Comorbidity of anxiety and depression - an examination of nosology, measurement and overlap.

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Prologue

Dr. John Langtry started his part-time Ph.D. in Psychology in September 2013 after 20 years in Northern Ireland Fire and Rescue Service (NIFRS). His career in the NIFRS was distinguished - in 2001 he was awarded an MBE for services to the Fire Service (he was one of the first two officers on the scene after the Omagh bombing). John's Ph.D. aimed to examine levels of occupational and psychological stress in the UK Fire Service, and how this was related to the existing provision of psychological support within different brigades. He had worked tirelessly on his Ph.D. and he had managed to successfully recruit 1,300 current and past members of the fire service to take part in an online survey. This was the largest and most comprehensive survey of its kind and has been facilitated and supported by the Fire Service and also the Fire Brigades Union.

John died in November 2017 after bravely battling cancer for a number of years. Shortly before this I had spoken with John, and he told me that he was keen that his work continued. I assured John that I would make sure that that happened. During 2018 a funded Ph.D. studentship at Ulster University was advertised to continue John’s research – the Faculty of Life and Health Sciences funded this. John was awarded a posthumous doctorate in July 2019, and his son Ethan collected the award during the graduation ceremony.

In September that year Marcin Owczarek started work on the Ph.D. project. Marcin worked tirelessly getting to grips with John's data, and he gradually started to see how the various parts of the survey could go together. The core psychological constructs were Posttraumatic Stress Disorder (PTSD) and Complex PTSD (CPTSD), and Marcin produced the first ever prevalence estimates of these disorders for UK firefighters. PTSD and CPTSD were assessed using a standardised measure, the *International Trauma Questionnaire*, and the ICD-11 PTSD criteria were met by 5.62% of the participants, and 18.23% met the criteria for CPTSD. The experience of increased traumatic work-related events increased the likelihood of both PTSD and CPTSD, however, non-work-related stressors were only associated with CPTSD. These findings were written up and published as a peer-reviewed journal article in the European Journal of Psychotraumatology (doi.org/10.1080/20008198.2020.1849524) and John was the lead author. The findings from this study have been subsequently cited in papers in prestigious journals such as *The Lancet*, *Journal of Traumatic Stress*, and *Frontiers in Psychiatry*. This comprehensive paper has highlighted John's important work and with 1788 reads from the journal website alone, the important message about the psychological impact of working in the emergency

services has been widely disseminated. I think that John would consider this '…a job well done'.

John had planned to supplement this quantitative research with interviews with current and retired firefighters. John was still in close contact with the NIFRS and the Fire Brigade Union and could have easily recruited participants. Unfortunately, Marcin would have struggled with this line of research, not through lack of effort, but rather we had no connections in NIFRS/FBU and no experience of the job as a firefighter. We decided to pivot and change the direction of the thesis. Marcin had an interest in common mental health disorders and decided to look at the phenomenological and statistical overlap between these disorders. What has resulted is a hugely impressive thesis that addressed some very basic, but fundamentally important, questions about the nature of psychopathology and how psychologists have conceptualised and quantified 'psychological distress'. Marcin has also developed and grown into a young scholar with enormous potential; he has published widely and has developed a broad network of national and international collaborators. I have no doubt that John would be proud that Marcin carried the mantle on his behalf, and I also know that Marcin has always been incredibly grateful and honoured for the opportunity that John afforded him.

On a personal note, it was an honour for me to have supervised John during the early parts of his doctoral research. He tackled his academic work in the same way that I suspect he approached everything else in life, with commitment, hard work, determination and good humour. He was well-liked and held in high regard by everyone who knew him in Ulster University. When I last spoke with John he was in hospital. He was characteristically positive, determined, and in true John fashion, his spirit was indomitable. He told me, with great understatement, that he had a tough few days. I can say without hesitation that in the face of such adversity he is the bravest man I have ever met. He faced his final challenges

with dignity and strength. Even then, John had the time to ask me how I was and enquired about my family. Quite simply John Langtry, now Dr. Langtry, was a gentleman.

Professor Mark Shevlin

Abstract

Depression and Anxiety are two of the most common internalising disorders in the world. Depressive and anxiety disorders are associated with significant impairments and lead to considerable personal, economic, and societal burden. Although these disorders are characterised by high comorbidity putting their validity as separate clinical categories into question, this is not reflected in the current diagnostic manuals – the DSM-5 and ICD-11. While depression and anxiety share common genetic, biological and societal underpinnings, only inconclusive evidence as to the distinction and similarity of their symptoms is available. The current series of studies aimed to remedy that by examining the possible reasons for their comorbidity through different methodologies. First, thematic coverage of systematically obtained scales that measure the two constructs was examined. Results highlight that not only do measures that supposedly measure the same constructs differ widely, but there is also a non-negligible cross-construct overlap in symptoms measured. Second, using multiple nationally representative and community samples from the UK and ROI, bifactor analyses examined whether depression and anxiety are better represented as a single measurement construct. Results suggest that treating the two constructs as unidimensional provides greater parsimony and higher convergent and divergent validity when compared to using both measures separately. Third, factor mixture models examined how anxiety and depression manifest within the population using a nationally representative sample of UK adults. The results suggested that symptoms of depression and anxiety co-occur more often than they occur as separate disorders with implications for how these disorders are specified within diagnostic manuals. Fourth, network analysis examination of comorbid depression and anxiety revealed a symptom network suggestive of depression and anxiety as being highly interwoven. This suggested that comorbidity is not simply a phenomenon of the two disorders co-occurring, but rather that they are intimately connected. The results have implications for the entire field of depression and anxiety science-beginning with conceptualisation, measurement methods, diagnosis, treatment and treatment evaluation.

Contents

1. Introduction

This chapter introduces the topic under investigation. Starting with a description of issues with how depression and anxiety are conceptualised, prevalence rates and their high comorbidity. Issues brought by their comorbidity along with potential reasons for it are outlined. Gaps in knowledge regarding the clinical validity of depression and anxiety differentiation are identified. Finally, this introductory chapter concludes with areas of investigation that inform further empirical chapters.

The description and representation of mental illness have seen substantial changes since the inception of psychopathology as a scientific venture. With the advent of the 'modern' diagnostic manuals in the form of the International Classification of Diseases (ICD) and the 3rd edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), the concept of 'anxiety neurosis' has been replaced with a plethora of disorders that, while linked, offer a systematic and distinct taxonomic approach to mental illness. The impetus for this distinction, beyond the will to describe reality in an accurate manner, lies within a notion that constructing a clearly delineated taxonomy of affective disorders, with distinct, operationally defined diagnostic criteria, will lead to better outcomes for the ones affected (Stavrakaki & Vargo, 1986). Under the conditions where any two disorders are distinct in terms of presented symptoms, risk factors, comorbidities, therapeutic outcomes (pharmacological and otherwise), underlying theoretical assumptions of cause, neurochemistry and genetic underpinnings– this is an easy task. Anxiety and depression, despite seeing their taxonomic departure from 'neurosis' close to 40 years ago, in 1980, are two disorders that may not easily fall into two easily distinguishable categories. Worldwide, many anxious patients present with concurrent symptoms of depression and many depressed patients present with concurrent symptoms of anxiety (Jacobson & Newman, 2017).

Depression and anxiety are among the most prevalent mental health disorders with around 20% of the global population suffering symptoms (Steel et al., 2014). In the United States, around 13.1 million adults suffer from a depressive episode and 40 million experience anxiety each year (Kessler et al., 2003; Kessler et al., 2012). Some sources suggest increased costs of healthcare for sufferers, estimated to be almost tripling the costs for those with depression (König et al., 2020) and more than doubling the costs for those affected by anxiety disorders (Konnopka & König., 2020). Findings from the Global Burden of Diseases Study in 2015 show that depressive disorders and anxiety disorders were the third and ninth leading causes of nonfatal burden, respectively (Mokdad et al.,

2018). The profound impact of these disorders is reflected not only in its economic costs, but in the many challenges and impairments experienced by individuals with depression across multiple life domains, including general health – with those affected being more likely to also suffer from sleep disturbance (Alvaro et al., 2013), substance use disorder (Regier et al., 1998), impaired social and workplace performance (Löwe et al., 2008) and suicide (Kalin, 2021) among others.

The severity of the impact depression and anxiety have on the sufferers is exacerbated by the comorbidity each of the disorders shares with the other. Comorbid depression and anxiety may occur at any age from childhood to adolescence through to old age. Those suffering from this comorbidity can expect a more disabling, more resistant to treatment form of illness with a greater risk of suicide, and more severe psychological, physical, social, and workplace impairment when compared to just experiencing one condition alone (Tiller, 2013). Depending on estimation, for those who received a diagnosis, up to 85% of patients with depression also show significant anxiety symptoms and similarly up to 90% of patients with anxiety show significant depression symptoms (Gorman, 1996).

So far, the field finds itself in an interesting conundrum. The two most common psychological disorders in the world, with severe impacts on both the economy and personal well-being, just 40 years ago used to be classified as one disorder and currently are separate disorders albeit with comorbidity of upwards of 80%. This raises the question of whether either one of these disorders meets the criteria of clinical validity. Kendell (1989) proposed that the clinical validity of a psychological disorder requires that it should meet certain criteria, among which (beyond simply formulating it) a disorder should demonstrate the boundaries between the disorder and other related disorders. These boundaries include: exhibiting different clinical outcomes, having different biological and genetic bases and different associated symptoms.

In a study involving over 5000 participants from the US as part of the National Comorbidity Survey, Kessler et al., (2008) found that the risk factors for developing symptoms of either anxiety or depression were similar and increased with similar magnitude for each of the risk factors present. Childhood adversities (including the divorce of parents, physical abuse, sexual abuse and neglect), and internalising disorders in parents

(including depression and anxiety disorders along with substance disorders) all increased the likelihood of reporting anxiety or depression symptoms.

The literature concerned with the therapeutic outcomes of those affected by either depression or anxiety is substantial while there is a scarcity of data on the treatment of patients with comorbid depression and anxiety. Therefore, clinical practice is determined by treating individual anxiety and depressive disorders, probably driven by the 'special status' of comorbidity (Tyrer et al., 2021). However, there exists substantial commonality in certain aspects of both. For most patients, no obvious medical aetiology can be established – meaning that the onset of both is very often indeterminate (Tiller, 2013). Furthermore, most effective treatments for depression also diminish anxiety symptoms and when comparing Cognitive Behavioural Therapy and antidepressants (Selective Serotonin Reuptake Inhibitors - SSRI) in the treatment of anxiety and depression, a meta-analytic study by Roshanaei-Moghaddam et al., (2011) showed no significant differences between the success rates in treating the two disorders – i.e. the effectiveness of either method was similar across the two psychopathological constructs. Furthermore, when compared to the pre-DSM-III studies, the reported longer-term outcomes for both anxiety and depression do not differ substantially with around 50% of individuals presenting with residual symptoms after 10–15 year follow-ups and having overall poorer non-psychiatric outcomes (Tyrer et al., 2021). While certainly not posing a strong piece of evidence, in the absence of modern "neurosis vs. depression and anxiety" studies, this can certainly act as an impetus for further research.

From a neurochemical point of view, managing brain oxidative stress through high dietary polyphenol intake has been shown to hold some promise in reducing the prevalence of anxiety and depression in population studies, suggesting a common pathology pathway between the two disorders (Es-Safi et al., 2021). Indeed, the past fifteen years yielded substantial evidence that the gut microbiome modulates brain function, including influencing brain chemistry (Jameson & Hsiao, 2018). Most probably the relationship between the gut, the brain and subsequent anxiety and depression is modulated by GABA-producing microbiota (Duranti et al., 2020) and the gut influence on brain serotonin levels (although the mechanism of action is still not well described; Jameson & Hsiao, 2018). Another biomarker shared between anxiety and depression lies within the C-reactive protein which is a marker of inflammation and can be used to predict both anxiety (Khandaker et al., 2016) and depression (Wium-andersen et al., 2013).

Furthermore, two studies examining twins, suggested that genetic predisposition to both anxiety and depression is governed by the same genes- obtaining a correlational unity (r=1) in their results (Kendler, 1996; Roy et al., 1995) with later studies reporting associations of .08 (Smoller, 2020). Therefore, overall, from a biological perspective, depression and anxiety appear to share a substantial amount of biological underpinnings. This poses a question of whether it is the psychological domain that separates them.

In theory, measures of depression and anxiety are designed to distinguish between disorders and exclude clinical features that are shared between the two. Therefore, criteria for depression, by design, should exclude common comorbid anxiety symptoms, and those for anxiety disorders should exclude symptoms of depression. Diagnostic criteria are however not the same as clinical presentations – some of which are often purely somatic (Tiller, 2013). These are also often shared between anxiety and depression and include: muscle aches and pains, muscle tension, headaches, dry mouth, choking sensation, "churning stomach" sensation, nausea, vomiting, diarrhoea, heart palpitations, tachycardia, chest pain, flushing, shortness of breath, dizziness, vertigo, blurred vision, paraesthesia and loss of libido (Tiller, 2013; Kapfhammer, 2022). It is important to note that there is no one somatic symptom associated with either anxiety or depression that can differentiate between the two, although there is some mixed evidence suggesting that, at the population level, the two disorders differ in magnitude (Bekhuis et al., 2015). It is also important to note that while most of the symptoms listed here could also be shared with other internalising disorders, the 'uniqueness' criterion for other disorders can be satisfied or their severity is diagnostically meaningful – respectively, partial sleep (sometimes called 'local sleep'- when the patient is partially asleep and partially awake) resulting from hypervigilance in PTSD (Gupta, 2013) and cachexia and appetite disorders in anorexia and bulimia (Van Rijn, 1998).

Therefore, the clinical validity of separate designations of anxiety and depression, given societal and genetic risk factors, epidemiology (high comorbidity) and similar underlying biological processed and somatic manifestations should be questioned. However, when examining the symptoms themselves, as expressed in psychometric scales, the same conclusions are not as easy to be made. A 10-year systematic review of a common measure of anxiety and depression - Hospital Anxiety and Depression Scale, suggested wide disparity when it comes to the factor structure of the measure with 2, 3 and 4 factors emerging (Cosco et al., 2012). The evidence for divergent or convergent validity of

anxiety and depression scales is equivocal, with some studies suggesting good divergence (Snyder et al., 2000; Osman et al., 1997), and others suggesting convergence (Lee, 2019), and others suggesting a measure-specific relationship (Koeter, 1992). There are regrettably fewer factor analytical studies. Again, some studies have suggested that anxiety and depression compose separate dimensions (Boelen & van den Bout, 2005; Stark & Laurent, 2001) and others conclude that anxiety and depression scales are essentially measuring the same underlying construct (Feldman, 1993; Bados et al., 2010). Other studies show inconclusive results (Chung & Kim, 2013). With the advent of network analysis in psychometric sciences, a new avenue of symptom-based research was made available. Interwovenness of symptoms of anxiety and depression was examined. However, the results are inconclusive with examinations suggesting a strong divergence of symptoms (Beard et al., 2016), symptom community overlap (Kaiser et al., 2021), and anxiety symptoms being highly central in a depression network (Fried et al., 2016), anxiety and depression forming a community in a network of distress symptoms (Price et al., 2019).

Taken together, despite posing a non-negligible economical and human suffering burden, depression and anxiety are surprisingly ill-examined 40 years after their differentiation from neurosis. While sharing common genetic, biological and societal underpinnings, the field of psychology, as it stands right now, provides only inconclusive evidence as to their distinction. With answers depending on how the question is asked methodologically. To remedy this, a comprehensive, evaluating look at the field is needed. The following studies aim to provide a nomological network of cumulative evidence, amassing knowledge using different samples and state-of-the-art methodologies to examine how depression and anxiety are best conceptualised. Starting with the very tools psychologists use to measure these constructs, to how anxiety and depression manifest within society, the uni- vs multi-dimensionality of the construct/s and interwovenness of the symptoms. It is hoped that the insights gained will yield important information for the diagnosis, prevention and, ultimately, the treatment of these debilitating conditions.

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Chapter 2: “Between apples to apples and apples to oranges” – a systematically informed examination of content overlap between and within self-report measures of anxiety and depression.

2.1 Introduction

Many self-report questionnaires have been developed purporting to measure negative emotional states. In the case of anxiety and depression, self-report measures are often used in studies either as an outcome, predictor, moderator, or covariate variables across numerous disciplines not just including psychology and psychiatry – e.g.: nutrition, epidemiology (Firth et al., 2012; Hettema et al., 2001). The process of using self-report measures often involves administering a measure, obtaining a score, and then making inferences about how the score reflects, or is reflected on, by other measures. However, anxiety and depression can be measured using a plethora of self-report measures which while well-validated and widely used, are not equal when it comes to the symptoms the measures purport to measure.

The proliferation of inventories, scales and measures in psychology is an issue that is rarely explored. For example, Santor et al., (2006) report that since 1918 more than 280 measures of depression have been developed and a number of them are still in use today. Similarly, a general anxiety disorder can be inferred by using a myriad of measures and while no studies exist establishing an approximate total number similar to Santor et al., the number of 'widely used ones' is higher than three (Julian, 2011; McHugh & Behar, 2009). While these numbers are surprising, it may be explained by the fact that as our understanding of psychological phenomena increases within the psychological literature, such developments also influence the development of more up-to-date measures. These then would be compared, refined and their purpose, strengths and downfalls would be taken into consideration when choosing them for use in research. While partially true when it comes to comparison (Julian, 2011; Preljevic et al., 2012) and refinement (Eaton et al., 2004; Reynolds & Richmond, 1979; Wells et al., 2013), the strengths, relationship to accepted definitions of disorders, and differences between the scales are rarely considered (Snaith, 1993; Keedwell & Snaith, 1996). Both in the research of anxiety and depression the researchers often assume that as long as a scale is validated and 'widely used' it is appropriate to use it as it is reflective of the underlying construct and bears no difference to other, similar scales. Therefore, the choice of a scale often falls to personal preference or convenience (Keedwell & Snaith, 1996). This may not be the case. There are multiple studies comparing the performance of scales supposedly measuring one underlying construct – recently, a study comparing four instruments measuring Covid-19 related

anxiety showed only moderate similarity (Kubb et al., 2020). Examples of these studies are numerous and extend to the measurement of depression (Cameron et al., 2008; Titov et al., 2011) and anxiety (Zimmerman et al., 2020; Clover et al., 2020) both in terms of scales measuring the same construct being discriminant to each other and differential identification of caseness (i.e. scales identify severity at different levels).

The distinctiveness of anxiety and depression is an object of debate (Tyrer, 2001). Although the two are separate in both main manuals for the classification of diseases (ICD-11 and DSM 5), they both often co-occur and share many symptoms (Pollack, 2005). In the National Comorbidity Survey conducted in the United States, 58% of individuals suffering from major depressive disorder (MDD) also presented with comorbid anxiety disorder and 67% of individuals with generalized anxiety disorder (GAD) presented with comorbid depression (Kessler et al., 1996; Judd et al., 1998). More recently prevalence of comorbidity for those diagnosed with either one of these disorders has been reported as 85-90% (Tiller, 2013), other reports yet report prevalences of between 25 and 50% (Johansson et al., 2013). Keeping in mind how different measures can produce different results while seemingly measuring the same disorders, these discrepancies may be a result of not only differences in sampled groups or current 'psychological zeitgeist' (i.e.: changing prevalence trends of psychopathology on society-wide scale) but may indeed lie in scale choice. While both anxiety and depression share a common core of negative affect (Pomerantz & Rose, 2014), the case may be that this core is 'polluting' developed and well-validated scales of one disorder with symptoms that would serve better as being diagnostically distinguishing for the other or even non-specific to either but rather reflective of psychopathology as a whole.

The landscape of research into anxiety and depression is therefore facing two major problems that may contribute to idiosyncrasy of results: a) within-construct well validated scales are used interchangeably while being dissimilar in terms of symptoms measured to each other – i.e. have the potential of producing varying results, b) scales measuring one of the disorders may capture symptoms of the other – for example, due to the scales containing items that represent symptoms which while present in both, are not specific to either of the disorders. To remedy these problems, the present study aims to examine symptoms measured by systematically obtained validated scales of depression and anxiety. The methodology will follow the example of Fried (2020) who examined 52 symptoms of depression across 7 scales and calculated their overlap using Jaccard indices. The present

study aims to improve and expand upon the paper by obtaining the scales used within the study through systematic means rather than using 'common' scales. In the light of the contested status of the depression-anxiety dichotomy, the study will also include measures of anxiety. It is predicted that the difference between measures within each of the constructs will be lower than the difference between the measures across the constructs of anxiety and depression but that the differences will be small.

2.2 Methods

The study design consists of 3 steps:

1) Systematic search - a systematic search of the published literature was performed to obtain developed, validated self-report measures of general anxiety and depression. To meet the selection criteria, the studies obtained also need to present consideration of the factor structure of the measure, be non-specific when it comes to age suitability of the scale (e.g. measures specifically designed for adolescents or older respondents were excluded), not be topical or attached to another disorder other than anxiety or depression, be published in English and not be a version or translation of another measure.

2) Content analysis- using the NVivo software the measure are then assigned codes based on the symptoms present.

3) Statistical analysis- Similarity indices were calculated for each scale when compared to another within both depression and anxiety scales.

2.2.1 Systematic search

A systematic search of published literature was conducted using the following databases: Web of Science, Pubmed and ScienceDirect. The following search strategy (expressed in Boolean syntax) was used for Web of Science and adapted for each of the databases used:

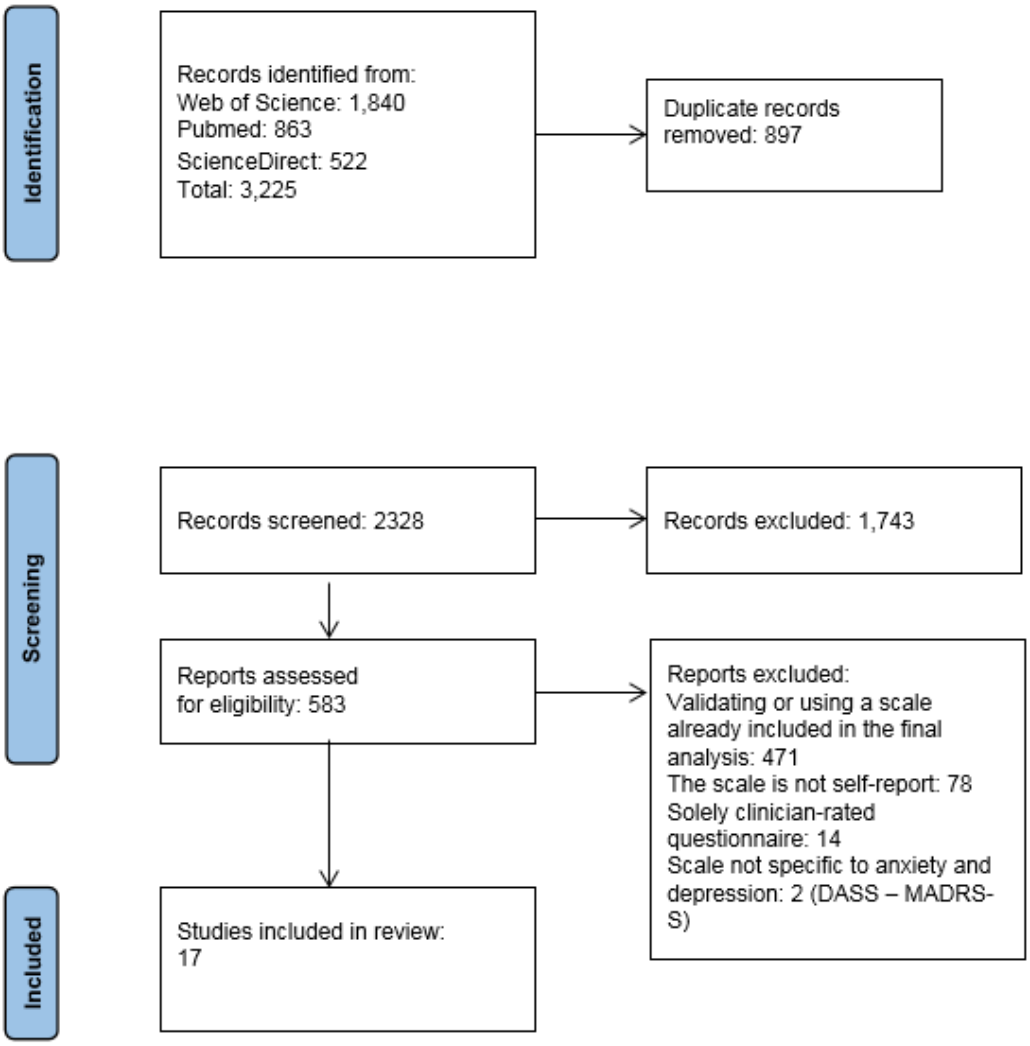
((ALL=(Anxiety OR Depression) AND ALL=(measure OR scale OR inventory) AND ALL=(Develop* OR Validation) AND ALL=(factor analysis OR factor structure) AND ALL=(self-report OR self-report) NOT ALL=(youth OR young OR adolesce* OR geriatric) NOT ALL=(meta OR review)) NOT ALL=(adaptation OR Language OR translat*)) AND LA=(English).

This search strategy was reflective of the search goals in that it involved selecting published papers that included developed and validated self-report measures of general anxiety and depression that had been established through the use of factor analysis and had not specified their use based on age. The exclusion criteria of not being used specifically for measuring anxiety and depression in 'special' populations could not be expressed in the search terms as it encompassed too broad of a range of topics (e.g. pregnant, ill, performing a specific job, being part of a certain population). Therefore, these cases were judged individually, on a case-by-case basis by examining the abstracts.

2.2.2 Study selection

The study selection process was done entirely by one author (the PhD researcher) – this is expanded upon in the limitations section. Initial search results were obtained from Web of Science, Pubmed and ScienceDirect databases and duplicates were removed (Figure 1). Results were then screened for eligibility. Studies not directly relevant to the review were excluded. Common themes of studies that were excluded involved: (1) Studies that explored themes of anxiety and depression where the main examined construct was not anxiety or depression (e.g. cancer and other diseases, alcohol and substance abuse), (2) specific anxiety disorders outside of general anxiety disorder (e.g. worry, social anxiety, etc.), (3) studies about general stress, (4) clinical interviews. Next, the final list of X studies was assessed for eligibility. A large number of studies included involved validation studies and factor analysis explorations of established scales. Therefore, a large number of studies were effectively 'duplicates' in that they utilised the same scales used in the final analysis. A number (N= 78) of the studies were not self-report scales and either involved a clinician-assisted interview or a clinician-filled checklist. Two scales presented a specific reason for exclusion: DASS (Lovibond & Lovibond, 1995) a scale involving 3 factors of depression, stress and anxiety – which was excluded due to the stress subscale potentially acting as a confounding factor when considering anxiety and depression subscales - e.g. items otherwise sufficiently loading on anxiety or depression subscales being co-opted into the stress factor; and MADRS-S which is part of a CPRS-SA (Svanborg & Åsberg, 1994) which also includes competing factors (Goekoop et al., 1992; Bertschy et al., 1992) and presents similar problems to DASS. The final list consisted of 17 scales listed in Table 1. The study selection process is shown in Figure 1.

Figure 1. Systematic search progression



2.2.3 Data Extraction

Data extraction was performed using the NVivo software. Content analysis of the scales involved extraction of measured symptoms based on the items in each scale. Given the nature of the analysis certain levels of subjectivity of the researcher were involved (see: limitations section). Similar items were collapsed into the same category, for example, the 'Trouble relaxing' item from the GAD-7 and the 'Unable to relax' item from BAI were both assigned the 'Unable to relax' code. Items that measured more than one symptom were assigned more than one code, for example, IDS-SR included an 'Aches and pains' item which involved answers pertaining to symptoms of headaches and joint pain – both of these were assigned a separate category. The methodology also allowed for one symptom to appear more than once within a scale, for example, IDS-SR includes two items 'Feeling sad' and 'Quality of mood' with answers for both including experiencing sadness. The scale was then assigned the code twice but the final analysis only considered the presence of a symptom within a scale and not its frequency. The items were reviewed to capture every linguistic nuance that the scales may present and collapsing of items into categories capturing the perceived meaning of the item was not performed – for example, experiencing 'The blues' and 'Sadness' were coded as separate symptoms. This was to ensure a low degree of reviewer bias. Finally, the present study avoids collapsing compound and specific symptoms into the same category. Items concerning somatic symptoms, different types of insomnia and changes in appetite were coded separately in accordance with how they were presented within the scale – for example, if a scale indicated trouble falling asleep the symptom assigned indicates 'early insomnia' but if the scale was nonspecific and asked about 'poor sleep' the category assigned is similarly nonspecific ('Poor sleep'). Similarly, different somatic symptoms present in different scales may influence the endorsement of an item- for example, headaches might be endorsed more widely than joint pain or a difference between their endorsement might be noticed when comparing anxiety and depression scales – a distinction that would be lost if both were assigned into a somatic symptom category. Another distinction lost if these items were collapsed into wider categories would be information about how these symptoms are measured in anxiety vs. depression scales- for example, if depression scales pose certain questions more broadly than anxiety scales and vice versa. While this may

lead to a proliferation of different symptoms and in consequence may lead to increased heterogeneity among the scales, it was decided that this fits with the premise of not assuming that similar items fit into the same categories for the benefit of comparison of what is being asked between anxiety and depression scales.

2.2.4 Statistical analysis

Similar to Fried (2017), the content overlap was estimated using the Jaccard Similarity Coefficient. In the present study, it represents the overlap between two scales and the values it can assume range from 0 (no overlap) to 1 (absolute overlap). For each of the scales used, a list of representations of the overall symptom pool was generated and a value was calculated based on the formula $J = s/(u1 + u2 + s)$ where J is the Jaccard coefficient value, s is the number of items the two lists share, u1 is the number of items unique to the first list and u2 is the number of unique items in the second list. For the sake of interpretability, it is important to note that items not present in both of the lists (i.e. not being present in either of the scales) are not considered in the equation and therefore despite the number of total symptoms among the scales, the Jaccard coefficient is not affected - i.e. if the two scales have a small number of items when compared to the total their similarity index is not affected by a shared number of overall values that are not present in both. Following the methodology in Fried (2017), the present study also uses cut-off points from Evans (1996) to interpret Jaccard values- very weak 0.00–0.19, weak 0.20–0.39, moderate 0.40–0.59, strong 0.60–0.79, and very strong 0.80–1.0.

2.3 Results

2.3.1 Systematic search results and scale performance

Systematic search yielded 17 scales across 15 inventories spanning 236 items- 99 total items for anxiety scales and 137 for depression scales. The scales included were divided into those measuring anxiety (N=8) and Depression (N=9). Two of the inventories included in the final analysis included subscales of anxiety and depression, namely: the Goldberg Anxiety and Depression Scale (Goldberg et al., 1987) and the Hospital Anxiety

and Depression Scale (Zigmond & Snaith, 1983) and therefore their respective subscales were used in the analysis.

Table 1. Measures included in the study.

