to the direct physiological effects of a substance or a recent bereavement – physical illness and recent deaths are common in old age. Depression symptom checklists do not impose such rules, and thus may produce inflated prevalence estimates. [383]

Strengths and weaknesses

This study reveals that depression in men is strongly linked with area disadvantage. It has several strengths. I had a large, population-based sample of middle- and older-aged adults and adequately adjusted for a range of possible confounders. I used a structured, self-reported questionnaire to assess presence of current MDD, and participants were followed for a long period of time. I overcame methodological limitations of previous studies by employing a commonly-used, theoretically-sound measure of area deprivation capturing important features of the environment, such as unemployment and non-home ownership. I also had a large list of self-reported physician diagnoses of chronic physical diseases that I used to establish medical histories. Despite this, the residual effect of diseases not captured by my study, but that are associated with MDD may be present. Past illness may also have been underreported, which may have introduced measurement error.

Any error in misclassifying people with respect to their exposure or outcome was non-differential and likely biased the effect estimates towards the null. Any measurement error for MDD was non-differential with respect to area deprivation and vice versa.

Although I controlled for important covariates in my analyses, I would have liked to additionally adjust for other anxiety and personality disorders (commonly co-occurring with GAD). I suspect that if I would have done so, the main effects estimates would have become even more attenuated in the progressively adjusted models.

A further point I would like to make in regards to the covariates concerns categorization. It is possible that the use of smaller categories (original form of social class rather than its dichotomous form as was used in analyses) might have resulted in less loss of information. This is discussed in chapter 5.

Participants were required to complete detailed dietary and lifestyle questionnaires and undergo periodic health assessments. Because those who participated in EPIC-Norfolk were somewhat less deprived and healthier than individuals living in other parts of England [166], my results may not generalise to people living in extremely deprived circumstances. Further detailed discussion on the associated biases and generalizability issues can be found in the previous chapter, which looked at a very similar research question: the association between area deprivation and GAD.

Another limitation is that some of the areas classified as deprived in 1991 might have shown an improvement in socioeconomic circumstances over time and become more affluent, and vice versa. Although this might present an issue for samples drawn from busy, urban environments, I expect changes in area-level circumstances for the EPIC-Norfolk cohort to have been small. Many EPIC-Norfolk participants come from rural areas, where significant urban development and change in the residential environment are unlikely to have occurred during the study period. [294] Nonetheless, to account for potential changes in MDD rates and area-level circumstances, future studies should assess the association between depression and area deprivation at multiple time points.

Although I have been discussing this research as if it were longitudinal (because area deprivation was indeed measured before depression), the limitation of the study design should be mentioned.

Because cases of MDD were prevalent, rather than incident cases, and some people could have had depression at the time that area deprivation was measured, this research should be considered cross-sectional. Temporality cannot be ascertained with a cross-sectional design, because the exposure and outcome are assessed at the same point in time, and reverse causality becomes an issue. Thus, instead of poor socioeconomic circumstances leading to depression, it could be that MDD causes a downward drift in social status/loss of resources and people are forced to move to deprived areas. The former explanation seems much more likely, though. However, to determine whether this is really the case, a longitudinal study is needed to measure the exposure, socioeconomic circumstances, before the outcome, incident MDD.

Placing my research in context

Although other studies have shown that the places where people live have a substantial impact on health [75, 79], studies on the links between area deprivation and mental disorders from a gendered perspective are limited. A recent study [384] of over 1000 African American and non-Hispanic white adults living in the US showed that men who had experienced stressful life events in 1983-1986 were more likely to have depression in 2011, while this was not observed in women. This study, however, has limited generalisability, because it excluded other ethnicities. Also, the reliability and validity of the measure of stressful life events was not reported – the measure was based on a checklist of 'major negative events' that had occurred in the previous 3 years. Finally, exposure to stressful life events at the individual-level were investigated, rather than the effect of the place people live in.

A number of studies have assessed individual-level risk factors of depression, but substantially fewer have examined the influence of the residential environment on mental health. Nonetheless, studies of individual-level risk factors provide an important starting point in understanding relationships. Another prospective UK study of over 500 people [364] showed that the socioeconomic status of men at midlife was associated with depression at midlife, while this was not observed in women. For women, their socioeconomic status at birth influenced their levels of depression at midlife. Also, men who had experienced downward social mobility or a reduction in their socioeconomic status from adulthood to midlife were at high risk of having poor mental health at midlife, but this was not found in women. [364] These results suggest that women are more sensitive to the social class group they are in very early in life, while for men, social mobility over the life course, as well as the socioeconomic status group they are in during later life are more important for their mental health. This study, however, was limited, because it was based on a small sample size, assessed only individual-level measures rather than area-level level effects, and failed to adjust for a number of important confounders, such as, demographic factors. Failure to properly adjust for potential confounders can lead to overestimation of the effect estimate. Finally, this study examined general mental health, rather than individual psychiatric disorders.

A recent US study showed that the types of stressors that influence men's risk of depression are those related to work, finances, and legal matters. [362] In this study, stressors were not linked to depression risk in women. Again, this research only assessed individual-level data. My study shows, for the first time that living in a deprived area increases the risk of depression in men, while less so in women. Area deprivation was measured in my study at midlife and beyond, the time period which seems to have the greatest influence on men's mental health [362].

8.5 Conclusion

Depression is a major cause of morbidity and mortality, and few studies have assessed the influence of the residential environment on risk of having this condition among women and men separately. Results from this study show that men seem to be particularly vulnerable to depression if living in deprivation, while this does not seem to be the case for women.

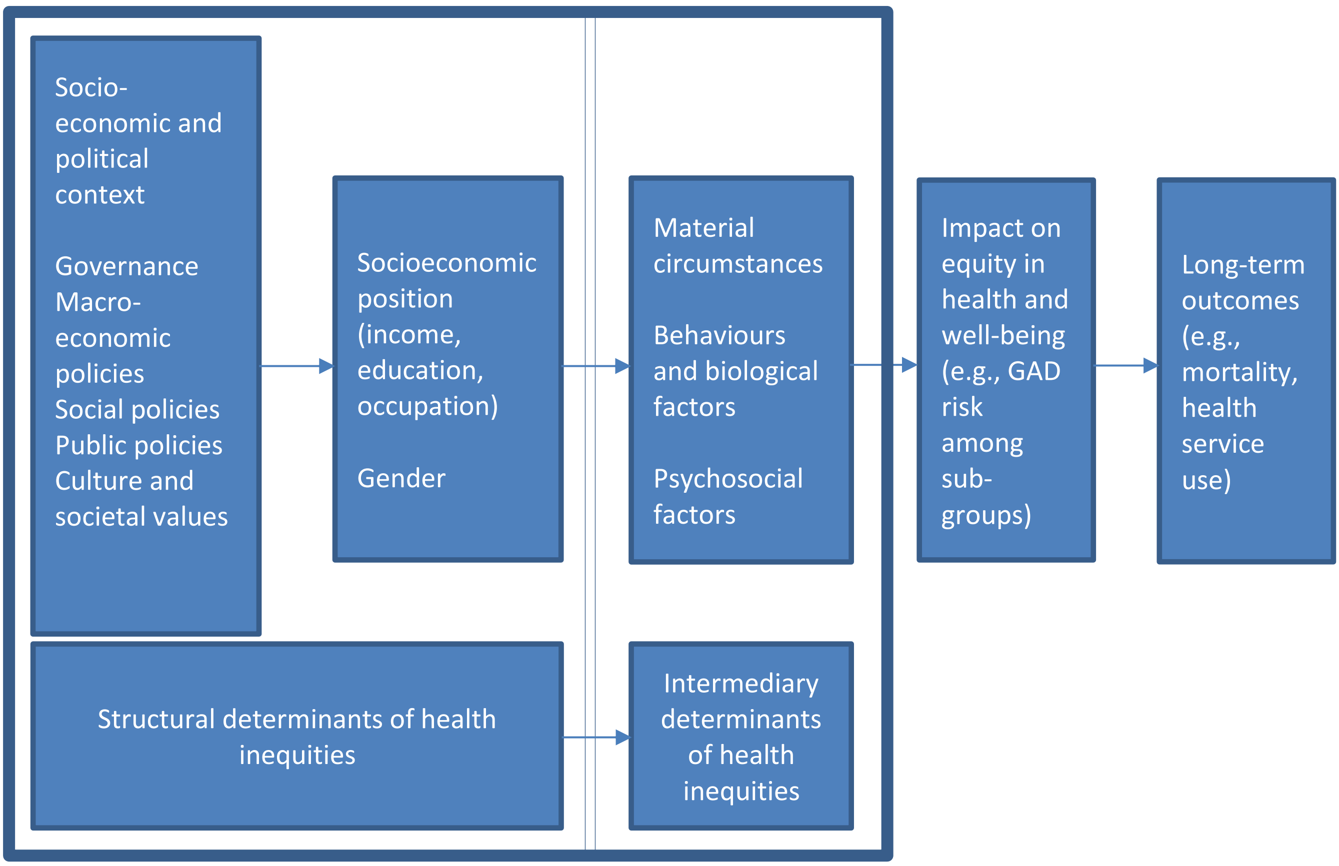
The previous chapter showed that women living in deprivation were more prone to having anxiety. The next chapter will examine ways of mitigating risks of anxiety among women living in deprivation.

9 Sense of coherence (SOC) as a coping mechanism for women with anxiety living in deprivation: British population study

Preface to chapter

The WHO framework indicates that people of lower socioeconomic circumstances have more stresses to face and circumstances which are more difficult to handle than their more affluent peers. I would like to determine whether personal dispositions can buffer the negative impact of living in disadvantage on mental health, namely risk of having GAD measured according to the Diagnostic and Statistical Manual of Mental Disorders, fourth version (DSM-IV).

The WHO maintains that deprived communities should be empowered to control their own health. If personal coping resources are found to positively influence health and mitigate risks of anxiety among those living in deprivation, then such coping skills may be encouraged and developed in people needing them the most – such as those that are part of disadvantaged contexts.



ABSTRACT

Introduction

Many patients receiving medical treatment for anxiety relapse or do not improve. Research has therefore been turning to coping mechanisms as a way to decrease anxiety rates. Previously, I showed that living in a deprived area significantly increases the risk of GAD in women, but not in men. The objective of this study is to assess whether SOC (coping mechanism) buffers the influence of area deprivation on women's risk of GAD using data from EPIC-Norfolk.

Methods

30,445 people over the age of 40 were recruited through general practice registers in England. Of these, 20,919 completed a structured HLEQ used to assess GAD and SOC. Area deprivation was measured using 1991 Census data, and SOC and anxiety were examined in 1996-2000. The outcome, GAD, was measured according to core criteria stipulated by the DSM-IV. 10,183 women had complete data on all covariates.

Results

In this study, 2.6% (263/10,183) of women had GAD. In those with a strong SOC, area deprivation was not significantly associated with anxiety (OR=1.28, 95% CI: 0.76, 2.16). However, among women with a weak SOC, those living in deprived areas were almost twice as likely to have GAD compared to those living in more affluent areas (OR=1.92, 95% CI: 1.32, 2.79).

Conclusion

The absolute number of women living in deprived conditions is large worldwide, and significant numbers are affected by GAD. SOC moderates the association between area deprivation and anxiety in women; therefore, interventions targeting coping mechanisms may need to be considered for people with anxiety. However, further research on this is needed using a larger number of anxiety cases before clinical and public health recommendations can be made.

9.1 Introduction

GAD is characterised by excessive and pervasive worry about a number of areas of life, and associated symptoms, such as, restlessness, irritability, muscle tension, sleep difficulties, and concentration problems. [5] If left untreated, this disorder can increase the risk for disability, impairment, and suicide. [187, 188, 260-262] Although treatment for anxiety exists in the form of psychotherapy and pharmacotherapy, very few people who need treatment actually receive it. [262] One of the reasons for this is that physicians under- and misdiagnose those affected, and few people experiencing symptoms seek help from the clinician. [2] Low rates of help-seeking is a result of low general awareness about the disorder and treatment options, and people perceiving their anxiety to be an intractable personality trait, rather than a condition that can be treated. These problems are further compounded by the fact that even after patients are treated, many relapse, while some do not experience improvement in symptoms. [2]

While it is not known what causes anxiety, most studies on risk have focused on individual-level determinants of anxiety disorders such as personal income, education and history of psychopathology. [309-311, 313] However, research has shown that the environment can have a profound effect on mental health, over and above individual-level circumstances. The living context, such as, living in a deprived area, can have harmful effects for mental health independently of personal socioeconomic status and lifestyle factors. [75, 79] Women have been reported to be particularly affected by their context or the environment in which they are living. [69, 333] Women living in poor areas seem to be disproportionately affected by mental disorders. Previously, I showed that women living in deprivation had a significantly higher risk of GAD, while this was not observed in men. If women are living in an area with low socioeconomic circumstances, they are more likely to be exposed to the stress and strain that arises from deprivation. [69] Exposure to stress can then increase the risk for central nervous system dysfunction and hypothalamic-pituitary-adrenal axis dysregulation, which may lead to the development of GAD. [336, 337]

To reduce the risk of mental disorders among women exposed to disadvantage or adversity, coping skills need to be considered. In particular, SOC, which is a way of viewing life as predictable, manageable, and meaningful, can lower the risk for poor health outcomes. [80, 84] Also, SOC is a flexible and adaptive dispositional orientation which enables coping with stressful situations. [84, 385]

Two systematic reviews [80, 81] showed that SOC is linked to quality of life. A strong SOC is related to good physical and self-perceived health, and is negatively associated with anxiety, depression, and PTSD. [81] In the EPIC-Norfolk study of over 18,000 people, a strong SOC contributed to a 20% reduction in all-cause mortality in adults. [82] SOC has also been shown to moderate the influence of disadvantage on mental health outcomes. In a study of people who had faced early childhood deprivation and trauma during the Holocaust, SOC moderated the association between early-life deprivation and posttraumatic stress in old age. [83] A strong SOC can therefore be a major coping resource for preserving health.

Previously, I have shown that women living in deprived areas were at increased risk for GAD. The stress of living in deprivation was harmful for women's mental health, while this association with deprivation was not apparent in men. For this reason, this study will focus on women. The objective of this study is to determine whether SOC moderates the link between area deprivation and GAD in women using a large, longitudinal, population cohort.

9.2 Methods

Study population

Although the methods were already described in a previous chapter, they will be briefly presented again.

Data were drawn from the population-based EPIC-Norfolk, described in detail elsewhere [166]. Between 1993 and 1997, 30,445 participants over the age of 40-74 years living in Norwich and the surrounding towns and rural areas were identified through general practice age-sex registers (77,630 people were initially invited to join EPIC-Norfolk). At baseline (1993-97), 30,445 participants consented to join the study and completed a postal HLQ questionnaire that captured information on sociodemographics, including sex, marital status, highest educational attainment, employment, and self-reported physician diagnoses of physical diseases. Using participants' postal codes, a measure of area deprivation was derived based on the 1991 Census [386]. Between 1993 and 2000, participants completed self-reported postal questionnaires provided they: 1) were still alive, 2) did not ask to be removed from the study's mailing list, and 3) had a valid mailing address.

All participants recruited through general-practice registers and who completed a baseline health questionnaire were eligible to be included in my study; those who completed a psychosocial questionnaire during follow-up were eligible to be included in my analysis.

Assessment of GAD – outcome

In 1996-2000, 20,919 men and women completed an HLEQ [387] used to identify those meeting criteria for DSM-IV GAD. The primary outcome in this study was past-year GAD. The HLEQ captured the onset and offset timings of episodes of GAD. [179] Past-year GAD consisted of at least one episode that had offset within 12 months of administration of the HLEQ. DSM-IV GAD was diagnosed if participants reported having uncontrollable, excessive worry for six months or longer on most days than not that resulted in disability or impairment. In addition, at least three of the following symptoms needed to have been present:

restlessness, irritability, muscle tension, fatigue, trouble concentrating because of worry, mind going blank, trouble falling asleep, trouble staying asleep, and feeling keyed up or on edge.

Assessment of potential confounders

Covariates were chosen a priori based on previous literature (as detailed in the chapter on area deprivation and GAD). Further explanations on the potential confounders and the categorization of the variables are given in chapter 7. The baseline HLQ was used to ascertain sex, education (highest level of education attained: no qualifications, educated to age 16 years, educated to age 18 years, or educated to degree level), marital status (single, married, widowed, separated, divorced), employment (yes, no), and self-reported physician diagnoses of major medical conditions (asthma, bronchitis, allergies, hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis). Social class (professionals, managerial and technical occupations, skilled workers divided into non-manual and manual, partly skilled workers and unskilled manual workers) was derived using the Computer-Assisted Standard Occupational Coding. [183]

The HLEQ was used to derive participant age, marital status, determine presence of lifetime MDD according to the DSM-IV, and disability based on the SF-36. To determine disability levels, I used the PCS of the SF-36, a widely-used, validated self-assessment tool. Higher scores indicate better health. [178]

Assessment of area deprivation – exposure

To examine area deprivation, I used the Townsend Index. [314] This index is a composite measure of four variables obtained from the 1991 Census: 1) percentage of economically active residents over age 16 who are unemployed, 2) percentage of households that do not possess a car, 3) percentage of private households that are not owner occupied, and 4) percentage of private households that are overcrowded (have more than 1 person per room). These variables were obtained at the level of the enumeration district. For each variable, Z scores were obtained by dividing the mean by the standard deviation (across enumeration districts in England). The Z-values of the four variables were added together to produce a Townsend index score. Positive values of the index indicate areas that are more deprived, while negative values indicate areas that are less deprived; 0 represents the national mean. The postal codes of participants were record linked to enumeration districts, and participants were considered to live in deprived areas depending on the Townsend index score assigned to their enumeration district.

Ascertainment of SOC

The HLEQ included a three-item SOC questionnaire [182] that assessed each of the SOC constructs. The following questions were used to assess each construct:

Comprehensibility:
Do you usually feel that the things that happen to you in your daily life are hard to understand?

Manageability:
Do you usually see a solution to problems and difficulties that other people find hopeless?

Meaningfulness:
Do you usually feel that your daily life is a source of personal satisfaction?

Participants were given the choice of responding to these questions with yes, usually; yes, sometimes; and no. Comprehensibility was reverse scored, and all items were then summed to provide a total SOC scale ranging from 0 to 6. Higher scores represent weaker SOC.

Statistical analysis

Characteristics of the participants were compared by GAD status – Pearson's chi-square test was used to determine whether differences were statistically significant for categorical variables. I used correlated data analysis to assess the association between individual- and area-level risk factors of GAD in women and men, separately. A population-average model was constructed, which accounted for the potential correlation introduced by the clustering of individuals within enumeration districts. To estimate the population-average effect of the risk factors of interest on past-year GAD, I used generalised estimating equations. As past-year GAD represents a binary outcome (yes/no) and the intra-cluster correlation is assumed to be equal, generalised estimating equations with a logit link and an exchangeable correlation structure was used. Adjusted OR and 95% confidence intervals based on robust standard errors were estimated.

Individual-level measures consisted of demographic, socioeconomic status, and health variables whereas the area-level measure was the Townsend index. Townsend index scores were used to create a dichotomous variable, with 0 as the cut-point (representing the national average).

SOC was split at the median (of 2) [388] and participants below this cut-point were classified as weak on SOC, while those above this cut-point had a strong SOC. The interaction between area deprivation and SOC in women was assessed. After this, analyses were conducted separately for those with strong and weak levels of SOC. First, unadjusted effect estimates were determined. Next, models were constructed that adjusted for 1) age, educational attainment, marital status, social class, and employment; then for 2) age, educational attainment, marital status, social class, employment, and MDD; and finally for 3) age, educational attainment, marital status, social class, employment, MDD, physical diseases, and disability level. Age was first assessed as a categorical variable and then in 10 year bands [177].

Models were constructed for participants with complete measurements on all covariates. The brackets show the reference categories that were used for each categorical variable when it was entered in the models – age: young (<65) vs. old (>=65) [ref]; education: high [ref] vs. low; marital status: married [ref] vs. not married; social class: non-manual [ref] vs. manual; employed: no vs. yes [ref]; lifetime MDD: no [ref] vs. yes; deprivation: no [ref] vs. yes; prevalent physical disease: no [ref] vs. yes; disability level: low [ref] vs. high. These reference categories were based on the literature. Choosing other groupings for the potential confounders would not have changed the results. It was not possible to group the GAD variable otherwise, and area deprivation was analysed in accordance with the literature.

To arrive at the study size, I went through the following steps: of the 30,445 who completed the baseline HLQ, I retained those participants (both men and women) who completed the HLEQ (20,919), and of these, I kept only women with complete data on all covariates (10,183).

9.3 Results

77,630 people from general practices in Norfolk were invited to take part in the study, and of these, 30,445 consented. The characteristics of responders versus non-responders are compared in appendix 4; compared to non-responders, those who took part consisted of slightly more women and slightly younger (than 50 years) participants. Of the 30,445 people recruited at baseline, 20,919 completed the HLEQ during follow-up. [179, 196] Of those who completed the HLEQ, 10,183 women were retained for analysis in this study, because they had complete data on all covariates. The number of missing observations for each covariate was: 1 for age, 7 for education, 23 for marital status, 303 for social class, 35 for employment, 46 for Townsend index, 883 for disability, 321 for MDD, 215 for SOC, and 300 for GAD. Participants were assessed between 1993 and 2000 (followed for 7 years).

In 1996-2000, GAD was present in 260 out of 10,183 (2.6%) women. Table 9.1 shows sociodemographic and health status characteristics for women with a weak and strong SOC.

Table 9.1 Distribution of characteristics for women (n=10,183) with weak and strong SOC who completed the HLEQ questionnaire in the EPIC-Norfolk cohort

	Weak SOC		Strong SOC	
Characteristic	**Number with characteristic**	**Percentage and number with past-year GAD**	**Number with characteristic**	**Percentage and number with past-year GAD**
Socio-demographics				
Age (years)				
<50	438	7.1 (31)[a]	999	2.2 (22)[b]
50-60	1126	7.1 (80)	2553	1.5 (39)
60-70	839	4.2 (35)	2286	1.1 (26)
>=70	588	2.9 (17)	1354	0.7 (10)
Education[‡]				
Low	1358	4.6 (62)	2619	0.8 (21)[b]
High	1633	6.2 (101)	4573	1.7 (76)
Marital status				
Married	2060	5.5 (113)	5590	1.2 (69)
Not married[*]	931	5.4 (50)	1602	1.7 (28)
Social class[¥]				
Manual	1261	4.9 (62)	2508	1.1 (27)
Non-manual	1730	5.8 (101)	4684	1.5 (70)
Employed				
Yes	1178	5.6 (66)	2852	1.4 (40)
No	1813	5.3 (97)	4340	1.3 (57)
Townsend index				
Deprivation				
Yes (>0)	534	8.4 (45)[a]	1083	1.8 (19)
No (<=0)	2457	4.8 (118)	6109	1.3 (78)
Health status				
Prevalent physical disease				
Yes[+]	1683	6.1 (103)	3922	1.8 (70)[a]
No	1308	4.6 (60)	3270	0.8 (27)
Disability level				
High[¶]	1717	6.2 (107)[b]	3493	1.8 (64)[a]
Low	1274	4.4 (56)	3699	0.9 (33)
Lifetime MDD				
Yes	737	13.8 (102)[a]	1180	5.4 (64)[a]
No	2254	2.7 (61)	6012	0.5 (33)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Single divorced, separated, widowed

¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

+ Prevalent physical disease: respiratory disease (asthma and bronchitis), allergies (allergies and hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

[a] $P < 0.001$

[b] $P < 0.05$

Among women with a weak SOC, those who also had GAD were more likely to be younger than 60 years of age, live in areas of high deprivation, and have high disability and lifetime MDD. There were a few differences with respect to strong SOC. In the group with strong SOC, women with anxiety were more likely to be younger than 50 years, have high educational attainment, high disability, prevalent physical disease, and lifetime MDD.

During the 6-year follow-up period, there were a total of 260 GAD cases in women. A weak SOC was found in 2,991 women, while a strong SOC was present in 7,192 women. When the interaction between area deprivation and SOC was assessed, the p-value was 0.226. Table 9.2 and table 9.3 show the unadjusted and adjusted OR (Models A-C) associated with GAD in those with a weak and strong SOC, respectively.

Table 9.2 Odds ratios for GAD in women with a weak SOC who completed the HLEQ questionnaire in 1996-00 (women with weak SOC sample size=2,991)

	Odds ratios and 95% CI				
Characteristic	**Unadjusted**	**Model A[1]**	**Model B[2]**	**Model C[3]**	**P-value for Model C**
Socio-demographics					
Age					
Per 10 years	0.66 (0.55, 0.79)	0.55 (0.44, 0.70)	0.66 (0.52, 0.84)	0.63 (0.50, 0.80)	0.0002
Education‡					
Low	0.73 (0.52, 1.00)	0.79 (0.57, 1.11)	0.83 (0.59, 1.18)	0.83 (0.59, 1.18)	0.3005
High	1.00	1.00	1.00	1.00	
Marital status					
Married	1.00	1.00	1.00	1.00	
Not married*	0.98 (0.69, 1.38)	1.03 (0.72, 1.48)	0.84 (0.58, 1.21)	0.83 (0.57, 1.20)	0.3169
Social class¥					
Manual	0.83 (0.60, 1.15)	0.82 (0.58, 1.15)	0.83 (0.59, 1.18)	0.80 (0.57, 1.14)	0.2198
Non-manual	1.00	1.00	1.00	1.00	
Employed					
Yes	1.00	1.00	1.00	1.00	
No	0.95 (0.69, 1.31)	1.80 (1.20, 2.70)	1.54 (1.02, 2.32)	1.46 (0.96, 2.20)	0.0735
Townsend index					
Deprivation					
Yes (>0)	1.82 (1.28, 2.61)	1.96 (1.37, 2.80)	1.90 (1.31, 2.77)	1.92 (1.32, 2.79)	0.0007
No (<=0)	1.00	1.00	1.00	1.00	
Health status					
Lifetime MDD					
Yes	5.77 (4.15, 8.03)		5.18 (3.67, 7.31)	5.00 (3.53, 7.06)	<0.0001
No	1.00		1.00	1.00	
Prevalent physical disease⁺					
Yes	1.36 (0.98, 1.88)			1.22 (0.86, 1.73)	0.2757
No	1.00			1.00	
Disability level					
High¶	1.45 (1.04, 2.01)			1.51 (1.05, 2.17)	0.0270
Low	1.00			1.00	

1. Adjusted for age, SES (education, marital status, social class, employment)
2. Adjusted for age, SES, lifetime MDD
3. Adjusted for age, SES, lifetime MDD, prevalent physical disease and disability

‡ High education: O-level, A-level, degree; low education: refers to no education

* Not married: single, divorced, separated, widowed

¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

⁺ Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

Table 9.3 Odds ratios for GAD in women with a strong SOC who completed the HLEQ questionnaire in 1996-00 (women with a strong SOC sample size =7,192)

	Odds ratios and 95% CI				
Characteristic	**Unadjusted**	**Model A[1]**	**Model B[2]**	**Model C[3]**	**P-value for Model C**
Socio-demographics					
Age					
Per 10 years	0.66 (0.52, 0.83)	0.55 (0.41, 0.73)	0.64 (0.48, 0.87)	0.59 (0.44, 0.80)	0.0006
Education‡					
Low	0.48 (0.29, 0.78)	0.58 (0.35, 0.96)	0.63 (0.38, 1.05)	0.64 (0.38, 1.08)	0.0956
High	1.00	1.00	1.00	1.00	
Marital status					
Married	1.00	1.00	1.00	1.00	
Not married	1.42 (0.91, 2.22)	1.63 (1.02, 2.60)	1.30 (0.81, 2.11)	1.27 (0.78, 2.05)	0.3319
Social class¥					
Manual	0.72 (0.46, 1.12)	0.83 (0.52, 1.33)	0.85 (0.52, 1.36)	0.81 (0.50, 1.32)	0.3949
Non-manual	1.00	1.00	1.00	1.00	
Employed					
Yes	1.00	1.00	1.00	1.00	
No	0.94 (0.62, 1.41)	1.87 (1.14, 3.05)	1.73 (1.06, 2.80)	1.53 (0.93, 2.51)	0.0925
Townsend index					
Deprivation					
Yes (>0)	1.38 (0.83, 2.29)	1.42 (0.85, 2.38)	1.31 (0.78, 2.20)	1.28 (0.76, 2.16)	0.3574
No (<=0)	1.00	1.00	1.00	1.00	
Health status					
Life-time MDD					
Yes	10.39 (6.79, 15.89)		9.18 (5.96, 14.15)	8.37 (5.38, 13.01)	<0.0001
No	1.00		1.00	1.00	
Prevalent physical disease⁺					
Yes	2.18 (1.40, 3.41)			1.80 (1.14, 2.84)	0.0122
No	1.00			1.00	
Disability level					
High¶	2.07 (1.36, 3.16)			1.97 (1.24, 3.12)	0.0039
Low	1.00			1.00	

1. Adjusted for age, SES (education, marital status, social class, employment)
2. Adjusted for age, SES, lifetime MDD
3. Adjusted for age, SES, lifetime MDD, prevalent physical disease and disability

‡ High education: O-level, A-level, degree; low education: refers to no education

* Not married: single, divorced, separated, widowed

¥ Manual: skilled manual, semi-skilled, non-skilled; non-manual: professionals, managerial, skilled non-manual

⁺ Prevalent physical disease: respiratory disease (asthma, bronchitis), allergies (allergies, hay fever), stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the PCS value of 50.6

Analyses that adjusted for age, education, marital status, social class, and employment status showed that area deprivation was significantly associated with increased risk for GAD in women with a weak SOC (OR=1.96, 95% CI: 1.37, 2.80) (table 9.2), but area deprivation was not significantly associated with anxiety in those with strong SOC (OR=1.42, 95% CI: 0.85, 2.38) (table 9.3). In women with a weak SOC (table 9.2), further adjustment for lifetime MDD slightly attenuated the effect estimate, though the association between area deprivation and anxiety remained highly significant (OR=1.90, 95% CI: 1.31, 2.77). When prevalent physical disease and disability level were added to the final model, the effect estimate remained almost unchanged compared to the previous model; among women with poor coping skills, those living in deprived areas had a 92% higher likelihood of having anxiety than women living in less deprived areas (OR=1.92, 95% CI: 1.32, 2.79). For women with a strong SOC (table 9.3), area deprivation was associated with a small increased risk of having GAD in progressively adjusted models; however, none of the effect estimates reached statistical significance. In the fully-adjusted model, women with a strong SOC and living in deprivation had a 28% higher chance of having GAD compared to women living in less deprived areas, but this did not reach statistical significance (OR=1.28, 95% CI: 0.76, 2.16).

Secondary findings – covariates and GAD

When I examined covariates that were related to GAD among women with a weak SOC, the following emerged as significant: increasing age (OR=0.63, 95% CI: 0.50, 0.80), MDD (OR=5.00, 95% CI: 3.53, 7.06), and disability (OR=1.51, 95% CI: 1.05, 2.17). The same pattern emerged among women with a strong SOC, with the exception of prevalent physical disease. The latter variable was statistically significantly associated with anxiety in women with a strong SOC (OR=1.80, 95% CI: 1.14, 2.84), but not in those with a weak SOC (OR=1.22, 95% CI: 0.86, 1.73). What is interesting in this chapter, is that even though MDD is associated with deprivation in women with both weak and strong SOC (OR=5.00, 95% CI: 3.53, 7.06 and OR=8.37, 95% CI: 5.38, 13.01, respectively), the effect estimate for depression is lower in the latter group (women with weak SOC).

9.4 Discussion

In this large, population-based study, I found that area deprivation significantly increased the risk for GAD in women, but particularly in those with poor coping skills. Coping skills or SOC appeared to moderate the association between area deprivation and anxiety. Women living in deprivation and with poor coping or a weak SOC were at a particularly high risk for having anxiety after controlling for important confounders. Although women with a strong SOC showed a slight increased risk of anxiety if living in disadvantaged circumstances, the association between area deprivation and GAD was statistically non-significant in women who were able to cope well and the effect estimate was much smaller than that of the former group (women with poor coping). A statistically significant association between area deprivation and GAD persisted in women with a weak SOC after adjustment for age, marital status, education level, social class, employment, MDD, chronic physical diseases, and disability. In contrast, having a strong SOC seemed to be protective for women living in deprived areas. Having a strong SOC rendered the association between area deprivation and anxiety statistically non-significant.

Although the interaction between area deprivation and SOC was not statistically significant, the effect estimates do suggest that there are differences between women with low and high SOC. My study sheds light on the importance of SOC when it comes to mitigating the risks of anxiety. Future research should replicate my study with a larger number of anxiety cases, perhaps by measuring 'total' or 'any' anxiety rather than individual disorders, such as GAD.

Deprived areas are often associated with low social integration and poor social control. Emile Durkheim showed that low social integration can lead to a sense of meaninglessness among individuals, and this can give rise to poor mental health and suicide. [389] SOC is a way of viewing life as meaningful and comprehensible, and my study shows that SOC can moderate the association between area deprivation and GAD in women.

Secondary findings – covariates and GAD

In this study, I also show that younger age, MDD, and disability are associated with increased risk of anxiety in women with both low and high SOC. These results are in line with the literature. Younger people are generally at higher risk of having anxiety than older people. The latter group tends to have lower levels of psychopathology, because of three possible factors. First, ageing has been linked to greater emotional control and decreased responsiveness to stressors; therefore, older people might be less likely to respond with anxiety when encountering stress. [198] Second, older people are more likely to be retired and therefore protected from situations which could be anxiety-inducing, such as interactions during employment. [128] Third, early mortality associated with poor mental health might mean that there are fewer cases of GAD among the oldest individuals.

Having MDD is also linked with anxiety as both conditions are highly co-morbid. Therefore, it is unsurprising that women with depression were at high risk of having anxiety in my study.

Another factor which was linked to anxiety in my study was disability. People with disability are at risk for serious illness, have fewer opportunities in life, and poorer access to health services than people without disability. [379, 380] Therefore, it is plausible that these factors (e.g., reduced opportunities, poor physical health) can also increase the risk of poor mental health among those with a disability.

The finding that prevalent physical disease was associated with a statistically significantly increased risk of GAD in women with a strong SOC only was surprising; though, women with a weak SOC also showed a small increased risk of anxiety if they had poor physical health.
It could be that people with a strong SOC also have greater concern about their well-being and may be more likely to think about possible solutions or ways of improving their health if diagnosed with a physical disease. Thus, the latter group might be more likely to respond with anxiety if sick. The reverse scenario – anxiety increasing the risk of disease only in people with a strong SOC is unlikely and will thus not be discussed. A more likely explanation for these findings could be sample size. There were a lot more participants with strong SOC than

those with a weak SOC. Future studies should re-examine this question using a higher number of cases with a weak SOC.