Scale/subscale used full name	Short Name	Measurement	Number of items	Number of symptoms	Number of idiosyncratic symptoms	Number of idiosyncratic items within a respective construct	Author
Generalized Anxiety Disorder 7	GAD-7	Anxiety	7	9	1	1	Spitzer et al., (2006)
Beck Anxiety Index	BAI	Anxiety	21	22	8	9	Beck et al., (1993)
Goldberg Anxiety and Depression Inventory (anxiety subscale)	GADS (ANX)	Anxiety	9	14	1	2	Goldberg et al., (1987)
Hospital Anxiety and Depression Scale (anxiety subscale)	HADS (ANX)	Anxiety	7	7			Zigmond & Snaith (1983)
ICD-11 Anxiety scale	ICD-11 ANX	Anxiety	5	5			Goldberg et al., (2017)
State-Trait Anxiety Inventory	STAI	Anxiety	20	16	4	8	Spielberger (1970)
Severity Measure for Generalized Anxiety Disorder	GAD-D	Anxiety	10	20	6	6	Lebeau et al., (2012)
Zung Self-Rating Anxiety Scale	Zung-ANX	Anxiety	20	26	3	7	Zung (1971)
Patient Health Questionnaire 9	PHQ-9	Depression	9	18			Löwe et al., (2004)
Beck depression inventory	BDI-II	Depression	21	28	4	5	Beck et al., (1987)

Quick Inventory of Depressive Symptomatology	QIDS	Depression	16	17			Rush et al., (2003)
Inventory of Depressive Symptomatology – self-report	IDS-SR	Depression	30	40	7	15	Rush et al., (1986)
Center for Epidemiological Studies-Depression scale	CES-D	Depression	20	18	4	4	Locke & Putnam (1971)
Goldberg Anxiety and Depression Inventory (depression subscale)	GADS (DEP)	Depression	9	11	1	1	Goldberg et al., (1987)
Hospital Anxiety and Depression Scale (Depression subscale)	HADS (DEP)	Depression	7	9	2	2	Zigmond & Snaith (1983)
ICD-11 Depression scale	ICD-11 DEP	Depression	5	6			Goldberg et al., (2017)
Zung Self-Rating Depression Scale	Zung-DEP	Depression	20	24		2	Zung (1986)

Included scales along with their abbreviations, what they measure, the number of items, symptoms derived from content analysis and Idiosyncratic symptoms (those that do not appear in any of the other scales) are presented in Table 1. The number of items vary across scales and while most scales include items that involve more than one symptom- e.g. questions about somatic symptoms or other compounded questions (e.g. 'Depressed or hopeless' in PHQ-9 or 'Loss of interest or pleasure in doing things' in ICD-11 DEP). Other items were coded as measuring the same symptom (e.g. 'I could not "get going"' and 'I felt that everything I did was an effort' were both coded as 'high effort in actions' in CES-D).

2.3.2 Scale overlap

Overlap among the scales was estimated using the Jaccard index. The results are presented in Table 2. The mean overlap when considering all scales included (overall overlap) is 0.137. Mean overlap was also estimated for within-construct similarity- it reflects how similar scales of anxiety are to other scales of anxiety and the same procedure was performed for depression scales. The mean within-construct overlap for anxiety scales was 0.211 and for depression scales, it was 0.255. Cross-construct mean overlap representing a mean value of similarity between anxiety and depression was 0.04. These results suggest that scales are overwhelmingly dissimilar to each other across constructs and are less dissimilar within constructs.

Specific overlap was also considered. Scale overlap ranged from 0 to 0.52. The highest similarity was observed between BDI-II and PHQ9 at 0.52. HADS (ANX) with ICD-11 (ANX) at 0.5 and PHQ-9 with QIDS at 0.5. The highest cross-construct similarity was observed for IDS-SR and Zung-ANX at 0.20, Zung-Dep with Zung-ANX at 0.16. It is important to note that despite the cross-construct similarities being low, they present some higher values than some of the within-construct values of which the weakest are: for anxiety- STAI and GADS (ANX) at 0.07 and BAI and ICD-11 ANX at 0.08 along with two pairs for depression – IDS-SR with ICD-11 (DEP) at 0.12 and CES-D with GADS (DEP) also at 0.12.

For anxiety, GAD-7 showed the highest mean similarity to other measures of the same construct, however, its difference to the 'runner-ups' was negligible and the overall similarity between the scales was weak to very weak. For depression, PHQ-9 and QIDS showed highest overall similarity to other measures of depression. The overall within-construct similarity for depression measures was weak to very weak.

The most commonly endorsed symptoms were 'Restlessness' and 'Concentration difficulty' – both endorsed by 11 and 10 different scales respectively. It is important to note that 'Concentration difficulty' was endorsed by all of the depression scales and only one anxiety measure (STAI). 'Restlessness' showed more heterogeneity in scale inclusion being included in GAD-7, HADS-ANX, ICD-11 ANX, STAI, GAD-D and Zung-ANX from the anxiety construct and PHQ-9, BDI-II, QIDS, IDS-SR and Zung-DEP from the depression construct (Figure 2).

2.4 Discussion

The study examined the content differences in anxiety and depression measures. The measures were obtained in a systematic way, their content was analysed qualitatively to obtain a list of symptoms for each. These were used to establish similarity indices (Jaccard) between the scales. The analysis identified 15 inventories for comparison of which, two (GADS, HADS) included separate anxiety and depression subscales. Content analysis of these 15 scales (17 when considering subscales of HADS and GADS) identified 99 symptoms. 11 subscales showed symptoms that were idiosyncratic when considering the entire symptom pool of both constructs. When examining within-construct idiosyncrasy, 6 anxiety scales and 6 depression scales showed idiosyncratic symptoms. The within-construct overlap was higher than the cross-construct overlap with notable exceptions (explored below). 'Concentration difficulty' and 'Restlessness' were included in the largest number of different scales, however, 'Restlessness' showed higher heterogeneity – being included across both constructs to a higher degree.

The key finding of the present study is that it identifies a high degree of heterogeneity both within and across the measures of anxiety and depression. The within construct disparity – i.e. the degree to which scales measuring either anxiety or depression are different from other scales measuring the same construct based on the symptoms measured; is considerable for both anxiety and depression scales. The similarity values when compared

to Fried (2017) are lower for the depression scales. This may be due to differences in methodology used, as the previous, similar examination considered items as opposed to symptoms, with one item being allowed to be only reflective of one symptom. Conversely, the assumption in the present study was that one item may include more than one symptom. Additionally, publication by Fried (2017) included a lower number of scales. In the light of previous studies finding a high correlation between the scales within a construct both for measured anxiety (Naeinian et al., 2011; Marcolino et al., 2007) and depression (Polaino & Senra, 1991; Marcolino et al., 2007), the within-construct disparity observed might be an indicator of the scales measuring an underlying construct through different means. For example, if the common cold was measured by four symptoms: cough, stuffy nose, muscle ache and high body temperature – different measures including a varying number of items (two or three out of the four) measuring these symptoms in any combination would, in theory, be a useful diagnostic tool – i.e. the tool would predict the common cold to a high degree of accuracy. However, mere usefulness does not always translate to a good diagnostic tool. For example, difference in identifying severity of a disorder might lead to diagnostic decisions based on imperfect information and might lead to patient outcomes that would change depending on the diagnostic tool used (for an example involving depression see: Cameron et al., 2008; anxiety: Clover et al., 2020). In the common cold example, hypothetically, including the 'stuffy nose' item might lead to overdiagnosis while 'muscle ache' might lead to underdiagnosis. An additional difficulty one should consider is how this hypothetical symptom set, sets the 'common cold' apart from other diseases, for example, the flu. Assuming high symptom similarity between these two diseases in an environment where diagnostic tools differ widely, the diagnostic outcomes as well as prevalence rates and potential overlap might differ based on diagnostic tools used. The present study highlights this issue by providing information about the symptom overlap for self-report scales within and between anxiety and depression.

Another consideration that could be entertained based on the results of the present study is 'in the light of high symptom disparity within the scales, should the research efforts be steered towards using measures that encompass all of the symptoms present within each of the two constructs?'. The casual and interchangeable use of sum score scales as all being sufficiently representative of the measured construct might impede the progress science makes in describing the disorders these constructs represent. In the light of some, perhaps

fringe, examinations supporting heterogeneity of depression (Van Loo et al., 2012) and anxiety (Hantouche et al., 2005; Ferdinand et al., 2007) sub-types, the use of scales not capturing the gross number of known symptoms is unwarranted if accuracy of description is the goal- i.e.: scales capturing more of the symptoms may be more suitable to capturing the different subtypes and, furthermore, may provide a more robust description of the state of mind of the patient.

The present study is the first one to examine cross-construct symptom overlap between anxiety and depression self-report measures. The study partially supports the notion that the high comorbidity between anxiety and depression is not majorly the result of measures of both asking the participants about experiencing the same symptoms. However, it may be a contributing factor, depending on the scale pairs used and it should be considered when administering pairs of scales that include the same symptom. Apart from 'restlessness' which was included in 6 anxiety scales and 5 depression scales, certain symptoms showed more cross-construct presence than others. 'Heart pounding' (included in both ZUNG scales), 'indecisiveness' and any indicators of sleep problems (poor sleep and different types of insomnias) are all examples of symptoms present across the two constructs (Figure 1). Overall, the cross-construct overlap values were lower than within-construct overlap values. However, some anxiety scales were more similar to measures of depression – e.g. the similarity of STAI and GADS (anxiety) was half of that observed between STAI and QIDS. Similarly, some measures of depression were more similar to measures of anxiety- e.g. the similarity of IDS-SR and ZUNG (anxiety) was higher than the similarity between IDS-SR and ICD-11 (DEP) as presented in Table 2. The disparity in these similarity scores may therefore present a challenge to the generalisability and replicability of the results depending on the scale pairs used with some presenting symptom overlap that, while low, is higher than zero and may contribute to, previously described, high variance in reported rates of comorbidity.

Considering the findings of this study, one has to tackle the question of whether high within-construct similarity and low cross-construct similarity are indeed desirable scale characteristics. High within-construct similarity would be indicative of an agreed-upon and well supported set of symptoms for both anxiety and depression. This is not the case. First, different scales may be constructed for different purposes. For example, BDI was initially developed to screen for the severity of depression in samples with the previous diagnosis and held population norms as its reference while PHQ-9 is used for population studies and

uses criterion-based DSM-IV (American Psychiatric Association, 2000) reference. Similarly, for anxiety, ZUNG (anxiety) uses a population norm as a reference and was conceived to clinically diagnose individuals while GAD-7 uses a criterion-based (DSM-IV; American Psychiatric Association, 2000) reference. Other methodological assumptions may contribute to scale effectiveness and should be focused on by future researchers in light of contextual scale appropriateness- for example, whether a scale is more suitable as a screener in the general population or whether it is better suited as a clinical tool. Both anxiety and depression may arise as comorbid disorders to other diseases and may share a fraction of the symptoms with them (e.g. diabetes - Smith et al., 2013; De Groot et al., 2001; high blood pressure- Hildrum et al., 2008) which in turn can impact which individual symptoms are associated with the disorder depending on when and on whom the scale is validated. Furthermore, scales should be cognisant of the time of onset, genetic, environmental and stage (time since onset) of each of the constructs measured to inform the appropriateness of their application. Access to this knowledge is still scarce but newer developments are beginning to consider these factors (Cai et al., 2020). However, current practices of using these scales interchangeably without consideration for their idiosyncrasies contribute to drawing conclusions about anxiety and depression based on a set of considerably different measurement tools that may in effect be no different from using one low reliability and low validity (i.e. 'blunt') tool. This is not appropriate and can jeopardise the generalisability and replicability of findings.

While low cross-construct similarity between anxiety and depression could be considered desirable, one has to consider the origins of these disorders. The origins of separation between the two from a diagnosis of 'neurosis' or 'cothymia' can be traced back to DSM-III which a) which assumed that the same symptom cannot be a part of more than one disorder (Robins, 1994). DSM-III was informed by separate committees with regard to mood and affective disorders (Shorter & Tyrer, 2003). More modern considerations of the diagnostic schemas are beginning to question the distinction in the light of unclear boundaries between disorders, disorder cooccurrence, heterogeneity within disorders and diagnostic instability (Kotov et al., 2017). In light of these insights, the separation of anxiety and depression may have influenced the methodology behind the development of scales. For example, both constructs present with similar somatic symptoms (Haug et al., 2004), and these show to be nonspecific when examining anxiety and depression (Stulz & Crits-Christoph, 2010). In practice, the extent of anxiety and depression separation may be

inflated and the observation within the present study that some measures of one construct are more similar to measures of the other rather than ‘sister’ measures of the same construct might be an artifact of this phenomenon. Therefore, while more research is needed, the low cross-construct similarity of scales might not be reflective of the underlying reality. Nevertheless, the present study supports the notion that, from the perspective of symptom content, anxiety and depression measures are largely separate. If the aim of a potential study within which the dissimilarity of anxiety and depression is desired (for example, comorbidity) the present study may serve as a guideline for deciding which scales have no overlap and should therefore be used.

The findings of the present study have to be considered with certain limitations in mind. The present study could have been improved by involving additional researchers in both the systematic review and symptom coding part of the analysis. Calculating researcher agreement would contribute greatly to the validity of these findings as other raters might evaluate both the screened papers and their contents differently. However, the aims of the study were aimed at providing dissimilarity in symptoms and, perhaps improving upon Fried (2017), the items themselves could be differentiated into different symptoms so that one item can measure more than one symptom and that allowed for a lower amount of grouping symptoms into higher, arbitrary categories based on an inevitable degree of personal preference. Another limitation lies within the inclusion criteria. The study evaluated only self-report scales and the full symptom spectrum that would have been obtained from interview schemas is omitted. Inclusion of these in the analysis might yield different results. However, self-report tools are cost-effective when compared to interviews performed by clinicians and see wide use. Therefore, they represent a considerable proportion of published papers on the subject and, in consequence, the field in its entirety.

2.4.1 Conclusion

Taken together, the scales presented with low levels of similarity to other measures within their respective constructs. This should be considered as a warning against using these scales interchangeably and as a call for more consideration of which scale is used for what

purpose. This disparity also extended into cross-construct evaluation. The effectiveness of using any measurement pair from across the two constructs should take into account symptom overlap and that can be examined using the results of the present study.

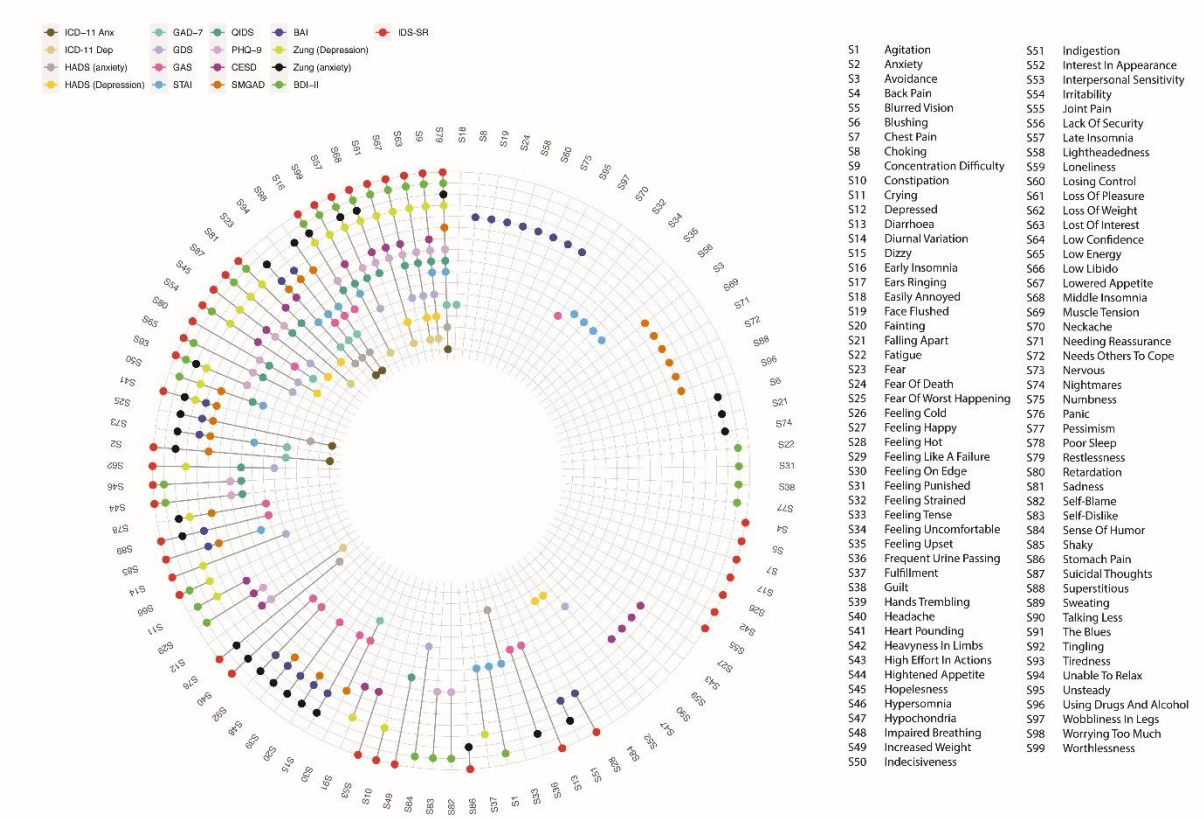
Table 2. Scale similarity.

	GAD-7	BAI	GADS (ANX)	HADS (ANX)	ICD-11 ANX	STAI	GAD-D	Zung-ANX
GAD-7	-							
BAI	0.11	-						
GADS (ANX)	0.21	0.16	-					
HADS (ANX)	0.33	0.12	0.11	-				
ICD-11 ANX	0.40	0.08	0.12	0.50	-			
STAI	0.25	0.12	0.07	0.28	0.17	-		
GAD-D	0.32	0.24	0.13	0.23	0.25	0.24	-	
Zung-ANX	0.17	0.30	0.29	0.18	0.15	0.11	0.28	-
PHQ-9	0.04	0.00	0.03	0.04	0.04	0.06	0.03	0.13
BDI-II	0.06	0.00	0.05	0.03	0.03	0.13	0.04	0.10
QIDS	0.04	0.00	0.03	0.04	0.05	0.14	0.06	0.10
IDS-SR	0.07	0.07	0.10	0.04	0.05	0.08	0.07	0.20
CES-D	0.08	0.03	0.03	0.04	0.00	0.10	0.03	0.05
GADS (DEP)	0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.03
HADS (DEP)	0.00	0.00	0.00	0.00	0.00	0.04	0.00	0.00
ICD-11 DEP	0.00	0.00	0.00	0.00	0.00	0.10	0.00	0.00
Zung-DEP	0.06	0.02	0.09	0.03	0.04	0.14	0.10	0.16
Mean Jaccard index- overall	0.13	0.08	0.09	0.12	0.12	0.13	0.13	0.14
Mean Jaccard index - anxiety	0.26	0.16	0.16	0.25	0.24	0.18	0.24	0.21

Table 3. Scale similarity continued

	PHQ-9	BDI-II	QIDS	IDS-SR	CES-D	GADS (DEP)	HADS (DEP)	ICD-11 DEP	Zung-DEP
PHQ-9	-								
BDI-II	0.52	-							
QIDS	0.50	0.45	-						
IDS-SR	0.34	0.33	0.39	-					
CES-D	0.23	0.24	0.17	0.18	-				
GADS (DEP)	0.30	0.18	0.33	0.21	0.12	-			
HADS (DEP)	0.23	0.13	0.19	0.14	0.18	0.27	-		
ICD-11 DEP	0.25	0.17	0.21	0.12	0.20	0.13	0.27	-	
Zung-DEP	0.31	0.44	0.41	0.42	0.31	0.25	0.19	0.20	-
Mean similarity indices									
Mean Jaccard index -overall	0.19	0.18	0.19	0.18	0.12	0.12	0.10	0.10	0.20
Mean Jaccard index -depression	0.34	0.31	0.33	0.27	0.20	0.22	0.20	0.19	0.32

Figure 2. Symptoms of anxiety and depression



Note: BAI - Beck Anxiety Index; GADS (ANX) - Goldberg Anxiety and Depression Inventory (anxiety subscale); HADS (ANX) - Hospital Anxiety and Depression Scale (anxiety subscale); ICD-11 ANX - ICD-11 Anxiety scale; STAI - State-Trait Anxiety Inventory; GAD-D - Severity Measure for Generalized Anxiety Disorder; Zung-ANX - Zung Self-Rating Anxiety Scale; PHQ-9 - Patient Health Questionnaire 9; BDI-II - Beck depression inventory; QIDS - Quick Inventory of Depressive Symptomatology; IDS-SR - Inventory of Depressive Symptomatology – self -report; CES-D - Center for Epidemiological Studies-Depression scale; GADS (DEP) - Goldberg Anxiety and Depression Inventory (depression subscale); HADS (DEP) - Hospital Anxiety and Depression Scale (Depression subscale); ICD-11 DEP - ICD-11 Depression scale; Zung-DEP - Zung Self-Rating Depression Scale.

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Chapter 3: Parsing depression and anxiety: a bifactor investigation of general and specific components using representative and community samples from the United Kingdom and the Republic of Ireland

3.1 Introduction

Anxiety and depression are two of the most common internalising disorders in the world. Anxiety lifetime prevalence in Europe was previously estimated to be 14.5 % and in the US was as high as 33.7% (Bandelow & Michaelis, 2015). Depression lifetime prevalence in Europe was estimated at 8.56% (Ayuso-Mateos et al., 2001) and in the US it reached 13.23% (Hasin et al., 2005). Global disease burden of anxiety disorders has been calculated at 335 Years Lived with Disability (number of years lost due to ill-health, disability but not early death) per 100,000 people and depression contributes 738 years per 100, 000 people which constitutes the single largest contributor to non-fatal health loss (World Health Organization, 2017). For comparison, in the UK, years of life lost per 100,000 people due to ischemic heart disease is 688 and 649 for trachea, bronchus and lung cancer (Steel et al., 2018). The impact these disorders have on human well-being is therefore substantial and its consequences span from prenatal development (with growing evidence that children born from mothers suffering from anxiety and depression are negatively affected; Kinsella & Monk, 2009), through childhood and adolescence (Johnson et al., 2000), negatively impacting quality of life well into adulthood (Koivumaa-Honkanen, et al., 2004).

To this day, the distinctiveness of anxiety and depression is still a subject of considerable debate. Comorbidity between these disorders is reportedly high and they share many common symptoms (Pollack, 2005). It has been reported that between 47 to 88% of individuals diagnosed with one disorder will meet the criteria for the other (Jacobson & Newman, 2017; Choi et al., 2020). High comorbidity rates present several issues in terms of drawing clean boundaries between the diagnoses. It has been previously suggested that treatment-resistant varieties of both anxiety and depression are often showing high comorbidity with the other respective disorder (e.g. depression with anxiety and vice versa). These show poorer responses to antidepressant therapies (Fava et al., 1997; Davidson et al., 2002) and cognitive behavioural treatments (Durham et al., 2012). Conversely, further strengthening the similarity between anxiety and depression, individuals with symptoms of either disorder were shown to respond favourably to similar lines of treatment such as exercise (Carek et al., 2011; Martinsen, 2008), selective serotonin reuptake inhibitors (SSRIs; Walkup et al., 2008) and CBT treatments which, while differing between anxiety and depression (severe depression warranting a

combination of CBT and SSRI treatment; Brent et al., 1998), both focus on adaptive thoughts and behaviour when faced with negative emotionality, problem-solving and assertiveness (Weersing, 2004).

In terms of nosology, there exists conflicting factor analytic evidence with some studies suggesting that the two disorders are indeed separate (Boelen & van den Bout, 2005; Stark & Laurent, 2001) and others that anxiety and depression scales are measuring the same underlying construct (Feldman, 1993; Bados et al., 2010). This conflicting evidence also extends beyond factor analytical methodology. Multiple network analysis approaches suggest inconsistencies in the way anxiety and depression are conceptualised and operationalised in terms of diagnostic schemas. Fisher et al., (2017) suggested that feelings of worry and depressed mood held the least influence over the overall network comprised of 21 descriptors of low mood and anxiety symptom nodes. It is important to note that worry and depressed mood are principally held as 'gatekeeping' questions in many diagnostic approaches (e.g. ICD: Goldberg et al., 2017; DSM: American Psychiatric Association, 2013). On the other hand, Garabiles et al., (2019) found strong bridging symptoms between the two scales with one of the network nodes being depressed mood – a symptom that is commonly conceptualised as central to depression but also one that suggests negative affect is captured by both anxiety and depression scales.

Both anxiety and depression have previously been suggested to be associated with a number of psychological or behavioural disorders and are well described in terms of their comorbidities and risk factors (e.g. Muyan et al., 2016; Weersing et al., 2012; Spinhoven et al., 2014). It appears that any threat or damage to one's psychological homeostasis may result in heightened anxiety and depression. This high interconnectedness between anxiety and depression and several external psychopathological factors serves as another point of contention against the distinctiveness of the two. While several studies report differences in the magnitude of how anxiety and depression are related to external phenomena, suggesting that either anxiety or depression plays a larger part in predicting or being predicted by said phenomena, the results, as discussed below, are not replicated in different studies.

Loneliness is widely cited as being predictive of both anxiety and depression (Muyan et al., 2016, Liu et al., 2016; Heinrich & Gullone, 2006). Loneliness itself is often considered when examining one's psychological resilience. Indeed, family cohesion and 'social resources' outside of family settings, in addition to personal dispositions, play a major part in one's resilience (Hjemdal et al., 2011). While its well-operationalised

taxonomy is still to be defined, resilience is perhaps best broadly defined by maintaining positive psychological outcomes despite adversity (Friborg et al., 2005). While resilience plays a role in anxiety and depression, a number of studies report stronger protective effects for anxiety (Bitsika et al., 2010, Roberts et al., 2020), others suggest that it plays a larger role in depression (Carvalho et al., 2016; Anyan & Hjemdal, 2016), while others yet suggest largely similar effects (Smith et al., 2008). Resilience as a protective factor is implied not only in anxiety and depression symptoms but its protective effects extend to other areas such as diminishing the fear of death (Fortner & Neimeyer, 1999) and increasing the tolerance of uncertainty (Arici-Ozcan et al., 2019).

Many measures of anxiety and depression involve an item, or items, that are aimed at assessing functional impairment (Julian, 2011; Kroenke et al., 2019). Anxiety has been previously shown to impair one's ability to perform in work and social duties (Löwe et al., 2008). Depression is also frequently associated with significant impairments in social functioning (Löwe et al., 2008). This encompasses an individual's overall interaction with their environment, involving work, social activities and familial relationships (Bosc, 2000; Mundt et al., 2002; Rosellini et al., 2018). Functional impairment resulting from both anxiety and depression, according to current theories, is a result of an interplay between biological predispositions to experience heightened stress, maladaptive cognitions (e.g. feelings of worthlessness, poor problem solving,) and behavioural maladaptations (e.g. avoidance; Weersing et al., 2012). Furthermore, indirectly suggesting a continuous relationship between functional impairment and both anxiety and depression, subthreshold anxiety and depression have been suggested to negatively impact both work and social functioning (Karsten et al., 2013).

The relationship between somatic symptoms, anxiety and depression has long been debated. While anxiety and depression are associated with increased somatic symptoms during adolescence (Ginsburg et al., 2006) and adulthood (Bekhuis et al., 2015), the causal relationship between the disorders is unclear. Studies of this relationship are ridden with major confounds, for example, anxiety and depression can exacerbate the perceived severity of somatic symptoms (Michaelides & Zis, 2019); an increased number of different somatic symptoms increases one's chance of being diagnosed with anxiety and depression (Little et al., 2007). The speculated mechanisms of these relationships are also a matter of discussion: onset of somatic symptoms might act as a triggering mechanism for vulnerable individuals and conversely the deterioration of an individual's health may lead to systemic changes and as a result be causal to depression and anxiety (Goodwin, 2006). Another

confounding aspect lies within both anxiety and depression being suggested as explaining similar variance in somatic symptoms in several studies (e.g. Haug et al., 2004; Creed et al., 2012) while other studies suggest that somatisation is explained better by depression than anxiety (Bekhuis et al., 2015) or that anxiety is a better predictor for poor physical health (Niles & O'Donovan, 2019). Taking into account the confounds outlined above, the current scientific consensus suggests that anxiety and depression both are strong predictors of somatic symptoms, however, the temporal ordering (i.e.: which disorder precedes the other), as well as 'a better predictor' of the symptoms are unclear.

The mechanism behind the comorbidity between anxiety, depression and post-traumatic stress disorder (PTSD) is a matter of debate. Reported comorbidity among individuals suffering from PTSD ranges from 39% to 97% for anxiety, and from 21% to 94% for depression (Ginzburg et al., 2010; Spinhoven et al., 2014). Spinhoven et al., (2014) suggested that this wide range can be explained by the use of a wide variety of methodological approaches: the disorders may be causally linked (i.e. one is a necessary prerequisite for the others to develop), the disorders may present a high degree of symptom overlap (Gros et al., 2012), or the symptoms of each disorder may be independent while sharing common risk factors (e.g. trauma). The causal relationship between anxiety and PTSD symptom severity was previously examined by Marshall et al., (2010) who suggest that the relationship is reciprocal – anxiety increases PTSD symptoms which in turn increases anxiety in a positive feedback loop manner. Similarly, the relationship between depression and PTSD was previously suggested to be involving bidirectional causality, common risk factors, and common vulnerabilities (Stander et al., 2014). Conversely, Breslau (2002) suggests that individuals who were exposed to a traumatic event and do not develop PTSD, are at no higher risk of developing anxiety or depression which indirectly stands against the 'common risk factors' explanation. Wild et al., (2016) suggest that, for the development of depression and PTSD, cognitive styles and resilience played a major part. The similarities between how anxiety and depression relate to PTSD are partially explained by Byllesby et al., (2016) who modelled the factors comprising PTSD and anxiety and depression in a bifactor model with the assumption that the 'general' factor represents negative affect. The results suggested some significant commonalities between the grouping factors (PTSD, anxiety and depression) but also suggested that PTSD was more distinct from anxiety and depression than the two were to themselves. Taken together, these studies suggest that the comorbidities may result from overlapping

symptoms – i.e. are an artifact of diagnostic specification of the disorders (Spinhoven et al., 2014).

While the role of anxiety and depression in psychotic-like experiences (PLE) is not well defined, their co-occurrence suggests that anxiety and depression are both predictors of PLEs. PLEs, which include delusions and hallucinations, are relatively common in the general population with an approximate 5% prevalence (van Os et al., 2009). While PLEs are usually associated with a diagnosis of psychosis, individuals who experience symptoms of anxiety and depression are also more likely to report experiencing them (Varghese et al., 2011). Depressive symptoms have previously been associated with auditory hallucinations (De Loore et al., 2011) and anxiety and depression symptoms were suggested to differentiate the content of those hallucinations (see Scott et al., 2020). Individuals reporting PLEs were reported to have elevated symptoms of anxiety and depression that remained stable over time (Mackie et al., 2011).

The problem of the perceived similarity between the two constructs is therefore supported both by research on the psychometric and symptomatic structures but also by comorbidities these constructs show with a myriad of other disorders. To solve the issue of high similarity between the two constructs, bifactor modelling was often employed (Simms et al., 2012; Simms et al., 2008; Gomez et al., 2020). Bifactor modelling provides a distinct alternative to traditional first-order and higher-order confirmatory factor analysis (CFA) models in that it allows for covariation among observed indicators to be explained by a general factor and specific factors. The factors are not hierarchical and the general factor is loaded on by each examined item while the items loading on specific 'grouping' factors are no different from previous conceptualisations with each item loading on the general factor and, at most, one additional orthogonal group factor (in this case two, anxiety or depression). Previous results of high comorbidity and conflicting results on the factor structure of the two scales, lead to much ambiguity in terms of the underlying structure of anxiety and depression. Therefore, it is appropriate to employ a bifactor methodology that allows for exploration of the commonality between the disorders while accounting for the extent to which they reflect a specific factor (their uniqueness).

Recent methodological insights, however have highlighted problems with common approaches to how the bifactor models have been evaluated and interpreted. Namely the bifactor's tendency to provide biased goodness-of-fit indices and over-interpretation of the bifactor model itself. One of the main criticisms is an overreliance on model fit indices (see Rodriguez et al., 2016b). This is due to consistent superior goodness-of-fit being

suggested to be often observed due to the model's ability to capture noise in the data (Bonifay & Cai, 2017; Bornovalova et al., 2020). This presents a problem in the field, as many publications use superior fit as undisputed support for a particular theory concerning the 'general' factor (Bonifay & Cai, 2017). Conversely, Morgan et al., (2015) in their Monte Carlo simulation study, suggest that the bifactor model is favoured when the simulated data is sampled from a truly bifactor structure and when sampled from a truly higher-order data. When samples were selected from a truly correlated factors structure, the fit indices were more likely to favour the correlated factors solution as the best fitting and not the bifactor solution. They also suggest that out of all the three models tested (higher order, bifactor and correlated factors) each of the models tended to fit the data well, opening up investigating the models based on investigations outside of model fit indices (e.g. usefulness, theoretical conceptualisation, substantiveness and parsimony).

Another major issue with using bifactor models lies with interpreting the general factor. Strong positive correlations (as observed with anxiety and depression) do not necessarily have to be indicative of a common causal structure but rather a common manifestation (Bonifay & Cai, 2017). Furthermore, the interpretation of the grouping factors presents a challenge as they may present unique subconstructs not captured by the general factor that is nonetheless useful if interpreted properly but can also reflect a realistically uninterpretable 'husk' when the general factor is too strong as it seeks to absorb as much variance as possible (Bornovalova et al., 2020).

These issues can be addressed. Assuming that a superior model fit of the bifactor model is to be expected, Bornovalova et al., (2020) propose that bifactor models can be used to inform the interpretation of multifaceted scales in terms of the utility of their summed scores versus subscale scores and to describe the measured construct's relations with external variables. Psychometric scales that are composed of multiple subscales pose a question of whether it is more meaningful to interpret their total, as opposed to subscale, score and to what extent each of these interpretations account for score variance. Factor loadings obtained using the bifactor analysis can be used to compute a number of indices that help inform the researcher in this regard. Omega Hierarchical Reliability (ΩHR) of the general factor is a statistic that estimates the proportion of total variance of total summed scores (raw) of a scale that can be attributed to the general factor (Rodriguez et al., 2016b). ΩHR with addition to Explained Common Variance (ECV) which informs about the ratio of variance explained by the general factor when compared to the overall variance of the model (i.e. including grouping factors) provides insights into whether the scale's summed

score should be used from a factor analytic perspective. Furthermore, the Percent of Uncontaminated Correlations (PUC) which represents the percentage of covariance terms that only reflect variance from the general dimension can be used in conjunction with ECV to establish the parameter bias of the unidimensional solution. Finally, the Average Relative Parameter Bias (ARPB) indicates the average difference between the scale's items loading on the unidimensional (one factor) solution with the general factor loadings in the bifactor, divided by the general factor loadings in the bifactor (Rodriguez et al., 2016a).

In the case of anxiety and depression, introducing an examination of the external validity of the bifactor model can provide nosological insights into the use of the scale and what exactly it is measuring. By examining differential relations of general and group factors to external, theoretically relevant constructs, the practical utility of using these models can be established. Keeping in mind that 'all models are wrong but some are useful' (Box, 1979), comparing predictive validity between the factor analysis and bifactor solutions, would determine how much (if any) 'practical' predictive validity is lost (or indeed gained) when treating the two constructs as one consistent measure. External validation establishes whether the grouping factors provide additional explanatory power. Additionally, it provides a 'by proxy' insight into if what they encompass after the introduction of the general factor into the model is informative. In short, what this means for the interpretation of total versus subset scores is that it allows for examining which of the two is more meaningful across different settings. For example, the general factor might provide more variance towards 'general' distress measures (e.g. well-being) while specific factors might be more informative of specific issues (e.g. uncertainty intolerance).

The present study expands upon anxiety and depression dimensionality research by examining whether the measurement of these two psychological disorders can be better modelled as one transdiagnostic latent variable encompassing the commonalities between anxiety and depression. Three hypotheses will be examined: (1) that anxiety and depression are essentially unidimensional, (2) that the unidimensional solution will perform better than either anxiety and depression alone when predicting comorbidities, (3) and that these results will find replication across different samples and measurement methods (different questionnaires). These research questions will be addressed by (1) examining the bifactor indices, (2) regression modelling, and (3) examining the results across samples and methods. The present study addresses a number of shortcomings that the bifactor analysis has previously faced (overreliance on model fit indices, and

interpretation of the results). To the knowledge of the authors, no other study has addressed this research question using the same samples for establishing both the construct and external validity of the analysis. Furthermore, in the context of anxiety and depression, this is the first examination that uses a state-of-the-art, strict methodology to assess the bifactor approach to the psychometric measurement of these disorders.

3.2 Methods

3.2.1 Participants

The present study involved 4 samples:

Irish community sample

This sample involved participants from the Republic of Ireland (N=1020). The participants were recruited by the Qualtrics© survey company and were drawn from a panel (provided by Qualtrics©) in a stratified random probability manner to obtain a sample that was representative of the general adult population in terms of sex, age, and geographical distribution in accordance with 2016 census.

UK community trauma sample

This sample (N=1051) involved participants drawn from an existing online research panel that was representative of the UK adult population. Three inclusion criteria were applied to the total panel of 2653 individuals - the participants needed to (1) be born in the UK, (2) be of 18 years of age at the time of the survey and (3) screened positive for at least one traumatic event using the Life Event Checklist (Weathers et al., 2013). The selection rate was 39.6%.

UK community COVID-19 lockdown sample

This sample (N=2025) involved participants from the UK. The sampling commenced on the day that the first COVID-19 ‘lockdown’ was announced (March 23rd, 2020) and commenced 5 days later (March 28th, 2020). Data gathering was performed by Qualtrics© company. The targeted population were individuals aged 18 years and older. Quota sampling methods were used to ensure that the sample was representative of this population in terms of age, gender and household income. These were based on 2016

population estimates from Eurostat, and the household income bands provided by the Office for National Statistics for the year 2017.

US community trauma sample

This sample (N=1839) involved a nationally representative household sample of non-institutionalised adults currently residing in the United States of America. Data was collected in 2017 using an online research panel from which a random sample was drawn using probability-based sampling (Initially N=3953). To be included, an individual had to be over 18 years old and under 70 years old at the time of the survey and must have experienced at least one traumatic event (as per the Life Event Checklist; Weathers et al., 2013). Minority populations and females were initially oversampled and appropriate weights were applied for the data to be representative of the entire US population.

3.2.2 Measures

Generalized Anxiety Disorder 7-item Scale (GAD-7)

The GAD-7 (Spitzer et al., 2006) was used to measure symptoms of generalized anxiety. The scale presents the participant with 7 items representing symptoms of general anxiety to which they were required to indicate how often it bothered them over the last two weeks. The answers were presented on a four-point Likert scale (0- "Not at all" to 3- "Nearly every day"). Possible scores ranged from 0 to 21, with higher scores indicative of higher levels of anxiety. The GAD-7 has seen wide use in psychiatric and community samples (Johnson et al., 2019) and the Cronbach's α score in the present samples was excellent (Irish community sample- .942, UK community trauma sample- .952, UK community COVID-19 lockdown sample- .944, US community trauma sample- .935).

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Kroenke et al., 2001) was used to assess the symptoms of depression. The scale presents the participant with 9 items representing symptoms of depression. Participants were asked to indicate how often they experienced each symptom over the past two weeks. The scale uses a four-point Likert scale (answers ranging from 0- "Not at all" to 3- "Nearly every day"). Possible scores range from 0 to 27, with higher scores being indicative of higher levels of depression. The use of PHQ-9 has been widely supported (Gilbody et al., 2007), and the Cronbach's α score in the present samples was excellent

(Irish community sample- .921, UK community trauma sample- .938, UK community COVID-19 lockdown sample- .921, US community trauma sample- .927).

Two 5-item ICD-11 Patient Health Questionnaires (WHO-10)

Depression and anxiety were assessed using two 5-item scales originally developed for use in validity studies of ICD-11 mixed anxiety and depression (Goldberg et al., 2012). The scale was designed for short interview purposes where the pen-and-paper method of answering is unfeasible, however, its similarity to a pen-and-paper scale allows for it to be used as a questionnaire (Goldberg et al., 2017). The scale presents the participants with two sets of five questions screening for symptoms of anxiety (Anx-5) and depression (Dep-5). The participants were asked to indicate the frequency that they experienced the symptoms on a 5-point Likert scale (ranging from 0=No days to 4= Every day) with higher scores indicating higher severity of the symptoms. The scale has not been widely used but was validated across 14 countries (Goldberg et al., 2012). The Cronbach's α in the Irish community sample was excellent for both of the subscales (anxiety- .930, depression- .921).

The Work and Social Adjustment Scale (WSAS)

The WSAS (Mundt et al., 2002) is a scale designed to capture the level of functional impairment caused by a mental health disorder. The scale presents the participants with five statements referring to how the way they feel influences different areas of their life. The participants are asked to express their level of agreement with the presented items on a 7-point Likert scale (1= Strongly Agree to 7= Strongly Disagree). Possible scores range from 5 to 35 with higher scores being indicative of lower functional impairment. The scale has shown high reliability and validity in predicting global dysfunction (Zahra et al., 2014). The Cronbach's α score in the current sample was excellent (.922).

The Trauma Symptom Inventory (TSI-2)

The TSI-2 (Briere, 2011) is a 136-item self-report scale measuring 12 different sets of symptoms that can occur after one has been exposed to a traumatic event. For this study, only the Somatic Preoccupation sub-scale was used. Participants were provided with a 10-item list of problems and complaints that people sometimes have. They were to indicate how often each of these experiences has happened to them in the last six months. The items were rated on a 4-point Likert scale (0- 'Never' to 3-'often'). The possible scores

ranged from 0 to 30 with higher scores being indicative of higher levels of somatic problems. The Cronbach's α score was high (.872).

International Trauma Questionnaire (ITQ-11)

The ITQ-11 was used to measure Post-Traumatic Stress Disorder and Complex Post-Traumatic Stress Disorder (ITQ-11; Cloitre et al., 2018). The scale presents the participants with 12 items - 6 items measuring 3 PTSD symptom clusters: Re-experiencing, Avoidance and Sense of Threat; and 6 items measuring 3 clusters of 'Disturbances in Self Organisation' (DSO): Affective Dysregulation, Negative Self-concept and Disturbed Relationships. The participants are asked to indicate how much have they been bothered by the problem in the past month by using a 5-point Likert scale (ranging from 0- 'Not at all' to 4- 'Extremely'). The possible scores for the PTSD and DSO subscales range from 0 to 24. For the present study, a probable diagnosis of both PTSD and DSO was established based on endorsement of at least one item from each of the respective symptom clusters with a score of 2 ('Moderately') or higher - This was used to calculate a binary variable used in the present analysis of 'No diagnosis' (0) and 'PTSD/CPTSD' (1). The scale has seen wide use and has been validated across cultures (Knefel et al., 2020). Cronbach's α was satisfactory for both PTSD (.890) and DSO (.887).

Adolescent Psychotic-like Symptom Screener (APSS)

The APSS (Kelleher et al., 2011) was used to assess psychotic-like symptoms. The scale presents the participants with 14 items assessing hallucinatory and delusional experiences in terms of frequency and distress (7 items each). For this study, only the 7 items asking about the frequency of symptoms were used. The participants are asked to endorse the presented items denoting different psychotic symptoms on a 4-point Likert scale representing the frequency of occurrence of said symptoms (ranging from 1- Never to 4- Nearly Always). The possible scores range from 7 to 28 with higher scores indicating a higher frequency of psychotic-like symptoms. Kelleher et al., (2011) reported good predictive validity and good specificity and sensitivity for the APSS in its ability to identify Psychotic-like Experiences in the population. The Cronbach's α in the sample was excellent (.903).

De Jong Gierveld Loneliness Scale – short form (GLS)

The short form scale of the De Jong Gierveld Loneliness Scale (GLS; Gierveld & Tilburg, 2006) was used to measure loneliness. The scale presents the participants with 6 statements about how they feel at the present moment and the participants are asked to indicate their agreement on a 5-point Likert scale (ranging from 1- 'yes!' to 5- 'no!'). Possible scores ranged from 6 to 30 with higher scores indicating lower levels of loneliness. Excellent psychometric properties of the measure were supported internationally (Gierveld & Tilburg, 2010). For this study Cronbach's α reliability was good (.808).

Death Anxiety Inventory – revised (DAI)

A revised version of the Death Anxiety Inventory (Tomas-Sabado et al.,2005) was used to measure the fear of death. The participants were presented with 17 statements about death-related phenomena (e.g. 'The idea of death frightens me') and were asked to indicate their agreement with the statements on a five-point Likert scale (ranging from 1- 'totally disagree' to 5- 'totally agree'). Possible scores ranged from 17 to 85 with higher scores being indicative of higher levels of death anxiety. The scale presented excellent Cronbach's α (.938) in the sample used.

Resilience (BRS)

Resilience was measured using the Brief Resilience Scale (BRS; Smith et al., 2008). It was designed to measure resilience understood as the subject's ability to deal with and recover from environmental obstacles and stressful circumstances. It is comprised of 6 items that are answered on a 5-point Likert scale ranging from (1)- 'strongly disagree' to (5) 'strongly agree' (also using reverse coded items). The high scores are suggestive of high levels of resilience. Cronbach's α of the measure was excellent (.919) in the sample used.

Well-being (WHO-5)

Well-being was measured using the World Health Organisation Well-being Index (WHO-5; WHO, 1998). WHO-5 is comprised of five items that are associated with positive mood, vitality and overall health. Each of the items, asking about the frequency of positive affective and behavioural experiences, is rated on a 6-point Likert scale ranging from (0)- 'at no time' to (5)- 'All the time'. High scores are suggestive of higher levels of well-being. Cronbach's α was excellent (.938) in the sample used.

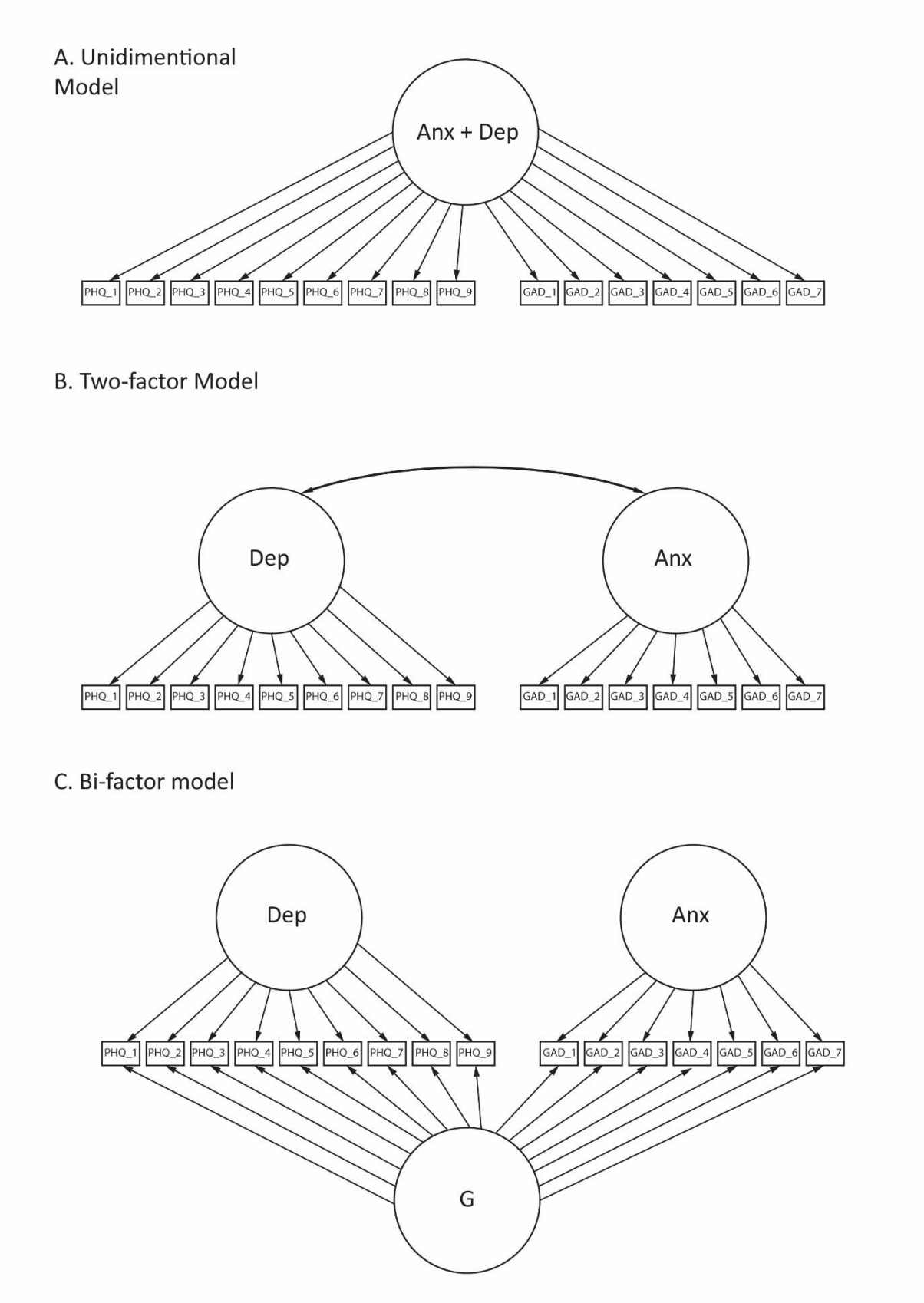
Uncertainty tolerance (IUS-R)

Intolerance of uncertainty was measured using The Intolerance of Uncertainty Scale-Revised (IUS-R; Bottesi et al., 2019). The scale presents the participants with 12 items to be rated as representing a characteristic that the participants see in themselves (e.g. “I always want to know what the future has in store for me.”, “I should be able to organize everything in advance.”). The scale is rated on a 5-point Likert scale (1) =“Not at all like me” to (5) =“Entirely like me”. The scale offered a good Cronbach’s α (.859) score in the sample used.

3.2.3 Statistical analysis

The analysis was conducted in three linked phases. First, a series of alternative factor analytic models were specified and tested. These models used either the PHQ-9 and the GAD-7 or the Dep-5 and Anx-5 to measure depression and anxiety respectively. The models are presented in Figure 3. Model A specified a model with one latent variable on which all the anxiety and depression indicators loaded. This model proposes that there is no distinction between anxiety and depression and that the latent variable represents a general dimension of psychological distress. Model B specified a model with 2 correlated latent variables, with all the anxiety indicators loading on an ‘anxiety’ latent variable and all the depression indictors loading on a ‘depression’ latent variable. Model C specified a bifactor model with a general factor affecting all items and two grouping factors, accounting for a specific anxiety and depression variance, respectively. This approach effectively models each item’s variance as the by-product of general and specific components.

Figure 3. The measurement models tested for anxiety and depression



Robust maximum likelihood estimation (MLR: Yuan & Bentler, 1997) was used as it was shown to be superior to other estimators when more than four ordered categories are used (Beauducel & Herzberg, 2006). The fit for the different models was based on the chi-square statistic with acceptable model fit being indicated by a chi-square-to-degree of freedom ratio of less than 3 to 1 (Hu & Bentler, 1999), the Comparative Fit Index (CFI; Bentler, 1990) and Tucker-Lewis Index (TLI; Tucker & Lewis, 1973) with values >.90 being indicative of acceptable fit and greater than .95 presenting excellent fit for both these indices. The Root Mean Square Error of Approximation (RMSEA) was also used, with values less than .05 indicative of excellent fit, and .05 to .08 indicating acceptable fit (Browne & Cudeck, 1993). Additionally, Standardized Root Mean Square Residual (SRMR) was calculated with values of less than .05 indicative of good fit (Byrne, 2014). The Bayesian Information Criterion (BIC) was also used for comparison of the models, models with the lower value were deemed as showing better fit (Raftery, 1995). All models were estimated using Mplus 6.12 (Muthén & Muthén, 1998).

In the second phase, for the bifactor model solutions, various bifactor reliability indices were calculated for each sample.

Omega Hierarchical Reliability (ΩHR).

ΩHR is a value that conveys the proportion of total variance of total summed scores on a scale that can be attributed to the general factor (Rodriguez et al., 2016b). High Omega Hierarchical Reliability of the general factor (ΩHR ; >0.7) is suggestive of a scale that should be interpreted based on the total scale score while low ΩHR supports considering subscale scores as a more suitable approach (Reise et al., 2013). An Omega statistic was also calculated for the grouping factors (ΩS) within the bifactor models to establish the proportion of independent variance provided by the anxiety and depression latent variables. Higher ΩS indicates that the raw subscale score consists mostly of the specific factor variance, as opposed to the general factor variance. This result would support the use of subscale scores.

Explained Common Variance (ECV).

The ECV is a ratio of variance explained by the general factor divided by the variance explained by the general and group factors (Reise, 2012). An ECV of .50 would suggest an equal distribution of common variance across general and group factors. No strongly

supported cut-off point exists for a high ECV score but Bonifay et al., (2015) suggest that values of over .70 are sufficient if other indices are used and supportive of a unidimensional approach.

Percentage of Uncontaminated Correlations (PUC).

The PUC value is the ratio of the number of uncontaminated correlations to the number of unique correlations. In other words, it represents the percentage of covariance items that only reflect variance from the general factor. PUC is also informative of appropriate ECV values to be considered when examining unidimensionality. For example, Reise et al., (2013) suggest that with PUC values lower than .80, general ECV values greater than .60 and ΩHR of the general factor higher than .70 suggest the presence of multidimensionality that is not "severe" enough to disqualify interpreting the scale as primarily unidimensional.

Average Relative Parameter Bias (ARPB)

ARPB is an average of differences between an item's loading in the unidimensional solution and the item's loading in on the general factor in the bifactor solution divided by the item's loading on the general factor. Muthén et al., (1987) suggest that values of this index that are below .10–.15 are acceptable (Rodriguez et al., 2016a).

Phase 3 involved specifying and estimating a series of regression models where factor scores from the best fitting factor analytic model from Phase 1 were specified as dependent variables. Across the 4 samples, some independent variables were common (age, gender, anxiety, depression) and some were unique to each sample (Ireland population; functional impairment, somatic symptoms; UK Clinical: psychotic-like experiences; UK population: Death Anxiety, Loneliness, Intolerance of Uncertainty, Resilience; US population: Well-being, PTSD/ CPTSD, Loneliness). The models were estimated using MLR and produced linear regression coefficients (reported as standardised for ease of comparison) and R-squared.

3.3 Results

3.3.1 Descriptive

This study used participants from four different samples (combined N= 5935). The mean age for the entire pool of participants was 45.85 years (SD= 15.39) and 59% were female (n=3502). Every individual in the UK community trauma sample (N=1051) and the US community trauma sample (N=1839) has endorsed at least one traumatic event. For additional demographic information: Irish community sample, see: Hyland et al., 2020; UK community trauma sample, see: Karatzias et al., 2019; Early UK community lockdown sample, see: Shevlin et al., 2020; US community trauma sample, see: Hyland et al., 2019. The UK community trauma sample showed the highest anxiety (M= 6.41, SD= 6.469) and depression (M=8.02, SD=7.651) scores. However, the depression scores obtained from the US community trauma sample used the PHQ-8 (other samples used PHQ-9; Kroenke et al., 2001), therefore the depression scores (M= 4.30, SD= 5.47) for that sample are not comparable to the other three samples. Descriptive statistics for the variables used within the analysis are provided in Table 4.

Table 4. *Descriptive statistics and sample characteristics for all samples*

Variables	Irish community sample (N=1020)		UK community trauma sample (N=1051)		Early UK community lockdown sample (N=2025)		US community trauma sample (N=1839)	
	Value in N (%) or Mean (SD)	Sample range	Value in N (%) or Mean (SD)	Sample range	Value in N (%) or Mean (SD)	Sample range	Value in N (%) or Mean (SD)	Sample range
Age	43.1 (15.12)	18-87	47.18 (14.998)	18- 90	45.55 (15.901)	18- 83	46.96 (14.62)	18- 70
Sex (female)	N= 520 (51%)	-	N= 719 (68.4)	-	N= 1047 (51.7%)		N= 1216 (66.1%)	
Anxiety (GAD-7)	5.65 (5.83)	0-21	6.41 (6.469)	0- 21	5.15 (5.68)	0- 21	3.76 (4.91)	0- 21
Depression (PHQ-9)	7.05 (6.84)	0-27	8.02 (7.651)	0- 27	5.37 (6.22)	0- 27	4.30 (5.47)*	0- 24
Anxiety (WHO-10: anxiety)	4.30 (5.16)	0-20						
Depression (WHO-10: depression)	4.06 (4.91)	0-20						
Functional impairment (WSAS)	23.19 (8.82)	5-35						
Somatic symptoms (TSI-2)	9.93 (6.52)	0-29						
APSS (frequency)			1.92	0- 14				
Fear of Death (FOD)					43.77 (14.90)	17- 85		
Loneliness (GLS)					4.77 (1.86)	3- 09	15.11 (4.99)	05- 27
Uncertainty intolerance (IUS-R)					42.87 (14.88)	12- 84		
Resilience (BRS)					19.61 (5.03)	6- 30		
Well-being (WHO-5)							15.00 (6.43)	0- 25
ITQ-11 (PTSD/ CPTSD)							154 (8.4%)	

*Note: *- the depression results for the US community trauma sample were based on PHQ-8, whereas the other samples used PHQ-9.*

Confirmatory factor analysis results

Results of the confirmatory factor analysis comparing the bifactor and two-factor models are presented in Table 5. For each sample, the bifactor model provided superior model fit when compared to two-factor and unidimensional models. TLI and CFI values were excellent (above .90) for both the bifactor and two-factor models. Similarly, for bifactor and two-factor models, all SRMR values were below .05 suggesting good model fit. RMSEA values suggested unacceptable model fits for the two-factor solution in the Early UK community lockdown sample (.098) and UK community trauma sample (.081) samples and all unidimensional models with the exception of the US trauma community sample (Two factors= .056; Unidimensional= .069). The superiority of model fit of the bifactor models was further supported by BIC which was consistently lower for the bifactor solutions when compared to the other two.

Table 5. CFA and bifactor model fit statistics

Sample	Method	Chi^2 (df)	CFI	TLI	RMSEA (90% CI)	SRMR	BIC
US community trauma sample	Bifactor	413.331 (75)	.956	.939	.050 (.045- .055)	.024	**43268.672**
	Two factors	594.036 (89)	.934	.923	.056 (.052- .060)	.034	43799.533
	Unidimensional	862.129 (90)	.900	.883	.069 (.065- .073)	.039	44537.152
Irish community sample ICD-11	Bifactor	133.210 (25)	.973	.952	.065 (.055- .076)	.020	**22564.091**
	Two factors	151.114 (34)	.971	.962	.058 (.049- .068)	.024	22583.494
	Unidimensional	260.098 (35)	.945	.929	.079 (.071- .089)	.030	22829.285
Irish community sample DSM	Bifactor	430.080 (88)	.957	.942	.062 (.056- .068)	.029	**31887.276**
	Two factors	547.927 (103)	.945	.935	.065 (.060- .070)	.032	32001.232
	Unidimensional	825.169* (104)	.910	.896	.082 (.077- .088)	.039	32465.852
UK community trauma sample	Bifactor	531.478 (88)	.955	.939	.069 (.064- .075)	.026	**33611.318**
	Two factors	814.976 (103)	.928	.916	.081 (.076- .086)	.038	33991.667
	Unidimensional	1208.690 (104)	.888	.871	.101 (.095- .106)	.043	34638.257
Early UK community lockdown sample	Bifactor	1039.789 (88)	.964	.951	.073 (.069- .077)	.026	**59407.380**
	Two factors	1895.035 (103)	.932	.921	.093 (.089- .097)	.042	60148.560
	Unidimensional	3469.715 (104)	.872	.852	.127 (.123- .131)	.054	61715.636

3.3.2 Bifactor indices

The bifactor indices were established using a bifactor indices calculator developed by Deuber (2017) and are presented in Table 6. ΩHR was lower for the specific factors than the general factor. The ECV computed for the general factors across the samples ranged from .840 (Early UK community lockdown sample) to .906 (ICD-11 Irish community sample) and overall suggests unidimensionality of the scales. ECV index was also computed for the grouping (specific) factors to indicate the unique variance provided by each (ECV-s). The ECV-s were negligible, ranging between .026 to .054 for depression and from .068 to .128 for anxiety. These results suggest that, across the samples, a larger percentage of variance provided by anxiety is not captured by the general factor when compared to depression. The ARPB index was within the suggested benchmarks of below 10% (Muthén et al., 1987).

Taken together, for each of the samples, PUC values were lower than .80 and ranged from .525 to .556. This, in addition to general ECV values being greater than .60 and high general factor ΩHR (>.85), suggest that despite showing some multidimensionality, anxiety and depression can be considered as a unidimensional construct.

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Table 6. Bifactor statistics for all samples

Sample	Factors	ECV/ ECV-s	Ω Hierarchical Reliability	PUC	ARPB
Irish DSM	G	.892	.932	.525	.035
	Anxiety	.071	.130		
	Depression	.038	.019		
Irish ICD-11	G	.906	.924	.556	.037
	Anxiety	.068	.126		
	Depression	.026	.016		
UK Community	G	.840	.914	.525	.087
	Anxiety	.120	.223		
	Depression	.040	.000		
UK Trauma	G	.887	.942	.525	.041
	Anxiety	.067	.120		
	Depression	.047	.015		
US community	G	.892	.927	.533	.077
	Anxiety	.041	.034		
	Depression	.067	.115		

Note: ECV/ ECV-s =Explained Common Variance; Ω Hierarchical Reliability/ Subscale Ω Hierarchical Reliability: PUC = Percentage of Uncontaminated Correlations

3.3.3 Regression models

The best fitting model obtained from CFA, the two-factor and the bi-factor models, were used in a regression analysis to predict external criterion variables. Age and gender were included in all the models as control variables. This was done separately for each of the samples and models. The results are presented in Table 7.

Table 7. Regression results for the bifactor and confirmatory factor analysis models

Sample	Model	Outcome	Controls				
			Gender	Age	G	Depression	Anxiety
Irish DSM	Bifactor	FI	.043	**.107****	**-.666****	.007	-.014
		Somatisation	.034	**.156****	**.662****	**-.138****	-.07
	CFA	FI	**.048***	**.107****	-	**-.680****	.014
		Somatisation	.045	**.164****	-	**.514****	**.167***
Irish ICD-11	Bifactor	FI	.036	**.107****	**-.587****	**-.210****	.032
		Somatisation	**.062***	**.156****	**.616****	.055	.088
	CFA	FI	.031	**.107****	-	**-.628****	.002
		Somatisation	**.057***	**.158****	-	.148	**.480****
UK Trauma	Bifactor	PLE frequency	**-.116****	**-.152****	**.412****	**.208****	**-.081***
	CFA	PLE frequency	**-.155****	**-.174****	-	**.276****	.086
UK Lockdown	Bifactor	Fear of Death	.021	**-.139****	**.338****	**.111****	**.154****
		Loneliness	.022	-.016	**.281****	-.025	.018
		Uncertainty intolerance	-.022	**-.141****	**.364****	-.032	**.164****
		Resilience	-.024	**-.169****	**-.420****	**.125****	**-.156****
	CFA	Fear of Death	.009	**-.151****	-	.051	**.321****
		Loneliness	.023	-.014	-	**.294****	-.005
		Uncertainty intolerance	-.019	**-.139****	-	.094	**.319****
		Resilience	-.038	**.157****	-	**-.192 ****	**-.281****
US community	Bifactor	PTSD/CPTSD	.023	-.013	**.507****	**.234****	.085
		Loneliness	-.035	**-.096****	**.593 ****	-.163	.017
		Well-being	.006	.005	**-.718****	**.365****	**-.100 ****
	CFA	PTSD/CPTSD	.015	-.032	-	.206	**.302***
		Loneliness	-.031	**-.091***	-	**.715****	-.106
		Well-being	.003	.016	-	**-.640****	-.124

*Note. CFA: confirmatory factor analysis; G: General Factor; PLE: Psychotic-like experiences; FI: Functional Impairment; *: p <.05; **: p<.01.*

The general factor (of the bifactor model) has shown better explanatory power than either of the two factors from the two-factor model when predicting a number of outcomes, notably, when predicting somatisation (both the DSM and the ICD-11 measures used in the Irish community sample- General factor β =.662 vs. Depression factor β = .514 and General factor β = .616 vs. Anxiety factor β = .480 respectively), PLE frequency (General factor β = .412 vs. Depression factor β = .276), Resilience (β = -.420 vs. Depression factor β = -.192 and Anxiety factor β = -.281) and PTSD/CPTSD. In other cases, it has performed marginally worse – e.g. when predicting Loneliness in the Early UK community lockdown sample or substantially worse- e.g. Loneliness in the US community trauma sample. Despite these discrepancies, when comparing the explained variance of the general factor in the bifactor model to the two-factor models across the analyses, there emerges a pattern of comparable performance between the two approaches. These results suggest that the general dimension, representing what is shared between anxiety and depression, offers a comparable or better explanation than the two-factor approach with a notable exception of Loneliness in the US sample.