Another interesting finding in this chapter is that the odds ratio for MDD was lower among women with a weak SOC compared to women with a strong SOC. A few explanations might provide insight into this. First, the sample size for those with a weak SOC was much smaller than the other group; if the sample size were increased for those with a weak SOC, I expect the associations with both MDD and GAD to become even stronger than they are. Second, the measure of MDD might be linked to greater recall error than that of GAD. In this research, participants were asked if they had "ever experienced an episode of depression" – this type of information might be much harder to remember than episodes of past-year GAD examined in the year immediately before the administration of the HLEQ. Third, participants in poorer health and likely with a weaker SOC might be even more likely to forget about past psychopathology than those with a strong SOC. Depression has been linked to memory problems [255]. I suspect that if these problems did not occur, the odds ratio for MDD among women with a weak SOC would be much greater than that reported.

Strengths and limitations of this study, and future research

This is the largest, population-based study of the association between area deprivation and GAD in women, and to determine whether coping resources or SOC moderates the association between area deprivation and anxiety. I had access to a large sample of over 10,000 women living in the community. I used a clinically relevant measure of anxiety, and GAD was defined according to the DSM-IV. Although GAD affects a substantial number of people, even more experience subthreshold cases of anxiety disorders. Subthreshold cases have also been associated with impairment and disability; therefore, future research should assess associations with subclinical anxiety.

I used detailed health and lifestyle questionnaires to extract information on sociodemographics and major chronic physical diseases, and controlled for these factors in my analyses. I used a validated and reliable measure of disability, which I adjusted for in my models. I had a large list of self-reported physician diagnoses that I used to establish medical histories for participants, though three issues might arise with this approach. First, the residual effect of diseases not captured by my study but that are associated with area deprivation and anxiety, may be present. Second, medical diagnoses were not verified by clinicians, leading to possible misclassification of medical history. Third, past illness may have been under-reported, leading to misclassification bias and attenuation of effect estimates. I may have overadjusted my models with the inclusion of disability, because this might be part of the expression of psychiatric illness. This may have reduced effect estimates. A detailed discussion of the associated biases can be found in chapter 7, which was the groundwork for this chapter. An additional point that I would like to raise is that any error in misclassifying people with respect to their exposure or outcome was non-differential and likely biased the effect estimates towards the null. Any measurement error for GAD was non-differential with respect to area deprivation and vice versa.

My objective was to assess the links between deprivation, SOC, and anxiety in women. Although it was out of scope for the present study, I was unable to examine the same objectives in men: there were very few men with a strong SOC living in deprivation and with GAD. Therefore, analyses in this sub-group would not have been robust. Future studies should undertake this assessment. It should also be mentioned that the internal consistency of the three-items SOC scale, as measured by Chronbach's alpha, was 0.35. [385] While the internal consistency of the shorter 3-item measure was low in this sample, this is likely to be partially due to the small number of scale items. Also, the original developers of the scale reported satisfactory short-term test-retest reliability and validity for the 3-item measure. [306, 385]

There were other limitations of this study, however that deserve mentioning. Although I had access to a number of covariates, I would have liked to control for other psychiatric comorbidities, such as other anxiety and personality disorders (frequently co-occurring with GAD, just like MDD). However, information on this was not available. I suspect if I would have adjusted for these additional variables, the main effect estimates would have diminished even more towards the null in the progressively adjusted models. Another point I would like to make in regards to the covariates is with respect to the categorization. It is possible that the use of smaller categories of variables (e.g., original form of social class rather than the dichotomous form I used) might have resulted in slightly less loss of information.

At baseline, people who consented to take part in EPIC-Norfolk agreed to fill out detailed health and lifestyle questionnaires over the duration of the study period; therefore, healthy volunteer effect may have biased my findings. Participants in EPIC-Norfolk tend to be somewhat healthier and more affluent than the general population, therefore, results from this study cannot be generalised to extremely deprived areas. If the most deprived areas would have been included, I would expect the association between area deprivation and anxiety to be even stronger in women with a weak SOC. Also, when comparing the demographic characteristics of responders versus non-responders (appendix 4), I found that participants were slightly younger (than 50 years) and slightly more women than men consented. Further detailed discussions of these limitations and generalizability issues can be found in chapters 5 and 7.

Also, although area deprivation was measured before GAD, this research should be considered cross-sectional. Cases of anxiety were prevalent, rather than incident cases. As such, it is possible that some people may have had anxiety at the time that the Census was undertaken. In cross-sectional research, it is difficult to determine the temporal ordering of variables: whether area deprivation indeed preceded GAD. Thus, reverse causality becomes a concern - instead of low socioeconomic circumstances increasing levels of anxiety, it may be that participants with poor mental health moved to more deprived neighbourhoods. Nevertheless, reverse causality seems unlikely as an explanation for my findings.

In addition, SOC was also measured at the same time point as GAD and “prevalent” cases of strong/weak SOC were assessed (people were asked about the presence of this construct at the time that EPIC-Norfolk was undertaken), making this research truly cross-sectional.

Despite these limitations, my study provides a valuable step forward and is the first to shed light on the importance of coping in people with GAD living in disadvantaged circumstances. Further longitudinal research is needed to confirm these findings.

Comparison with other studies

This is the largest, population-based study to consider the association between area deprivation and GAD in women, and to determine whether SOC moderates this association. Most of the literature on coping and SOC specifically is limited. Most studies have small sample sizes, and measure people's coping abilities in relation to feelings of stress, history of stressful life events, or exposure to stressful circumstances, such as, wars. There is a paucity of research examining the living context, such as, area deprivation, and no studies have assessed whether the link between area-level circumstances and anxiety disorders can be moderated by coping mechanisms. The literature on coping uses highly select samples; therefore, results cannot be generalised to the larger population. Also, incomplete adjustment of covariates makes it difficult to determine whether findings from these studies are not better explained by the residual effect of other factors that have not been accounted for, such as, lifestyle and personal socioeconomic circumstances. Across studies, there is large heterogeneity in the definitions used to define coping, with many focusing on factors, such as, hardiness, optimism, and negative emotions, rather than SOC. In sum, it is difficult to understand the links between the living context, coping abilities, and mental health from the literature; however, the studies that have been conducted are a good starting point.

A UK study of over 3000 people [390] showed that SOC was linked to self-rated health; however, the moderating effect of coping was not assessed. Research on people living in Negev communities in Israel showed that those exposed to trauma and severe stress-provoking situations, but who had a strong SOC, were least likely to develop stress. [86] In a study of French adults [391], SOC buffered the effect of adversity on psychological well-being. In another study of Holocaust survivors [83], SOC moderated the association between early childhood deprivation and posttraumatic stress in old age. Both of these latter studies, however, were small, failed to adjust for important confounders, such as sociodemographic factors and disability, and did not examine individual psychiatric disorders diagnosed according to valid and reliable criteria, such as, the DSM. In the study on child Holocaust survivors [83], exposure to trauma was measured in early life, while posttraumatic stress in old age. Since participants were required to report traumas experienced in childhood, this might have led to recall bias. My study expands on previous research and is the first to investigate the moderating effect of coping skills (SOC) on the risk of developing GAD in women living in deprived circumstances.

Mechanism of effect

Living in a deprived area can increase anxiety in women because of biological and social factors, as described in an earlier thesis chapter. The stress of living in deprivation can increase the risk for inflammation and HPA axis dysregulation, which can lead to GAD. [336, 337] This, combined with the multiple roles that women are increasingly taking on (income earner, child-bearer, and carer of elderly relatives), means that coping is particularly relevant for women living in disadvantaged circumstances. A strong SOC is linked to high quality of life, and good physical and mental health. [80, 81] My study shows that SOC can buffer the effect of area deprivation on risk of anxiety.

9.5 Conclusion

SOC is a coping resource which allows individuals to overcome stressful situations. Although results from this study represent an important starting point, further research on this topic is needed using a larger number of anxiety cases before clinical and public health recommendations can be made.

10 General Discussion

10.1 Introduction

Anxiety disorders are characterised by fear and hyperarousal, and represent some of the most common mental health problems today. [2, 5] If untreated, they can lead to disability, impairment, and risk of suicide. [11, 187, 261, 306] Despite these serious consequences, knowledge gaps regarding the risk factors and outcomes associated with these conditions remain. Before undertaking further research on this, however, it is important to determine whether anxiety represents a problem in the population. To do this, I conducted a review of reviews on the burden of anxiety disorders worldwide. I searched for studies conducted in clinical and population-based settings, and recruiting young and old samples with a range of physical health and psychiatric conditions. I found that anxiety affected approximately 4 out of every 100 people around the world [8], with women, young people, and those living in Western countries being particularly affected. Anxiety also affected those with chronic health conditions, such as cancer, diabetes, and CVD, and was present in vulnerable populations, such as those exposed to trauma from wars.

One of the most common anxiety disorders that emerged from this review was GAD; however, not much was known regarding this condition. Further research on the consequences of GAD was needed. If GAD could be linked to serious health outcomes, such as early death and health service use, then it would have public health importance and would need to be taken into consideration by clinicians and public health authorities. [17] Using the EPIC-Norfolk study, a population-based study of British people over the age of 40 living in Norwich and the surrounding towns and rural areas, I examined just that – whether GAD is associated with increased risk of premature mortality and non-psychiatric hospital admissions. My findings showed that people with an episode of anxiety in the past year were at a significantly increased risk for all-cause mortality and deaths from cancer. Other findings showed that people with more severe forms of GAD such as those whose anxiety was comorbid with depression had an increased risk for non-psychiatric hospital admissions. These findings highlight the potential impact that GAD has on our society and that it should be taken into consideration by other researchers, physicians, and other stakeholders.

Next, I wanted to determine the factors that could increase the risk for this condition, so that prevention and intervention efforts could be developed or further refined. One of the first factors I examined was area deprivation and its effects on mental health. To place findings into context, I used the WHO population health framework. [72] This framework shows that the context within which we live influences our socioeconomic position, which in turn makes us more or less susceptible to exposures, stressors, lifestyles or risk behaviours, and finally, health outcomes. The framework refers to individual-level socioeconomic status as a structural determinant, which is affected by the context. For instance, governance patterns as well as economic, public and social policies are capable of influencing the distribution of material and social resources across population sub-groups. Unequal distribution of resources amongst sub-groups contributes to differences in health across populations or health inequities. [72]

People of lower socioeconomic status experience lower levels of power and prestige, and are more likely to feel ashamed and excluded from society than those who are more affluent. [72] People of lower social standing are more likely to be exposed to health-damaging work and home environments and encounter stress in life; as a result of these environments and to cope with the stresses, they are also more likely to smoke, have poor diets, and drink alcohol in comparison with others. [72] All of these factors can lead to deleterious health outcomes, such as early mortality and health service use in disadvantaged groups.

The WHO framework posits that socioeconomic position can be measured at the individual, household, or neighbourhood (area level), and is usually represented by indicators of education, income, and occupation. If these indicators are not available, then proxies such as living standard (ex. non-home ownership and non-car ownership) can be used. [72] In the EPIC-Norfolk study, I had access to both individual social class and an area-based measure of deprivation composed of non-home ownership, non-car ownership, unemployment, and household overcrowding. Because a number of studies have already shown that individual-level socioeconomic status can negatively influence mental health and increase anxiety risk, I wanted to determine if living in a deprived area has an effect on mental health over and above personal circumstances. A wealth of research has indicated that the places in which we live can impact our health, independently of individual-level factors. In accordance with the WHO framework, I used proxies of SES indicators, such as non-home ownership and non-car ownership to examine the influence of area deprivation on anxiety levels.

I assessed the link between the area deprivation and GAD for men and women separately. This was important to do, because the WHO framework considers gender to be a structural determinant of health inequities. Women have historically been the target of discrimination and have had less access to education and employment opportunities in comparison with men. Because of the lower levels of power, prestige, and reduced control over resources, women have had less access to health-promoting goods and services, and this has resulted in poorer health outcomes in the latter. Men, on the other hand, have also been negatively influenced by gender stereotypes. [72] The WHO framework provides some examples – heavy drinking and violent behaviour patterns are found in some men who ascribe to masculine identities. [72] In my analyses, I took gender into account and conducted analyses for women and men separately. This was done for both the chapters on area deprivation in relation to GAD, and area deprivation in relation to depression. Results showed that living in disadvantage increased the risk of GAD in women, but not in men. Women living in an area of lower socioeconomic circumstances had a 63% higher chance of having GAD than women living in more affluent areas. When the index of deprivation that was used to measure area-level socioeconomic circumstances was disaggregated, none of its constituent components (non-home ownership, non-car ownership, unemployment, overcrowding) were strongly related to GAD; it appears that it is the overall effect of living in a deprived area that is harmful for women's mental health. The association with deprivation was not statistically significant in men. In relation to the analysis on depression, I showed that living in disadvantage was associated with a significantly increased risk of MDD in men, while this was not observed in women. When the index was disaggregated into its constituent components, unemployment was significantly related to increased risk of having MDD in men living in disadvantage.

Finally, I took the analysis on the residential environment and anxiety in women further and examined coping circumstances. According to the WHO framework, people living in disadvantage face a significantly higher number of stressors and encounter circumstances that are more difficult to cope with than people living in more affluent areas. [72] I wanted to determine if women living in disadvantage - in spite of their detrimental situation - could maintain good mental health through coping mechanisms. To do this, I turned to research on SOC and Antonovsky's salutogenesis theory [392]. Results from my research showed that women with a strong SOC did not have anxiety even though they were living in deprivation, while women with a weak SOC were at a significantly increased risk of having anxiety.

10.2 Strengths and limitations

This thesis has several strengths, and also limitations. First, the overall strengths and limitations of the review of reviews are presented, followed by those pertaining to the research using EPIC-Norfolk.

The review of reviews was based on extensive searching of databases for primary studies on the prevalence of anxiety. Despite this, there was high heterogeneity in burden estimates making comparability of findings within and across reviews difficult. It is also possible that some reviews may have been missed. Also, most studies were conducted in predominantly Western settings, limiting generalisability to the rest of the world.

The EPIC-Norfolk study has several strengths. It uses a large population-based sample, a structured self-assessment approach to measuring psychiatric disorders based on the DSM-IV, and allows adjustment for several important covariates, such as social class, disability, MDD, and medical history. Despite these strengths, the study also has several limitations. First, although I had access to a large list of self-reported physician diagnoses which I used to construct medical histories, it is possible that some diseases associated with GAD may have been underreported. This might have introduced residual confounding in the analyses and attenuated effect estimates towards the null. Second, to derive the measure of MDD, a structured postal questionnaire was used. Although psychiatric information was based on a self-assessment approach rather than a clinical interview, previous research showed that the prevalence of MDD obtained using EPIC-Norfolk methods is similar to that obtained using interviewer-based assessment methods in UK studies. [177] Third, participants were required to complete detailed health and lifestyle questionnaires and attend regular health checks in order to take part in EPIC-Norfolk; as such, healthy volunteer effect might have biased the sample towards healthy and motivated participants. Indeed, findings show that the EPIC-Norfolk sample has fewer current smokers compared to the general population of England. The study sample is representative of the general population with respect to anthropometric measures, blood pressure and serum lipid levels. [166] Further discussion on generalizability is found in the individual thesis chapters.

Fourth, EPIC-Norfolk participants were aged 41 years and older at recruitment, were mostly of non-manual social class and came from predominantly rural areas. [166] As such, results might not be generalisable to very young people such as children and teenagers, those of manual social class, and people living in urban cities. Fifth, EPIC Norfolk may be population derived, but it is not population representative (except with respect to anthropometric measures), because of the low response rate and differential participation. People who took part in this study were slightly younger (than 50 years) and slightly more women participated compared to non-responders. There may also have been differential response in different social groupings. Nevertheless, I do not expect the associations in non-responders to be in a completely different direction to those found in responders.

There are other strengths and limitations related to this research, however which deserve mentioning. The following sections present the strengths and limitations that are specific to each of the EPIC-Norfolk analyses within the thesis.

10.2.1 Anxiety and mortality

Strengths related to the mortality study include the use of data from large, administrative health databases maintained by the UK ONS. Participants were also followed for a long time, allowing enough cases to be accrued for measures pertaining to mortality from all-causes and cancer specifically.

Despite these strengths, some of the limitations of this research include the small number of outcome cases for other endpoints, such as mortality from respiratory disease, CVD, and other causes for those with GAD.

10.2.2 Anxiety and health service use

One of the strengths of the health services study is the long follow-up period, which allows for the accrual of enough outcome events. A number of previous studies on health services and mental health used short follow-up periods, which failed to capture potentially chronic effects of psychopathology. Second, this study captured information on non-psychiatric hospitalisation using large, national administrative health databases maintained by the East Norfolk Primary Health Care Trust. [186] Using administrative databases avoids the self-reporting bias present in previous research on health service use. The databases used in this study captured inpatient episodes and outpatient visits for participants treated anywhere in England and Wales, not just in Norfolk. Nevertheless, most of the hospitalisations were linked back to the Norfolk and Norwich University Hospitals NHS Foundation Trust. [186] A limitation is that a negligible proportion of participants may have obtained care outside of the UK [196] or at private facilities.

Another weakness is that this study did not link hospitalisation databases to primary care service use databases; thus, I could not provide a more complete picture of the health care obtained by participants with anxiety. GAD is one of the most common mental health problems in primary care [28, 390], and including information on primary care service use would have added further insight into the health service use patterns among those with this condition.