3.4 Discussion

The present study aimed to evaluate whether anxiety and depression can be better psychometrically expressed as one factor encompassing the commonalities between the two disorders. To this end, bifactor analysis was employed. The study addressed the shortcomings of a number of previous studies (e.g. Zanon et al., 2020; Bianchi, 2020; Giusti et al., 2020) namely, the overreliance on goodness-of-fit indices when using the bifactor model and not evaluating the usefulness of the general factor (Bornovalova et al., 2020). These issues were addressed by examining several bifactor indices which were calculated to establish model reliability and dimensionality providing support for the unidimensionality of the disorders. In addition, the study involved regression models using the general and specific factors from the bifactor solution and (separately) the previously established two-factor approaches to establish predictive validity which provided support for the usefulness of the aggregate scoring of the scales. The model fit statistics suggested the superiority of the bifactor models. Bifactor indices suggest high reliability of the scale and that it can be interpreted as primarily unidimensional. Examining the predictive validity of both the bifactor and two-factor approaches suggests comparable predictive

validity of the models. Furthermore, the results were replicated in all four of the samples used and across two different measurement methods reflecting the ICD-11 and DSM-5 conceptualisations.

The first stage of the analysis was concerned with model fit. The results suggest that the bifactor model presented a superior model fit to a two-factor model constituted by anxiety and depression. This finding, while being consistent with a number of previous studies (Osman et al., 2012; Schonfeld et al., 2019) needs to be interpreted with the tendency for the methodology to favour the bifactor model over a two-factor approach. This phenomenon is attributable to the methodology used because the only constraints imposed upon the model are the grouping factors, the general factor is free to absorb the maximum amount of variance possible (Bornovalova et al., 2020). To resolve this, phases two – examining bifactor indices and three- examining convergent validity were employed.

The ΩHR/ΩS, ECV, and PUC indices did not support the use of separate composite subscale scores for anxiety and depression. While the results support the use of a total score of the two scales, some multidimensionality was suggested. In practice, these results suggest that the measures used are unable to sufficiently differentiate between the two constructs and/or that the two constructs are reflective of a common underlying core with the general factor representing overwhelming commonality between anxiety and depression. These results are in line with a previous study by Zanon et al., (2020) who examined the Depression, Anxiety, and Stress Scale–21 across 8 countries and found that the bifactor indices did not support the use of composite subscale scores and this is also suggested by the present study. These results present several challenges to present conceptualisations of the disorders both in terms of nosology and diagnostic schemas. The current psychometric scales of anxiety and depression may benefit from a re-examination of utility. Beyond the present results, other studies report high correlations between the two (up to 74%; Bjelland et al., 2002). Additionally, it was previously suggested that trait neuroticism may largely or entirely predict one's levels of internalising symptoms (Ormel et al., 2004). Therefore, a question of what is currently being measured using the available scales is not out of place. While the current measures seem to be capturing a large portion of commonalities between anxiety and depression, effectively meaning that the measures do not discriminate between what they intend to measure, a psychometric focus on what is unique to the two beyond the general factor, conceptualised as an internalising factor might provide more accurate diagnoses, treatment and positive therapeutic outcomes.

In light of these findings suggesting that anxiety and depression are indeed better conceptualised as being reflective of a common underlying factor (or overarching spectrum, see: Kotov et al., 2017), the results need to be viewed in light of the methodological shortcomings of self-report measures. Namely, these results might be attributable to the inability of the self-report scales to differentiate between the two constructs. Previous examinations have found discrepancies between self-report measures and structured interviews when it came to the diagnostic prevalence of anxiety and depression in clinical samples (Ferentinos et al., 2011; Whelan-Goodinson et al., 2009). While the superiority of structured interviews over self-report measures in accurately describing the reality is often assumed (Teymoori et al., 2020), the construct reflected by the general factor in the present study might be instead reflective of 'general distress' (Clark & Watson, 1991) or the 'internalising spectrum' (Kotov et al., 2017) rather than just being an artifact of the methodology used. The criticism of self-report measures is also not supported by common brain regulatory mechanisms for both of the disorders (Tronson et al., 2008) and anxiety and depression's similar response to SSRI treatment (Gorka et al., 2019).

The third phase examined the convergent validity of the factors obtained. Overall, these results suggest that the total score of the scales presents a comparable way of predicting several previously theorised outcomes. The general factor has consistently shown better or comparable loadings (Table 7) with a notable exception of Loneliness in the US community trauma sample (Bifactor regression coefficient: .507, Two-factor depression regression coefficient: .715). In the cases of somatisation (DSM measurement), PTSD diagnosis, psychotic episode frequency, fear of death, well-being and uncertainty tolerance, the bifactor grouping factors also showed significant effects that, when considering their overall small contribution to model variance, support the notion that anxiety and depression can be interpreted as a unidimensional scale while still retaining limited multidimensionality. While the current study does not entail the explanation of what remains in the grouping factors after accounting for the general factor, the negative effects of the grouping factor of depression on somatisation (i.e. reduction of somatic symptoms) could be informative on an aspect of depression that is not captured by the usual measurement. For example, while pain complaints are likely characteristic of depressed individuals, decreased sensitivity to pain was also reported and as such the general factor could capture one aspect of this phenomenon but not the other based on the type of pain experienced (Bär et al., 2005). While speculative, this effect is lost when the

general factor is not present. Similarly, the grouping factor of depression, when predicting resilience, showed an effect that increases resilience. Hypothetically, this effect may be due to the emotional numbness aspect of depression which includes 'being less bothered by things than other people' and having 'no feelings' (Leahy, 2002). Keeping in mind that within the samples used, the general factor captured between 84% and 90% of the variance, these results suggest that there are some empirically distinguishable aspects of anxiety and depression that need further empirical research and that the present study reveals due to accounting for the general factor. As such these results might be a call for future research to rethink the way we approach what is captured and, perhaps more importantly, what is 'bi-factorially latent' and therefore not captured by the measures in use today and how these grouping factors relate to clinical reality. This line of research also highlights certain implications for treatment. For example, can the general factor be used to predict treatment outcomes or do the specific factor need to be accounted for? Similarly, are specific lines of treatment targeting the specific factors more effective or, as tentatively suggested by the present results, is internalising the better target? It is hoped that this study is one of the first steps toward answering these questions.

Another aspect to consider when deciding whether to consider current measures of anxiety and depression as a primarily unidimensional measurement instrument is parsimony. Beyond bifactor indices suggesting treating the two scales as one measure, both approaches performed similarly when examining the goodness-of-fit indices and in terms of their predictive validity. While the bifactor model itself shows lower model parsimony, the lack of support for the use of subscale scores suggests treating the scale as an effectively more parsimonious, unidimensional instrument.

The major strength of the present study is that it used 4 different samples and two different measures of depression. The results were replicated across these samples. In the Irish sample the use of summed scores of GAD-7 and PHQ-9, as well as the summed score of ICD-11 ANX5 DEP5 were both suggested. The UK community trauma sample and the US community trauma sample included participants who have previously suffered a traumatic event and were at higher risk of developing PTSD. Replicating the results across a mixture of general and higher risk populations addresses the concern of the general 'anxiety and depression' factor being overestimated due to capturing multi-morbidities stemming from current, acute distress as opposed to 'persistent psychopathology' (Bornovalova et al., 2020).

Despite these strengths, this study is not free of certain limitations. First, due to using secondary data, the results of the specific outcomes were not able to be tested and retested in different samples. Loneliness, being the exception to this issue, was used in two of the samples and provided vastly different results. Second, despite examining a wide variety of samples, the stability of the general factor should also be tested within populations with a diagnosis of either only depressive and only anxiety disorders to examine whether these effects hold within individuals who are expected to score high on either anxiety or depression measures. While issues surrounding how the sample can affect the results are not exclusive to bifactor studies, data gathered from individuals diagnosed with Generalised Anxiety Disorder or Major Depressive Disorder would increase the external validity of the claims made. Finally, the present study examined only a limited number of ways anxiety and depression are measured. While anxiety and depression measures used in the present study stand in accordance with DSM and WHO specifications, effectively spanning both North American and European practices, there exist other measures of these constructs which do not necessarily have to conform with the present results. A myriad of measures of anxiety and depression that extend beyond the ICD-11 and DSM classifications and use items measuring different symptoms that do not overlap between the measures (Anxiety: Julian, 2011; Depression: Fried, 2017) are currently being used within the field. Replicating the results suggesting that the general factor performs similarly or better across different measures when examining external validity addressed that point only partially due to this proliferation of measures in the field.

In conclusion, this study expanded upon research into the dimensionality of anxiety and depression by examining whether the measures of the two constructs can be better operationalised as one scale. This was addressed using the bifactor analysis with special attention placed upon addressing the limitations of this type of analysis. The study involved four different samples from Ireland, the UK and the United States with the Irish sample including two different anxiety and depression inventories that conform with the DSM and ICD-11 conceptualisation of anxiety and depression. Both confirmatory factor analysis model fit indices and reliability and dimensionality bifactor indices support the use of a unidimensional measure. Practical utility of a unidimensional approach was further supported by examining its convergent validity against a two-factor approach. The results support the notion that psychometrically, a summed score of anxiety and depression

performs comparably to a two-factor approach while offering a more parsimonious solution.

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Chapter 4: Distinguishing Anxiety and Depression using Factor Mixture Models

4.1 Introduction

Globally, almost one fifth of the population suffers from either anxiety or depression (Steel et al., 2014), out of those, between 47% and 88% will experience comorbidity with the other disorder (Jacobson & Newman, 2017). This 'mixed' (comorbid) diagnosis, when compared to a non-comorbid diagnosis of either anxiety or depression, is characterised by poorer response to treatment (Fava et al., 2008; Howland et al., 2009), higher suicidal ideation and odds of surviving a suicide attempt (Seo et al., 2011; Fava et al., 2006), poorer quality of life (Lin et al., 2014) and poorer disease course trajectories both in terms of chronicity and long-lasting symptoms (Rhebergen et al., 2011; Melartin et al., 2004). Despite the challenges a comorbid diagnosis presents, the two diagnostic systems, the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), have only recently begun to rediscover the utility of the unique classification of comorbid anxiety and depression.

The symptoms of anxiety and depression are often co-occurring (Gorman, 1996; Fava et al., 2000; Simon et al., 2003; Zimmerman et al., 2000) and this finding has been described throughout the past century from a variety of perspectives. First, it has been described from a psychoanalytical designation of neurosis (Slater & Slater, 1944), and through descriptive studies of 'depression with tension' (Harrowes, 1933; Muncie, 1934), as well as through psychometric means arrived at using statistical methods such as principal component and factor analysis (Kendall & Watson, 1989; Dobson, 1985) and more recently through network analytic approaches (Fried et al., 2016; Beard et al., 2016). Historically, the development of nosology of anxiety and depression as separate disorders has been described as mainly stemming from 3 sources. First, different psychopharmacological treatments available at the time, namely- benzodiazepines (anxiolytic drug), monoamine oxidase inhibitors (MAOIs; with efficacy for both anxiety and depression) and tricyclic antidepressants, all purported to affect different symptoms (Tyrer & Shawcross, 1988). Second, a psychometric bias against non-discriminating (low specificity) symptoms that appear with both anxiety and depression - examples including changes in appetite, concentration issues, somatic symptoms, gastrointestinal or genitourinary symptoms and low libido (Steer, 1987; Snaith et al., 1976). Third high association between anxiety and depression not invalidating the classification of these disorders as separate - e.g. under the condition of all possible comorbidities of around 600

disorders classified in the DSM-5, a classification including all of different combinations of disorders would perhaps defeat the validity of such classification (Tyrer, 2001). Based on these three points and factor analysis studies (Costello & Comrey, 1967; Mendels et al., 1972), with the publication of DSM-III in 1980, two independent committees were formed to inform the diagnostic manual about mood (Depression) and anxiety (Generalised Anxiety Disorder) separately. The ICD-10 which was published 10 years later, largely conformed to this established separation but added a Mixed Anxiety and Depressive Disorder (MADD) classification in the anxiety disorder section with a description of "The patient presents with a variety of symptoms of anxiety and depression" (WHO, 1993). Later, with the publication of the DSM-IV, a Mixed Anxiety and Depressive Disorder (MADD) classification was reviewed for addition as a diagnosis separate from Major depressive disorder (MDD) and Generalised Anxiety Disorder (GAD) but existed only in the research appendix as the review of published work at the time revealed poor inter-rater reliability and low validity (First, 2011, Mulder et al., 2019). The concept was revisited in the DSM-5 in which a "with anxious distress" specifier was added to the mood disorder section. With the still recent advent of ICD-11 in 2018, another designation was added moving the diagnosis from anxiety into the mood disorder category and changing the name to Mixed Depressive and Anxiety Disorder (MDAD). With this revision, came a subsyndromal designation of "Neither set of symptoms (anxiety and depression), considered separately, is sufficiently severe, numerous, or persistent to justify a diagnosis of another depressive disorder or an anxiety or fear-related disorder". The comorbid classifications face additional problems relating to their implementation. While a comorbid diagnosis is reported to be more severe in terms of symptoms and treatment outcomes (Fava et al., 2006; Fava et al., 2008), most of the global mental health provision is provided by primary care workers who most likely are not trained mental health professionals and a comorbid diagnosis is rarely made (Lam et al., 2012).

While MDAD has been recognised as a separate disorder in ICD-11, after its introduction into diagnostic manuals, only a limited amount of research has been devoted to describing its prevalence and symptom profiles. The DSM-5 designation faces a similar issue. The research surrounding both of the diagnostic designations for mixed anxiety and depression in its syndromal and subsyndromal states is inconclusive. Goldberg et al., (2017) studied anxiety and depression in primary care settings in four large middle-income

countries (Brazil, China, Mexico and Pakistan). They reported that a comorbid anxiety and depression was the most common (48.7%) diagnosis among the sample of 'psychologically distressed' participants with depression (7.8%) and anxiety (20%) being yet more common than a subclinical mixed depression and anxiety diagnosis (2.7%). While the study was confined to primary care settings where individuals were selected for screening, these results do not reflect prevalence rates. The study also employed two 5-item scales for anxiety and depression (one scale each) that had not received psychometric validation. While the scales represented symptoms of anxiety and depression specified in ICD-11, the items of the scales were answered in a dichotomous way (yes/no) which the methodological literature advises against due to loss of information, spurious statistical significance and low measurement reliability (MacCallum et al., 2002). Another study involving MDAD diagnosis was performed by Das-Munshi et al., (2008) who reported an 8.8% one-month prevalence for MDAD (subsyndromal) and a 1.5% prevalence for comorbidity in a representative sample from the UK. Conversely, the anxious specifier of the DSM characterised 75% of all depression cases in a national survey of over 36 thousand adults from the United States of America (reported 12-month prevalence for depression in the sample was 10.4%; Hasin et al., 2018).

Aside from diagnostic designations, Hettema et al., (2015) in their analysis of latent profiles of symptoms associated with anxiety and depression reported profiles of mixed anxiety and depression that differed in magnitude but were not qualitatively different. Their results put the 'comorbid' designation into question as symptoms of both anxiety and depression were found to be co-occurring across ordinal classes. They however did not use validated measures in their analysis and the sample was constrained to individuals with no prior diagnosis of either anxiety or depression.

To the detriment of patients around the globe and despite reports of high severity and common occurrence, the mixed anxiety and depression designation remains an 'unwanted child' of both major diagnostic manuals. As discussed above, the field surrounding the subject could be enriched by studies using representative samples and validated measures to determine whether the 'mixed' designations deserve their place in the diagnostic manuals. To this end, the present study employed Factor Mixture Modeling (FMM) which is both a person and variable-centered approach in that it utilises factor analysis to cluster items into factors and then uses latent profile analysis to describe resulting groups with different factor mean scores.

Based on designations available in the DSM-5 and ICD-11, it was predicted that a total of 2 factors and 5 classes would emerge. Symptoms of Anxiety and Depression would constitute the two factors and the five classes would represent (1) no symptoms, (2) subsyndromal anxiety and depression (ICD-11 MDAD), (3) high depression, (4) high anxiety and (5) High depression with elevated anxiety symptoms (DSM-5 "anxious distress" specifier).

The second aim of the analysis was to determine whether demographic and psychological variables were able to predict latent class membership in a significant way. Previous research suggests that symptoms of both anxiety and depression are negatively associated with age and that being female is a risk factor (Tuohy et al., 2005; Faravelli et al., 2013). Furthermore, low external locus of control and low self-esteem were hypothesised to predict the symptoms of both anxiety and depression (Kennedy et al., 1998; Sowislo & Orth, 2013).

The third aim is to establish the diagnostic relevance of arrived at solutions. A number of psychological variables were selected for this purpose. Mean differences between classes were tested: somatic symptoms, loneliness, uncertainty tolerance and resilience as they all are associated with heightened anxiety and depression symptoms (Löwe et al., 2008; Zawadzki et al., 2013; Carleton, 2012; Min et al., 2013).

4.2 Methods

4.2.1 Sample

The sample involved UK participants (N=2025). The sampling started on March 23rd, 2020, which was the day that the first COVID-19 'lockdown' was announced in the UK, and finished on March 28th, 2020 (5 days duration). Data gathering was performed using the Qualtrics© online survey platform. The targeted population included individuals aged 18 years and older. Representativeness of the sample was ensured by using quota sampling methods. Age, gender and household income were based on 2016 population estimates from Eurostat with household income ranges being provided by the Office for National Statistics for the year 2017.

4.2.2 Measures

Generalized Anxiety Disorder 7-item Scale (GAD-7)

The GAD-7 (Spitzer et al., 2006) was used to measure symptoms of generalized anxiety. The scale presents the participant with 7 items representing symptoms of general anxiety to which they were required to indicate how often it bothered them over the last two weeks. The answers were presented on a four-point Likert scale (0- "Not at all" to 3- "Nearly every day"). Possible scores ranged from 0 to 21, with higher scores indicative of higher levels of anxiety. The GAD-7 has seen wide use in psychiatric and community samples (Johnson et al., 2019). The Cronbach's α score in the present sample was excellent (.944).

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Kroenke et al., 2001) was used to assess the symptoms of depression. The scale presents the participant with 9 items representing symptoms of depression. Participants were asked to indicate how often they experienced each symptom over the past two weeks. The scale uses a four-point Likert scale (answers ranging from 0- "Not at all" to 3- "Nearly every day"). Possible scores range from 0 to 27, with higher scores being indicative of higher levels of depression. The use of PHQ-9 has been widely supported (Gilbody et al., 2007). Cronbach's α score in the sample was excellent (.921).

The Brief Locus of Control Scale (BLOC)

The Brief Locus of Control Scale (Sapp & Harrod, 1993) was used to measure external locus of control. The brief version of the scale was adapted from Levenson's (1974) original scale. The participants were presented with 9 questions about the degree of control that they have in their life. The answers were given on a 7-point Likert scale (ranging from 1- 'strongly disagree' to 7-'strongly agree'). After reverse coding items measuring internal locus of control, possible scores ranged from 9 to 63 with higher scores being indicative of external locus of control. Cronbach's α score in the sample was good (.804).

De Jong Gierveld Loneliness Scale – short form (GLS)

The short form scale of the De Jong Gierveld Loneliness Scale (GLS; Gierveld & Tilburg, 2006) was used to measure loneliness. The scale presents the participants with 6 statements pertaining to how they feel at the present moment and the participants are asked to indicate their agreement on a 5-point Likert scale (ranging from 1- 'yes!' to 5- 'no!'). Possible scores ranged from 6 to 30 with higher scores indicating lower levels of loneliness. Excellent psychometric properties of the measure were supported

internationally (Gierveld & Tilburg, 2010). In the sample, Cronbach's α reliability was good (.808).

Resilience (BRS)

Resilience was measured using the Brief Resilience Scale (BRS; Smith et al., 2008). It was designed to measure resilience understood as the subject's ability to deal with and recover from environmental obstacles and stressful circumstances. It is comprised of 6 items that are answered on a 5-point Likert scale ranging from (1)- 'strongly disagree' to (5) 'strongly agree' (also using reverse coded items). The high scores are suggestive of high levels of resilience. In the present sample, Cronbach's α of the measure was excellent (.919).

Uncertainty tolerance (IUS-R)

Intolerance of uncertainty was measured using The Intolerance of Uncertainty Scale-Revised (IUS-R; Bottesi et al., 2019). The scale presents the participants with 12 items to be rated as representing a characteristic that the participants see in themselves (e.g. "I always want to know what the future has in store for me.", "I should be able to organize everything in advance."). The scale is rated on a 5-point Likert scale (1) ="Not at all like me" to (5) ="Entirely like me". In the present sample, the scale presented a good Cronbach's α (.859) score.

Somatic symptoms (TSI-2)

The Trauma Symptom Inventory (TSI-2; Briere, 2011) consists of 136-item self-report items measuring 12 different sets of symptoms that can occur following traumatic exposure. 14 items representing Somatic Preoccupation were adapted for this study. The instructions the participants were provided read as follows: "During the past 7 days, how much have you been bothered by any of the following problems?" Participants were presented with a list of physical problems: (1) Stomach pain, (2) Back pain, (3) Pain in your arms, legs, or joints (knees, hips, etc.), (4) Headaches, (5) Chest pain, (6) Dizziness, (7) Fainting spells, (8) Feeling your heart pound or race, (9) Shortness of breath, (10) Pain or problems during sexual intercourse, (11) Constipation, loose bowels, or diarrhoea, (12) Nausea, gas, or indigestion, (13) Feeling tired or having low energy, (14) Trouble sleeping. The items are rated on a 3-point Likert scale (0-2) ranging from 'Not bothered at all' to

'Bothered often'. The scores were summed up and an aggregate was used in the analysis. The reliability in this sample was high, with a Cronbach's α of .910.

4.2.3 Statistical analysis

The analysis was conducted in three linked phases using Mplus software version 8.1 (Muthén & Muthén, 2017). First, following the guidelines proposed by Clark et al., (2013), the initial analyses involved establishing confirmatory factor analysis (CFA) and latent profile analysis (LPA) solutions using the PHQ-9 and GAD-7 response data. The CFA and LPA models were estimated using robust maximum likelihood (Yuan & Bentler, 2000). CFA was performed to establish whether the latent structure of the data fits with theoretical assumptions. To this end two models were tested: a one-factor model with items from the PHQ-9 and GAD-7 loading onto one factor, and a correlated two-factor model with the items loading on their respective factors of Depression and Anxiety. All unique variances were uncorrelated. The CFA models were assessed in a comparative manner using standard criteria: a non-significant chi-square (χ^2) test, Comparative Fit Index (CFI; Bentler, 1990), and Tucker Lewis Index (TLI; Tucker & Lewis, 1973) with values greater than .90; Root-Mean-Square Error of Approximation (RMSEA: Steiger, 1990) with 90% confidence intervals (RMSEA 90% CI); and Standardized Root-Mean-Square Residual (SRMR) values of .08 or less reflect acceptable model fit (Hu & Bentler, 1999). The CFA models were further compared using: Akaike Information Criterion (AIC; Akaike, 1987), the Bayesian Information Criterion (BIC; Schwartz, 1978) and the sample size adjusted Bayesian Information Criterion (ssaBIC; Sclove, 1987) with lower values indicating superior fit.

In order to determine if there was significant heterogeneity in the responses, models with 2 through to 5 classes were fitted in the LCA part of the analysis. Within-class correlations were all fixed to zero. Model fit was assessed using Akaike Information Criterion and Bayesian (BIC, ssaBIC) fit statistics in addition to the Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-A; Lo, Mendell, & Rubin, 2001). The LMR-A was used to compare models with increasing numbers of classes, and when a non-significant value ($p > .05$) occurs this suggests that the model with one less class should be used. The degree of correct classification of participants was established using entropy for each solution with values closer to one being indicative of better classification (Ramaswamy et al., 1993). To

avoid LPA solutions based on local maxima, 2000 random sets of starting values were initially used and 100 final stage optimizations.

When the best fitting CFA model was determined, and if heterogeneity was evident based on the LPA, FMMs were estimated testing increasing number of classes (2 to 7). Type-2 FMMs (Clark et al., 2013) were used with class invariant intercepts, class invariant factor loadings, class invariant factor covariance matrices, and class-specific factor means being estimated. The factor means for a reference class were fixed at zero. This specification was used as it maximised statistical power. An alternative specification (e.g., FMM-3) would require the estimation of all intercepts in each class whereas the FMM-2 only estimates factor means. Fewer free parameters are, therefore, being estimated when using FMM-2. The estimation and assessment of model fit for the FMMs was the same as for the LPAs.

In the second phase, the covariates (sex, age, locus of control, self-esteem) were used as predictors of the latent classes. Using the R3STEP method meant that the analysis is correspondent with a multinomial logistic regression. The method does not influence the estimation of the latent class part of the model and accounts for the uncertainty of class membership (Asparouhov & Muthén, 2014).

Third phase was concerned with diagnostic relevance of the classes obtained through the FMM. Summed scores of the scales measuring somatic symptoms, loneliness, uncertainty intolerance and resilience were specified as distal outcomes predicted by the latent classes using the DU3STEP method (holding unequal means and variances across classes as an assumption; Asparouhov & Muthén, 2014). This method allows for testing for the equality of means across classes obtained through FMM. A Wald test and subsequent pairwise comparisons inform about equality of means between the classes (Asparouhov & Muthén, 2014).

4.3 Results

4.3.1 Descriptive statistics

The descriptive statistics for the sample are provided in Table 8. These were stratified by the diagnostic criteria being met based on a cut-off score of 10 for both the GAD-7 and PHQ-9 (Spitzer et al., 2006; Manea et al., 2012). The stratification kept independence of observations so that no participant was a member of more than one group- those who satisfied both anxiety and depression criteria were assigned to an independent group. The groups showed significant differences across all variables. It is important to note that this stratification is presented for descriptive purposes only and does not bear on methods used in further analyses. The sex of the participants was nearly evenly split with women constituting 51.7% of the sample. The mean age of the participants was 45.44 (SD= 15.90). Additionally, a number of participants did not endorse any of the anxiety symptoms (31.3%, N= 633), which was also observed with symptoms of depression (28.5%, N=557).

Table 8. Descriptive statistics

	No diagnosis (N= 1516)	Depression cut-off met (N= 124)	Anxiety cut-off met (N= 105)	Depression and anxiety cut-offs met (N= 280)	Difference test	Total (N=2025)
	N (%)	N (%)	N (%)	N (%)	Chi^2 (df)	
Female	754 (49.74%)	68 (54.84%)	77 (73.33%)	148 (52.86%)	37.18 (12) , p< 0.01	51.7% (N= 1041)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	ANOVA	
Age	47.79 (15.69)	39.73 (14.85)	42.3 (15.67)	36.47 (13.43)	F(3, 2021)=50.99, p< 0.01	45.44 (SD= 15.90)
Locus of Control	29.13 (8.08)	34.81 (6.46)	33.62 (8.26)	37.71 (6.98)	F(3, 2021)=110.35, p< 0.01	30.89 (SD= 8.46)
Self-esteem	3.82 (2.15)	3.59 (2.44)	4.98 (2.77)	3.56 (2.45)	F(3, 2002)=10.96, p< 0.01	3.83 (SD= 2.26)
Somatic Symptoms	2.57 (3.64)	7.85 (5.88)	3.8 (3.3)	9.58 (6.98)	F(3, 2021)=235.1, p< 0.01	3.92 (SD= 5.10)
Loneliness	4.31 (1.59)	5.92 (1.83)	5.26 (1.85)	6.55 (1.87)	F(3, 2021)=168.23, p< 0.01	4.76 (SD= 1.86)
Uncertainty Intolerance	39.83 (13.8)	48.88 (14.37)	49.98 (14.28)	53.99 (13.96)	F(3, 2021)=101.03, p< 0.01	42.86 (SD= 14.87)
Resilience	18.37 (2.19)	18.86 (2.94)	18.96 (2.14)	19.81 (3.34)	F(3, 2021)=28.66, p< 0.01	18.63 (SD= 2.87)
Anxiety	2.5 (2.84)	7.1 (2.8)	13.68 (2.53)	15.5 (3.2)	F(3, 2021)=1969.88, p< 0.01	5.37 (SD= 6.31)
Depression	2.48 (2.83)	13.56 (2.55)	6.4 (2.87)	17.05 (4.34)	F(3, 2021)=2093.05, p< 0.01	5.15 (SD= 5.68)

4.3.2 FMM results

Table 9 shows the fit statistics for all models that were tested.

Table 9. Fit Statistics for the CFA, LCA and FMM of ICD-11 Anxiety and Depression.

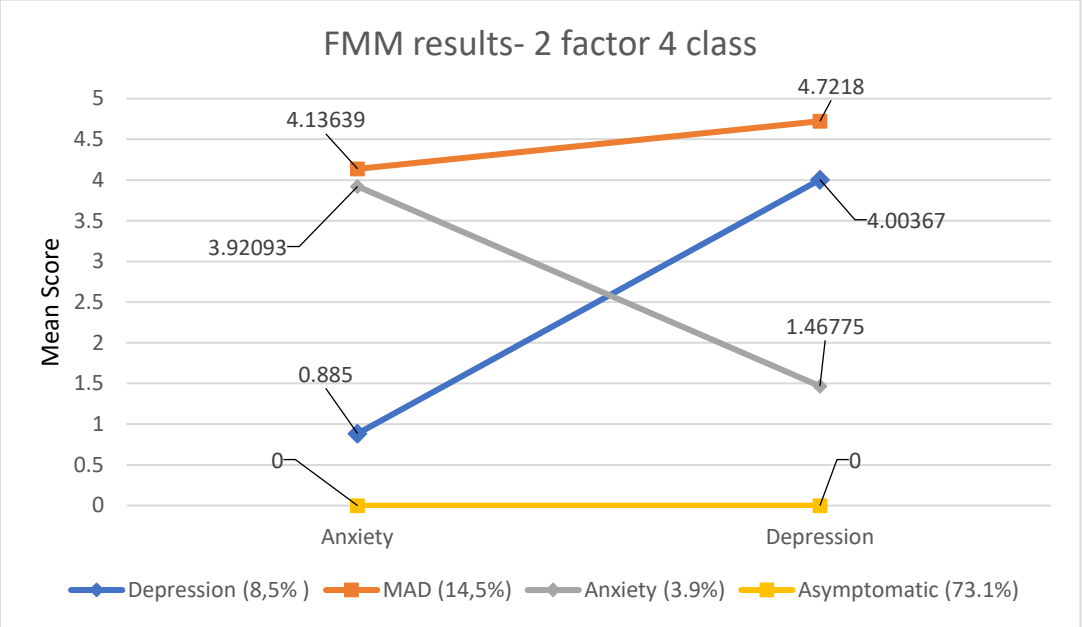
Model	Log-likelihood	AIC	BIC	ssaBIC		
CFA					CFI	TLI
1 factor	-30675.312	61446.625	61715.636	61563.137	0.873	0.853
2 factors	**-29887.972**	**59873.944**	**60148.560**	**59992.884**	**0.933**	**0.922**
LPA					Entropy	LMR-A (p)
2 classes	-33386.870	66871.740	67146.355	66990.680	0.975	17354.752 (0.0000)
3 classes	-31095.269	62322.537	62692.427	62482.741	0.958	4548.022 (0.3149)
4 classes	-30168.042	60502.083	60967.248	60703.552	0.940	1840.219 (0.1228)
5 classes	-29382.615	58965.229	59525.669	59207.963	0.952	1558.796 (0.0016)
6 classes	-28822.548	57879.096	58534.810	58163.094	0.953	1111.535 (0.0635)
FMM						
2 factors 2 classes	-29523.386	59150.772	59442.201	59276.994	0.894	698.552 (0.0000)
2 factors 3 classes	-29342.724	58795.448	59103.690	58928.952	0.909	346.150 (0.0001)
2 factors 4 classes	**-29223.917**	**58563.834**	**58888.889**	**58704.620**	**0.913**	**227.636 (0.0020)**
2 factors 5 classes	-29117.729	58357.459	58699.327	58505.526	0.897	192.146 (0.2432)

Note: AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, ssaBIC = sample size adjusted Bayesian Information Criterion, LMR-A Lo-Mendell-Rubin adjusted likelihood ratio test. Best-fitting models for each approach (CFA, LPA, FMM) are shown in bold.