10.2.3 Area deprivation in relation to GAD and MDD

The studies on deprivation and GAD/MDD used the Townsend index [185] to measure area-level socioeconomic disadvantage. The Townsend index is a commonly-used, theoretically sound index which captures key aspects of deprivation, making this instrument an attractive option for measuring ecologic-level circumstances. Nevertheless, some of its limitations include the fact that it is Census-based and areas are defined according to administrative boundaries. The Census might not capture other important aspects of deprivation, such as lack of green space or cycle lanes, and dilapidated housing. Also, using administrative boundaries, which are defined for practical purposes rather than research [391], might not delineate areas which participants consider to be their neighbourhoods.

Other weaknesses include the lack of generalisability of study findings to people living in extreme disadvantage and the cross-sectional nature of the research. Although psychopathology was measured in 1996-2000 and area deprivation in 1991, it is possible that some participants meeting criteria for past-year GAD or current MDD in 1996-2000 might have had episodes of psychopathology in 1991 or earlier. A cross-sectional design makes it difficult to determine whether living in a deprived area increases the risk of anxiety and depression, or whether poor mental health leads to downward social mobility and forces people into deprivation.

10.2.4 Coping as a moderator of the association between area deprivation and GAD

As in the previous chapter, one of the strengths of this study is the use of a common, theoretically-sound measure of area deprivation, the Townsend index. To explore coping mechanisms, a robust measure of SOC with satisfactory short-term test-retest reliability and validity [82] was used. Previous research and several papers based upon the EPIC-Norfolk cohort used this three-item measure of SOC [182, 385, 388].

One of the limitations of this research is its cross-sectional nature. As such, it was not possible to determine temporality effects: whether area deprivation indeed increases the risk of anxiety. This is because prevalent cases of GAD were measured, and as a result, some participants may have had anxiety at the time that area deprivation was assessed. This was discussed in chapters 7 and 9. Essentially, cross-sectional research takes a snapshot of the population at one point in time and measures the exposure and outcome in the same instance. Therefore, it is difficult to determine which came first: the exposure or the outcome. To overcome this limitation, longitudinal research would be needed which would examine area deprivation in relation to *incident* cases of GAD.

Another limitation is that there were very few men with a strong SOC and living in deprivation; therefore, it was not possible to examine the moderating effect of SOC in relation to area deprivation and GAD in this gender group.

10.3 Results in the context of evidence

To make sense of the findings obtained in this thesis, it is important to present results in the context of evidence, as follows.

10.3.1 The burden of anxiety around the world

Anxiety is one of the most common mental health complaints today. Although many reviews have been undertaken on the burden or prevalence of this condition in populations around the world, it is difficult to compare findings because of differences in sampling, case definitions of anxiety disorders, follow-up periods, and instruments used to measure psychiatric symptoms or disorders. Furthermore, the lack of measurement equivalence between cultures makes it difficult to determine whether the anxiety measured in one country is the same as that experienced by a different population. However, the anxiety assessed within different samples of the same culture may also vary depending on the case definitions and tools used. In addition to the heterogeneity arising from the use of different psychopathology measuring instruments, many studies lump anxiety symptoms or disorders together into one category and include an assessment of 'any' or 'total' anxiety, which might not be clinically meaningful, while other studies examine individual anxiety disorders. Inconsistency in measuring instruments and anxiety case definitions are some of the issues that hamper comparability of the burden of this mental health problem across studies.

The systematic review of reviews that I conducted showed that, when all evidence is considered, anxiety is indeed prevalent in populations around the world. The global synthesis of the literature also indicated that there are gaps in knowledge when it comes to the burden of anxiety in vulnerable populations, such as Indigenous people around the world (e.g., Aboriginal people in Canada), sex workers, and injection drug users.

10.3.2 The link between anxiety and early death

A recent systematic review of clinical and community-based studies showed that anxiety was linked to all-cause mortality. [45] When community studies were examined separately, the association disappeared. These studies, however were limited. Some used old diagnostic criteria with low reliability, such as DSM-II or DSM-III, small sample sizes which lack the power to detect significant associations, symptom checklists or scales to assess anxiety symptoms, and failed to assess individual disorders.

The most recent research on anxiety and mortality showed that people with GAD were at a significantly increased risk of all-cause mortality after adjusting for depression. [55] When total anxiety disorders were examined as one category, they failed to be associated with increased risk of cancer deaths. The separate effect of GAD on cancer mortality was not examined, and the exposure in this study was treatment for anxiety. [55] Using administrative databases to ascertain treatment for anxiety is problematic, because of issues with coding accuracy and recording bias, as detailed in the introduction.

My study used a large, population-based, cohort of over 20,000 people. Anxiety was measured using DSM-IV criteria, and I adjusted for a range of important confounders, including depression, medical history, and disability. Results showed that anxiety increased the risk of all-cause mortality and deaths from cancer. There are several reasons why anxiety could lead to premature mortality. People with anxiety might be more likely to have underdiagnosed and undertreated medical comorbidities compared to people without psychiatric problems [2, 55]. Anxiety can lead to risk behaviours, such as unhealthy diets which can increase the risk for adverse outcomes. Having a psychiatric disorder can also make compliance with treatment for psychiatric or physical health conditions more difficult [52] and it can lead to reduced treatment-seeking [393]. Anxiety has also been linked to dysregulation of the HPA axis and the release of pro-inflammatory cytokines, which can also lead to poor health and early death. [2]

10.3.3 Health service use among those with anxiety

The evidence base on health service use and anxiety is small and limited, and most of the recent studies have focussed on PTSD in war veterans. [61, 394] Most studies are based on clinical populations, cross-sectional designs, small samples, short follow-up periods (usually one year), do not adequately control for confounders, and use self-report to assess frequency of stay in the clinical setting. Samples recruited from clinical settings tend to have a higher symptom severity, potentially biasing the association with health service use, and the use of cross-sectional designs makes it difficult to determine whether anxiety was present before the patient was admitted to the hospital. [62, 63] Studies that collect health service use data through self-report are subject to recall bias, and the use of short follow-up periods does not allow sufficient time for the accrual of enough outcome events (e.g., admissions).

GAD is one of the most common anxiety disorders in the general population and the primary care setting [2], and has been associated with high economic and human burden. However, it has been neglected in the health services literature, with the exception of studies that have shown GAD to contribute to higher use of primary care services in primary care samples. [28, 62, 63, 278] Whether GAD leads to non-psychiatric hospital admissions is unknown. The study I carried out is a large, population-based, longitudinal study which overcomes many of the limitations of previous research. It uses large, administrative health databases to ascertain non-psychiatric hospital admissions and follows participants for a long time (9 years) to determine whether anxiety is associated with an increased risk of health service use. It adjusts for a number of important confounders, including socioeconomic circumstances and medical history.

Results showed that people with a more severe course of anxiety, such as that characterised by comorbidity with MDD have a higher risk of being admitted to hospital. There are three possible reasons as to why people with a more severe course anxiety are more likely to use health services than others. Psychiatric comorbidity has generally been associated with poor prognosis; anxiety which increases the risk for depression could be a marker for poor underlying physical health – however, further longitudinal research is needed to disentangle these relationships. [395] Anxiety has been linked to a host of physical health problems, including cancer, CVD and diabetes, as was shown in my systematic review; therefore, it seems plausible that psychiatric morbidity would lead to even poorer health. GAD-MDD comorbidity might also be linked to undiagnosed physical health problems or sub-clinical disease which might prompt affected individuals to seek health care. There could be other reasons, though, for the higher health service use among those with anxiety and depression. Heightened sensitivity to bodily changes [2, 395] might lead to the perception that normal bodily sensations need clinical attention. Also, the stigma associated with seeking psychological help might lead some with poor mental health to interpret their symptoms somatically and seek help from their general practitioner. [2, 395] The physician might then begin searching for a physical cause through expensive medical work-ups and referrals to hospitals, thus contributing to increased health care use.

10.3.4 Area deprivation as a risk factor for anxiety

Previous studies have shown that living in disadvantage or in areas of high inequality increases the risk of early death [315], depression [64], and common mental disorders [68], with some of this research exploring gender effects. Previous literature, however, has not examined the association between the residential environment and GAD from a gendered perspective; therefore, it is difficult to place findings into context.

For the first time, I showed that women living in a deprived area were at a significantly increased risk of having anxiety, while this association was not observed in men. This could be because the genders are differentially affected by the living context and are exposed to stressors in their environment at varying frequency and intensity. [65, 333] Women are more likely to spend time in their community because of part-time work compared to men [334]; women are also more likely to be woven into the social fabric of their neighbourhoods [69, 70, 335]. Thus, if they are part of disadvantaged contexts, women might be more likely to experience the associated stresses and strains and develop poor mental health.

10.3.5 Area deprivation as a risk factor for depression

Compared to anxiety, there is much more research on depression making it easier to place findings into context.

Three systematic reviews [76-78] found associations between neighbourhood characteristics and depression. For example, in one review [76] of adolescent and adult populations living in high-income countries, individuals living in areas of poor socioeconomic conditions had higher odds of psychopathology than those living in more affluent areas (OR=1.14, 95% CI: 1.01, 1.28) in about half the studies. In all reviews [76-78], there was high heterogeneity between primary studies, making comparison of findings difficult. There were differences in follow-up time, definitions of neighbourhood socioeconomic conditions, types of boundaries used to define neighbourhoods, control of confounding, and study design. Some studies used short follow-up periods, while others followed participants for at least 5 years; some measured socioeconomic conditions using indices constructed of disparate components while others used single items such as neighbourhood unemployment history; some authors defined neighbourhoods according to administrative or statistical boundaries such as census units while others used residence-centred buffers and self-reported subjective delimitations of neighbourhoods. Some studies used self-reported neighbourhood variables, and this is a limitation, because data on self-reported features might be more closely tied to depression risk than objective measures. There were also differences in study design, with cross-sectional studies being potentially affected by reverse causality. Reverse causality may occur when individuals with poor mental health may select into more deprived neighbourhoods.

Although a wealth of literature has established a link between neighbourhood characteristics and depression, there is much less research on this association from a gendered perspective. A recent study [384] of 1,129 White and Black individuals living in the US showed that exposure to individual-level stressful life events increased depression risk in men, but not in women. Another study [362] of 1,057 opposite-sex dizygotic twin pairs from a population-based US register showed that history of stressful life events, such as financial problems, unemployment and legal problems was linked to depression in men, while problems with interpersonal relationships and intimacy were linked to depression in women. For the first time, I show that living in a deprived area increases the risk of having depression in men, but not women over and above individual-level social class, other demographics factors, and medical history. In my study, men living in areas of high unemployment had a particularly high chance of having psychopathology. In line with the twin pairs study [362], men seem to be more affected by failure at key instrument tasks that focus on occupational and financial success. Living in an area of high unemployment can promote emotional distress and anticipatory stress about losing one's job in the latter (particularly if men are seen as head of household). [369] Women, on the other hand, are more likely to develop anxiety if living in disadvantage. Although the reasons for the gender differences are complex and need further research, this study provides compelling evidence that men and women might be differentially affected by the living context.

10.3.6 Coping as a moderator of the association between area deprivation and anxiety in women

Several studies have been undertaken on coping mechanisms in relation to stress and fewer have focused on mental disorders. Many of the studies used disparate case definitions and referred to coping factors, such as hardiness, optimism, and resilience; the heterogeneity made it difficult to synthesise the literature.

The evidence base on SOC in relation to mental health is limited, and research on this construct with respect to anxiety and the residential environment is scarcer. In fact, no studies have been undertaken on the moderating effect of SOC in relation to area deprivation and risk of having GAD. In my study, I showed that SOC can buffer the harmful effect of living in deprivation on women's mental health. Women living in disadvantage who perceived their environment to be controllable, comprehensible, and meaningful were least likely to have GAD. This is because SOC is a coping resource that allows people to overcome stressful situations [85, 86, 392], such as those encountered when living in deprivation, and maintain good mental health.

Further information on the meaning and implications of findings is provided in the next section, as well as a discussion of future research. This is presented for each of the chapters.

10.4 Meaning and implications of findings, and future research

10.4.1 Systematic review of reviews

The meaning and implications of the review of reviews is that anxiety is a prevalent condition in countries around the world; therefore, it should be taken into consideration by clinicians, researchers, and policy-makers. Anxiety can affect people at any age, of any gender and ethnicity, and is linked to detrimental health outcomes. Further efforts to identify those at risk for anxiety should be made and appropriate treatment provided.

Recommendations for future research made by review authors included the use of longitudinal designs to address temporality issues; population-based research that is less susceptible to the help-seeking/self-selection bias often present in clinical studies; and the use of valid and reliable instruments and consistent approaches to examine anxiety levels pre- and post-disease. The measure of 'total' or 'any anxiety' is not clinically meaningful and is discouraged in favour of the assessment of individual disorders. Consensus on definitions used to define study samples (e.g., sexual orientation) and diagnostic standardization with respect to the measurement of psychiatric disorders were also emphasized, as well as research into the risk factors, illness trajectory, hereditary and biological markers of anxiety, and the appropriateness of anxiety screening measures in the context of physical diseases and cultures around the world (who may express distress differently). Research questions should be structured around theories. Recommendations were made for the inclusion of appropriate control subjects in studies to determine whether prevalence differs between exposed and comparison groups. Finally, further treatment or intervention studies are needed to alleviate anxiety.

Clinical recommendations included the administration of targeted anxiety screening and, if necessary, treatment. For example, suggestions were made for the screening of substance users at treatment entry or patients with non-cardiac chest pain presenting to acute care. It was also shown that certain anxiety disorders were more common in certain groups, such as OCD in schizophrenia, panic disorder and GAD in CVD, and specific phobia in diabetes. Additional research on individual anxiety disorders is needed to confirm these findings, but once this is underway, further impetus will be provided for the targeted screening of high-risk groups in relation to individual anxiety disorders.

10.4.2 Anxiety and mortality

GAD is a debilitating and impairing condition that has been linked to risk of suicide. [11, 187, 261, 306] The finding that GAD is associated with all-cause and cancer mortality is highly important and can have policy and clinical implications. GAD, hypothesized to be linked to inflammation and other harmful biological processes, could be a warning signal for future poor health and general practitioners should be vigilant for this. It is important to note that subthreshold GAD is much more common in the general population and has been associated with substantial disability and impairment. Given the strong association I found with threshold cases of GAD, other studies should repeat this study using subthreshold GAD which is much more common in the general population. In light of my findings with respect to mortality, it may be that anxiety represents more than just worry-related symptoms that need to be treated with psychotropic medications and psychotherapy. GAD could be a warning signal for something more serious that might occur down the line. Additional studies are needed to determine why anxiety is linked to cancer processes specifically.

10.4.3 Anxiety and health services

Population-based research on anxiety is lacking, and thus far, no studies have assessed the association between GAD and non-psychiatric hospitalisation. Clinicians should consider that it may not be the diagnosis of the individual disorder at one point in time (ex. past-year GAD) that is predictive of deleterious health outcomes; rather, different forms of the disorder may be more important. GAD has a waxing and waning course throughout a patient’s life, and many of those affected experience relapse after psychiatric treatment or develop psychiatric comorbidities.

These findings from EPIC-Norfolk are important for clinicians and policy-makers. Large numbers of people are affected by anxiety-depression comorbidity. [2] As such, clinicians should consider more widespread screening for mental health problems and if appropriate, the examination of any underlying health conditions that may require treatment in order to prevent future hospital admissions. Policy-makers should also consider rolling out more widespread anxiety and depression prevention and screening programmes.

Future research, however needs to examine the reasons for the increased non-psychiatric hospital service use in those with GAD-MDD comorbidity (this can provide additional insight into clinical recommendations). To provide a better understanding of the links between mental and physical health, the bidirectional links between anxiety and physical health problems should also be examined. Finally, future research should merge a population-based cohort with primary and secondary care administrative health databases to provide a more complete picture of the burden of different forms of anxiety on the health care system.

10.4.4 Area deprivation and GAD

The consequences of living in deprivation are far-reaching and can affect future generations. Repeated exposure to socioeconomic disadvantage in childhood is a consistent predictor of poor mental health in adolescence and young adulthood, particularly for young girls. [396] Since anxiety disorders tend to emerge in early adolescence, repeated exposure to socioeconomic disadvantage in childhood can increase the risk for more severe, early-onset forms of the disorder. Early-onset forms are the most difficult to treat and have a poor prognosis. [2] My study is the largest to date to examine the link between area deprivation and GAD.

The absolute numbers of people living in deprived conditions are large worldwide. This, combined with a growing mental health burden means that the findings obtained in this study remain highly relevant. The WHO [397] has emphasised the need to reduce social and health inequalities. My findings provide a strong evidence base to this call, showing that “perhaps the most important risks to health are beyond people’s immediate control” [398] and that the environment needs to be taken into account when developing mental health policy. Gender is clearly an important factor when it comes to assessing the impacts of the environment, and promoting good mental health.

Future research should consider assessing the risk of GAD in countries with high social and material inequalities, such as the United States, where the rates of anxiety are also some of the highest in the world. [2] Although the 12-month prevalence of GAD in the US is estimated to be 2.2% [399], substantially more people are affected by subthreshold disorder. [2] It would be especially informative to repeat this study in less developed parts of the world, where poverty is strongly linked to the development of mental disorders, and women’s unequal status and social roles in society represent important additional issues. [400] Findings from such research can be used to inform mental health policy, it can be used to inform clinical practice about the population sub-groups that are most affected by anxiety, and it can be used to inform the targeted investment of mental health resources to those areas needing them most.