The fit statistics for both 1-factor (χ^2 (104) = 1820.292, p < .001; CFI = .873, TLI = . .853; RMSEA = .091 (90%CI = .087, .094), SRMR= .054) and 2-factor (χ^2 (103) = 1009.424, p < .001; CFI = .933, TLI = . .922; RMSEA = .066 (90%CI = .063, .070), SRMR= .042) solution have shown sufficient fit. Based on the three information theory statistics, however, as presented in Table 9, a 2-factor model was shown to be superior. Additionally, the standardised factor loadings for the depression items were all positive and ranged from .68 to .84 and all were statistically significant (p < .001). Considering anxiety, the standardised factor loadings were all positive and ranged from .75 to .90 and all were statistically significant (p < .001). The correlation between the latent variables was very strong (r = . 86, p < .001). The fit statistics for the LPA models showed a decreasing BIC with an increasing number of classes. Significant LMR-A results were obtained for the five- and two-class solutions with nonsignificant results including 3- and 4- class solutions. The CFA solution indicated that the depression and anxiety items measure two separate-but-highly correlated dimensions. Supporting the use of FMM, the LPA solution showed that there was significant heterogeneity in responses.

The FMM results are presented in Figure 4. Class 1 (n = 71, 3.5 %) comprised of individuals presenting low factor mean for anxiety (M = 0.885, SE = 0.224) and a high factor mean for depression (M = 4.004, SE = 0.281). Based on those results, Class 1 was labelled ‘Depression’. Class 2 (n = 296, 14.7%) included individuals with high factor means for both anxiety (M = 4.136, SE = 0.156) and depression (M = 4.722, SE = 0.192). Class 2 was labelled as the ‘MAD’ (Mixed Anxiety and Depression) class. Class 3 (n = 161, 8%) was characterized by involving individuals with high factor mean for anxiety (M = 3.921, SE = 0.190) and a low factor mean for depression (M = 1.468, SE = 0.202). Class 3 was thus labelled the ‘Anxiety’ class. Class 4 (n = 1479, 73.8%) had its factor means fixed to zero. It was the largest class and served as the reference group. This class was labelled the ‘Asymptomatic’ class.

Figure 4. FMM results



4.3.4 Predictors

The second phase of the analysis added a number of predictors (sex, age, locus of control, self-esteem) added to the model. Class membership was set as the outcome variable with the Asymptomatic class providing reference. Table 10 presents the results as odds ratios (OR). Older age significantly decreased the odds of belonging to the MAD class (OR= 0.95) Being female increased the odds of belonging to the Anxiety class (OR= 2.33) as did higher scores of self-esteem (OR=1.09). Exhibiting higher external locus of control increased the odds of belonging to the Depression, MAD and Anxiety classes respectively when compared to the asymptomatic class with odds ratios ranging from 1.07 to 1.18 and showing the highest effect for belonging to the MAD class.

Table 10. Predictors of Class Membership

	Class 1 Depression	Class 2 MAD	Class 3 Anxiety	Class 4 Asymptomatic (reference)
Age	0.98 (0.96- 1)	0.95 (0.93- 0.96)*	0.98 (0.97- 1)*	-
Gender (being Female)	1.24 (0.6- 2.56)	0.79 (0.56- 1.1)	2.33 (1.58- 3.45)*	-
External locus of control	1.07 (1.03- 1.11)*	1.18 (1.15- 1.22)*	1.07 (1.03- 1.11)*	-
Self-esteem	0.96 (0.83- 1.11)	1 (0.93- 1.07)	1.09 (1.02- 1.16)*	-

*Note: * significant at the 0.05 level (p<0.05).*

4.3.5 Outcomes

The sum scores of Somatic, Loneliness, Uncertainty intolerance and Resilience were added as distal outcomes, and results from the tests of mean differences across classes are presented in Table 11. All scales presented overall significant effects. Symptomatic classes were significantly different from the Asymptomatic class across measured outcomes. The Depression class and the MAD class showed significantly elevated levels of Somatic symptoms when compared to the Anxiety class while not exhibiting significant differences between themselves. For Loneliness and Uncertainty intolerance, the MAD class was significantly higher when compared to other classes. Conversely, the Asymptomatic class was significantly higher than symptomatic classes when considering resilience with the Depression class showing higher resilience than the MAD class.

Table 11. Class-dependant scores and Wald Test results.

Outcome	Class 1 Depression Mean (S.E.)	Class 2 MAD Mean (S.E.)	Class 3 Anxiety Mean (S.E.)	Class 4 Asymptomatic Mean (S.E.)	Overall Chi Squared	Wald Test ($p < .05$)
Somatic symptoms	3.378 (0.292)	3.294 (0.145)	1.831 (0.316)	0.761 (0.088)	269.610**	1,2>3>4
Loneliness	6.463 (0.246)	9.131 (0.709)	5.529 (0.167)	4.246 (0.053)	138.330**	2>1>3>4
Uncertainty intolerance	47.497 (2.081)	54.289 (0.946)	50.835 (1.300)	39.521 (0.396)	244.505**	2>1,3>4
Resilience	17.932 (0.668)	15.662 (0.280)	16.539 (0.424)	20.822 (0.126)	356.822**	4>1,2,3; 1>2

*Note: **- Significant at the 0.01 level ($p<0.01$).*

4.4 Discussion

The primary aim of the study was to determine the underlying categorical and dimensional structure of anxiety and depression within a nationally representative sample. To this end, Factor mixture modelling was utilised allowing for both person- and variable-centered descriptions. As per Clark et al., (2013) CFA, LPA and FMM were all determined for comparison. The best fitting solution involved the FFM solution including 4 classes and two factors. The estimated two factors were consistent with constructs of Anxiety and Depression. The classes estimated by the FMM revealed an 'Asymptomatic' class characterised by low anxiety and depression, a high anxiety class, a high depression class and a MAD class characterised by levels of anxiety and depression that were higher when compared to the other classes. This finding stands in opposition to the conceptualisation provided by the ICD-11 in that a subsyndromal class was not part of the optimal FMM solution. As for the interpretation of these results in relation to the DSM-5, the 'anxious

distress' specifier places the diagnosis in a psychometrically ill-defined spot as the designation may include a range of symptoms between subsyndromal and clinically relevant levels (Mulder et al., 2019). The present results, however, suggest that when the symptoms of anxiety and depression are largely co-occurring it is on an ordinally higher level when compared to either anxiety or depression putting the utility of the specifier into question. Beyond symptom severity, the present analysis also provided an estimate of the prevalence of individuals most likely belonging to one of the four estimated classes. The class composition suggests that a mixture of anxiety and depression symptoms is a more frequent occurrence when compared to symptoms of 'pure' anxiety or depression. The present study, involving a representative UK sample, suggests that 14.5% of participants would belong to the MAD class with 8.5% showing more dominant depression symptoms and only 3.9% showing mostly anxiety symptoms. These findings contribute to the notion that a MAD designation is more commonly occurring with individuals exhibiting 'pure' anxiety or 'pure' depression symptoms being rarer.

The secondary aim of the study was to determine predictors of the classes obtained from the FMM. The results suggest that age, gender, locus of control and self-esteem were all significant predictors of belonging to the class characterised by higher anxiety levels. External Locus of control and age were both significant predictors of MAD with the former having a positive effect (increasing the odds of exhibiting MAD symptoms) and age showing small negative effects. Interestingly, for depression, exhibiting an external locus of control was the only significant predictor. These results are largely conflicting with the initial hypotheses. However, the low significance and strength of gender (being female) may be attributable to external locus of control being exhibited more often in women (Churchill et al., 2020). Additionally, external locus of control has previously been suggested to be strongly associated with low self-esteem (Tamta & Rao, 2017). Taking these considerations into account together with locus of control showing the highest effects for MAD, the results underline the importance of locus of control as a universal risk factor for developing the examined constructs.

Finally, the study examined the diagnostic relevance of the FMM results. For each class, a mean of somatic symptoms, loneliness, uncertainty intolerance and resilience was established along with an estimation of significant differences between the classes. The MAD and depression classes showed significantly higher levels of somatic symptoms when compared to both anxiety and asymptomatic classes. In other cases, the MAD class

has shown the highest severity of negative symptoms- highest loneliness, highest uncertainty intolerance and lowest resilience. These results support the notion that a mixture of anxiety and depressive symptoms contributes to higher severity of additional, co-occurring phenomena (Löwe et al., 2008; Zawadzki et al., 2013; Carleton, 2012; Min et al., 2013).

These findings highlight certain diagnostic considerations. First, ever since the DSM-III was introduced, there has been an effort to differentiate anxiety and depression by developing scales of anxiety and depression that are increasingly more orthogonal to one another (Dobson, 1985; Wetzler & Katz 1989; Watson et al., 1995; Cosco et al., 2012) which may have warped our understanding of the disease as evidenced by 'mixed' diagnoses being more common than their 'pure' manifestations. The results of the present study suggest that specifications provided by both the DSM-5 and ICD-11 do not accurately map onto how these symptoms are manifested in the used sample (representative UK sample). This presumed misspecification provided by the statistical manuals may be attributable to a number of possible reasons: (1) Anxiety and depression are reflective of one psychopathological entity (Simms et al., 2008), (2) Anxiety and depression are separate entities with 'soft' overlapping boundaries explaining the disconnect between factor analytical studies and symptom manifestation. For example, they may arise due to individual differences not captured by the current methodology (e.g. maladaptive response patterns of either giving rise to the other over time; Dalal & Sivakumar, 2009), (3) The psychopathology is not accurately captured by the DSM-5 nor ICD-11 due to anxiety and depression not being discreet disease entities. As such, anxiety and depression (or another designation) might be better conceptualised as being informed by causal systems of symptoms rather than an underlying disease (Borsboom, 2008). Secondly, current results might be used to encourage examinations of diagnostic barriers. With MAD being a more severe and more common designation, future research endeavours might examine whether a clearer and more parsable designations might lead to a more accurate diagnoses being made by mental health professionals. Lastly, the results of the present study reinforce the notion that MAD, beyond being a more common diagnosis, is also characterised by higher severity of accompanying symptoms (e.g. somatic).

This study is not free of certain limitations that need to be considered. The measures used, while measuring anxiety and depression found within the DSM-5 and ICD-11, do not map exactly onto the diagnostic specifications outlined within them. For example, the DSM-5

anxiety specifier was not examined through a prescribed interview schedule (Brown & Barlow 2014). Future research endeavours could focus on replicating present findings using methods that are more closely aligned with the diagnostic specifications. However, it is important to note that both the GAD-7 and PHQ-9 have been previously used in research concerning both DSM-5 and ICD-11 (e.g. Kladnitski et al., 2020 ; Goldberg et al., 2012) and were therefore treated as 'universal'. Furthermore, concerns can be raised about the dataset being procured shortly after the start of the COVID-19 lockdown which may have elevated the symptoms due to additional stress (Hyland et al., 2020).

4.4.1 Conclusion

Taken together, the present findings support a re-evaluation of how MAD is represented in the two most commonly used diagnostic manuals. A class comprising elevated symptoms of anxiety and depression that was both larger and more severe when compared to classes representing anxiety and depression was part of the optimal model. The MAD class was also associated with more numerous somatic symptoms, higher levels of loneliness, lower resilience and higher intolerance of uncertainty.

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Chapter 5: Unravelling the symptom structure of anxiety and depression: a network study of a nationally representative sample stratified by symptom intensity

5.1 Introduction

A great wealth of empirical research stands behind the notion that comorbidity exists between anxiety and depressive disorders. It has been reported that between 30 to 67% of individuals meeting the criteria for either one of the disorders will be suffering from comorbidity of the other (Jacobson and Newman, 2017). Because high comorbidity of symptoms presents a challenge to how we diagnose, differentiate and conceptualise the two highly intimately associated disorders of anxiety and depression (Tyrer, 2001), there have been numerous attempts at parsing through this issue using a wide range of methodologies.

Before examining the frontier approaches, it might be useful to recognise how Anxiety and Depression are approached from the standpoint of diagnostic manuals - the ICD-11 and the DSM-5. Beyond diagnoses of Major Depressive Disorder (MDD) and General Anxiety Disorder (GAD), both manuals recognise a 'mixed' manifestation of the disorders. The ICD-11 includes a diagnosis of Mixed Depression and Anxiety Disorder (MAD) and the DSM-5 recognises a 'with anxious distress' specifier in its mood disorder category. Beyond those, the classification is widely supported by clinicians, as exemplified in Lam et al., (2013) reporting overwhelming support for the designation. However, while the designation is common and supported, the questions of the best course of treatment are still debated- for example, whether to treat the common underlying mechanisms of both disorders or to focus on them sequentially (Craske, 2012). Furthermore, as reported in Spijker et al., (2020), disorder-specific guidelines are based on randomised control trials that frequently exclude severe comorbidities aimed at obtaining optimal effect sizes in homogeneous patient samples. Therefore, the field is presented with a conundrum of recognising a common diagnosis that is supported by clinicians while simultaneously offering little in terms of guidelines. This issue might be solved by examining how symptoms of anxiety and depression interact with each other based on symptom severity or probable diagnosis.

A novel approach to how anxiety and depression are related lies within analyses informed by network theory. An approach that offers both framework and statistical techniques to describe and explore the underlying structure of connections between the symptoms of constructs of both anxiety and depression (Borsboom, 2017). There exists a substantial number of publications describing this symptom-level relationship between anxiety and depression with a high degree of heterogeneity of methods but with largely homogeneous

results – anxiety and depression are related closely, but within construct connections are mostly stronger than between construct connections. In other words, a separation between these constructs is evident by their respective symptoms being more closely connected within rather than across the constructs (Beard et al., 2016; Van den Bergh et al., 2021; McGlinchey et al., 2021). Conversely, recent investigations into anxiety and depression in adolescence, showed that the symptom network is largely suggestive of a homogeneous construct that does not differentiate between anxiety and depression (McElroy et al., 2018; McElroy & Patalay, 2019). Taken together, these suggest that anxiety and depression coexist, first, as a general distress to later (in adulthood) differentiate into anxiety, depression or a comorbid form. However, to the knowledge of the author, no study has explored how anxiety and depression in their comorbid forms differ in terms of symptom manifestation depending on symptom intensity (network analysis).

Another mode of this type of inquiry is found in bifactor examinations- a bifactor model sets out to establish a general factor, reflecting common variance among all included items, simultaneously with specific factors, reflecting variance among specified subsets of indicator (e.g. indicators of anxiety and depression) to essentially 'compete' for explanatory power (Bornovalova et al., 2020). Bifactor investigations regarding anxiety and depression mostly suggest that the specific factors are of little utility and therefore a sum score of anxiety and depression should be considered instead when using these scales (Iani et al., 2014; Luciano et al., 2014). There also exists research suggesting that even subclinical levels of anxiety and depression are also a source of significant distress to the individuals suffering from both (Das-Munshi et al., 2008; van Lang et al., 2006). However, a recent investigation including a representative adult sample from the Republic of Ireland and utilising factor mixture models (a method that allows the underlying structure of a set of symptoms to be represented simultaneously as categorical and dimensional), the representation of the subclinical diagnosis within the population was put into question with no subclinical class being identified (Shevlin et al., 2021).

Taking these points into account, an exploratory research endeavour into how symptoms of anxiety and depression manifest are warranted. The present study aims to utilise network theory based on probable diagnostic classification in line with recent suggestions of the high utility of conceptualising anxiety and depression as a unidimensional construct. Such exploration might shed light on the underlying structure of MAD and the description of

that structure might additionally inform future clinical endeavours on how to tailor future interventions.

5.2 Methods

5.2.1 Sample

UK participants (N=2025) were involved in the study. Data gathering procedures started on March 23rd, 2020, on the same day that the first COVID-19 'lockdown' announcement was made. Data gathering finished on March 28th, 2020. Data was gathered using a service provided by Qualtrics© – an online survey company. The population only involved adult individuals - aged 18 years and older. Quota sampling methods (based on age, gender and household income) were used to ensure the representativeness of the sample based on 2016 population estimates from Eurostat with household income ranges being provided by the Office for National Statistics for the year 2017.

5.2.2 Measures

Generalized Anxiety Disorder 7-item Scale (GAD-7)

The GAD-7 was used to measure symptoms of generalized anxiety (Spitzer et al., 2006). The scale presents the participant with 7 items representing symptoms of general anxiety to which they were required to indicate how often it bothered them over the last two weeks. The answers were presented on a four-point Likert scale (0- "Not at all" to 3- "Nearly every day"). Possible scores ranged from 0 to 21, with higher scores indicative of higher levels of anxiety. The GAD-7 has seen wide use in psychiatric and community samples (Johnson et al., 2019). The Cronbach's α score in the present sample was excellent (.944).

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Kroenke et al., 2001) was used to assess the symptoms of depression. The scale presents the participant with 9 items representing symptoms of depression. Participants were asked to indicate how often they experienced each symptom over the past two weeks. The scale uses a four-point Likert scale (answers ranging from 0- "Not at all" to 3- "Nearly every day"). Item scores are added together and possible scores range from 0 to 27, with higher scores being indicative of higher levels of depression. The use of

PHQ-9 has been widely supported (Gilbody et al., 2007). Cronbach's α score in the sample was excellent (.921).

5.2.3 Statistical analysis

First, a network of the symptoms of anxiety and depression as measured by GAD-7 and PHQ-9 was estimated. This was performed to establish the overall connectedness of the symptoms regardless of probable diagnostic classification (anxiety, depression or MAD). Then, based on the results from Chapter 4 - the participants were assigned to the most probable class and networks were established for those. Additionally, as suggested by the results of Chapter 3 – anxiety and depression measures were treated as a sum-scored one-dimensional scale. Following this – the groups obtained were as follows – *baseline* with low scores, *medium* which previously represented both the anxiety and depression groups and *MAD* which represents high anxiety and depression scores (Chapter 4). This was performed to compare the networks for different groups present within the population in accordance with suggestions obtained from the bifactor analysis. These groups were used in further analysis (Network comparison and clique percolation).

Network Estimation

Networks were estimated, using R and the package 'qgraph' (Epskamp et al., 2012). This package visualises networks as nodes, in this case - points in space representing symptoms, and edges represented by lines linking symptoms. The edges can be interpreted as partial correlation coefficients, with thickness of the line being reflective of the strength of the association (between two nodes) while controlling for all other effects. Additionally, the networks were visualised using the 'spring' layout which places strongly associated nodes closer together (Epskamp et al., 2018). Parsimony of the network was ensured by utilising LASSO (a least absolute shrinkage and selection operator) – an operator which reduces the number of edges within a given network by 'shrinking' the lowest edges to zero (Epskamp et al., 2012). Negative edges were represented in red and positive edges were represented in blue.

Network Centrality

The importance of each node within the networks were estimated using two centrality indices – expected influence and betweenness. Expected influence refers to a nodes

(symptoms) influence with its neighbouring nodes based on raw edge strength. Betweenness indicates the importance of a node in connecting other, unconnected symptoms in the network and is calculated based on the number of times a node lies on the shortest path between two nodes. Both were estimated using the 'qgraph' R package (Epskamp et al., 2012).

Network Stability

The R 'bootnet' package was used to establish the stability and accuracy of each of the estimated networks (Epskamp et al., 2018). This was performed in three steps: (1) 95% confidence intervals (CI) of the edge weights were obtained through bootstrapping, (2) the correlation stability co-efficient for centrality indices were estimated (with values below 0.25 implying inadequate stability while values exceeding 0.5 implying adequate stability), (3) an edge-weights difference test for each network estimated was also computed. The analyses each used 1000 iterations of bootstrapping.

Network Comparison Test

The networks were compared using a 'Network Comparison Test' (NCT; van Borkulo et al., 2017). NCT utilises non-parametric permutation testing to compare edges across networks and tests invariance in overall connectivity and structure tests. In the present study, these comparisons were performed to establish whether there are structural differences between symptom networks representing different groups of probable anxiety and depression diagnoses.

Clique percolation

Clique Percolation Method (CPM) for weighted networks (Palla et al., 2005; Farkas et al., 2007) was used to help identify communities of symptoms of anxiety and depression in the estimated networks. The R package CliquePercolation (Lange, 2019) was used. When compared to most other methods (e.g. walktrap), CPM is useful for psychometric networks because it allows a node to belong to more than one community. The method works by identifying k-cliques, which are fully connected networks with 'k' number of nodes. The cliques can be defined as adjacent when they share all but one node in which case these cliques are formed into communities. Two parameters have to be set for weighted CPM: the mentioned parameter *k* and the intensity parameter *I* which determines the strength of average relations among a community needed for that community to be detected. For small networks, using an entropy permutation test, can establish an optimal value for these

(Lange, 2019). In the present study, K was allowed to vary between 3 and 7 and *I* between 0.01 and 0.40 with each iteration between these being tested by increments of 0.005. Permutation tests were performed on the medium and MAD networks.

5.3 Results

The descriptive statistics for GAD-7 and PHQ-9 are available in Table 12.

Table 12. Descriptive statistics for the overall sample and its subgroups

	Overall N= 2007		Baseline N= 1479		Medium N=232		MAD N=296	
	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation	Mean	Std. Deviation
PHQ 1	0.702	0.919	0.370	0.635	1.216	0.996	1.959	0.771
PHQ 2	0.735	0.918	0.358	0.562	1.435	0.890	2.071	0.802
PHQ 3	0.851	1.000	0.513	0.753	1.427	1.058	2.088	0.847
PHQ 4	0.829	0.982	0.475	0.686	1.414	1.078	2.135	0.825
PHQ 5	0.572	0.901	0.258	0.563	0.948	1.051	1.851	0.905
PHQ 6	0.532	0.888	0.192	0.472	0.944	1.007	1.909	0.914
PHQ 7	0.568	0.880	0.231	0.494	1.039	0.995	1.885	0.883
PHQ 8	0.286	0.692	0.066	0.272	0.405	0.773	1.294	1.069
PHQ 9	0.299	0.704	0.067	0.273	0.409	0.784	1.372	1.040
GAD 1	0.878	0.969	0.478	0.605	1.793	1.049	2.159	0.763
GAD 2	0.734	0.957	0.312	0.507	1.737	1.046	2.061	0.792
GAD 3	0.790	0.967	0.360	0.525	1.733	1.043	2.199	0.716
GAD 4	0.766	0.948	0.358	0.543	1.651	0.951	2.111	0.810
GAD 5	0.501	0.837	0.181	0.426	1.009	0.962	1.706	0.977
GAD 6	0.728	0.938	0.368	0.601	1.362	1.001	2.030	0.845
GAD 7	0.767	0.958	0.385	0.602	1.586	1.045	2.034	0.835
Depression	5.370	6.219	2.530	2.957	9.237	5.356	16.560	4.339
Anxiety	5.164	5.691	2 .440	2.751	10.870	5.337	14.300	3.672

5.3.1 Network estimation

Figure 5 depicts the network structure for the entire sample. The possible number of edges for the network was 120 out of which, after LASSO, 86 (71.67%) were above zero. The strongest overall edge was observed between GAD2-GAD3 items (0.401) followed by PHQ3- PHQ4 (0.375) and PHQ1-PHQ2 (0.356). The strongest between construct edge was observed between PH8-GAD5 (0.265).

The edge weights bootstrap (Figure 6) showed that the 95% confidence intervals for many of the edges were overlapping. Furthermore, there were few significant differences between the strongest edges; this therefore indicates that the ranking of edge weights should be interpreted with care (Figure 7).

Figure 5. Full Sample Network Structure of Anxiety and Depression-based Symptomatology

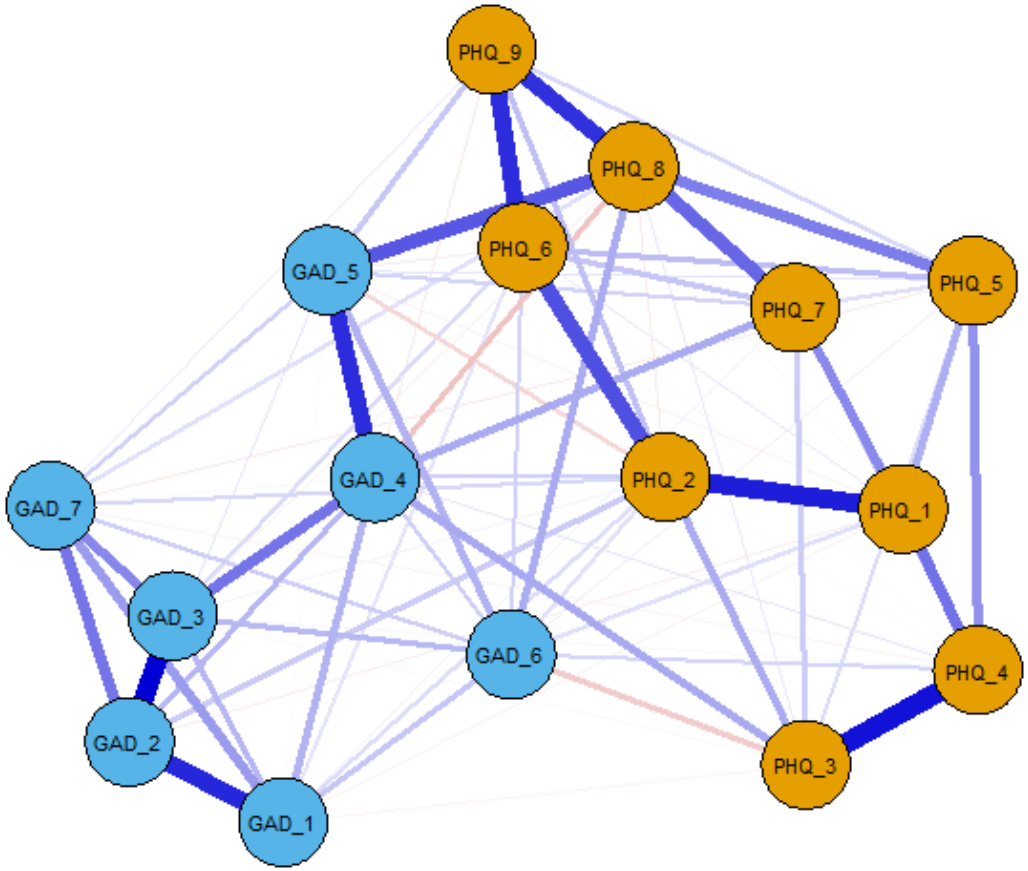


Figure 6. Results from tests of edge weight accuracy for the overall (entire sample) network structure

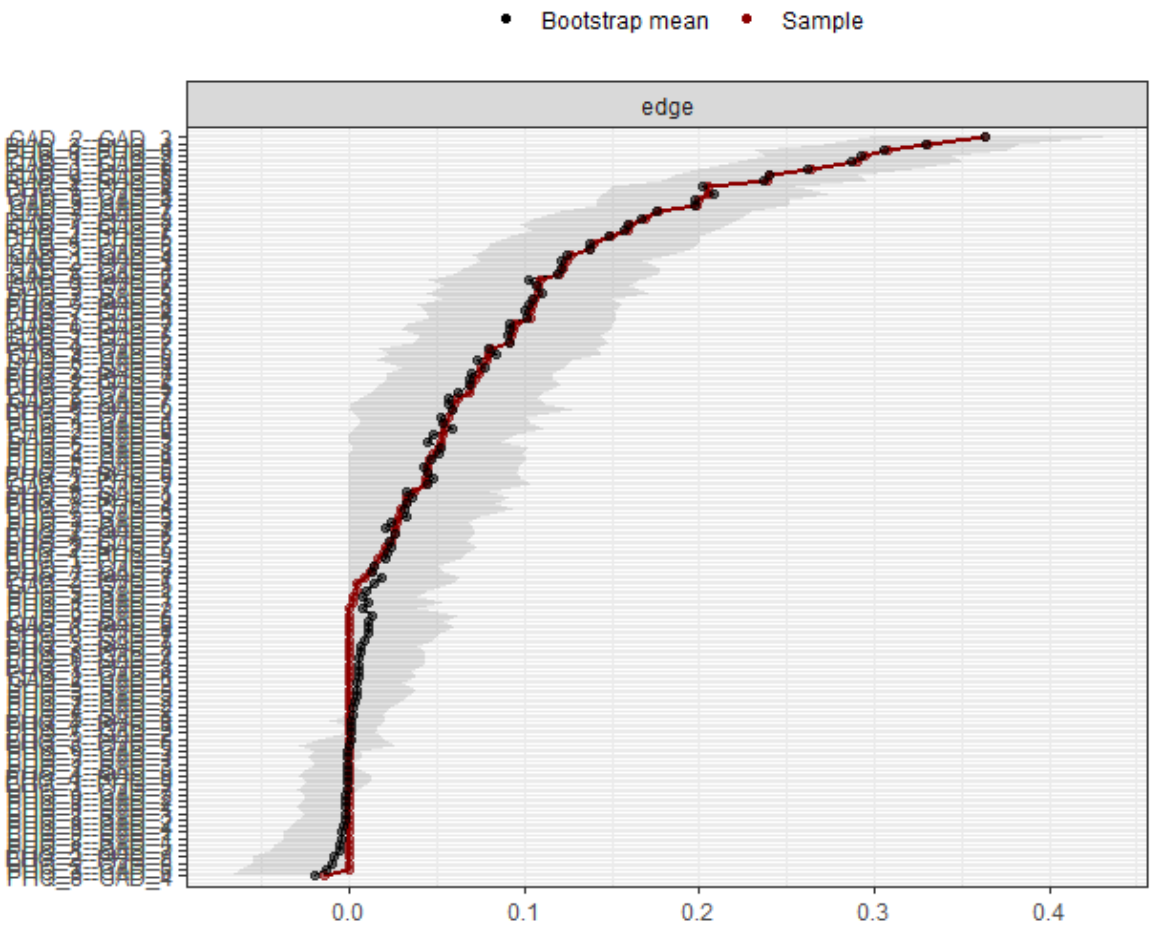
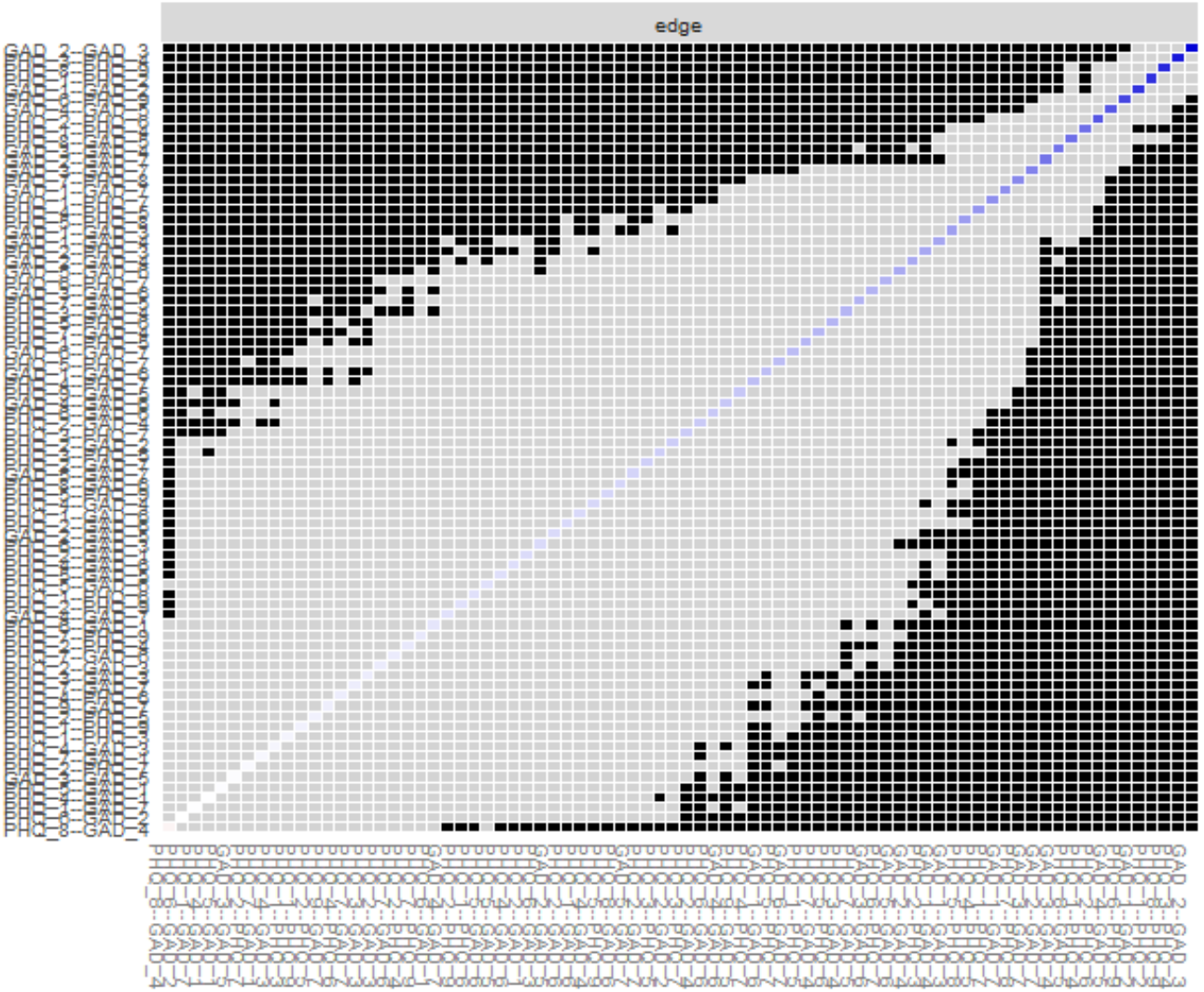


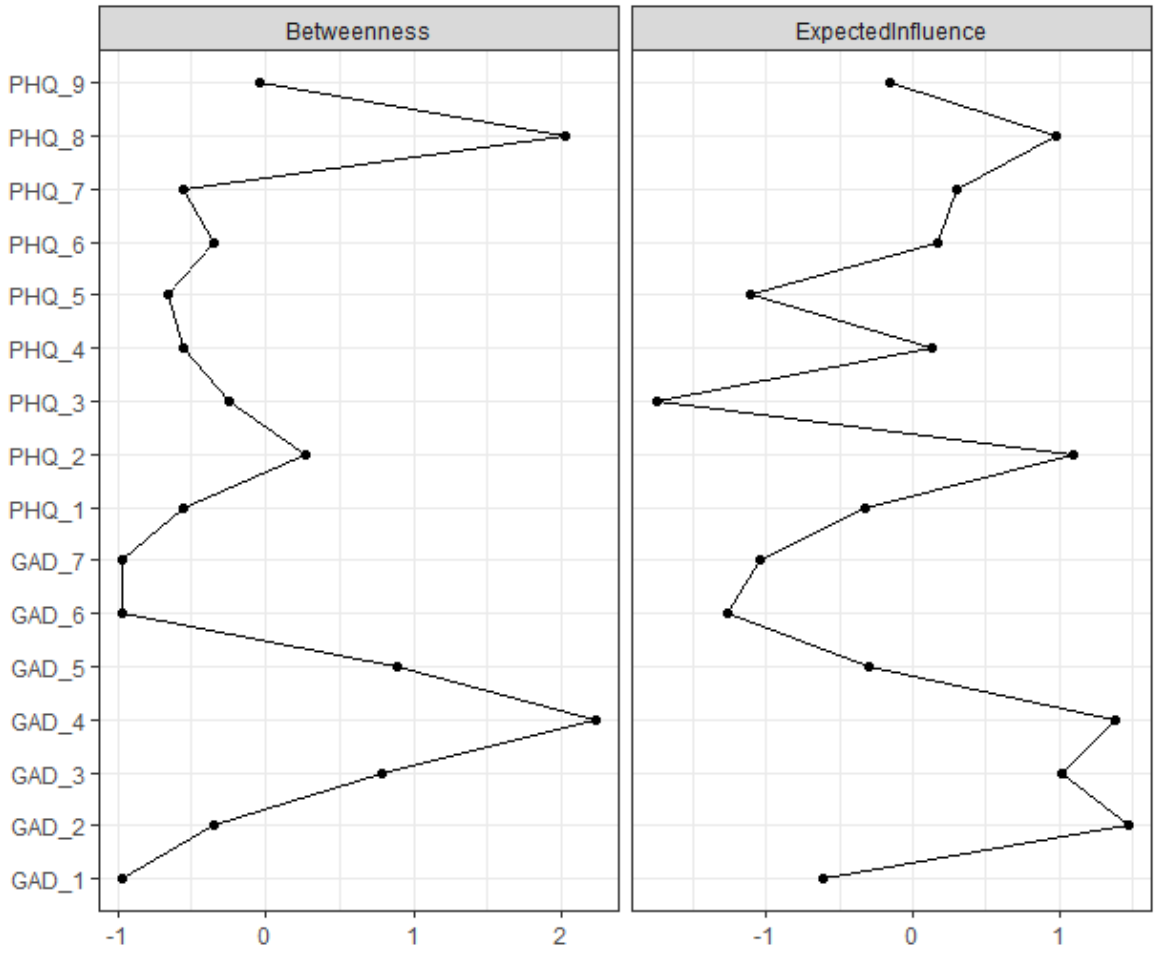
Figure 7. Bootstrapped difference tests between non-zero edges for the full sample



5.3.2 Centrality Indices

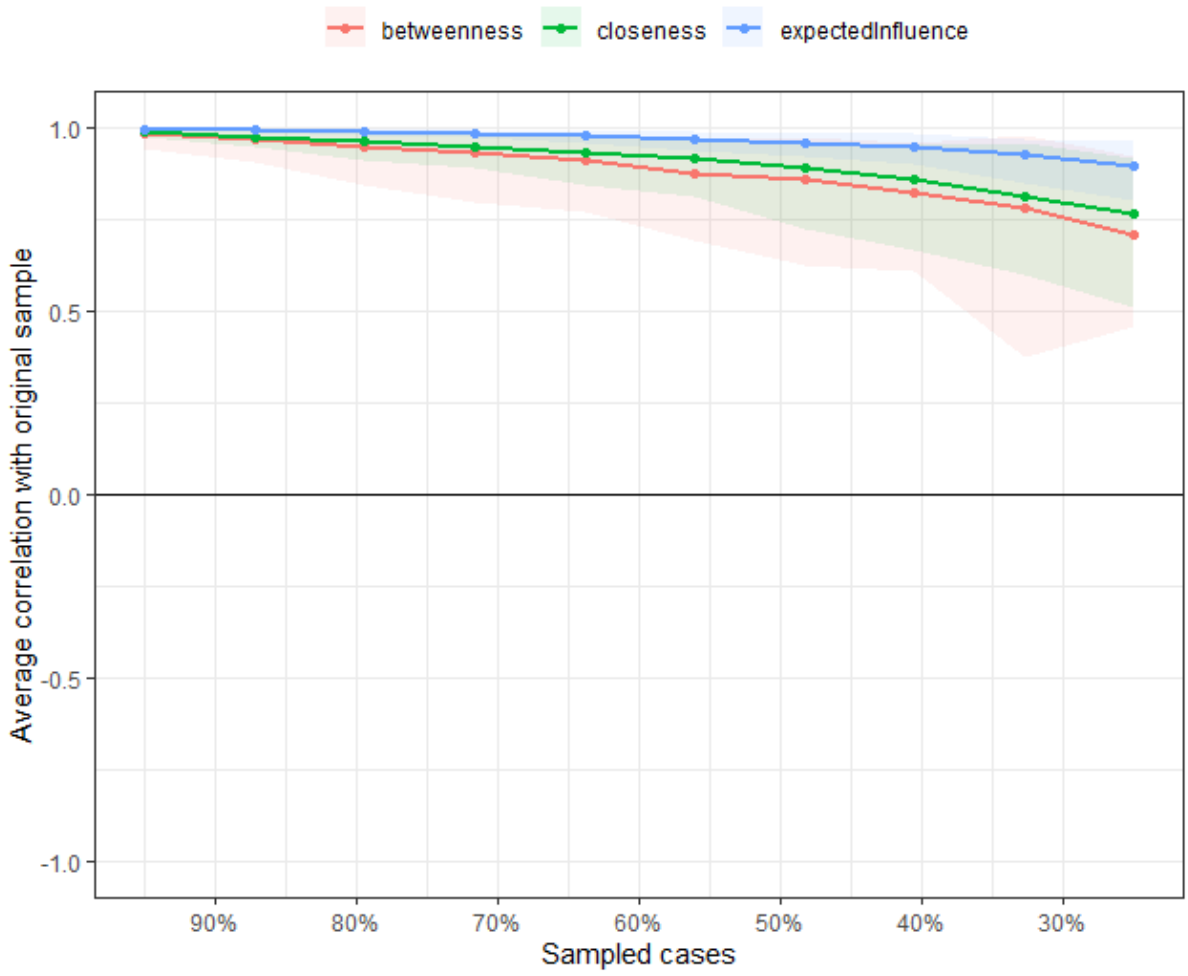
Centrality indices are presented in figure 8 and the stability is presented in figure 9. Stability analyses indicated a stable order of expected influence and betweenness with a CS coefficient above 0.5. Symptoms of GAD2 (1.47), GAD4 (1.38), PHQ2 (1.09) and GAD3 (1.02) had the highest expected influence and GAD4 (2.23) and PHQ8 (2.02) showed the highest betweenness.

Figure 8. Centrality Estimates for the Overall Network Structure.



Note: Centrality values are presented as Z-scores.

Figure 9. Mean correlations between centrality values of the full sample and bootstrapped samples with different degrees of persons dropped.

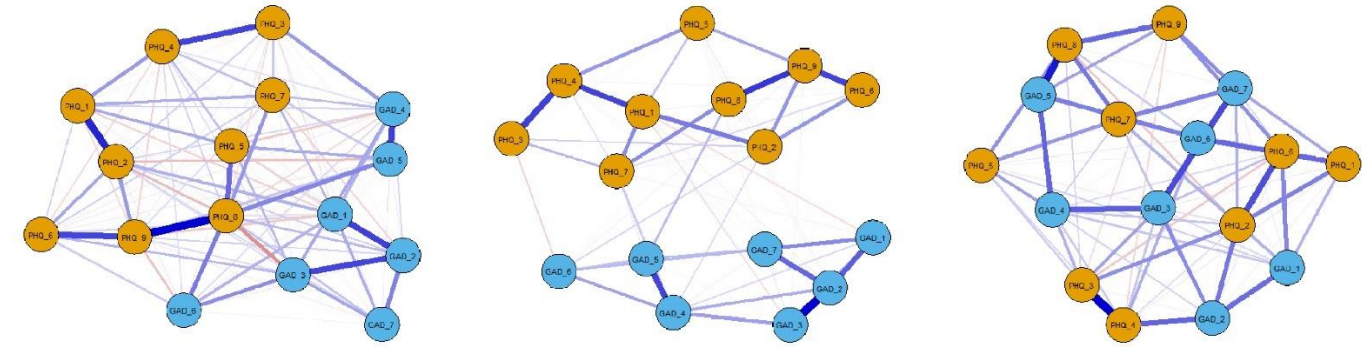


5.3.3 Network analysis of Baseline, Medium and MAD groups

Network estimation

Figure 10 depicts the network structure for the three different symptom intensity groups.

Figure 10. Network structure of Anxiety and Depression symptoms stratified by symptom intensity



Note. Depression symptoms are depicted in orange, Anxiety symptoms are depicted in blue. Network layout was established separately for each network using 'spring' layout.

Baseline

The possible number of edges for the network was 120 out of which 111, after LASSO, 111 (92.5%) were above zero. Edge strength ranged from -0.204 to 0.471. There were more positive than negative edges and negative edges were weak – all below -0.3. The strongest edges were observed for PHQ8- PHQ9 (0.471), and PHQ1- PHQ2 (0.402) The strongest between-construct edge was PHQ8-GAD-6 (0.243) with all between construct edges being weak – below 0.3.

Medium

The possible number of edges for the network was 120 out of which, after LASSO, 61 (50.83%) were above zero. Edge strength ranged from -0.088 to 0.468. There were more positive than negative edges and negative edges were weak – all below -0.3. The strongest edges were observed for GAD2-GAD3 (0.468) and PHQ8- PHQ9 (0.366). The strongest between-construct edge was PHQ8-GAD-5 (0.123) with all between construct edges being weak – below 0.3.

MAD

The possible number of edges for the network was 120 out of which, after LASSO, 77 (64.17%) were above zero. Edge strength ranged from -0.075 to 0.339. There were more positive than negative edges and negative edges were weak – all below -0.3. The strongest edges were observed for PHQ3-PHQ4 (0.339) and GAD5-PHQ8 (0.306) which was the strongest between-construct edge as well.

For each of the groups, the edge weights bootstrap (Figures 11-13) showed that the 95% confidence intervals for many of the edges were overlapping. Furthermore, there were few significant differences between the strongest edges. This therefore indicates that the ranking of edge weights should be interpreted with care (Figures 14-16).

Figure 11. Results from tests of edge weight accuracy for the Baseline network structure

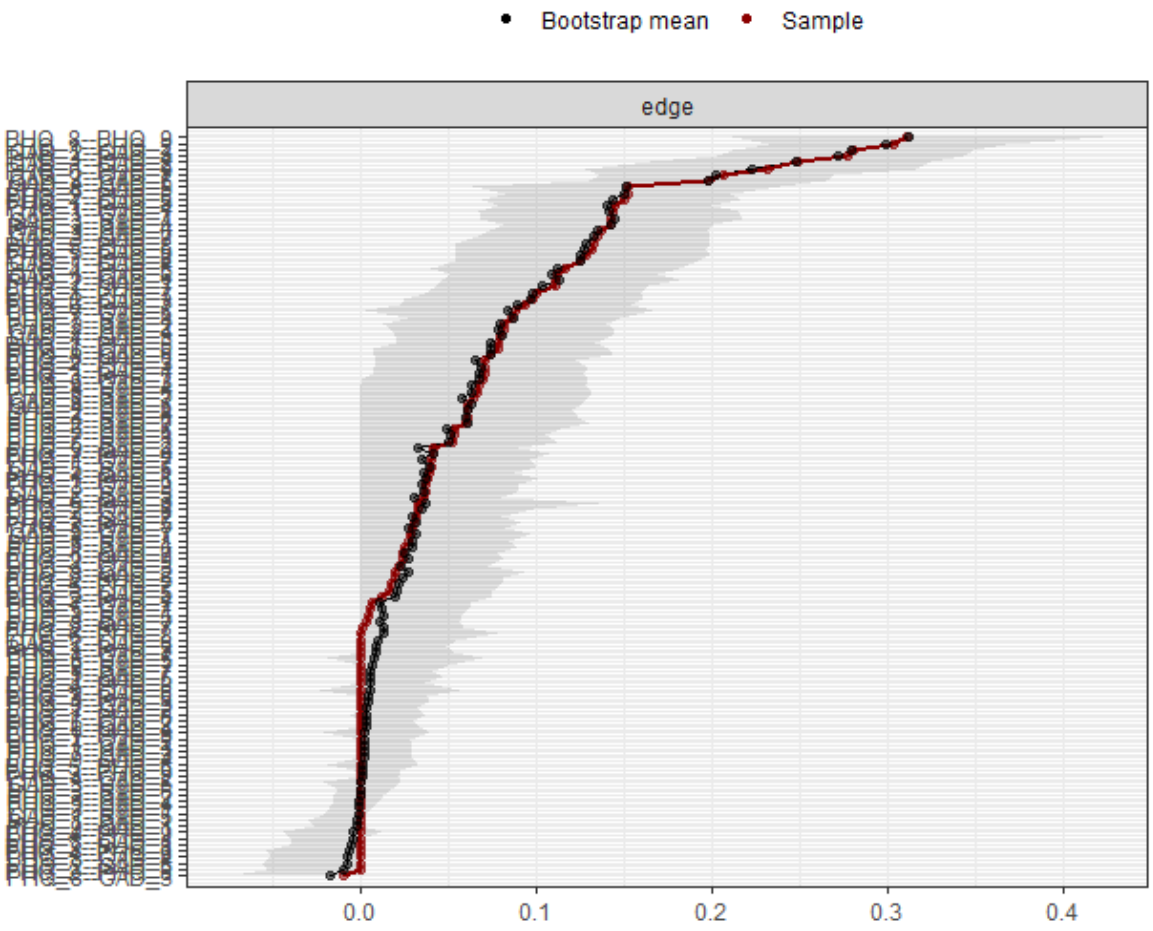


Figure 12. Results from tests of edge weight accuracy for the Medium network structure

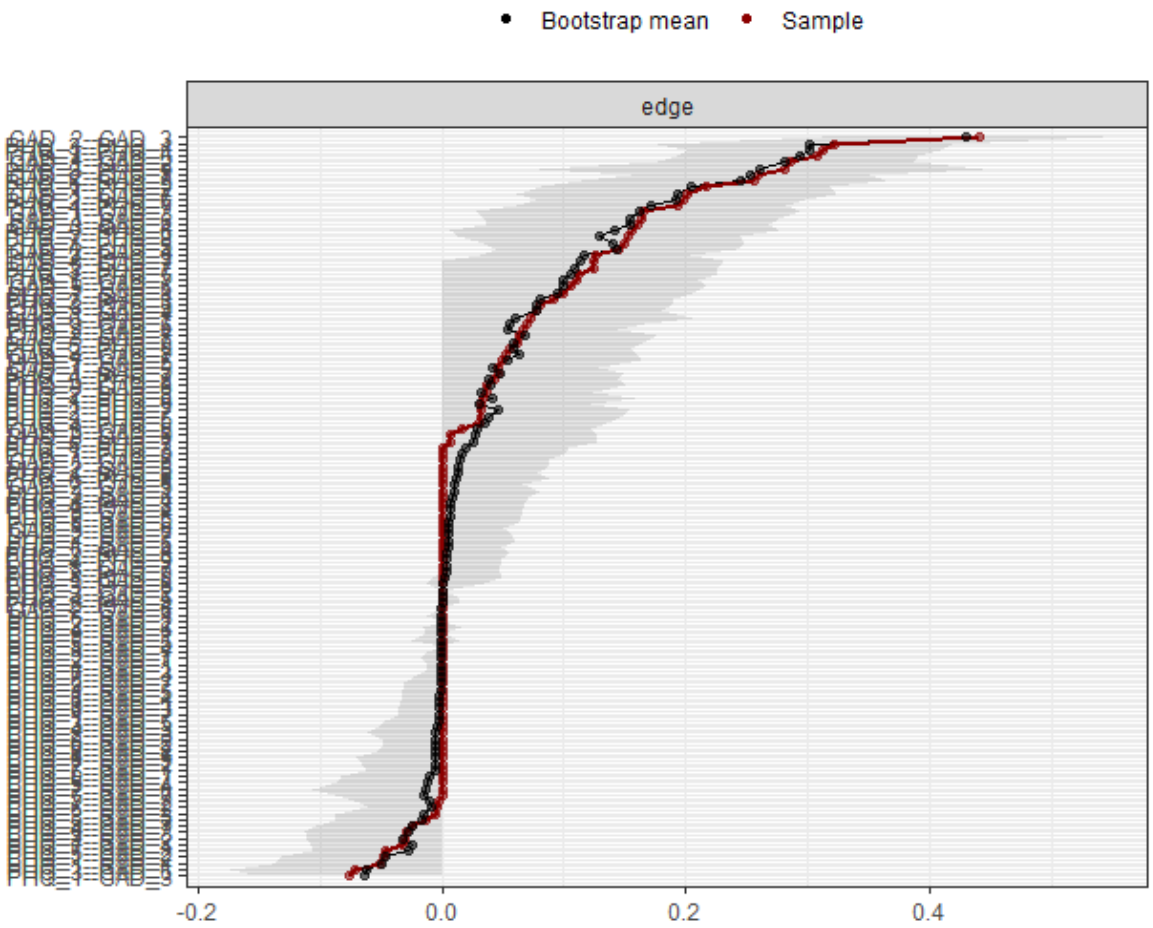


Figure 13. Results from tests of edge weight accuracy for the MAD network structure

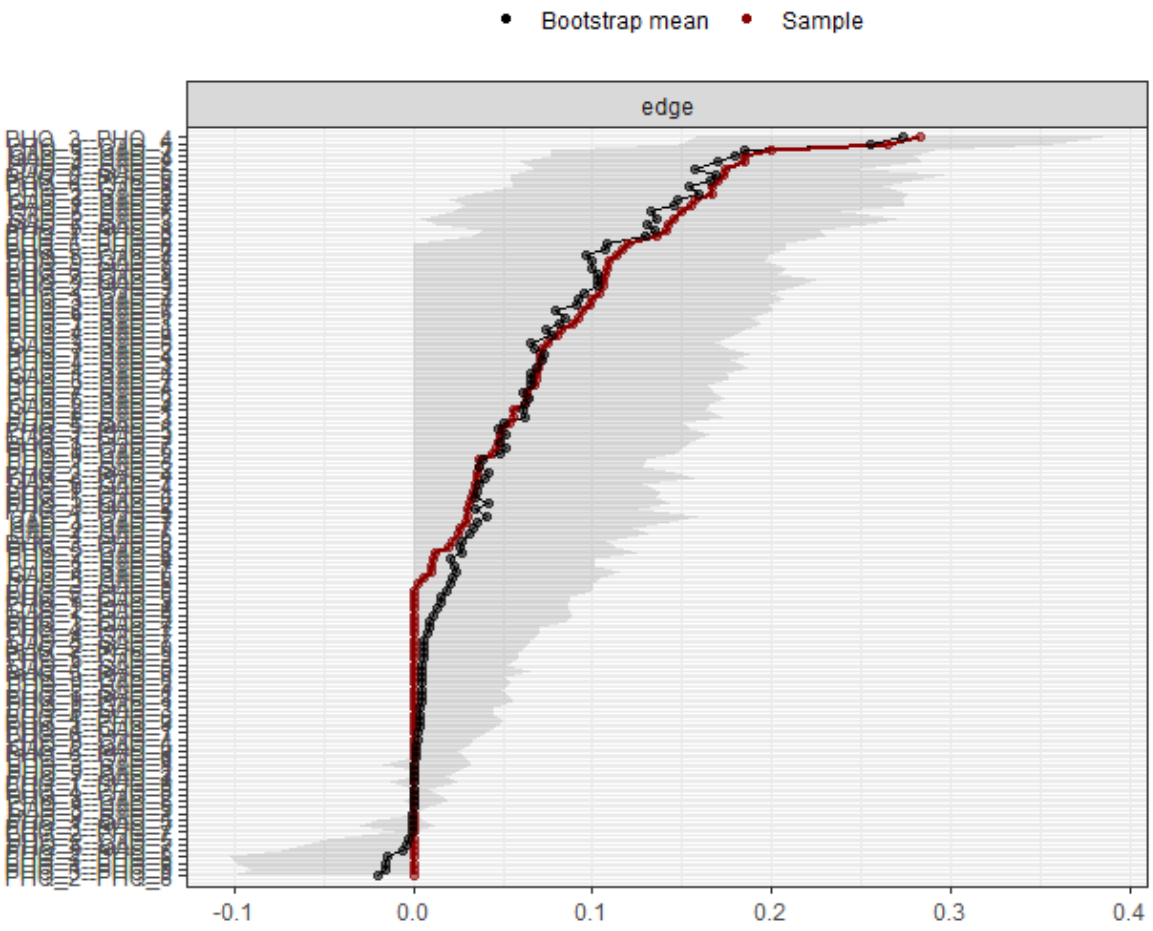


Figure 14. Bootstrapped difference tests between non-zero edges for the Baseline group.

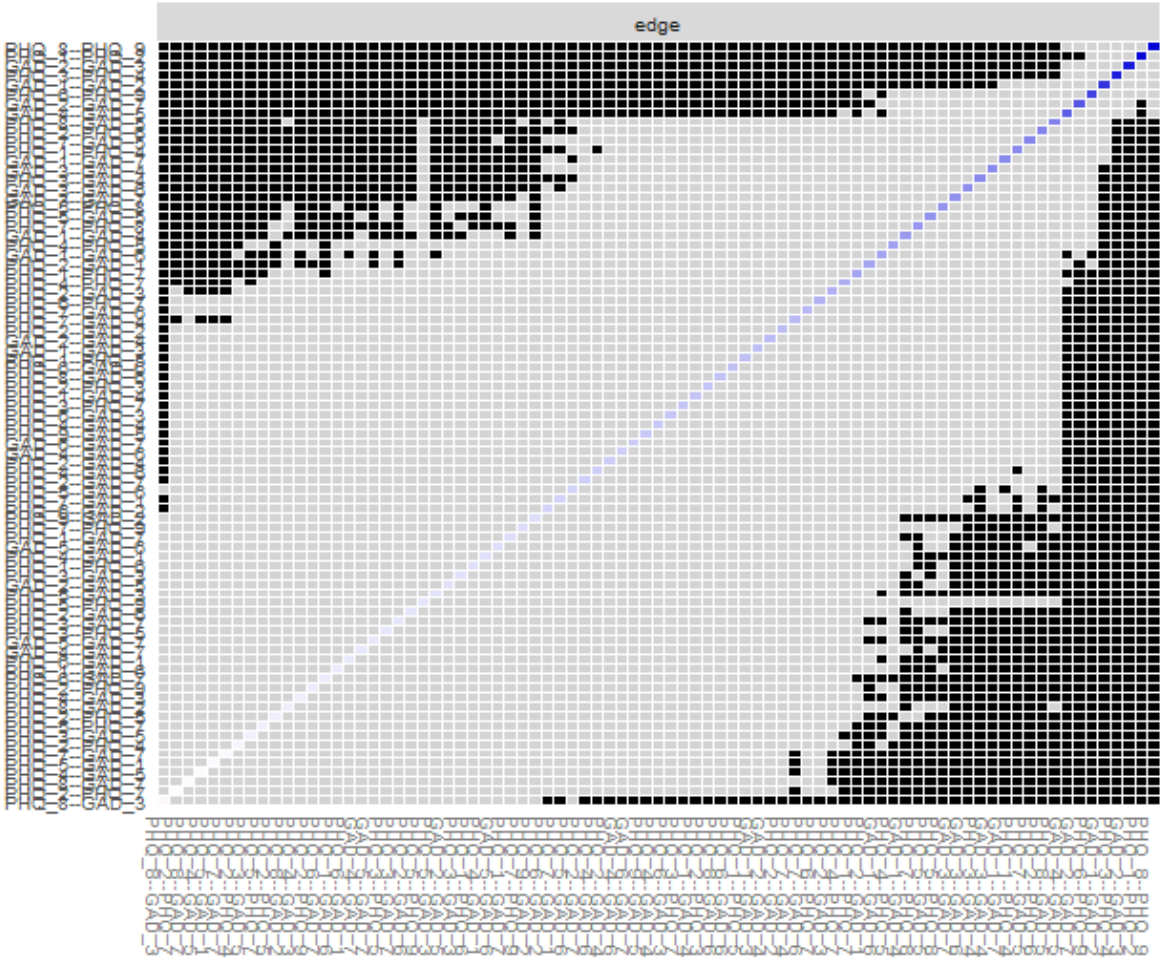


Figure 15. Bootstrapped difference tests between non-zero edges for the Medium group.

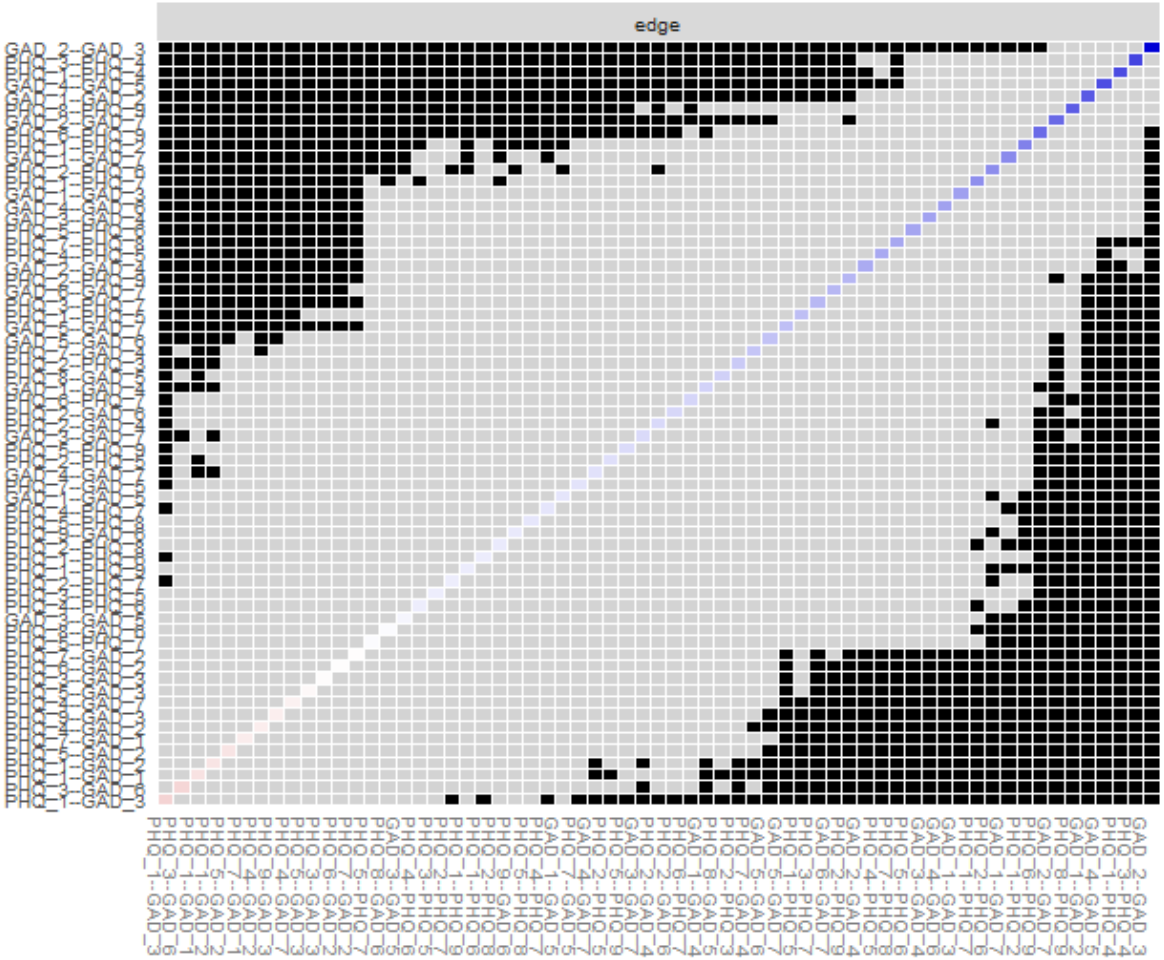
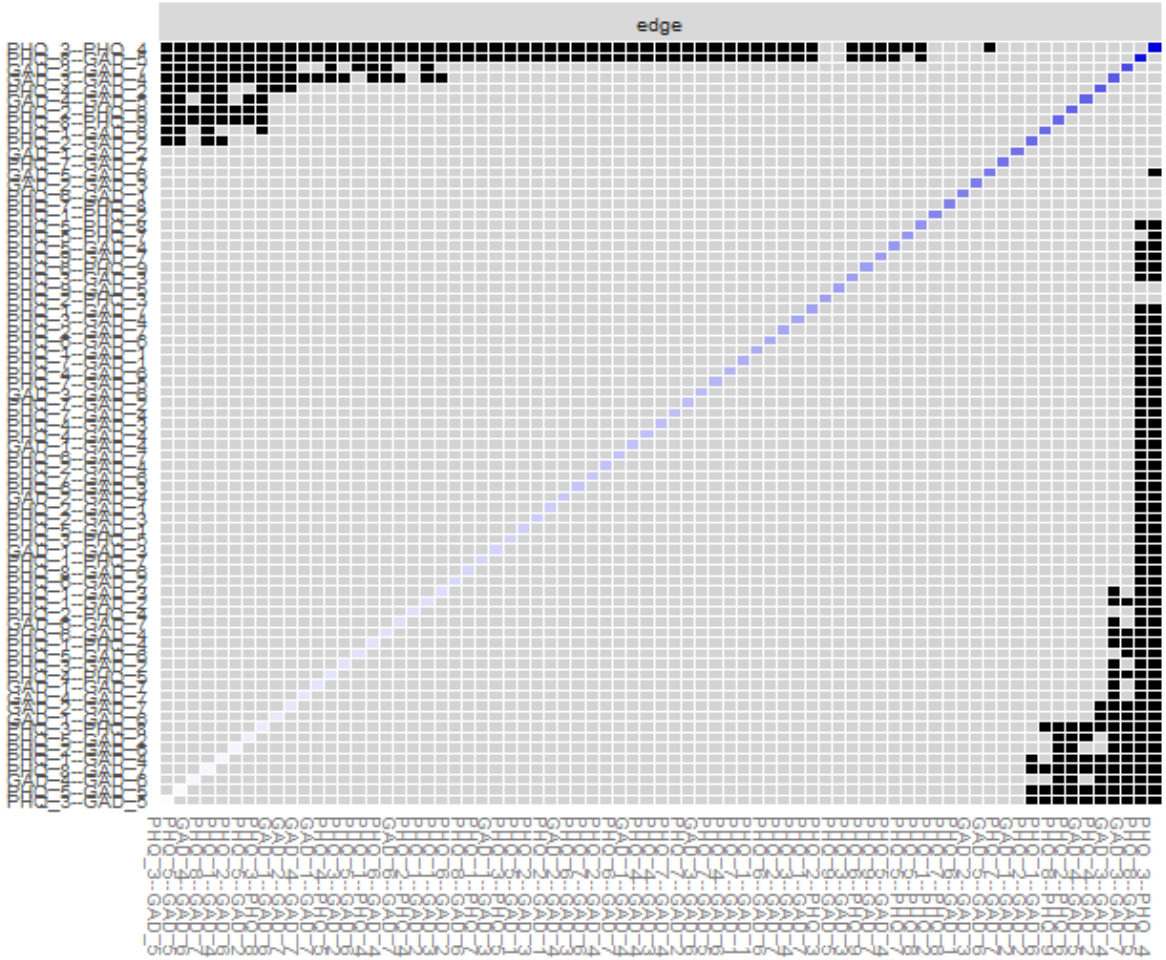


Figure 16. Bootstrapped difference tests between non-zero edges for the MAD group.