10.4.5 Area deprivation and depression

Many people across the globe live in deprivation and experience poor mental health. There is a need to reduce social and health inequalities and my findings provide support for this. Policy-makers need to consider the places which people inhabit and greater investment towards employment opportunities in deprived communities need to be made. Findings from my thesis show that men living in disadvantaged contexts are particularly prone to depression. This suggests that financial investments made to local areas may not benefit population sub-groups equally, which is important at a time of scarce economic- and health-related resources. Regarding clinical implications, health professionals should be aware that men living in deprived areas may be at higher risk of having depression.

Future research should assess the risk of depression not only in countries, such as the US or UK where there is higher gender equality, but also in parts of the world where social roles and gendered norms for men and women have shown much less change over time. Countries with higher gender equality also show some of the highest rates of depression and other mental disorders in the world. In Europe, the discrepancy in depression rates between men and women in highly-developed countries is greater than in less-developed countries where there is also greater gender inequality. [401] In Eastern European countries, levels of depression are similar between men and women [401], while in Western Europe, women are twice as affected as men. [201] More studies are needed to explore the influence of area deprivation on the mental health of men and women separately, and to do this in different contexts (ex. rural, urban) and countries around the world. Further, the reasons behind gender differences need to be better elucidated.

Another direction for future research is the assessment of comorbid anxiety and depression. GAD and MDD frequently co-occur and may represent a more severe sub-type than each disorder on its own. [402] As such, studies should examine the link between psychiatric comorbidity and area deprivation from a gendered perspective to further inform policy and clinical practice. It would be especially informative to determine whether secondary anxiety or depression is more likely to develop in one of the genders when exposed to adverse circumstances, however, longitudinal research is needed to answer such a question.

10.4.6 Coping as a moderator of the association between area deprivation and GAD

For the first time, I show that SOC moderates the association between area deprivation and anxiety in women. Generally speaking, my results show that people who believe they are in control of their lives, who believe that life has purpose and meaning, and who believe that challenges are worthy of effort have better mental health than those without these traits.

Future research should replicate my analysis using larger samples with larger numbers of anxiety cases and determine the specific components of SOC that attenuate the effect of deprivation on mental health. Interventions can then be developed to target components of

SOC to increase people's coping resources. Treatment for GAD exists, with psychotherapy and pharmacotherapy being commonly prescribed. However, success rates are fairly low, patients relapse, and some fail to experience any symptom improvement. Costs to the health care system related to anxiety are substantial. Therefore, targeting people's coping resources could represent another option for people with anxiety, including those who do not experience symptom improvement following commonly-prescribed therapies. Targeting SOC could also represent a better option for people who have faced extreme circumstances and adversity, and who may have difficultly dealing with the traumas directly, as during psychotherapy. Mental health policy should also consider improving living environments to decrease the burden of anxiety in women.

11 Conclusion

This thesis explored anxiety's effects on society and the factors that can increase its risk so that prevention and intervention efforts can be targeted. The systematic review of reviews showed that anxiety disorders represent a burden in countries around the world and affect people with a wide range of health problems; however, the comparison of findings between studies is hampered by methodological heterogeneity across studies.

One of the most common mental health problems today is GAD. As such, I decided to focus on it and used the EPIC-Norfolk study, a large, population-based study to research it. I found that GAD is 1) linked to early death from all-causes and cancer over 15 years of follow-up. However, despite potentially poorer health, people with GAD were not high consumers of hospital care resources. GAD was not associated with non-psychiatric hospital admissions over 9 years; only people who had comorbidity with MDD were more likely to make contact with hospitals. I believe further research on this is needed to confirm the findings, and especially using a more complete ascertainment of health service use through linkage with primary care databases.

As anxiety is clearly associated with detrimental health outcomes, such as mortality, it was important to examine its risk factors so that prevention efforts can be directed. I turned to the residential environment as a possible determinant of health and focused on area deprivation. My findings showed that women living in deprived areas had a 63% higher chance of having GAD than women living in more affluent regions, while this result was not observed in men. Men living in deprivation, particularly in areas with high unemployment rates, seemed to be more prone to having depression. This might tie in with expectations regarding gender roles and differential ways of responding to adversity in the environment by women and men. The former have traditionally had the responsibility of caring for the young and ensuring the survival of future generations [372]; if women are not able to make ends meet on a day-to-day basis, they can be at risk for having anxiety. Men, on the other hand, have traditionally been head of household and expected to provide for the family [362], and if they are not able to fulfill these roles, they can be prone to serious sequelae, such as depression. Additional longitudinal research on these topics is needed. To take these findings further, it would be interesting to determine whether anxiety or depression among those living in deprivation are associated with increased risk of mortality and health service use- and to do this for women and men separately. This would show the impact of having GAD in one of the genders, if exposed to adversity.

Finally, in my research, I wanted to know whether there are ways of mitigating the risks of anxiety, and turned to Antonovsky's research on SOC [84] to do this. Earlier studies showed that some people exposed to adversity were able to harness their inner resources and maintain good health, while others went on a downward spiral and developed mental disorders. Using the EPIC-Norfolk study, I showed that women who have these inner resources-which is a strong SOC- did not have anxiety even if they were living in deprivation, while women without these resources had GAD. These resources represented by a strong SOC meant having a sense of control, believing that challenges in life are worthy of pursuit, and believing that life has purpose and meaning. Although this research was limited by its cross-sectional nature, I believe it represents an important starting point in such research.

No prior studies have answered the questions I posed in this thesis. Despite the shortcoming associated with the EPIC-Norfolk study, it is a useful resource for examining the links between GAD and several factors in depth.

There is increased the recognition of the importance of public mental health worldwide and there are signs that research funders are following suit with targeted calls. This makes the study of the environment conducive to furthering our understanding of the causes and risks of anxiety to mitigate its impact on society and people's lives.

Appendices

Appendix 1: **Checklist of items to include when reporting a systematic review or meta-analysis.**

According to PRISMA, “a systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies.” [94]

Section/Topic	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16])
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Appendix 2: Search terms used for systematic review of reviews

Embase

1. exp Meta Analysis/
2. ((meta adj analy$) or metaanalys$).tw.
3. (systematic adj (review$1 or overview$1)).tw.
4. or/1-3
5. cancerlit.ab.
6. cochrane.ab.
7. embase.ab.
8. (psychlit or psyclit).ab.
9. (psychinfo or psycinfo).ab.
10. (cinahl or cinhal).ab.
11. science citation index.ab.
12. bids.ab.
13. or/5-12
14. reference lists.ab.
15. bibliograph$.ab.
16. hand-search$.ab.
17. manual search$.ab.
18. relevant journals.ab.
19. or/14-18
20. data extraction.ab.
21. selection criteria.ab.
22. 20 or 21
23. review.pt.
24. 22 and 23
25. letter.pt.
26. editorial.pt.
27. animal/
28. human/
29. 27 not (27 and 28)
30. or/25-26,29
31. 4 or 13 or 19 or 24
32. 31 not 30
33. anxiety/ or generalised anxiety disorder/ or anxiety disorder/
34. prevalence.mp.
35. 32 and 33 and 34
36. prevalen*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
37. 32 and 33 and 36

Medline

1. Meta-Analysis as Topic/
2. meta analy$.tw.
3. metaanaly$.tw.
4. Meta-Analysis/
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature as Topic/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list$.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. relevant journals.ab.
21. manual search$.ab.
22. or/17-21
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. Review/
27. 25 and 26
28. Comment/
29. Letter/
30. Editorial/
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34
37. exp Anxiety/ or exp Anxiety Disorders/
38. 36 and 37
39. prevalence.mp.
40. 36 and 37 and 39
41. 37 and 39
42. 36 and 41
43. prevalen*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
44. 36 and 37 and 43

PsycInfo

1. exp Meta Analysis/
2. meta analy$.tw.
3. metaanaly$.tw.
4. (systematic adj –n - (review$1 or overview$1)).tw.
5. exp "Literature Review"/
6. or/1-5
7. cochrane.ab.
8. embase.ab.
9. (psychlit or psyclit).ab.
10. (cinahl or cinhal).ab.
11. science citation index.ab.
12. bids.ab.
13. cancerlit.ab.
14. reference list$.ab.
15. bibliograph$.ab.
16. hand-search$.ab.
17. relevant journals.ab.
18. manual search$.ab.
19. or/14-18
20. selection criteria.ab.
21. data extraction.ab.
22. 20 or 21
23. exp "Literature Review"/
24. 22 and 23
25. comment/
26. letter/
27. editorial/
28. human.po.
29. animal.po.
30. (animal not (human and animal)).po.
31. 25 or 26 or 27 or 30
32. prevalence.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
33. exp Anxiety Disorders/ or exp Anxiety/
34. 6 or 19 or 24
35. 32 and 33 and 34
36. 35 not 31

Appendix 3: Table 1 - Systematic reviews describing the prevalence of anxiety disorders

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Global distribution of anxiety disorders				
Somers 2006 *Search:* 2004 *# incl. studies* 39 *Meta-analysis:* yes	- Adults - Range: 500-20,000	- Community surveys using probability sampling	- Diagnostic criteria, standardized instruments or clinician diagnosis	Pooled one-year and lifetime prevalence of: - Total anxiety disorders: 10.6% (7.5, 14.3), 16.6% (12.7, 21.1) - PD: 1.0% (0.6, 1.5), 1.2% (0.7, 1.9) - Agoraphobia: 1.6% (1.0, 2.3), 3.1% (2.1, 4.4) - SAD: 4.5% (3.0, 6.4), 2.5% (1.4, 4.0) - SP: 3.0% (1.0, 5.8) and 4.9% (3.4, 6.8) - OCD: 0.5% (0.3, 0.9), 1.3% (0.9, 1.8) - GAD: 2.6% (1.4, 4.2), 6.2% (4.0, 9.2) - Anxiety higher in women - SAD rates decline with age - Switzerland, US: 23-28.7; Korea: 9.2
Baxter 2013 *Search:* 2009 *# incl. studies* 87 *Meta-analysis:* yes	- 44 countries across the globe - Median: 2419	- Community samples	- Interview schedules, semi-structured instruments, diagnostic instruments that mapped to DSM or ICD	- Global prevalence: 7.3% (4.8-10.9) - 5.3% (3.5, 8.1) in African & 10.4% (7.0, 15.5) in Euro/Anglo cultures - Women 2x men; younger people more affected - Adults 55+ 20% less anxiety than 35-55 - 20-50% lower risk in cultures compared to Euro/Anglo
Mirza 2004 *Search:* March 2002 *# incl. studies:* 20 *Meta-analysis:* no	- Adults ages 18-65 years from community and clinical settings - Range: 113-2620	- Population-based, community, primary care samples; patients presenting to traditional or faith healers; psychiatric outpatients or inpatients - Clinical and community settings in Pakistan	- Psychiatric diagnoses, diagnoses made by trained workers using validated instruments	- Anxiety prevalence: 1.76%-25% - Middle-aged more affected
Vehling 2012 *Search: not rep.* *# incl. studies* 89 *Meta-analysis:* yes	- Adults 38 -73 years - Sample size not rep.	- Mostly US studies	- Structured clinical interviews	- 4-week prev. of anxiety disorders: 10.2% (6.9, 14.8) [International & German]; 13.5% (7.1, 24.3) [German only] - Germans with breast cancer: anxiety 28-33%; SP 5.2% (3.3, 8.2) & GAD 3.7% (2.3, 6.0) common
Baxter 2014 *Search:* 2009 *# incl. studies* 91 *Meta-analysis:* yes	- DSM/ICD community studies on people, all ages; GHQ for studies on secular trends - Range: 116-78,290	- Community-based studies	- Surveys, diagnostic criteria	- Age-standardized global point prev.: 3.8% (3.6-4.1%) in 1990; 4.0% (3.7-4.2%) in 2005 and 2010 - Anxiety women:men ratio of 1.9:1 - Sharp rise in adolescents; highest prev. 15-35 years - Prev. lowest in East Asia [2.8% (2.2-3.4%)] and highest in North America & North Africa/Middle East [7.7%, (6.8-8.8%) vs.7.7% (6.0-10%)]

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Global distribution of anxiety disorders				
Haller 2014 *Search:* 2006 *# incl. studies:* 18 *Meta-analysis:* no	- Pop-based studies of subthreshold DSM/ICD GAD in adults 15-96 years - Range: 90-17,739	- General population and primary care sample - Clinical and community settings - Mostly North American and European data	- Diagnostic criteria	- 12-month median prev. - 3.9% (range: 2.1-6.6%) - When GAD duration criterion relaxed, prev of subthreshold GAD increased: 12 month prev. with 3+ mo. vs. 1+ mo. duration: 3.6% vs. 6.1% - Higher prev in younger people in clinical samples, but higher in older people in community (3%) - Median point prev. in primary care: 5.9% (1.3-8.3%) - Women higher prev than men - 42% of young women with subthreshold GAD also had other subthreshold mental disorders - Subthreshold GAD mostly comorbid with other anxiety disorders
Steel 2014 *Search:* Jan 2014 *# incl. studies* 174 *Meta-analysis:* yes	- 26 high-income and 37 LMIC countries - Mostly 16-65 years - Samples of 450+ people - Median n: 2314	- Population sample; Census or probabilistic epidemiological procedures used in surveys - Community settings		- Period prev of anxiety disorders in men 4.3% (3.7-4.9%), 8.7% (7.7-9.8%) in women - Lifetime prev of anxiety disorders in men 10.1% (8.8-11.6%), 18.2% (16.2-20.4%) in women - Same pattern of gender differences in HIC and LMIC countries
Addiction				
Fatseas 2010 *Search:* Jan. 2009 *# incl. studies* 18 *Meta-analysis:* no	- All-age participants with opiate dependence - Range: 50-716	- Clinical samples from drug treatment programs	- Structured interviews and diagnostic criteria	- Lifetime prev: 2-58% and 5-67% - SP, SAD, GAD common - Narrower prev with recent DSM criteria
Fischer 2012 *Search:* Dec. 2011 *# incl. studies* 9 *Meta-analysis:* yes	- Adults - Range: 1,086-166,453	- General population samples - Community settings - All North American, mostly US studies	- Standardized (clinical diagnostic) and nonstandardized indicators or symptoms	- Symptoms prev in general pop: 16% (1-30)
Goldner 2014 *Search:* April 2012 *# incl. studies* 11 *Meta-analysis:* yes	- Patients at admission or in treatment for substance abuse problems from US and Canada - Sample size not rep.	- Chart review of admissions and discharges, survey of people entering treatment programs - Clinical settings - All North American, mostly US studies	- Clinical diagnostics based on DSM, other clinical assessments, or symptom self-reports	- Prev of diagnosis and symptoms: 38% (14-63) - Diagnosis prev: 29 (14-44); symptoms: 50% (16-84) - No significant age or sex-effects
Lorains 2011 *Search:* Sept. 2010 *# incl. studies* 11 *Meta-analysis:* yes	- Adults - Range: 2417-43,093	- General population samples/surveys - Community settings - Mostly US studies	- Validated screening tool /standardized measurement tools	- Prev: 37.4%

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Other mental and neurological disorders				
Fajutrao 2009 *Search:* past 10 years *# incl. studies* 26 *Meta-analysis:* no	- Patients with bipolar disorder - Range: 72-1,631,462	- Surveys; general population, inpatients - Clinical and community settings - European studies	- DSM diagnoses	- 13%-28% of bipolar patients with anxiety - GAD and PD common - 70%, 24%, 16% for Italy, France, Germany
Amerio 2014 *Search:* Mar 2013 *# incl. studies:* 64 *Meta-analysis:* no	- Pop-based and hospital-based studies on DSM OCD in bipolar disorder (BD), ages 6+ - Range: 15-1416	- Clinical and community settings - Most studies conducted in Europe and North America	- Interviews, DSM criteria	- Pop-based US, Italian studies: lifetime prev of OCD in BD: 11.1-21% - Hospital-based studies: lifetime prev: 1.8-35.1% - OCD onset usually concomitant with first mood episode
Swets 2014 *Search:* Dec 2009 *# incl. studies* 43 *Meta-analysis:* yes	- Schizophrenia patients -18-509	- Mainly clinical settings	- Interviews, symptom scales, DSM	- Prev of OCD and OCS in schizo. - 12.3% (9.7-15.4%) & 30.7% (23-39.6%); meta-regression: prev of OCS: 30.3% - Lower OCD prev: Sub-Saharan African origin, recent onset schizo. - Higher OCD prev: DSM-IV and Y-BOCS; after adjustment: OCD prev 13.6% (11.8-15.8%) - Higher prev with Y-BOCS, OCI - Prev of OCD/OCS in studies using YBOCS/OCI : 16.9% (13.25-21.1%) vs studies not using YBOCS/OCI: 8.0 (5.3-11.9%) - Higher the YBOCS threshold, lower OCS prev
Marrie 2015 *Search:* Nov. 2013 *# incl. studies* 118 *Meta-analysis:* yes	- MS populations; all ages - Range: not rep.	- Population-based, possibly other sampling - Some studies conducted in community settings - Most studies from Central or Western Europe or parts of North America	- Structured diagnostic interviews, medical records review, self-reported diagnoses, validated instruments	- Prev. of anxiety disorders & symptoms in MS: 31.7% vs 63.4%; Higher anxiety in MS than in controls - Anxiety at MS symptom onset: 2.72% vs 6.23% at diagnosis; prev. of health anxiety in MS: 26.4% - Pop-based studies – anxiety prev: 21.9% (8.76-35.0%) - Anxiety prev questionnaires vs admin data/medical records: 25.5% (16.7-34.3) vs. 15.4% (0-39.0)