Centrality Indices

Centrality indices are presented in Figure 17 and the stability is presented in figures 18-20.

Baseline

Stability analyses indicated a stable order of expected influence and betweenness with a CS coefficient above 0.5 up until 70% of the sample was dropped. PHQ8 (1.91) had the highest expected influence as well as the highest betweenness (2.917).

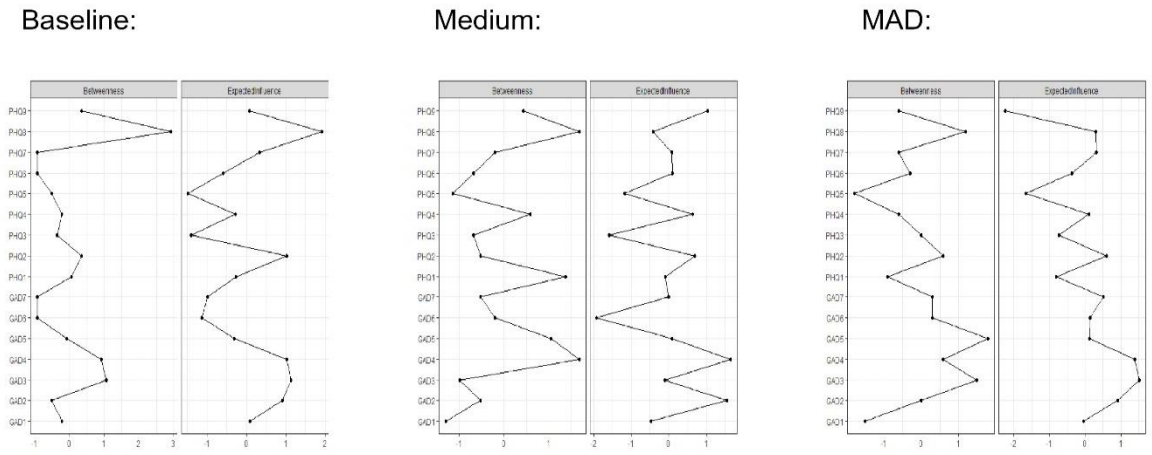
Medium

Stability analyses indicated a moderately stable order of expected influence and betweenness with a CS coefficient above 0.5 up until 60% of the sample was dropped. GAD4(1.636) and GAD2(1.543) showed the highest values of expected influence. GAD4 and PHQ8 both showed the highest betweenness (1.682; same value for both).

MAD

Stability analyses indicated an order of expected influence and betweenness that is moderately stable- betweenness retained CS coefficient above 0.5 with 50% of the sample dropped and expected influence retained the CS coefficient above 0.5 with 40% of the sample dropped. These suggest that the centrality indices should be interpreted with care. Symptoms of GAD3 (1.506) and GAD4 (1.386) had the highest expected influence and GAD 5 (1.782) and GAD3 (1.485) showed the highest betweenness.

Figure 17. Centrality indices for the networks based on symptom groups.



Note. Centrality scores are presented as Z-scores.

Figure 18. Mean correlations between centrality values of the Baseline group and bootstrapped samples with different degrees of persons dropped.

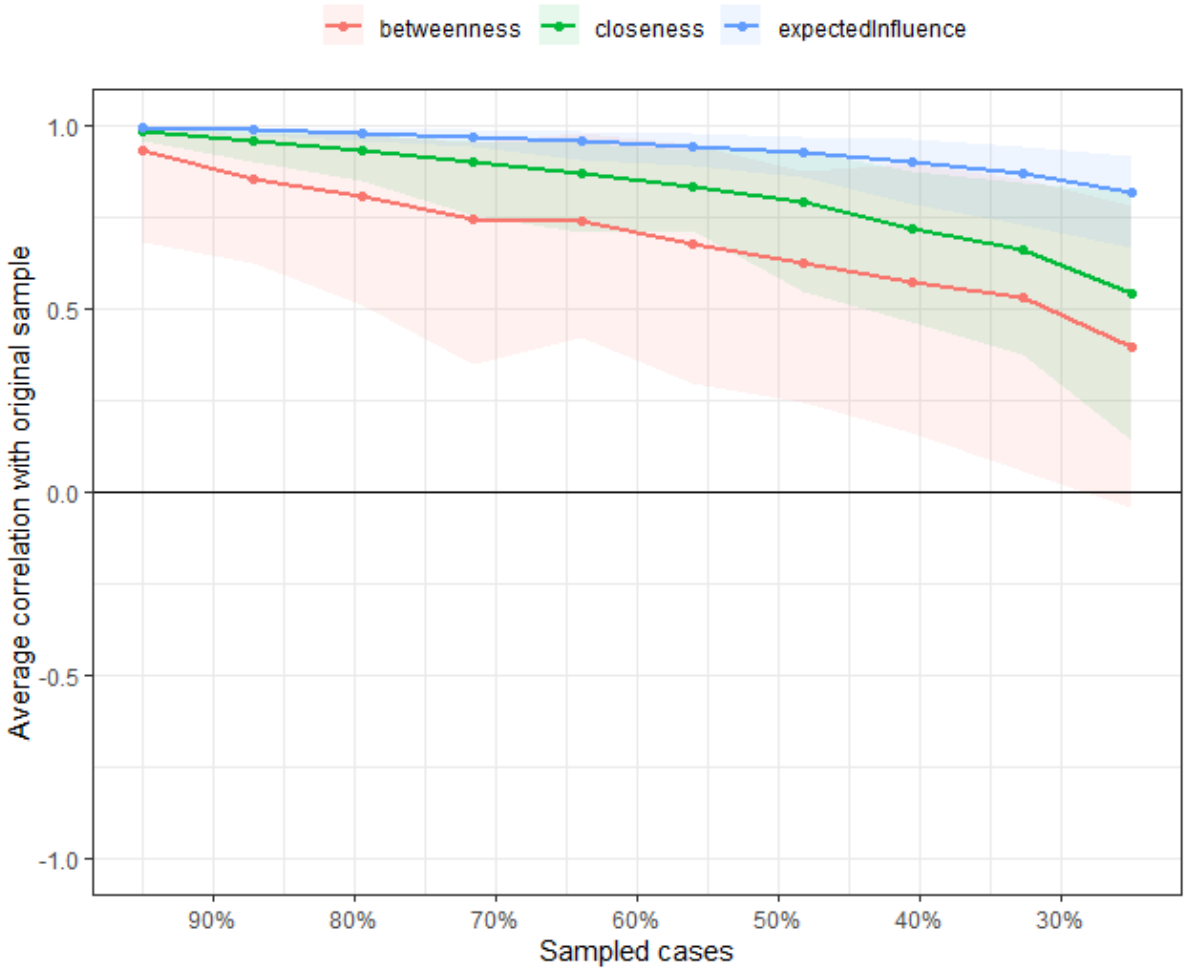


Figure 19. Mean correlations between centrality values of the Medium group and bootstrapped samples with different degrees of persons dropped.

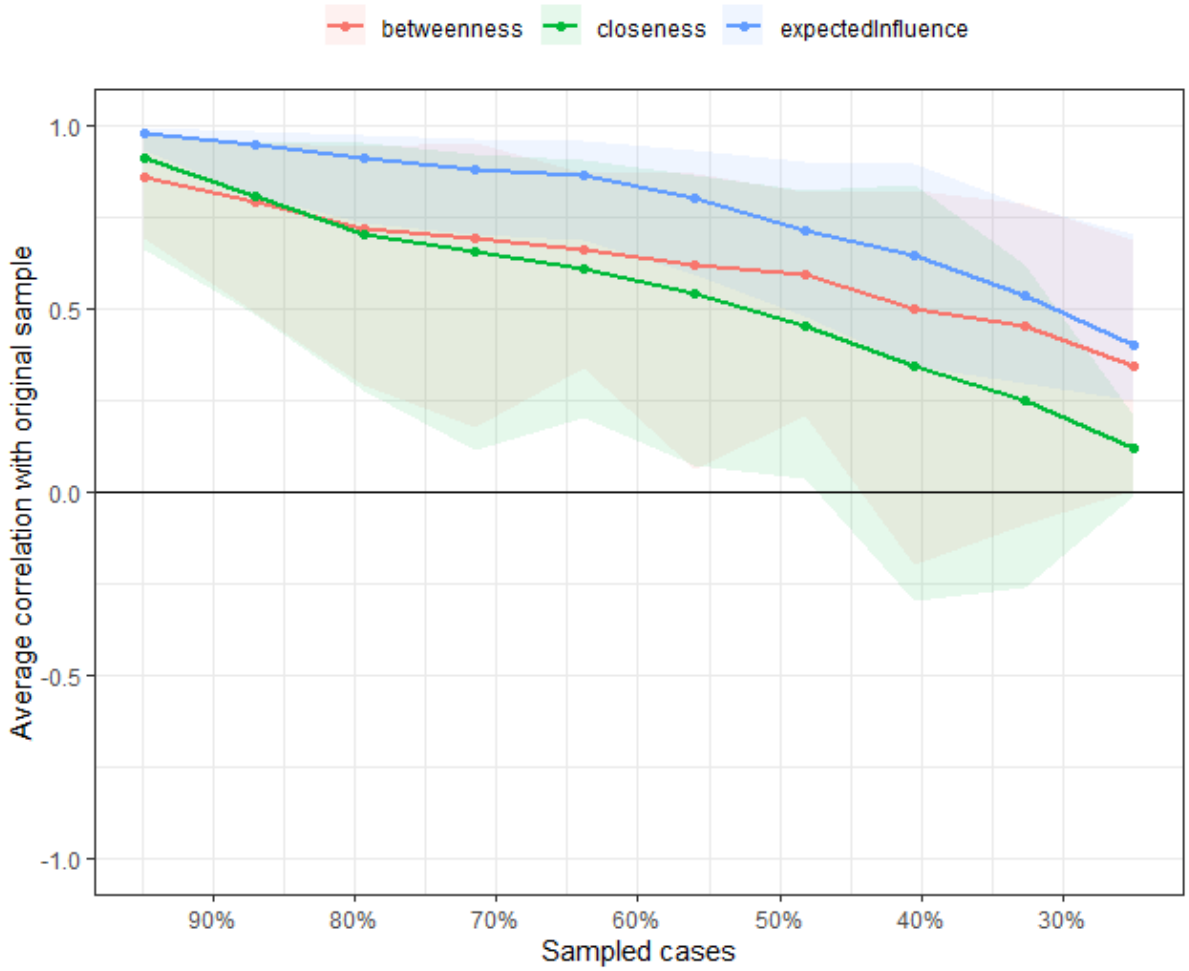
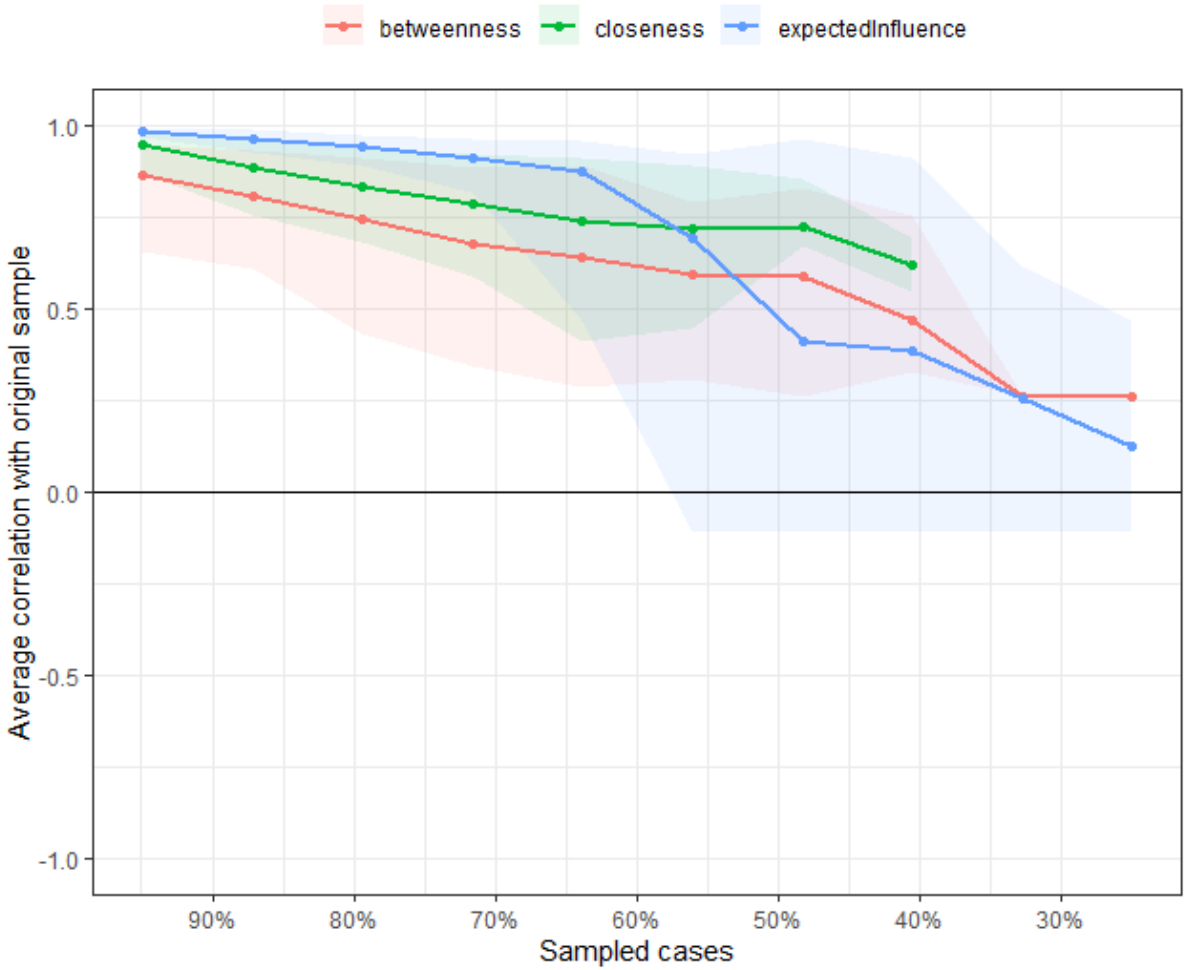


Figure 20. Mean correlations between centrality values of the MAD group and bootstrapped samples with different degrees of persons dropped.



5.3.4 Network comparison tests

To compare the symptom groups, network comparison tests were performed. No significant differences were found between the Baseline group and other groups in terms of the overall network structure. There was a significant difference found between the Medium and the MAD groups (M=0.295, p = 0.004). However, the global strength invariance test was nonsignificant (S= 0.466, p= 0.179). The edge difference results, presented in Table 13, reveal that most differences between the Medium and the MAD groups were found in the cross-construct edges.

Table 13. Cross- and Within-construct edge comparisons between Medium and MAD groups

Cross-Construct comparisons			Within-construct comparisons		
Symptom 1	Symptom 2	P value	Symptom 1	Symptom 2	P value
PHQ_1	GAD_1	0	PHQ_1	PHQ_2	0.291
PHQ_2	**GAD_1**	**0.007**	PHQ_1	PHQ_3	1
PHQ_3	GAD_1	1	PHQ_2	PHQ_3	0.868
PHQ_4	GAD_1	1	**PHQ_1**	**PHQ_4**	**0**
PHQ_5	**GAD_1**	**0.005**	PHQ_2	PHQ_4	0.577
PHQ_6	**GAD_1**	**0**	PHQ_3	PHQ_4	0.654
PHQ_7	**GAD_1**	**0**	PHQ_1	PHQ_5	0.18
PHQ_8	GAD_1	1	PHQ_2	PHQ_5	0.058
PHQ_9	GAD_1	1	PHQ_3	PHQ_5	0.83
PHQ_1	**GAD_2**	**0.023**	PHQ_4	PHQ_5	0.153
PHQ_2	**GAD_2**	**0**	PHQ_1	PHQ_6	0.692
PHQ_3	**GAD_2**	**0.03**	PHQ_2	PHQ_6	0.768
PHQ_4	**GAD_2**	**0**	PHQ_3	PHQ_6	1
PHQ_5	**GAD_2**	**0.005**	PHQ_4	PHQ_6	0.718
PHQ_6	**GAD_2**	**0**	PHQ_5	PHQ_6	0.098
PHQ_7	**GAD_2**	**0**	PHQ_1	PHQ_7	0.066
PHQ_8	GAD_2	1	PHQ_2	PHQ_7	0.575
PHQ_9	GAD_2	1	PHQ_3	PHQ_7	0.074
PHQ_1	**GAD_3**	**0**	PHQ_4	PHQ_7	0.597
PHQ_2	**GAD_3**	**0.003**	PHQ_5	PHQ_7	0.199
PHQ_3	**GAD_3**	**0**	PHQ_6	PHQ_7	0.41
PHQ_4	**GAD_3**	**0.001**	PHQ_1	PHQ_8	1
PHQ_5	GAD_3	0.065	**PHQ_2**	**PHQ_8**	**0.005**
PHQ_6	**GAD_3**	**0.007**	PHQ_3	PHQ_8	0.775
PHQ_7	GAD_3	1	PHQ_4	PHQ_8	1
PHQ_8	GAD_3	1	PHQ_5	PHQ_8	0.322
PHQ_9	**GAD_3**	**0.008**	PHQ_6	PHQ_8	1
PHQ_1	**GAD_4**	**0.016**	PHQ_7	PHQ_8	0.859
PHQ_2	GAD_4	0.98	PHQ_1	PHQ_9	0.663
PHQ_3	GAD_4	0.082	**PHQ_2**	**PHQ_9**	**0.035**
PHQ_4	GAD_4	0.056	PHQ_3	PHQ_9	1
PHQ_5	GAD_4	0	PHQ_4	PHQ_9	1

PHQ_6	GAD_4	0.207	PHQ_5	PHQ_9	0.456
PHQ_7	GAD_4	0.731	**PHQ_6**	**PHQ_9**	**0.045**
PHQ_8	GAD_4	1	PHQ_7	PHQ_9	1
PHQ_9	GAD_4	1	PHQ_8	PHQ_9	0.194
PHQ_1	GAD_5	1	GAD_1	GAD_2	0.159
PHQ_2	GAD_5	1	GAD_1	GAD_3	0.227
PHQ_3	GAD_5	0.215	**GAD_2**	**GAD_3**	**0.001**
PHQ_4	GAD_5	1	GAD_1	GAD_4	0.934
PHQ_5	GAD_5	0.341	GAD_2	GAD_4	0.303
PHQ_6	GAD_5	1	GAD_3	GAD_4	0.761
PHQ_7	GAD_5	0.701	GAD_1	GAD_5	0.517
PHQ_8	**GAD_5**	**0.019**	GAD_2	GAD_5	1
PHQ_9	GAD_5	0.178	GAD_3	GAD_5	0.623
PHQ_1	**GAD_6**	**0.005**	GAD_4	GAD_5	0.059
PHQ_2	GAD_6	0.468	GAD_1	GAD_6	0.781
PHQ_3	**GAD_6**	**0.009**	GAD_2	GAD_6	1
PHQ_4	**GAD_6**	**0.013**	GAD_3	GAD_6	0.312
PHQ_5	GAD_6	0.404	GAD_4	GAD_6	0.092
PHQ_6	GAD_6	0.225	GAD_5	GAD_6	0.615
PHQ_7	**GAD_6**	**0.042**			
PHQ_8	GAD_6	0.617			
PHQ_9	GAD_6	0.546			
PHQ_1	**GAD_7**	**0**			
PHQ_2	**GAD_7**	**0.042**			
PHQ_3	GAD_7	1			
PHQ_4	GAD_7	0.084			
PHQ_5	GAD_7	1			
PHQ_6	**GAD_7**	**0.005**			
PHQ_7	**GAD_7**	**0**			
PHQ_8	GAD_7	0.562			
PHQ_9	**GAD_7**	**0.005**			

5.3.5 Clique Percolation

Medium

The permutation test resulted in an optimal value of $k = 3$ and I=0.155. Clique percolation analysis resulted in four communities presented in Figure 21. PHQ8 and PHQ3 were two items that did not belong to any community and GAD4 and PHQ5 both belong to two communities. Communities and their full symptom description are presented in Table 14.

Table 14. Symptom Description of Communities for the Medium group

Community	Symptom	Code	
A	‘Feeling down, depressed, or hopeless’	PHQ2	
	‘Poor appetite or overeating’*	PHQ5*	Shared with B
	‘Feeling bad about yourself – or that you are a failure or have let yourself or your family down’	PHQ6	
	‘Thoughts that you would be better off dead, or of hurting yourself in some way’	PHQ9	
B	'Little interest or pleasure in doing things'	PHQ1	
	'Feeling tired or having little energy'	PHQ4	
	'Poor appetite or overeating'	PHQ5*	Shared with A
	'Trouble concentrating on things, such as reading the newspaper or watching television'	PHQ7	
C	'Feeling nervous, anxious, or on edge'	GAD1	
	'Not being able to stop or control worrying'	GAD2	
	'Worrying too much about different things'	GAD3	

	'Trouble relaxing'	GAD4*	Shared with D
	'Feeling afraid as if something awful might happen'	GAD7	
D	'Trouble relaxing'	GAD4*	Shared with C
	'Being so restless that it's hard to sit still'	GAD5	
	'Becoming easily annoyed or irritable'	GAD6	

*Note: * indicates that a node is shared.*

MAD

The permutation test resulted in an optimal value of $k = 4$ (minimum clique size was 3 nodes) and I=0.110. Clique percolation analysis resulted in three communities presented in Figure 18. PHQ1, PHQ5, PHQ9 and GAD7 were not assigned any community and one item – GAD2 belonged to two communities. Results are presented in Table 15 and Figure 22.

Table 15. Symptom Description of Communities for the MAD group

Community	Symptom	Code	
A	'Not being able to stop or control worrying'	GAD2*	Shared with C
	'Worrying too much about different things'	GAD3	
	'Trouble relaxing'	GAD4	
	'Trouble falling or staying asleep, or sleeping too much'	PHQ3	
	'Feeling tired or having little energy'	PHQ4	
B	Being so restless that it’s hard to sit still'	GAD5	
	Becoming easily annoyed or irritable'	GAD6	
	'Trouble concentrating on things, such as reading the newspaper or watching television'	PHQ7	
	'Moving or speaking so slowly that other people could have noticed or the opposite – being so fidgety or restless that you have been moving around a lot more than usual'	PHQ8	
C	'Feeling nervous, anxious, or on edge'	GAD1	
	'Not being able to stop or control worrying'	GAD2*	Shared with A
	'Feeling down, depressed, or hopeless'	PHQ2	
	'Feeling bad about yourself – or that you are a failure or have let yourself or your family down'	PHQ6	

Figure 21. Clique Percolation Results for the Medium group

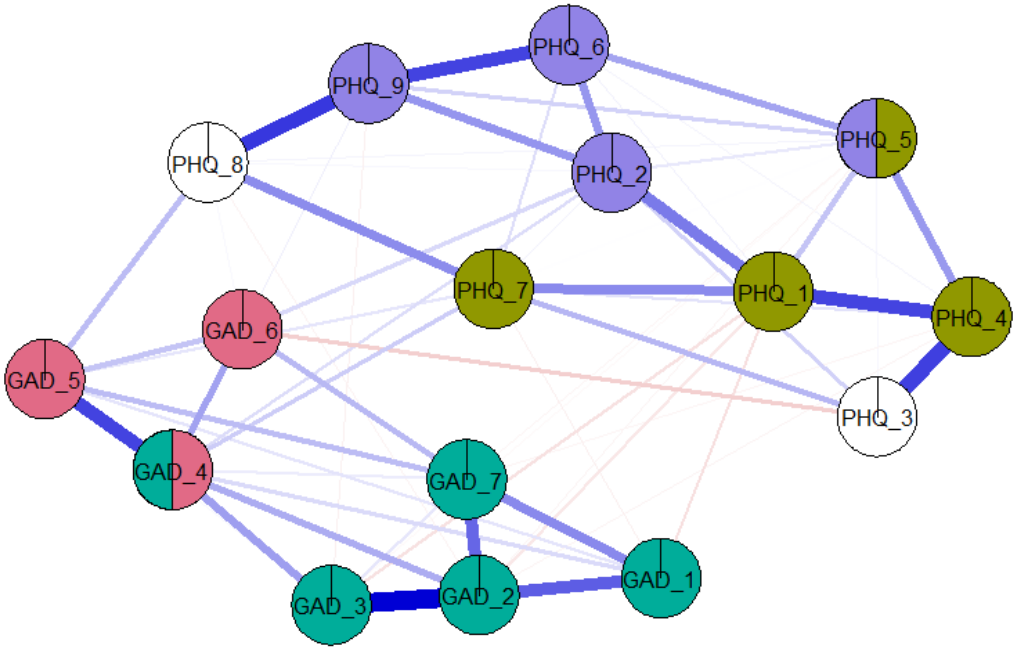
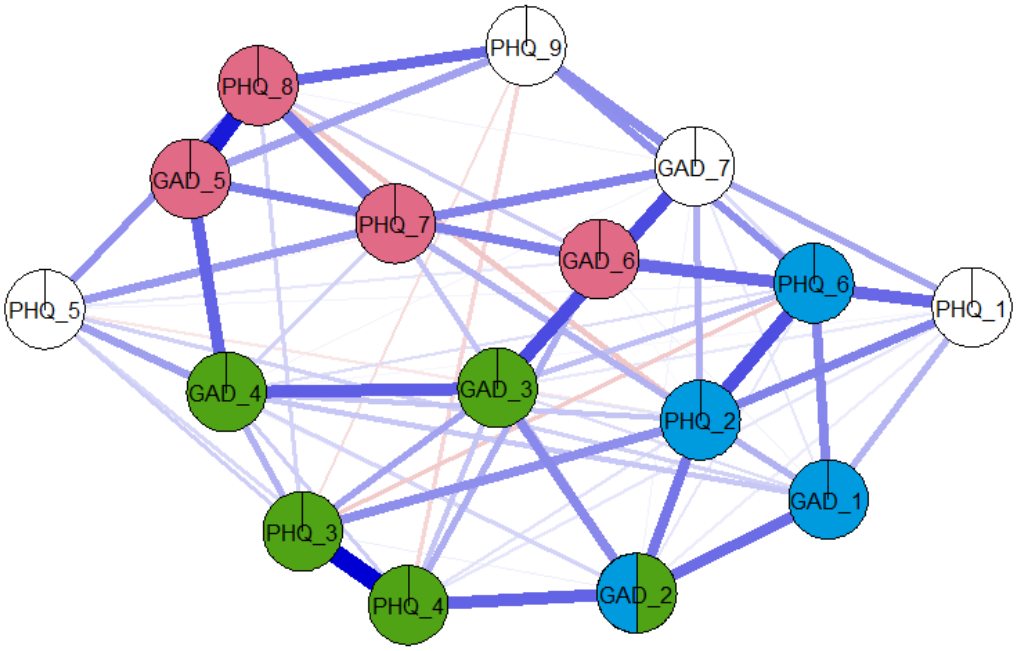


Figure 22. Clique Percolation Results for the MAD group



5.4 Discussion

The present study aimed to utilise network theory based on probable diagnostic classification in line with recent suggestions of high utility of conceptualising anxiety and depression as a unidimensional construct. To this end, the network structure of depression and anxiety symptoms in a large, nationally representative sample of UK participants was established both for the overall sample and using subsamples stratified by symptom intensity established in Chapter 4. Depression and anxiety were treated as a unidimensional construct based on the results of the bifactor analysis in Chapter 3, therefore the stratification was as follows: the Baseline group (N= 1479) involved individuals with virtually no symptom intensity (Asymptomatic), the 'Medium' group involved individuals with medium symptom intensity of anxiety and depression and comprised of both 'Depression' and 'Anxiety' groups from Chapter 3, and 'MAD' group included individuals with high symptom intensity in both constructs (comorbidity). The resulting networks showed sufficient stability. Further comparisons have been made between the 'Medium' and 'MAD' networks with significant differences being observed for the overall network structure, individual edges, and results of the clique percolation. Results suggest that the comorbidity of anxiety and depression has a qualitatively different symptom manifestation when compared with medium symptom intensity.

The overall network was established for future comparisons with subsample analyses. The overall network showed good stability. The two strongest relationships between nodes were observed between GAD2 ("Not being able to stop or control worrying") and GAD 3 ("Worrying too much about different things") items and PHQ3 ("Trouble falling or staying asleep, or sleeping too much") and PHQ4 ("Feeling tired or having little energy") nodes. These strong relationships are thematically meaningful as the strongest relationship within anxiety construct is related to worry and the strongest edge within the depression construct is related to tiredness. The strongest cross-construct edge was observed between the PHQ8 ("Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual") and GAD5 ("Being so restless that it's hard to sit still"). Interestingly, as noted in Chapter 1 – this relationship may be explained by both items measuring the same theme of restlessness. A strong relationship between these symptoms was also observed in previous studies. For example, in the Kaiser et al., (2021) paper, it was one of the strongest edges in a sample of treatment-seeking individuals in Germany. It

was also the strongest cross-construct edge in Beard et al., (2016). Assuming that the goal of the developed measures of depression and anxiety that are often paired when utilised in studies, future revisions of the measures, as well as present researchers, should be cognisant of this thematic overlap that may inflate symptom overlap.