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Chronic physical diseases				
Cardiovascular disease				
Janssen 2008 *Search:* 2007 *# incl. studies* 39 *Meta-analysis:* no	- End-of-life CHF, COPD, CRF patients - Mean age: 38-86 - Sample size: not rep.	- Proxies and patients recruited, chart /medical record review		- CHF: 2-49% (anxiety prev) - COPD: 32-57% - CRF: 20-41% - CRF terminal: 25%
Solano 2006 *Search:* June 2004 *# incl. studies* 64 *Meta-analysis:* no	- Adults with advanced cancer, AIDS, heart disease, COPD, renal disease - Range: 19-10,379	- Medical records, interviews with patients' families, proxies used, prescriptions for psychotropic drugs - Some studies conducted in clinical settings		- Prev of anxiety symptoms: - Cancer: 13-79% - AIDS: 8-34% - Heart disease: 49% - COPD: 51-75% - Renal disease: 39-70%
Tully 2013 *Search:* May 2011 *# incl. studies* 12 *Meta-analysis:* yes	- Older people: median age: 60 years - Range: 86-1015	- Primary care sample, CHD patients attending rehab, outpatient clinic, people going in for surgery - Clinical studies - Mostly US studies	- Diagnostic interview tools	- GAD prevalence: 10.94% (7.8, 14.0) - Lifetime GAD: 25.8% (20.84, 30.8)
Clarke 2009 *Search:* May 2003 *# incl. studies* 159 *Meta-analysis:* no	- Sample size: not rep.			- Heart disease - PD: 10-50% - Diabetes mellitus: 14% with GAD - Cancer: 15-23%; more advanced stage: 69% - Arthritis and osteoporosis link to anxiety - Women more anxiety than men (55.3% vs 32.9%)
Webster 2012 *Search:* Nov. 2010 *# incl. studies* 12 *Meta-analysis:* no	- Adults with (non-specific) acute chest pain in acute care - Range: 50-1300	- Patients admitted to ED - Clinical studies	- Symptom checklists	- 21-53.5% of NCCP patients had probable anxiety - Women and younger patients - elevated anxiety - Anxiety levels in NCCP similar to or higher than in CCP or healthy controls
Campbell Burton 2013 *Search:* March 2011 *# incl. studies* 44 *Meta-analysis:* yes	- Mean age: 66-71 years - Range: 15-498	- Population-based (all stroke patients recruited from particular geographical area), hospital- and rehabilitation-based (inpatients or those attending rehab facilities), community-based (did not attempt to capture all stroke cases in geographic area) - Clinical and community settings	- Anxiety symptom scales, clinical diagnoses, single question measure, researcher-developed questions	- Prev of anxiety disorders: 18% (8-29) - PD & GAD common - Anxiety caseness (rating scales): 25% (21-28) - 1/3 of patients with post-stroke anxiety had pre-stroke mood or anxiety - High anxiety-depression comorbidity

Review details	**Population characteristics and sample size**	**Sampling methods**	**Anxiety assessment methods**	**Anxiety prevalence (prevalence %, [95% CI]) and summary of results**
Cancer				
Clarke 2009 – previously described				
Solano 2006 – previously described				
Yang 2013 *Search:* Sep. 2012 *# incl. studies* 17 *Meta-analysis:* yes	- Adults 18+ years from Mainland China - Range: 380-2554	- Unclear (assessed 'patients') - Mainland China studies	- Clinical diagnosis, symptom checklists, self-report questionnaires	- Anxiety prev: 49.7% (range: 20-89.1) in cancer, and 17.50% in the non-cancer control group
Vehling 2012 – previously described				
Lim 2011 *Search:* 2010 *# incl. studies* 10 *Meta-analysis:* no	- Patients 21-65 on treatment for early-stage breast cancer - Range: 48-332	- Women who were undergoing/had undergone breast cancer treatment (ex. RCT studies: patients from centre randomly selected to receive various treatment types; non-RCT studies: women undergoing various cancer treatments/surgeries, patients from oncology clinics; patients assessed at home) - Clinical and community settings	- Symptom checklists	- 20% to 58% - Less anxiety if given treatment choice - More state/trait anxiety during chemo than radiotherapy - Greater trait anxiety in young women during chemo
Arden-Close 2008 *Search:* May 2007 *# incl. studies* 18 *Meta-analysis:* no	- Ovarian cancer patients - Range: 9-246	- Unclear (included patients, cancer survivors) - Mostly US studies	- Standardized and non-standardized assessment tools, symptom checklists	- Prev: 47% at 3 months following treatment - Anxiety levels increased from treatment completion date to 3-month follow-up - Young age groups disproportionately affected
Mitchell 2013 *Search:* March 2013 *# incl. studies* 43 *Meta-analysis:* yes	- Adult patients compared with spouses, IQR sample size: 145-270 - Adult patients and healthy controls IQR:1328-25,245	- Cases: outpatient clinic, database/cancer registry, hospitals, general population; - recruitment: random sample (population-based), patients treated in a certain time period; prescription for psychotropic drugs; Controls: comparator matching by sociodemographics, convenience sample, matched partner pair - Clinical and community settings	- Symptom checklists, structured questionnaire for DSM, prescription of psychotropic drugs, clinical diagnosis	- Prev. long-term cancer survivors vs. healthy controls: 17.9% (12.8-23.6), 13.9% (9.8-18.5); anxiety higher in cancer patients regardless of methodological factors - Long-term cancer survivors vs. spouses: 28% (22.3-33.9), 40.1% (25.4-55.9); age/sex effect not rep.

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Respiratory disease				
Janssen 2008 - previously described				
Solano 2006 - previously described				
Davydow 2008 *Search:* April 2007 *# incl. studies* 10 *Meta-analysis:* no	- Adult survivors in US and Germany - 321 patients	- Sampling not mentioned – assessed patients following ICU discharge - US and German studies	- Symptom checklists	- 23 - 48%
Diabetes				
Smith 2013 *Search:* July 2012 *# incl. studies* 12 *Meta-analysis:* yes	- Adults ages 16+ years - Range: 635 - 217,379	- Sampling not mentioned/ unclear - Mostly North American and European studies	- Surveys, clinical interview(s), validated scale	- Prev (HADS-A): 15-73% in diabetic patients and 19.9-43.1% in ref groups - Prev of anxiety disorders (clinical interviews): 1.4-15.6% in diabetic patients; 1.6-8.8% in ref
Grigsby 2002 *Search:* 2001 *# incl. studies* 18 *Meta-analysis:* yes	- Adults ages 18+ - Range: 20-634 (for diabetic subjects)	- Most studies based on primary care/clinical samples	- Structured or semi-structured diagnostic interviews, self-report measures	- Current and lifetime prev (%) of anxiety in diabetes: GAD: 13.5, 20.5; panic: 1.2, 1.9 OCD: 1.3, 1.1; Agoraphobia: 4.6, 10.2 SP: 21.6, 24.8; SAD: 7.3, 9.3 Any phobia: 6.8, 10.4 Any anxiety disorder: 14.0, 25.8 Anxiety not otherwise specified: 26.5, 39.0 Elevated symptoms: 39.6 - Higher prev of anxiety symptoms in women than in men: 55.3 vs. 32.9 - No diff by diab. Type; GAD most prevalent - Anxiety dis. & symp: 25.8% & 39.6%
Clarke 2009 - previously described				
Other chronic physical diseases				
Dokras 2012 *Search:* April 2011 *# incl. studies* 9 *Meta-analysis:* yes	- PCOS subjects and non-PCOS controls - Range: 44-206	- Screened clinic populations, 1 study used telephone screening - Mostly clinical settings - Mostly Western studies	- Anxiety screening tool	- Anxiety prev: 1-37.5% in PCOS; 0-13 in controls - Prev of generalised anxiety symptoms in PCOS and controls: 20.4% vs 3.9% - SAD and OCD more common in PCOS; age effects not rep.
Smith 2014 *Search:* January 2013 *# incl. studies* 14 *Meta-analysis:* yes	- Mostly adult, Medi-terranean pop. - 30 BJHS people & 25 controls-182 people BJHS & 1123 controls	- Clinically representative participants - Recruited participants from school settings, university, primary care/community health care settings, hospital outpatient departments		- Anxiety prev: 5-68% in BJHS; 5-32% in non-BJHS - BJHS have more PD, agoraphobia and fear than non-BJHS

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Other chronic physical diseases				
Andersen 2014 *Search:* Sept. 2012 *# incl. studies* 24 *Meta-analysis:* no	- Adults (mean age: 43-50) from Western countries with musculoskeletal pain >= 3 months - Range: 84-3,928	- Primary care clinics or hospital services; recruitment: general population, through ads.; mostly outpatients - Western studies	- Symptom checklists and structured clinical interview	Pooled one-year and lifetime prevalence of: - Clinical and general anxiety levels: 0-20.9% (highest prev. with SCID) - Highest anxiety prev. in fibromyalgia
Dawson 2014 *Search:* Feb 2012 *# incl. studies* 16 *Meta-analysis:* no	- Adults with age-related macular degeneration (AMD) age 18+ Range: 51-32,702	- Recruited from eye clinics, GP clinics - Clinical/specialist setting - Western studies, many US	- Almost all symptom checklists, structured clinical interview	- Generally no link with anxiety found, but one study reported prev of 30.1% in AMD
Other chronic physical diseases in end-stage				
Mitchell 2011 *Search:* Nov. 2010 *# incl. studies* 94 *Meta-analysis:* yes	- 4007 adults age 18+ in palliative care; 10,071 adults 18+ in palliative care and oncological settings	- Patients from oncological, haematological, and palliative-care settings - Mostly western studies	- Psychiatric interviews	- 9.8% (6.8-13.2) in palliative-care, and 10.3% (5.1-17.0) in oncological and hematological settings
Janssen 2008 - previously described				
Murtagh 2007 *Search:* April 2005 *# incl. studies* 60 *Meta-analysis:* No	- Adult patients diagnosis of end-stage renal disease - Range: 19-5,256	- Clinical settings	- Standardized psychiatric interview, survey, validated screening tools	- Anxiety prev: 38% (12-52)
Solano 2006 - previously described				
Trauma				
Mckechnie 2014 *Search:* June 2013 *# incl. studies* 13 *Meta-analysis:* no	- Traumatic limb amputees, age 18+ - Range: NR	- Military patients (including veterans from Vietnam, Iraq, Afghanistan) - Mostly UK and US studies	- ICD or DSM diagnoses, symptom checklists	- Anxiety ranged from 25.4-57% in this pop
Chen 2010 *Search:* Dec. 2008 *# incl. studies* 37 studies *Meta-analysis:* yes	- Individuals with history of sexual abuse compared to those without - Range: 34 -1,574,100	- Registries, school health or GP records; referral from rape crisis centre, conscripts, voters, general population, friends of victims (controls) - Clinical, community settings	- Mostly structured diagnostic interview	- Lifetime anxiety in people with sex abuse: 2-82% - Associations between sexual abuse and MD persisted regardless of sex of survivor and age at which abuse occurred
Fazel 2005 *Search:* Dec. 2002 *# incl. studies* 20 *Meta-analysis:* yes	- Adult refugees from southeast Asia, former Yugoslavia, middle east, Central America; weighted mean age=27 - 6743 adult refugees	- Opportunistic sampling (ex. student enrolment lists, health-screening programs) - High-income western countries; ¾ participants from southeast Asia - Community settings	- Clinical interview, trained interviewers using validated diagnostic methods	- 4% (3-6) of refugees diagnosed with GAD

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Vulnerable population sub-groups				
Older people and their caregivers				
Bryant 2008 *Search:* 2007 *# incl. studies* 49 *Meta-analysis:* no	- People 60+ years in community or clinical settings - Range: 286-10,641	- Community surveys, GP lists, geriatric hospital, general hospital, case register, clinic referrals, consecutive series; participants included institutionalized older adults, nursing home residents	- Checklists, self-report, clinical record review, clinical diagnoses	- Anxiety in community: 1.2-14%; anxiety in clinical samples: 1-28% - Anxiety symptoms: 15-52.3% in community and 15-56% in clinical samples * PD: 1.4-25.6%; Agoraphobia: 0.4-20% * SP: 5.9-13.1%; SAD: 0.0-18.7% * OCD: 0.6-1.8%; PD: 0.0-10.5% - GAD commonest & more women with anxiety
Volkert 2013 *Search date:* Dec. 2011 *# incl. studies* 25 *Meta-analysis:* yes	- Older people 50+ years mainly from Germany, US, Sweden - Range: 242-22,777	- Mostly random samples, representative samples, 1 study contacted all elderly of one town, sample stratification according to various criteria - Community settings	- Diagnostic interviews, dimensional instruments	- Current and lifetime - PD: 0.88% (0.76, 0.99), 2.63% (2.43, 2.84) - Agoraphobia: 0.53% (0.39, 0.66), 1.00% (0.54, 1.45); SP: 4.52% (4.15, 4.89), 6.66% (6.17, 7.15) - SAD: 1.31% (1.18, 1.44), 5.07% (4.82, 5.32) - GAD: 2.30% (2.03, 2.57), 6.36% (5.57, 7.14) - OCD: 0.90% (0.63, 1.17), 0.97 (0.55, 1.38) - Lower SP prev in old
Monastero 2009 *Search:* Aug. 2008 *# incl. studies* 27 *Meta-analysis:* no	- Mean age at baseline ranged from 65-80 years - Range: 44-2879	- Hospital-based samples with MCI, population-based samples with MCI, clinical trial of MCI subjects - Clinical and community settings	- Behavioural instruments including diagnostic interviews (clinical interview, trained interviewer)	- Prev: 11-74% - Anxiety is common in Alzheimer's disease
Yates 2013 *Search:* Nov. 2012 *# incl. studies* 18 *Meta-analysis:* yes	- Clinical samples with MCI or community samples of older people - Range: 18-6892	- People self-referred or referred by GP to memory clinics; people recruited from general population	- Anxiety symptom scales	- Prev. of anxiety: 11-75% in elderly with MCI - Women and younger caregivers higher anxiety
Cooper 2007 *Search:*2005 *# incl. studies* 33 *Meta-analysis:* no	- Caregivers of people with dementia - Range: 34-979	- Case-note review to identify caregivers of old people referred to psychiatry service; cohort studies - UK and US studies	- Diagnostic interview schedules, symptom scale	- 3.7-76.5% - Prev depended on study time period, sample, anxiety caseness definition
Pregnant women				
Russell 2013 *Search:* August 2012 *# incl. studies* 17 *Meta-analysis:* yes	Russell 2013 *Search:* August 2012 *# incl. studies* 17 *Meta-analysis:* yes	Russell 2013 *Search:* August 2012 *# incl. studies* 17 *Meta-analysis:* yes	Russell 2013 *Search:* August 2012 *# incl. studies* 17 *Meta-analysis:* yes	Russell 2013 *Search:* August 2012 *# incl. studies* 17 *Meta-analysis:* yes

Review details	Population characteristics and sample size	Sampling methods	Anxiety assessment methods	Anxiety prevalence (prevalence %, [95% CI]) and summary of results
Pregnant women				
Molyneaux 2014 *Search:* Jan 2013 *# incl. studies* 62 *Meta-analysis:* insufficient studies for meta-a for anxiety	- Overweight or obese women at start of pregnancy vs normal weight control women - Total 540,373 women	- Medical records; women seeking prenatal care; primary are or hospital centre sample; all women living in Avon expected to deliver in a certain time period; Recruitment from prenatal exercise classes, obstetrician and gynaecologist waiting rooms (through newsletter), women with low-income insurance - Clinical and community - Mostly Western studies (esp. UK and US)	- Diagnostic and screening measures; did not include measures of state anxiety	- Low-income Brazilian women: anxiety prev 35% obese, 35.7% overweight, 31% normal weight - Postpartum anxiety prev: symptoms across studies ranged from 4.7% in obese (4% in overweight, 4.2% in normal weight) to 33.3% (13.3% in overweight, 16.4% normal weight)
Sawyer 2010 *Search:* January 2009 *# incl. studies* 35 *Meta-analysis:* yes	- Ethiopian and Nigerian women - Range: 101-632 (anxiety studies)	- Antenatal and postnatal health clinics, community - All studies from Africa, most from Nigeria	- Most used structured clinical interviews, many used self-administered measures, some used both	- Pre- and postnatal anxiety prevalence: 14.8% (12.3-17.4) and 14.0% (12.9-15.2) - Younger women more anxious
LGB and self-harm patients				
King 2008 *Search:* 2005 *# incl. studies* 25 *Meta-analysis:* yes	- Anxiety in LGB and heterosexual groups - Range: 79-194 (for anxiety studies)	- Random sampling, multi-stage sampling, snowball sampling, some primary studies did not specify method - Community settings	- Standardized scales	- Anxiety prev: 3-20% and 3-39% in men and women - Stigma and discrimination contributors
Hawton 2013 *Search:* Nov. 2011 *# incl. studies* 50 *Meta-analysis:* yes	- All age patients presented to hospitals following self-harm (self-poisoning, self-injury, suicide attempt) - Range: 22-1158	- Consecutive admissions to different departments, recruitment on specific days, consecutive referrals to suicide unit, random sample - Clinical samples - All studies of non-western countries from Asia, most western studies from UK	- Research diagnostic criteria and clinical diagnoses converted to DSM-IV	- Prev of anxiety disorders: 34.6% (21.9-48.6) - Anxiety prev in women and men: 42% & 38% - Small sex-based diff.; prev high in young and old

*SP= specific or simple phobia; PD=panic disorder; GAD=generalised anxiety disorder; SAD=social anxiety disorder; OCD=obsessive compulsive disorder; anx=anxiety; NR=not reported

Appendix 3: Table 2 – Directions for future research and reported limitations

Review details	**Directions for future research**	**Reported limitations**	**QA***
Global distribution of anxiety disorders			
Somers 2006 *Search:* 2004 *# incl. studies* 39 *Meta-analysis:* yes	- Incidence and onset studies needed - Research on anxiety risk & protective factors, and social variables as mediators - Prev of anxiety in special groups (e.g., medical patients, residents of nursing homes) - Clarify epidemiology of anxiety to help with deployment of treatment	*Original studies* Heterogeneity: diagnosis criteria and instruments used (ex. lower estimates with use of DIS and DSM-III than CIDI and DSM-III-R) *Review* - Heterogeneity: diff countries, response rate, sample size	5
Baxter 2013 *Search:* 2009 *# incl. studies* 87 *Meta-analysis:* yes	Further research on: - Impact of conflict on mental health - Aspects of wealth related to anxiety - Cultural aspects (ex. psycho-stressors) related to anxiety - Further studies using consistent anxiety definition and methodologies in 1) developing and emerging countries; 2) populations exposed to conflict - Interactions of factors associated with prevalence of anxiety	*Original studies* - Limited measurement equivalence across cultures – results should be interpreted with caution - Rural study results – should be interpreted with caution - Study design differences *Review* - NR	10
Mirza 2004 *Search:* March 2002 *# incl. studies:* 20 *Meta-analysis:* no	- Robust evidence (ex. conduct national, mental health epidemiology surveys) to develop mental health policy with strategic implementation plan for Pakistan - More outcome studies, prevention and treatment trials needed	*Original studies* - Most studies from Punjab and Sindh - Heterogeneity in study design and instruments – limited generalisability *Review* - Publication and selection bias - Small number of included studies	5
Vehling 2012 *Search: not rep.* *# incl. studies* 89 *Meta-analysis:* yes	- Representative studies	*Original studies* - Estimate heterogeneity and study quality - Limited generalisability *Review*	7
Baxter 2014 *Search:* 2009 *# incl. studies* 91 *Meta-analysis:* yes		*Original studies* - Limited or no data from Central Asia, Andean Latin America, Oceania, Central Sub-Saharan Africa, Central Europe, South-east Asia - Possibly biased population samples (ex. conflict region studies may have oversampled those exposed to conflict) *Review* - NR	10

Review details	Directions for future research	Reported limitations	QA*
Global distribution of anxiety disorders			
Haller 2014 *Search:* 2006 *# incl. studies:* 18 *Meta-analysis:* no	- Clarify subthreshold GAD vs. non-pathological anxiety – use impairment criterion for this - Should treatment strategies used for threshold disorders be used for subthreshold cases?	*Original studies* - Inadequate study response rates - Heterogeneous definitions of subthreshold GAD *Review* - Some studies missed - Difficult to define search terms for subthreshold GAD - Insufficient studies for subpopulations - Different study quality	7
Steel 2014 *Search:* Jan 2014 *# incl. studies* 174 *Meta-analysis:* yes		*Original studies* - Some recall bias with 12-month estimates - Different study age structures contributing to different prev - Higher prev with smaller sample sizes - Different estimates with the use of different instruments - Adaptation of surveys to culture and context & measurement equivalence issues *Review* - Some studies may have been missed - Untested search strategies - Assessment equivalence across cultures - Can only generalise findings to adults	5
Addiction			
Fatseas 2010 *Search:* Jan. 2009 *# incl. studies* 18 *Meta-analysis:* no	- Effectiveness of treatment for phobias in opiate-dependent patients	*Original studies* - Reliability and validity of diagnostic tools (ex. difficult to distinguish substance-induced anxiety from independent disorders with pre-DSM-IV criteria) - Heterogeneity in sample characteristics - Different time frames for prev of anxiety *Review*	6

Review details	Directions for future research	Reported limitations	QA*
Addiction			
Fischer 2012 *Search:* Dec. 2011 *# incl. studies* 9 *Meta-analysis:* yes	- Longitudinal studies to assess reasons for using NMPOU in individuals with mental health problems	*Original studies* - Heterogeneity: operationalization of anxiety and NMPOU - Many screener or epidemiological instruments used (possible overestimation), instead of clinical diagnostic tools - All North American studies – limited generalisability - Small number of studies *Review* - Between-study heterogeneity	8
Goldner 2014 *Search:* April 2012 *# incl. studies* 11 *Meta-analysis:* yes	- Relationship between NMPOU and mental illness - Retrospective and prospective studies to examine development of mental health problems and NMPOU in those receiving POAs - Use standardized and comparable diagnostic instruments - Link between chronic pain and mental illness - Alternative treatments for and outcomes of patients with both mental health problems and NMPOU	*Original studies* - Cross-sectional data, thus temporality issues between NMPOU and mental illness - Diff instruments used *Review* - Publication bias - High between-study differences - Heterogeneity: defining and measuring NMPOU psychiatric problems	8
Lorains 2011 *Search:* Sept. 2010 *# incl. studies* 11 *Meta-analysis:* yes	Health care workers should: - Assess for comorbidities - Determine whether anxiety developed before gambling problem and should be treated first	*Original studies* - Lifetime estimates may be confounded by age - Diff tools (ex. SOGS – satisfactory psychometrics in populations surveys; discordance between NODS and DSM-IV) - Most general population prevalence surveys conducted in US and Canada, small sample sizes *Review* - NR	5
Ho 2014 *Search:* 2012 *# incl. studies* 8 *Meta-analysis:* yes	- Genetic transmission of IA - Patients with IA should be screened for anxiety and vice versa & integrated treatment recommended - Further studies on moderators; other ethnic groups in Europe and North America; older adults - Studies on interactions between IA and anxiety (aetiology, illness trajectory, treatment outcomes) - Consensus on definition of IA - Prospective studies - Link between anxiety and IA-specific behaviours (ex. use of social media)	*Original* - Heterogeneity: age of sample, different psychiatric questionnaires, mostly cross-sectional studies, uncontrolled confounding (ex. environmental stress, parenting) - Young patients mainly from Asian countries *Review* - Small number of studies - Unable to assess how estimates differ with use of self-reported questionnaires vs. structured interviews	8

Review details	**Directions for future research**	**Reported limitations**	**QA***
Other mental and neurological disorders			
Fajutrao 2009 *Search:* past 10 years *# incl. studies* 26 *Meta-analysis:* no	- Bipolar disorder in Europe	*Original studies* - Anxiety assessment and reporting methods diff - Retrospective and non-representative samples *Review* - Focus on electronic databases; language selection criteria	5
Amerio 2014 *Search:* Mar 2013 *# incl. studies:* 64 *Meta-analysis:* no	- Assess history of mood disorders in OCD patients - Treatment research (ex. use of mood stabilizers) - Studies on hereditary and biological markers, diagnostic validity of BD-OCD comorbidity and its treatments	*Original studies* - Differences in evaluation, diagnosis, reporting - Mostly observational, retrospective studies, lack of control group, small sample size, sampling bias *Review* - NR	5
Swets 2014 *Search:* Dec 2009 *# incl. studies* 43 *Meta-analysis:* yes	- Use random sampling - Training needed to assess OCS - Diagnostic standardization needed, careful patient selection - Detailed assessment of OCD; use SCID OCD def. followed by Y-BOCS administration - Assess OCS in patients with psychosis - Shift from descriptive to treatment studies	*Original studies* - Different instruments and criteria used (ex. lower estimates with DSM-III-R than later versions; lower prev with DIGS) - Sampling variability (different patient characteristics) - Possible sampling bias, help-seeking/patients selection can influence prev rates - Limited data on: Sub-Sahara African countries, gender, ethnicity, use of meds (ex. antipsychotics) *Review* - NR	5
Marrie 2015 *Search:* Nov. 2013 *# incl. studies* 118 *Meta-analysis:* yes	- Be consistent: compare psychometric properties of instruments and use same instrument to assess anxiety - Standardize estimates to common (world) population	*Original* - Differences in study design: different data sources, populations, definitions of psychiatric disorders - Little info on age-, sex-, or ethnicity-specific estimates *Review* -NR	5

Review details	Directions for future research	Reported limitations	QA*
Cancer			
Clarke 2009 – previously described			
Solano 2006 – previously described			
Yang 2013 *Search:* Sep. 2012 *# incl. studies* 17 *Meta-analysis:* yes	- Use control groups with diseases other than cancer	*Original studies* - Anxiety assessed using different instruments - Studies were cross-sectional so cannot determine temporality between anxiety and cancer development *Review* - Few studies & lacking international literature - Potential publication bias	9
Vehling 2012 – previously described			
Lim 2011 *Search:* 2010 *# incl. studies* 10 *Meta-analysis:* no	- Studies in different settings assessing effect of cancer treatment on anxiety - Interventions for anxiety in women with breast cancer - Ways to decrease state anxiety and help women cope with chemotherapy, despite their level of trait anxiety	*Original studies* - Small sample sizes *Review* - Difference in treatment, tools & timing of measurement	6
Arden-Close 2008 *Search:* May 2007 *# incl. studies* 18 *Meta-analysis:* no	- Longitudinal studies and RCTs needed to clarify directionality between immunity and mental illness - Prospective research needed to test trajectories of change in mental illness following cancer diagnosis and treatment - Interventions targeting distress (ex. coping) - Attention to sample size and validation of questionnaires - Theory-driven research needed - Authors should state limitations/directions for future research	*Original studies* - Certain correlates of mental illness tested in too few studies - Lack of validation of assessment tools - Small sample sizes - Residual confounding - Limited generalisability (US) *Review* - Published studies	6
Mitchell 2013 *Search:* March 2013 *# incl. studies* 43 *Meta-analysis:* yes	- Link between health-related quality of life and anxiety - Studies on anxiety in palliative settings or in patients with advanced cancer - More reliable estimates by use of interview methods	*Original studies* - Differences in: quality of matching with healthy controls, study quality, study design, case ascertainment - Possible uncontrolled factors - Heterogeneity in healthy controls (review authors had limited info on recruitment of healthy controls in studies) *Review* - NR	11
Respiratory disease			
Janssen 2008 - previously described			
Solano 2006 - previously described			
Davydow 2008 *Search:* April 2007 *# incl. studies* 10 *Meta-analysis:* no	- Risk factors for psychopathology - More rigorous assessment of psychopathology - Anxiety in ICU as risk factor for post-ALI/ARDS psychopathology - To what extent are risk factors for ALI/ARDS related to development of mental illness in those without ALI/ARDS	*Original studies* - Mostly psychiatric questionnaires used with diff. sensitivities, ex. screening instruments or measures of symptom severity (not necessarily validated for ARDS survivors) - Small sample sizes *Review* - Small number of studies	5

Review details	Directions for future research	Reported limitations	QA*
Diabetes			
Smith 2013 *Search:* July 2012 *# incl. studies* 12 *Meta-analysis:* yes	- Individual anxiety disorders associated with diabetes - Relevant confounders should be included - Studies on diabetes and anxiety using accurate measurements - Prospective studies to clarify directionality between anxiety and diabetes	*Original studies* - Different time frames resulting in different likelihood of capturing symptoms - Measurement differences - Cross-sectional data - Temporality between diabetes and anxiety *Review* - Publication bias, language biases	10
Grigsby 2002 *Search:* 2001 *# incl. studies* 18 *Meta-analysis:* yes	- Longitudinal studies to identify behavioural and physiological mechanisms related to anxiety in diabetes - More community-based studies to estimate anxiety prev in diabetes - Assess potential moderators - Studies on causal mechanisms	*Original studies* - Small sample sizes - Lacking data on race/ethnicity influence on anxiety prev - Differences in scales used to measure anxiety and in aggregation/reporting of results (ex. assessment of 1 anxiety disorder vs. aggregate of several anxiety disorders) - Lack of data on prev of anxiety by diabetes type *Review* - Small number of studies - Few studies included nondiabetic comparison group	6
Clarke 2009 - previously described			
Other chronic physical diseases			
Dokras 2012 *Search:* April 2011 *# incl. studies* 9 *Meta-analysis:* yes	- Effect of clinical or biochemical factors in relation to hyperandrogenism and anxiety in PCOS - Link between PCOS-specific characteristics and anxiety - Larger sample sizes - Longitudinal studies for insight into etiology and trajectory of anxiety in PCOS	*Original studies* - Few studies on prev on anxiety in PCOS using validated anxiety screening tools - Mostly cross-sectional studies *Review* - Small sample sizes, possible publication bias	5

Review details	Directions for future research	Reported limitations	QA*
Other chronic physical diseases			
Smith 2014 *Search:* January 2013 *# incl. studies* 14 *Meta-analysis:* yes	- Degree of BJHS related to mental illness - Biological link between BJHS and anxiety (ex. abnormal reactive autonomic nervous system) - Influence of non-pharmacologic treatment on alleviating anxiety in those with BJHS - Anxiety in BJHS in other cultures	*Original studies* - Limited generalisability (mainly Mediterranean adult populations), mostly cross-sectional designs - Possible cross-cultural differences in expression of anxiety *Review*	7
Andersen 2014 *Search:* Sept. 2012 *# incl. studies* 24 *Meta-analysis:* no		*Original studies* - Different recruitment methods, study inclusion criteria - Most study patients were women, thus, possible overestimation of significance of results - Different measurement methods: questionnaires, clinical evaluations, structured interviews (some methods not validated for pain patients) *Review* - Search strategy	6
Dawson 2014 *Search:* Feb 2012 *# incl. studies* 16 *Meta-analysis:* no	- Does anxiety come before onset of AMD? - Link between length of time since AMD diagnosis and AMD treatments in relation to patient's mental health - Include control group to compare prev of anxiety between AMD and non-AMD populations - Use tools with clear cut-off for clinical anxiety	*Original studies* - Is anxiety different in different forms of AMD? - Different definition and measurement of anxiety - Comparison group may not be representative *Review* - Small number of studies	5

Review details	Directions for future research	Reported limitations	QA*
Other chronic physical diseases in end stage			
Mitchell 2011 *Search:* Nov. 2010 *# incl. studies* 94 *Meta-analysis:* yes		*Original studies* - No consensus about optimum psychiatric diagnostic approach in cancer settings - Studies of variable quality, mostly cross-sectional designs, some used convenience sampling, different anxiety measurement methods - Could not determine correlates of anxiety - Few studies with defined period of prevalence *Review* - Possible publication bias	8
Janssen 2008 - previously described			
Murtagh 2007 *Search:* April 2005 *# incl. studies* 60 *Meta-analysis:* No	- Studies on incidence and prevalence of symptoms in ESRD, their causes, and interventions - Population-based, longitudinal studies - More information on generalisability of available studies - How do symptoms vary between those managed without dialysis and those withdrawing from dialysis? - Symptom burden in ESRD - Symptoms experienced at end of life - Identify what is common and different between those dying from ESRD and other palliative populations	*Original studies* - Heterogeneity: symptom definition, who defines a symptom (reporting), different periods over which prevalence is measured, different tools used - No population-based studies *Review* - Search strategy	6
Solano 2006 - previously described			
Trauma			
Mckechnie 2014 *Search:* June 2013 *# incl. studies* 13 *Meta-analysis:* no	- Prospective studies assessing long-term levels of anxiety in post-traumatic amputees, and whether rehab programmes are successful and mental health issues continue after the programme ends	*Original* - No info on how prev changes with time since amputation (anxiety assessed at fixed time point) - Different scoring systems in different populations at various follow-up times - Selected specialist samples not representative of all traumatic amputees - Sampling – possible selection bias - Attrition during follow-up *Review* - Some studies may have been missed	8

Review details	Directions for future research	Reported limitations	QA*
Trauma			
Chen 2010 *Search:* Dec. 2008 *# incl. studies* 37 studies *Meta-analysis:* yes	- Interplay between stressful life events, vulnerability genes, and development of psychiatric disorders (gene-environment interactions)	*Original studies* - Self-report (recall bias), abuse underreport - Anxiety affected by unmeasured forms of abuse? *Review*	8
Fazel 2005 *Search:* Dec. 2002 *# incl. studies* 20 *Meta-analysis:* yes		*Original studies* - Measurement equivalence issues: differences in sampling methods, diagnostic instruments - Insufficient data on refugees in developing countries, asylum seekers, people internally displaced in their own countries - Updated info on recently displaced refugees *Review* - NR	5
Vulnerable population sub-groups			
Older people and their caregivers			
Bryant 2008 *Search:* 2007 *# incl. studies* 49 *Meta-analysis:* no	- Hypothesis-driven research with late-life anxiety as primary focus - Longitudinal designs - Studies on anxiety in old age - Prevention and early treatment should target old people in poor health and who are at risk for anxiety	*Original studies* - Differences in definition and measurement of anxiety - Measurement equivalence issues in elderly – is anxiety experienced differently in elderly? (case definition) - Difficult to disentangle physical symptoms & anxiety in elderly - Possible selection bias - Older people may underreport anxiety - Mostly cross-sectional studies *Review*	5
Volkert 2013 *Search date:* Dec. 2011 *# incl. studies* 25 *Meta-analysis:* yes	- Studies on anxiety in elderly using improved methodology and accounting for changes in old age (adapted instruments)	- Differences in instruments and diagnostic criteria - Difficult to disentangle anxiety from physical diseases, somatoform disorders, and depression in elderly - Instruments not designed for elderly – what constitutes anxiety in elderly? - Heterogeneity: studies of different geographic and cultural regions and using different case definitions and case identification methods - Difficult to recruit elderly for studies *Review* - Studies in English and German – limited generalisability - No missing data analysis	8
Monastero 2009 *Search:* Aug. 2008 *# incl. studies* 27 *Meta-analysis:* no	-Health care worker to distinguish primary behavioural changes from cognitive impairment - Large, cohort studies using standardized instruments to assess NPS as prognostic factors in MCI - Optimum ways to assess NPS in those with MCI - Genetic and biological markers linking NPS to MCI and dementia	*Original studies* - Possible selection bias - Differences in age and sex distributions within studies - Differences in instruments used/methods of reporting symptoms *Review* - NR	5