The centrality of the symptoms also largely replicate previous findings. For depression, PHQ2 ("Feeling down, depressed, or hopeless") presented with the highest Expected Influence replicating results of both Kaiser et al., (2021) and Beard et al., (2016). Similarly, GAD2 ("Not being able to stop or control worrying") presented the highest anxiety construct influence, also replicating the two previous studies. The replication of the results is important in the case of this study as future stratification requires validity of the initial analysis which these results support.

The results of the networks of stratified samples showed sufficient stability. Initial inspection of the graphical expression of the networks revealed differences in the network structure, namely that the 'Medium' network showed few cross-construct edges. For the 'Baseline' network which comprised of individuals that were most likely to be asymptomatic (Chapter 4), PHQ8 ("Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual") had the highest expected influence as well as the highest betweenness. Network comparison tests found no difference between symptom structure between the baseline and the two other groups. While outside the scope of the present study, this phenomenon might be further explored by examining the temporal continuity of symptom development. Because examining symptoms within populations that are theoretically asymptomatic has limited interpretability, the 'Baseline' network was exempt from further analysis.

For the 'Medium' network, GAD4 ("Trouble relaxing") and GAD2 ("Not being able to stop or control worrying") showed the highest values of expected influence with GAD2 also showing high betweenness suggesting that these items of the Anxiety construct could be prime targets for intervention. However, given that the constructs within the network are clearly separated, there might be a reason to hypothesise that symptoms of anxiety do not reinforce symptoms of depression in a meaningful way – warranting further study. Conversely, the 'MAD' network showed high interwovenness of nodes and GAD3 ("Worrying too much about different things"), GAD4 ("Trouble relaxing") and GAD5

("Being so restless that it's hard to sit still") are all suggested to be the most central to the network. Notably, these variables represent symptoms of anxiety perhaps revealing that in the 'comorbid' samples, these symptoms are the drivers of psychopathology. Importantly, PHQ8 ("Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual") also showed high betweenness and expected influence, however, as mentioned before, this might be due to it representing similar themes to GAD5. These results suggest that, when treating depression and anxiety as a unidimensional continuum, there are differences in symptom expression between medium and high symptom endorsement groups. Further research might seek to replicate these results in samples involving treatment-seeking and previously diagnosed individuals. For these initial findings to be utilised in clinical practices, such research is crucial. Nevertheless, network comparison revealed a difference between the 'Medium' and 'MAD' networks. This difference is suggestive of differential symptom interaction among those with high and medium symptom endorsement with differences lying mostly in the cross-construct interactions. Compared to Kaiser et al., (2021) and Beard et al., (2016), the 'MAD' network reveals an interwoven pattern of symptoms – further reinforcing the notion that symptom expression in individuals depends on symptom intensity.

Examining results of the clique percolation revealed that the communities within the 'Medium' group did not include any cross-construct symptoms. Conversely, every community within the 'MAD' network included nodes spanning both constructs. Communities in both groups are highly interpretable. For the 'Medium' network, community A involves negative affect, community B involves low excitability, community C focuses on worry with anticipation of future harm and community D involves restlessness and irritability. Compared to the theoretical framework of the Tripartite Model of Anxiety and Depression (Clark & Watson, 1991), community A and community B could be theorised to map onto negative affect and low positive affect respectively. However, community C and community D suggest that the 'anxious arousal' dimension of the model might be further split into two aspects – one anticipatory of harmful events, the other, representing arousal in the here and now. Another interpretation might place community D as part of the negative affect, however, this would also warrant two 'aspects' of the negative affect – one better represented by internalising (community A) and the other by externalising (community B). This is of course highly speculative, however,

arriving at a similar solution to the Tripartite Model through a different methodology cannot be ignored and these results might inform future research.

The communities within the 'MAD' network mapped differently onto the symptoms when compared to the 'Medium' group. Three communities were obtained, community A involving symptoms of worry, being unable to relax, having low energy and sleep problems; community B involving restlessness, irritability, concentration problems and psychomotor retardation; and community C involving nervousness, anxiety, low mood and guilt. Interestingly, these communities do not map onto the Tripartite Model, each involving symptoms spanning the three dimensions of the model. This finding reinforces that the symptom expression for the comorbid, high symptom sample is unique. Furthermore, this also does not directly support the Tripartite Model revealing how the symptoms in this group reinforce each other in a more complex manner.

The present results stand in opposition to the notion that 'Mixed Anxiety and Depression' is simply a comorbid and/or subsyndromal manifestation of anxiety and depression. The results suggest that, among the individuals who endorse symptoms of both constructs to a high degree, the symptoms follow complex patterns of reinforcement and are much more interwoven than investigations into syndrome-wide populations might suggest. Furthermore, the results support the notion that treating depression and anxiety as a unidimensional construct, has utility.

This study is not free from certain limitations. First, the 'Medium' group is an aggregate of the results of Chapter 2 which were not established using a validated unidimensional measure of depression and anxiety. However, given the exploratory nature of the present examination and endorsement of both anxiety and depression symptoms by individuals in the 'Medium' group as well as results from Chapter 3, such aggregation was justified. Nevertheless, given that the present results provide utility for treating depression and anxiety unidimensionally at higher endorsement levels, future research endeavours could seek to replicate these results using different methodologies. Second, the present study utilised a sample representative of the general population. The results obtained here might present differently in individuals who meet the diagnostic criteria for both depression and anxiety. Third, the symptoms elected by centrality measures have been criticised in terms of their utility in actual interventions (McNally, 2021) and as such the recommendations of targeting symptoms for treatment should be considered tentatively.

Overall, this exploratory study suggested that symptoms of anxiety and depression at higher levels of endorsement manifest differently and are more interwoven. The results supported the utility of a unidimensional approach to depression and anxiety. Additionally, the study was the first to map the symptom structure of an empirically derived class of individuals suffering from comorbid depression and anxiety and as such presents clinical utility.

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6 Overview and General Discussion

6.1 Overview

The primary goal of the present series of studies was to clarify the nosological nature of depression and anxiety with attention put on measurement methods, factor structure and symptom manifestation within the general population. An intention behind this thesis has been that of clarifying what the qualitative and quantitative features of overlap between the two constructs might be. Starting with examining the very tools used to measure them, through how anxiety and depression manifest within the general population, whether the constructs are better conceptualised as a unidimensional entity and, lastly, how the symptoms of depression and anxiety interact within samples stratified by symptom intensity. A final intention was to provide a comprehensive nomological network of cumulative evidence that will guide future research into these constructs.

In the next sections a summary of the main findings of the empirical work carried out is provided along with an evaluation of the extent of its contribution to addressing the question of mixed anxiety depression.

6.2 Summary of the main findings

Chapter 1.

The key finding of Chapter 1 is that it identifies a high degree of disparity both within and across the measures of anxiety and depression. This is relevant both for clinical practice and for the future academic pursuits into anxiety and depression for a number of reasons. Firstly, if the goal of measuring a psychological construct is to capture its essence in the most objective manner, a hypothesis that we are missing the mark is strongly supported by the results. For a measure to be considered valid, it needs to capture all of the components outlined for a construct. From this point of evaluation, there are then two pitfalls a measure can fall into – over- and under- depiction of a construct. With over-depiction, the measure includes items that are construct irrelevant (i.e. redundant or repetitive items) with under-depiction the measure should include items that are construct representative. In both cases, the accuracy of the measure in question suffers and with it our ability to accurately represent reality. The results of Chapter 1 show that the within-construct overlap of the themes measured across the scales was at best 52% (Jaccard index). Therefore, a problem

facing the field right now is that the scales that we use to measure the two, perhaps most common manifestations of mental ill-health, measure, essentially, different types of constructs. While it is true that different scales were designed to be used within different settings and for different purposes, going by the scales alone, it is impossible to establish which themes of symptoms comprise 'real' depression or 'real' anxiety. Secondly, the chapter also stresses that when examining comorbidity of anxiety and depression, the measures should not be used interchangeably due to these disparities. Third, current practices of using scales measuring a construct of either anxiety or depression interchangeably, without consideration of their idiosyncrasies, contribute to drawing conclusions about anxiety and depression based on a set of considerably different tools of measurement. In practice, the disparity this flawed approach produces may be no different from the field being equipped with one tool of low reliability. To gauge the consequences of the current state of measurement in our studies of anxiety and depression was outside the scope of the current series of studies. However, misidentification of severity, symptom pools, comorbidity levels and symptoms that are discriminating between constructs are just some of the risks to which the field is seemingly blind. Conversely, one has to acknowledge that a proliferation of measures may be a consequence of the scientific method being applied properly. As our understanding of these constructs increases, so should newer methods of measurement replace the old and without a multiplicity of tools, this might not be feasible. Efforts towards a more measure-aware methodology are however, something that the results support.

Chapter 2.

The primary aim of the study in chapter 2 was to determine the underlying categorical and dimensional structure of anxiety and depression within a representative sample. This research is an important contributor to the current understanding of anxiety and depression as it taps into how these disorders manifest together within the general population. Furthermore, the study put the 'Mixed anxiety and depression' designation of the ICD-11 into question, replicating the results of Shevlin et al., (2022), by revealing that symptoms of anxiety and depression more frequently co-occur in the general population and on an ordinally higher level when compared to either symptoms of anxiety or depression. As for the DSM-5, the 'anxious distress' specifier, in the light of present results, might not be diagnostically optimal. Firstly, the comorbidity of the disorders being more common is not reflected by the manual. Secondly, anxious distress might suggest a

range of symptoms spanning subsyndromal to ‘syndromal’ levels and as such is not reflective of how the symptoms manifest most commonly in the general population (Mulder et al., 2019).

With the DSM-III’s ‘split’ of neurosis into anxiety and depression, our understanding of these two internalising disorders might have been hampered, as suggested by the results of the study. Results suggest that the comorbid configuration of symptoms occurs more frequently in the population than both of the ‘pure’ (depression and anxiety were shown to always occur with some symptoms of the other disorder) configurations. While one might speculate if such a split would occur today in light of these results, the question of whether depression and anxiety are discrete disorders with clear boundaries should not be ignored moving forward.

The results also support previous suggestions that when the symptoms of both constructs co-occur, the issues associated with both are more severe. Somatic symptoms, loneliness, uncertainty intolerance and low resilience were all characteristic of the comorbid class of participants to a larger extent than most other classes. With similar levels of somatic symptoms and low resilience with the depression class as suggested by previous examinations (Löwe et al., 2008).

Taken together, Chapter 2 paved the way for further examination of the two constructs. With the high co-occurrence of symptoms of both constructs, a question about the misspecification of the nosological landscape of the two most prevalent psychological ailments was highlighted as a necessity.

Chapter 3.

This chapter set out to examine whether depression and anxiety can be better specified as a unidimensional entity. With conflicting evidence, both from the factor analytic studies (Boelen & van den Bout, 2005; Stark & Laurent, 2001; Feldman, 1993; Bados et al., 2010) and network analyses (Fisher et al., 2017; Garabiles et al., 2019), further examination of this phenomenon was warranted.

Over the past decade, bifactor model analysis has become the go-to method as a statistical approach to describe shared as well as unique elements of psychopathological phenomena (Bornovalova et al., 2020). However, recent insights highlighted potential problems with common approaches to evaluating and interpreting bifactor models.

Namely, the model's tendency to provide inflated goodness-of-fit and overinterpretation of the results. The study in chapter 3 aimed to solve this problem by using a number of methodological endeavours. Firstly, the study utilised four different samples (two community and two representative samples of UK and ROI populations) and two different methods of measurement (for the Irish community sample) – this ensured that the results could be replicated and held when measurement was performed using a different method (with potential measurement method-based disparities in results highlighted by Chapter 1). Secondly, rather than relying on model fit, the results were validated against a range of previously suggested comorbidities. This ensured that the results were not just an artifact of the bifactor model's tendency to overfit but provided actual utility. Third, the bifactor results were not interpreted as the end-all-be-all but rather as an indicator of the utility of treating the measures as unidimensional. Fourthly, several bifactor indices were calculated to further validate the results of the analysis beyond model fit (Rodriguez et al., 2016). To the knowledge of the author, no previous bifactor examination of depression and anxiety was performed using such a rigorous methodology.

Overall, the results strongly supported the use of a unidimensional approach to measuring anxiety and depression. Bifactor indices and goodness-of-fit indices provided strong support for the unidimensional approach across samples and measurement methods while predictive validity analyses suggested that both approaches (two dimensions vs. one dimension) performed similarly. However, the lack of support for the use of subscale scores (depression and anxiety scores separately), suggests the superiority of treating the scale as an effectively unidimensional instrument.

Given that the comorbidity of depression and anxiety is indeed the more common manifestation of the symptoms with more severe complications and resistance to treatment (Coplan et al., 2015), the clinical utility of these results might prove impactful. Implications for diagnosis include an awareness that the symptoms often co-occur which might shorten the pathway to effective treatment. While the effectiveness of using the unidimensional approach in evaluating treatment outcomes has to be evaluated by future studies, the results of the study imply that this avenue of research might prove to be more aligned with clinical reality.

Chapter 4

Chapter 4 aimed to utilise network theory based on probable diagnostic classification in line with the results of chapter 2. Comorbidity of depression and anxiety is often understood by assuming a common underlying cause. The network theory offers an alternative to this assumption by representing comorbidities as mutually reinforced symptoms. Network analysis was utilised to examine symptom expression based on symptom severity.

In light of the findings of chapter 3, suggesting the utility of a unidimensional approach to anxiety and depression, participants representative of the UK population, were assigned into three groups differing in symptom configuration and severity as informed by the results of chapter 2. The 'Baseline' group represented the asymptomatic individuals, 'Medium' was representative of those who endorsed the symptoms of depression or anxiety to a larger degree than symptoms of the other construct, and 'MAD' which comprised individuals experiencing a degree of comorbidity of the symptoms. This allowed for the examination of how the individual symptoms of both constructs reinforce the overall network of symptoms. The study presented an opportunity to examine which symptoms are the most influential within a network. Furthermore, the study could provide insight into whether the clinical reality of the 'Mixed Anxiety and Depression' designation is better conceptualised as a co-occurrence of two discrete disorders (suffering from depression AND anxiety) or as a complex disorder where symptoms of one construct reinforce the other (sometimes called 'Cothymia'; Tyrer et al., 2003).

The results supported the notion that with comorbidity, depression and anxiety symptoms form an interwoven network of reinforcing symptoms. This notion also provides support for a unidimensional approach to the disorder. However, with a lower degree of symptom endorsement, the results indeed suggested that the symptoms are better conceptualised as co-occurring. Symptoms of anxiety related to being unable to relax and excessive worry were found to be most central to the 'Medium' group while, similarly, worry, restlessness and being unable to relax were more central in the 'MAD' group. This has implications for clinical practice as, because of higher cross-construct connections present in the 'MAD' group, targeting these symptoms might unravel the entire network of reinforcing symptoms as opposed to the 'Medium group' where the cross-construct connections were sparse.

The communities detected within the network also serve as a critique of the dimensional approach to anxiety and depression – the Tripartite Model of Anxiety and Depression (Clark & Watson, 1991). While the communities of the 'Medium' group approximately mapped onto the concepts of low positive affect, high negative affect and anxious arousal, no clear mapping of these symptoms could be observed within the 'MAD' group. These results suggest that the Tripartite model has limited utility in comorbid anxiety and depression while supporting the unidimensional approach.

6.3 Implications

The overall implications of the present series of studies are vast. While the present results might be considered initial, on balance, the suggestion that our current classification of depression and anxiety as separate is not precisely reflective of reality may only bring a positive change in the field. The scope of the present results supports a reconceptualising of how we approach the two constructs from the 'ground-up'.

Measurement of the two constructs is in disarray in two main areas – low content overlap between the scales measuring a specific construct and content overlap between the constructs. Low content overlap between the scales within a specific construct is problematic as the measures seem to be capturing information that is not essential for a diagnosis. Considering idiosyncratic symptoms included in the scales such as 'blushing', 'drug and alcohol use', 'neckache', 'superstitious beliefs' - raises questions regarding the specificity of these symptoms and how they contribute to discriminant validity of the two constructs and beyond. For example, drug and alcohol use is a transdiagnostic phenomenon associated with both internalising disorders (PTSD; Taylor et al., 2017), thought disorders (psychosis; Margolese et al., 2004), and personality disorders (narcissistic personality disorder; Stinson et al., 2008). Similarly, somatic symptoms are associated with a wide range of diagnoses: PTSD (Gupta et al., 2013), psychosis (Rimvall et al., 2019), and personality disorders (Kealy et al., 2016) to name a few. Therefore, when relying only on self-report measures that have not been examined against other measures, regardless of whether they are 'sister' disorders like depression and anxiety, comorbidity and overlap might be inflated. This is important for public health as misspecification of diagnoses might lead to worse patient outcomes, both directly, through treatment choice, and indirectly, through imprecise evaluation methods being based on the 'purity' of diagnoses. Therefore, assuming that symptoms of psychopathology that can be measured by self-report measures fall into discrete diagnoses, more emphasis could be placed on

increasing the precision of the tools we use to measure them. Conversely, the findings of the bifactor analysis from multiple nationally representative and community samples (Chapter 3) suggest that depression and anxiety are better represented by a shared underlying condition. New methods of measuring the joined underlying construct should be developed and tested against existing methods, preferably in clinical settings, in terms of sensitivity and subsequent monitoring of the outcomes against treatment. This is especially important as present conceptualisations lead to interventions showing poor long-term outcomes (Rubio & López-Ibor, 2007; Chambers et al., 2004).

In an attempt to distinguish Depression and Anxiety symptoms in a general population (Chapter 4), the present results suggest that most individuals affected by depression and anxiety symptoms will fall into the 'mixed' category. Therefore, 'pure' anxiety and 'pure' depressive disorders are rarer than the mixed condition suggesting that, for most sufferers, the diagnostic distinction is misleading (Tyrer, 1990). Given that the implicit assumption that disease entities of anxiety and depression are entirely self-contained is questionable and based on how they manifest within the population. Moving forward while holding to that assumption is unjustified. The problem of pure classification might be deeply rooted within the diagnostic systems. Most lack explicit exclusion criteria (Pincus et al., 2004). Comorbidities are also underreported by unstructured clinical interviews and abundant in structured clinical interviews (Zimmerman & Mattia, 1999) leading to another source of conflicting information as the same person might be diagnosed with a single 'pure' disorder or a comorbid one depending on the method and these diagnoses might then inform how the disorders are conceptualised within the diagnostic manuals. Furthermore, high rates of comorbidities (Pincus et al., 2004) themselves provide a challenge to the notion of 'criteria list' disorders. Therefore, to proceed, the current approach to psychopathology might need to be revised.

Currently, two approaches are gaining prominence (Carcone & Ruocco, 2017; Michelini et al., 2021): The National Institute of Mental Health's Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP). RDoC is a research framework rooted in neuroscience that aims to increase the understanding of transdiagnostic biological and behavioural systems underlying psychopathology to inform future nosology. HiTOP is a dimensional classification system, with a basis in the high covariation among symptoms of psychopathology, aimed at providing more informative research and treatment targets. Both support an examination of psychopathology in a

dimensional, rather than classificational, manner. This is aimed at increasing the precision of diagnosis and moves the field closer to precision medicine with patients diagnosed and treated according to fine-tuned assessments. The present series of studies supports this notion with bifactor results suggesting that depression and anxiety are better represented by a single underlying construct explaining most of their variance. However, this is still unsatisfactory as even when conceptualised as dimensional, a decision would need to be made whether the field should consider a single dimension (e.g.: cothymia or neurosis; Tyrer, 1990), two dimensions (e.g.: anxiety and depression) or three dimensions (as represented by tripartite model: positive affect, negative affect and anxious arousal; Clark & Watson, 1991). The present research (Chapter 5) provides support for the use of a single dimension- showing that the individual symptoms within a comorbid sample do not adhere to either two-dimensional or the tripartite conceptualisations. In light of the present findings, future research should strongly consider comparing the utility of these conceptualisations.

6.3 Summary of Strengths and Limitations

The major strength of the current series of studies is approaching the issue of the comorbidity of depression and anxiety from different methodological avenues. Each chapter aimed to contribute to a nomological network of cumulative evidence when examining the comorbidity, structure and measurement of depression and anxiety. Each approach supported a different reason for the high comorbidity of these constructs. Chapter 1 revealed measurement inconsistencies by psychologists who examine depression and anxiety. It is important to note that academic pursuits in the realm of psychopathology often utilise self-report measures due to their cost-effectiveness and ease of implementation. These in turn inform clinical practice, policy and nosology as defined in diagnostic manuals. With high discrepancies in the way we gather this knowledge, the borders between the disorders might be blurred. Especially under the conditions where tools of measurement are so vastly different and used interchangeably. Chapter 2, examined how, in light of diagnostic specifications of DSM-5 and ICD-11 clearly separating anxiety and depression, the symptoms of anxiety and depression are manifested within a nationally representative sample. Results of this chapter suggest that the ‘mixed’ manifestation is indeed more common than the ‘pure’ manifestations. This suggests that the diagnostic manual specification does not apply to majority of individuals ailed by these

symptoms. Building on that notion, Chapter 3 attempted to examine the utility of treating depression and anxiety as a unidimensional entity. Support for that notion was obtained, suggesting that a unidimensional approach showed utility while being a more parsimonious solution. Finally, Chapter 4 examined whether the symptom expression of the constructs supports 'true' comorbidity – i.e. suffering from two distinct disorders at the same time. Results mostly supported the notion. They showed that, at higher levels of symptom severity, symptoms of depression and anxiety reinforce each other.

Each chapter therefore pointed towards a direction of re-evaluating our current understanding of anxiety and depression and supported the notion that these disorders might be reflective of a unitary phenomenon. However, this series of studies is not free from certain limitations. While specific chapter limitations were elucidated within said chapters, an overarching limitation of the studies is that clinical samples with an already existing diagnosis were not involved, rather, the studies utilised nationally representative and community samples. One differentiating factor of clinical samples might lie in symptom severity and as such whether the present findings hold in high severity samples is an avenue for future research. As the case may be, despite what is suggested by the results of Chapter 3, 'pure' or 'purer' manifestations of the disorders might be more frequent in clinical samples (Hirschfeld, 2001). Furthermore, the present series of studies also did not examine how symptoms of anxiety and depression manifest longitudinally. Despite some existing evidence that anxiety and depression become more strongly interwoven with time (McElroy et al., 2018), the clinical reality may be that symptom clusters of one of the constructs become more dominant as the disease progresses or, conversely, suffering mostly from symptoms of one cluster may lead to developing symptoms of the other (Wetherell et al., 2001).

6.4 Concluding Comments

Throughout the present series of studies, issues of measurement and classification of depression and anxiety were highlighted. Results support re-evaluating how the field of psychology approaches these two highly prevalent constructs. Furthermore, the present results support the notion that depression and anxiety are better conceptualised as a single diagnostic entity. Validating the present findings in the development, selection and evaluation of treatments is the logical next step for this line of research.

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Appendix A. Published work during the Ph.D.

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MDPI

Article

Dietary Phytoestrogen Intake and Cognitive Status in Southern Italian Older Adults

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Abstract: Background: Aging society faces significant health challenges, among which cognitive-related disorders are emerging. Diet quality has been recognized among the major contributors to the rising prevalence of cognitive disorders, with increasing evidence of the putative role of plant-based foods and their bioactive components, including polyphenols. Dietary polyphenols, including phytoestrogens, have been hypothesized to exert beneficial effects toward brain health through various molecular mechanisms. However, the evidence on the association between dietary phytoestrogen intake and cognitive function is limited. The aim of this study was to investigate the association between phytoestrogen intake and cognitive status in a cohort of older adults living in Sicily, Southern Italy. Methods: Dietary information from 883 individuals aged 50 years or older was collected through a validated food frequency questionnaire. Cognitive status was assessed through the Short Portable Mental Status Questionnaire. Results: The highest total isoflavone (including daidzein and genistein) intake was inversely associated with cognitive impairment compared to the lowest (odds ratio (OR) = 0.43, 95% confidence interval (CI): 0.20–0.92). Higher intake of total lignans and, consistently, all individual compounds (with the exception of secoisolariciresinol) were inversely associated with cognitive impairment only in the unadjusted model. Conclusions: A higher intake of phytoestrogens, especially isoflavones, was associated with a better cognitive status in a cohort of older Italian individuals living in Sicily. Taking into account the very low intake of isoflavones in Italian diets, it is noteworthy to further investigate selected populations with habitual consumption of such compounds to test whether these results may be generalized to the Italian population.

Keywords: phytoestrogens; isoflavones; lignans; genistein; daidzein; cohort; population; cognitive status; cognition; brain

check for updates

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1. Introduction

Over the last century, there has been a notable increase in life expectancy, especially in the developed countries, contributing to the rise of both the size and the proportion of older people in the global population [1]. An aging society faces significant health challenges and an increase in chronic diseases, including conditions affecting the cognitive function [2]. Non-communicable diseases have become the leading cause of mortality in industrialized nations, as well as the leading cause of disease-related life-years lost

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Testing the Factor Structure of the International Trauma Questionnaire (ITQ) in African Community Samples from Kenya, Ghana, and Nigeria

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ABSTRACT

The aim of this study was to test the factorial structure of Posttraumatic Stress Disorder (PTSD) and Complex PTSD (CPTSD) as outlined in the 11th revision of the International Classification of Diseases (ICD-11) in three African community samples using the International Trauma Questionnaire (ITQ). Four models were tested using confirmatory factor analysis based on a total sample of 2,524 participants, and the two-factor second-order model, representing PTSD and Disturbances in Self-organization (DSO), was the best fitting model. The factors were validated using demographic and trauma-related variables, supporting the use of the ITQ for English-speaking participants in these African countries.

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Posttraumatic stress disorder (PTSD); Complex PTSD; International Trauma Questionnaire (ITQ); Africa

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Brief-Report Covid-19

COVID-19-related anxiety predicts somatic symptoms in the UK population

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This study aimed to estimate the association between anxiety associated with COVID-19 and somatic symptoms, using data from a large, representative sample (N = 2,025) of the UK adult population. Results showed that moderate to high levels of anxiety associated with COVID-19 were significantly associated with general somatic symptoms and in particular with gastrointestinal and fatigue symptoms. This pattern of associations remained significant after controlling for generalized anxiety disorder (GAD), pre-existing health problems, age, gender, and income. This is the first evidence that anxiety associated with COVID-19 makes a unique contribution to somatization, above and beyond the effect of GAD.

Children Australia

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Review Article

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What do young people worry about? A systematic review of worry theme measures of teen and preteen individuals

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Abstract

Excessive worry can negatively influence one's developmental trajectories. In the past 70 years, there have been studies aimed towards documenting and analysing concerns or 'worries' of teen and preteen individuals. There have been many quantitative and qualitative approaches established, suggesting different themes of contextual adolescent worry. With the hopes of future clinical utility, it is important to parse through these studies and gather what is currently known about what teens and preteens worry about and what is the state of methods used to gather that knowledge. Studies were searched for using Web of Science, PubMed, PsycINFO, Scopus and ScienceDirect databases and selected on systematic criteria. Data regarding the country in which the study took place, participants, methods of collection, worry themes and conclusions and limitations were extracted. Data were synthesised in a narrative fashion. It was concluded that currently available methods of measuring themes of adolescent worry face certain problems. Themes of worry differ substantially between the studies, with the exception of school performance seeing stable high endorsement across cultures and ages. Issues with ordering worry themes and implications for future understanding of adolescent and preadolescent worry are discussed.

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Predictors of PTSD and CPTSD in UK firefighters

Predictores de PTSD y CPTSD en bomberos del Reino Unido
英国消防员中PTSD和CPTSD的预测因子

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ABSTRACT

Background: Globally, professional firefighters are often exposed to traumatic events and are at high risk of developing posttraumatic stress disorder (PTSD) symptoms.

Objective: With the publication of the 11th edition of the International Classification of Diseases (ICD-11) there arose a need for research based on the new diagnostic criteria, and the associated disorder, Complex PTSD (CPTSD).

Method: Participants were 1300 former or present firefighters from the UK. Prevalence rates of PTSD and CPTSD were estimated using International Trauma Questionnaire in accordance with ICD-11 criteria, and service related and personal trauma exposure were also assessed using an anonymous online questionnaire. Multinomial logistic regression was performed to assess how service and personal trauma exposure predicted PTSD and CPTSD.

Results: CPTSD criteria were met by 18.23% (95% CI 16.13–20.33%) and PTSD criteria were met by 5.62% (95% CI 4.37–6.87%) of the sample. Experiencing higher levels of service-related trauma significantly increased the risk for both PTSD and CPTSD, and nonwork related trauma uniquely predicted CPTSD but not PTSD.

Conclusions: This study provided the first examination of the new ICD-11 criteria for PTSD and CPTSD in a large sample of firefighters, and CPTSD was more common than PTSD. Exposure to multiple different types of trauma increased the odds of PTSD and CPTSD.

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ICD-11 'mixed depressive and anxiety disorder' is clinical rather than sub-clinical and more common than anxiety and depression in the general population

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Background. The new International Classification of Diseases was published in 2018 (ICD-11; World Health Organization, 2018) and now includes 'Mixed depressive and anxiety disorder' (6A73: MDAD) designated as a mood disorder. This disorder is defined by symptoms of both anxiety and depression occurring more days than not, for a period of two weeks, and neither set of symptoms considered separately reaches a diagnostic threshold for either disorder. However, to date no study has examined the validity of these guidelines in a general population sample.

Methods. Using Goldberg et al.'s (2017) guidelines regarding measurement of depression and anxiety, this study used factor mixture modelling (FMM) to examine the validity of the ICD-11 criteria of MDAD. Symptom endorsement rates are provided as well as demographic predictors and somatization outcomes.

Results. Fit indices suggested the two-factor four-class solution was the best balance between model complexity and model fit. The results did not support a class that is subsyndromal to both anxiety and depression. On the contrary, we suggest that there exists a 'Comorbid' class that represents endorsement of both anxiety and depression symptoms at a higher level when compared to both 'anxiety' and 'depression' groups. Demographic predictors, as well as somatization and functional impairment outcomes, provided support for this FMM solution.

Conclusions. The 'Comorbid' group was the largest symptomatic group and had the highest levels of both anxiety and depression symptoms. Importantly, this group was larger than either the 'anxiety' or 'depression' group and was associated with high levels of functional impairment and somatization.

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How is loneliness related to anxiety and depression: A population-based network analysis in the early lockdown period

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High risk of mental health problems is associated with loneliness resulting from social distancing measures and "lockdowns" that have been imposed globally due to the COVID-19 pandemic. This study explores the interconnectedness of loneliness, anxiety and depression on a symptom level using network analysis. A representative sample of participants ($N = 1041$), who were of at least 18 years of age, was recruited from the Republic of Ireland (ROI). Loneliness, anxiety and depression were assessed using validated instruments. Network analysis was used to identify the network structure of loneliness, anxiety and depression. Loneliness was found to be largely isolated from anxiety and depression nodes in the network. Anxiety and depression were largely interconnected. "Trouble relaxing," "feeling bad about oneself" and "not being able to stop or control worrying" were suggested as the most influential nodes of the network. Despite the expectation that loneliness would be implicated more robustly in the anxiety and depression network of symptoms, the results suggest loneliness as a distinct construct that is not interwoven with anxiety and depression.

Keywords: Anxiety; Depression; Loneliness.

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Fish and human health: an umbrella review of observational studies

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ABSTRACT

Fish represents one of the most important dietary sources of omega-3 polyunsaturated fatty acids, which are known to be associated with various health benefits. This study aimed to systematically review existing meta-analyses of observational studies exploring the association between fish intake and various health outcomes. A systematic search of electronic databases was conducted to retrieve a total of 63 studies. Evidence was deemed as possible for the association between higher fish intake and decreased risk of the acute coronary syndrome, liver cancer, and depression, and limited for other outcomes (including age-related macular degeneration, Alzheimer's disease, heart failure, all-cause and coronary heart disease mortality, total and ischaemic stroke) due to heterogeneity between results and potential otherwise inexplicable confounding factors. In conclusion, results from epidemiological studies support the mechanistic effects associated with omega-3 fatty acids from high fish consumption, but evidence needs to be further corroborated with more reliable results.