Review details	Directions for future research	Reported limitations	QA*
Older people and their caregivers			
Yates 2013 *Search:* Nov. 2012 *# incl. studies* 18 *Meta-analysis:* yes	- Anxiety and depression should both be considered - Classification systems for MCI should consider anxiety - Clarify directionality between anxiety and MCI	*Original studies* - Heterogeneity: sampling differences, small samples (may not be representative), different ways of assessing mood/NPS - Lacking info on link between anxiety and MCI subtypes *Review* - Possible publication bias, English articles	5
Cooper 2007 *Search:*2005 *# incl. studies* 33 *Meta-analysis:* no	- Cohort studies - Research on coping in relation to anxiety (this could be intervention target)	*Original studies* - Lack of info on determinants of anxiety caseness in caregivers *Review* - NR	5
Pregnant women			
Russell 2013 *Search:* August 2012 *# incl. studies* 17 *Meta-analysis:* yes	- Prospective studies examining OCD during pregnancy and postpartum period - Incidence studies needed - Course of OCD across reproductive events - Influence of biological determinants on OCD exacerbation throughout reproductive period	*Original studies* - Small samples - Difficult to match control studies on various factors - Possible overestimation of OCD prev in some control studies - OCD evaluated at different pregnancy time points, making comparisons difficult *Review* - Published studies	8
Molyneaux 2014 *Search:* Jan 2013 *# incl. studies* 62 *Meta-analysis:* insufficient studies for meta-a for anxiety	- Validation of anxiety scales for specific populations needed, ex. women in early pregnancy	*Original* - Heterogeneity: different screening measures and cut-offs *Review* - English language papers only - Published studies eligible - Few studies carried out in low and middle-income countries	6
Sawyer 2010 *Search:* January 2009 *# incl. studies* 35 *Meta-analysis:* yes	- Longitudinal studies to determine anxiety prev at different time points during and after pregnancy - Develop cross-cultural measures of mental health	*Original studies* - Small number of studies - Measurement issues, timing of mental health assessment varied (thus, anxiety trajectory over time is unclear) - Few studies on antenatal mental health and associated risk factors in African women - Insufficient info on how maternal psychological problems impact children *Review* - NR	6

Review details	**Directions for future research**	**Reported limitations**	**QA***
LGB and self-harm patients			
King 2008 *Search:* 2005 *# incl. studies* 25 *Meta-analysis:* yes	- Prospective studies to determine risk factors of mental disorders - Refine definition of sexual orientation	*Original studies* - Difficult to recruit and define LGB group - Study design heterogeneity - Heterogeneity in definitions of exposure and outcome *Review* - Heterogeneity: study designs and LGB definition - Small number of studies included	7
Hawton 2013 *Search:* Nov. 2011 *# incl. studies* 50 *Meta-analysis:* yes	- Studies on mental disorders in those who repeat self-harm	*Original studies* - Measurement equivalence issues - Heterogeneity: methods used to recruit participants, different diagnostic measures used, differences in study participant gender ratios - Cross-sectional studies -*Review* - English language studies	6

*prev=prevalence; anx=anxiety; NR=not reported; QA=quality assessment based on AMSTAR criteria

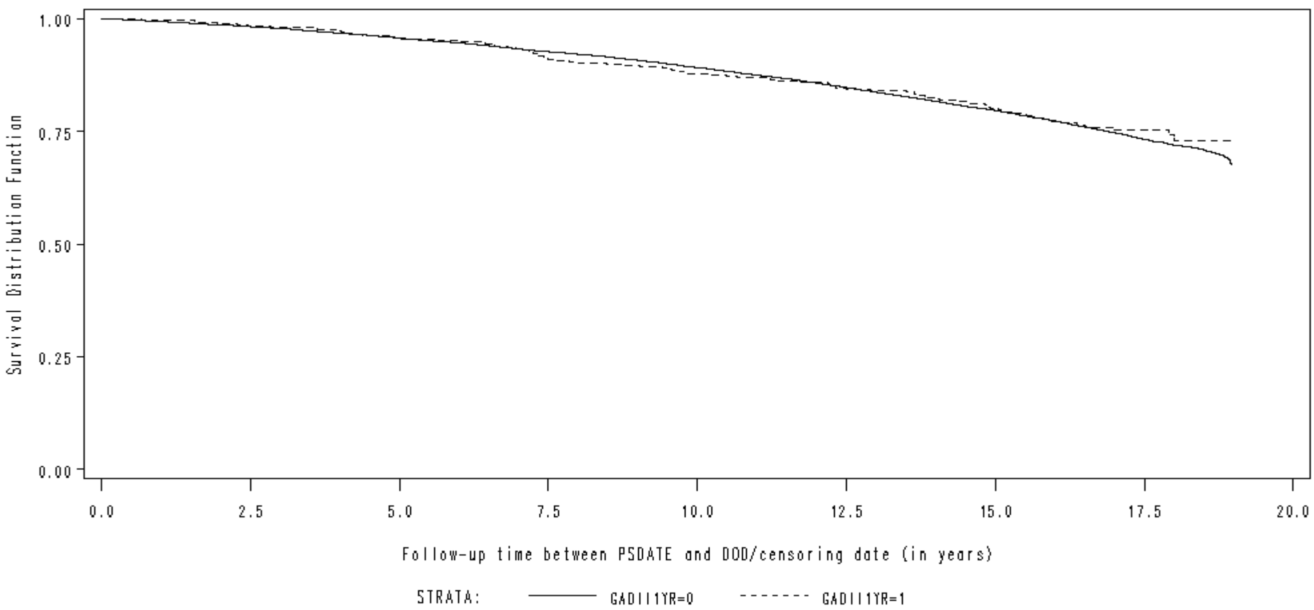
Appendix 4: Characteristics of participants who consented (n=30,445) and refused (n=43,452) to take part in the EPIC-Norfolk cohort study

	Percentage (number)	
Characteristic	**Consented**	**Did not consent**
Age		
<50	27.5 (8366)	33.7 (14647)
50-60	30.3 (9230)	29.5 (12819)
60-70	32.5 (9879)	27.4 (11898)
>=70	9.8 (2970)	9.4 (4088)
Sex		
Female	55.0 (16744)	49.0 (21296)
Male	45.0 (13701)	51.0 (22156)

Appendix 5: Kaplan Meier plots of people with and without GAD

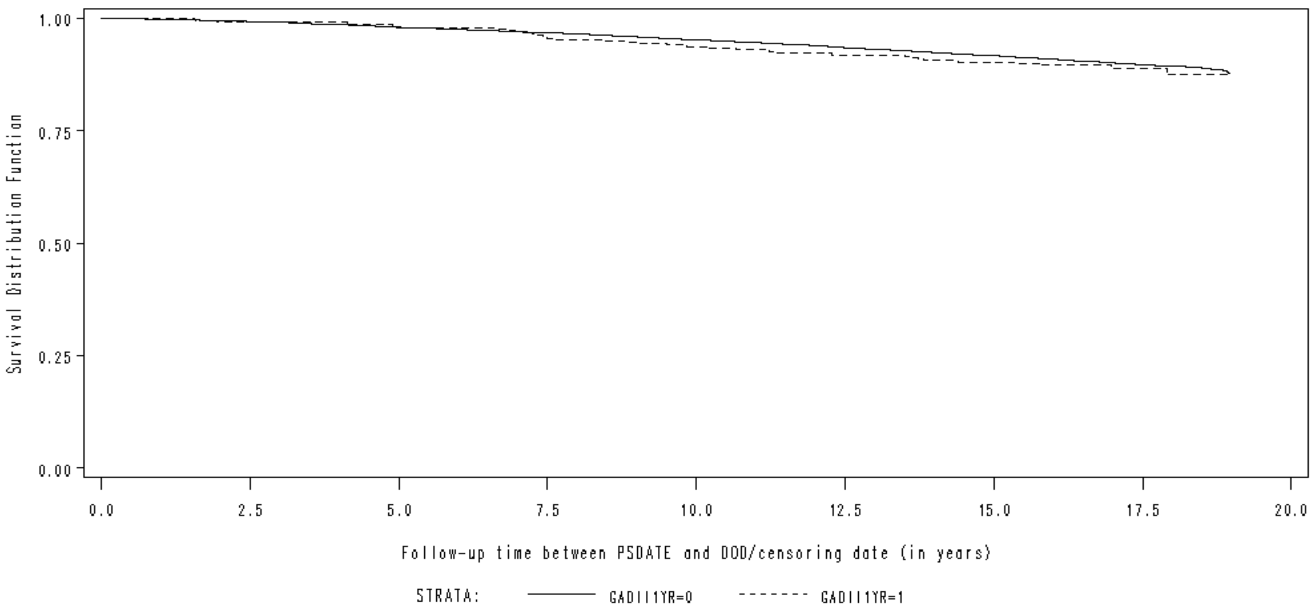
The Kaplan Meier curves, which are not multivariate-adjusted show that there is almost no difference between people with and without GAD. However, after adjusting for age, the association with all-cause mortality is evident (HR=1.51, 95% CI: 1.22, 1.88), as is the association with cancer mortality (HR=1.55, 95% CI: 1.11, 2.16). This is because age is a negative confounder. Age is highly associated with mortality, but people with anxiety are younger (and younger people in general tend to have low mortality rates). After the effect of age is taken into account and adjusted for, the strong association between anxiety and mortality becomes apparent.

All-cause mortality: Kaplan Meier curve of people with and without GAD



The dotted line represents people with anxiety (GADII1YR=1), while the thicker line represents people without anxiety (GADII1YR=0). PSDATE is the date when the HLEQ was completed and GAD ascertained, while DOD means date of death.

Cancer mortality: Kaplan Meier curve of people with and without GAD



The dotted line represents people with anxiety (GADII1YR=1), while the thicker line represents people without anxiety (GADII1YR=0). PSDATE is the date when the HLEQ was completed and GAD ascertained, while DOD means date of death.

Appendix 6: Percentage and number of people with missing past-year GAD reported in 1996-2000 according to sociodemographic factors, health status, and behaviour risk factors for the European Prospective Investigation of Cancer in Norfolk cohort

Characteristic	Total number with characteristic	Percentage and no. with missing past-year GAD
Socio-demographics		
Age (years)		
<65	10428	1.0 (107)
>=65	5869	1.4 (80)
Education[‡]		
Low	5377	1.2 (64)
High	10920	1.1 (123)
Marital status		
Single	593	1.7 (10)
Married	13270	1.1 (140)
Other[*]	2434	1.5 (37)
Social class		
Manual	6031	1.2 (70)
Non-manual	10266	1.1 (117)
Health status		
Physical conditions		
Yes[+]	1498	1.5 (23)
No	14799	1.1 (164)
Disability level		
High[¶]	8179	1.5 (123) [a]
Low	8118	0.8 (64)
Lifetime MDD		
Yes	2604	3.1 (80) [a]
No	13693	0.8 (107)
Lifestyle		
Category of body mass index		
Higher (>=26)	7693	1.1 (81)
Lower (<26)	8604	1.2 (106)
Physical activity level		
Inactive	4496	1.1 (48)
Active[¥]	11801	1.2 (139)
Smoking status		
Current	1667	1.6 (26)
Former	6836	1.1 (77)
Never	7794	1.1 (84)
Alcohol intake		
>=21[α]	1313	1.1 (14)
14-21	1385	0.7 (10)
7-14	3198	1.0 (32)

<7	10401	1.3 (131)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: stroke, heart attack, cancer

¶ Below the median PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

[a] $P < 0.001$

[b] $P < 0.05$

Appendix 7: Multiple imputations for missing data

I imputed missing data separately for men and women. Based on the literature, I identified 22 potential auxiliary variables; however, I retained eight variables that were correlated with the variables in my model and were good predictors of the missing status (based on statistical tests). My imputation model included all variables in the analysis model, the auxiliary variables, the Nelson-Aalen estimate of cumulative hazard, and the event indicator.

To retain as much information as possible, I conducted the imputations on non-transformed data-the original variables in my dataset. I imputed data using the fully conditional specification, and specified a linear regression model for continuous data that were normally distributed; predictive mean matching for continuous data that were not normally distributed; and logistic regression for categorical variables. Variable estimates were subsequently averaged from 5 imputed datasets using Rubin's rules [226] (I transformed the data before running the analytic model of interest within each of the imputed datasets).

I checked whether the imputations were acceptable by comparing 1) the means, standard deviations, and plots of recorded and imputed values for continuous variables, and 2) the frequencies and percentages of recorded and imputed values for each level of categorical variables.

Analyses were done using Statistical Analysis Software (SAS) Version 9.3 (SAS Institute, Cary, NC) and p-values less than 0.05 were considered statistically significant.

Auxiliary variables used in the imputation model

Variable	Questionnaire	Description of variable
Psychological factors		
SOC	HLEQ	Self-reported. This concept was coined by Antonovsky and represents a construct of salutogenic theory. [227] It is an individual's ability to cope with stressful life circumstances, which in turn, has an influence on health and health behaviours. An individual with a strong SOC believes that what happens in his or her life is comprehensible, manageable, and meaningful. A strong SOC facilitates adaptive coping when confronted with difficult situations.
Mastery	HLEQ	Self-reported using the Pearlin and Schooler Mastery Scale. Mastery is having a sense of control over one's life or the belief that one has control over future important life circumstances. It represents a coping resource that people use to manage or attenuate the impact of stressors, and this in turn, has an influence on health and health behaviours. [228, 229]
Neuroticism	HLEQ	Self-reported using the Eysenck Personality Inventory. A tendency towards experiencing negative, distressing emotions. [230]
Sociodemographic factors		
School age	HLQ Questionnaire	Self-reported age when participant left school.
Index of Multiple Deprivation (IMD)	2001 Census	The IMD [231] was derived from 2001 Census data and linked to the EPIC-Norfolk cohort using participants' postal codes. The IMD is one of the most commonly used measures of area deprivation in the UK. It is an aggregated measure of income, employment, health, education, housing and services, crime, and the living environment. [231]
Physical health		
History of psychiatric illness	HLQ	Self-reported history of other psychiatric illness
History of arthritis	HLQ	Self-reported history of arthritis
History of back pain	HLQ	Self-reported history of back pain

The following auxiliary variables were not included in the imputation model, because they were not correlated with the variables in my model and were not good predictors of the missing status (following tests using Pearson's/Spearman's correlation coefficient and t-tests/chi-square tests): composite measures of maternal and paternal affection using the Rossi scale [232], systolic and diastolic blood pressure measured using an Accutorr noninvasive oscillometric blood pressure monitor, self-reported ethnicity, and self-reported history of: cholesterol, migraine, diabetes mellitus, thyroid problems, hay fever, asthma, bronchitis, allergies, and benign tumours.

Appendix 8: Percentage and number of people with missing past-year GAD reported in 1996-2000 according to sociodemographic factors, health status, and behaviour risk factors for the EPIC-Norfolk cohort

Characteristic	Total number with characteristic	Percentage and no. with missing past-year GAD
Socio-demographics		
Age (years)		
<50	2385	1.1 (26)
50-60	6279	1.1 (70)
60-70	5787	0.9 (54)
70+	3685	1.3 (47)
Sex		
Women	10055	1.2 (118)
Men	8081	1.0 (79)
Education[‡]		
Low	6178	1.2 (72)
High	11958	1.1 (125)
Marital status		
Single	695	1.3 (9)
Married	14687	1.0 (149)
Other[*]	2754	1.4 (39)
Social class		
Manual	6918	1.2 (82)
Non-manual	11218	1.0 (115)
Employment		
Yes	7775	0.8 (63)[b]
No	10361	1.3 (134)
Health status		
Physical conditions[+]		
Yes	9285	1.3 (119)[b]
No	8851	0.9 (78)
Disability level		
High[¶]	9030	1.4 (130)[a]
Low	9106	0.7 (67)
Psychiatric conditions		
Past-year MDD		
Yes	983	5.0 (49)[a]
No	17153	0.9 (148)
Behaviour risk factors		
Physical activity		
Active[¥]	12963	1.1 (141)
Inactive	5173	1.1 (56)
Smoking status		
Current smoker	1922	1.5 (29)
Former smoker	7543	1.0 (73)
Never smoker	8671	1.1 (95)

Alcohol intake		
>=21[α]	1423	0.9 (13)
14-21	1525	0.7 (10)
7-14	3523	0.9 (32)
<7	11665	1.2 (142)

‡ High education: O-level, A-level, degree; low education: refers to no education

* Other: divorced, separated, widowed

+ Physical conditions: respiratory disease (asthma and bronchitis), allergies and hay fever, stroke, heart attack, cancer, diabetes, thyroid conditions, arthritis

¶ Below the median PCS value of 50.6

¥ Moderately inactive, moderately active, active

α 1 pint beer=2 units, 1 glass wine=1 unit, 1 glass sherry=1 unit, 1 glass spirits=1 unit

[a] $P < 0.001$

[b] $P < 0.05$

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