Generalized Anxiety Disorder (GAD) and Anxiety Symptoms in Older Adults

Johan Nilsson

Department of Psychiatry and Neurochemistry
Institute of Neuroscience and Physiology
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg 2019

Generalized anxiety disorder (GAD) and anxiety symptoms in older adults

johan.nilsson@neuro.gu.se

ISBN 978-91-7833-530-5 (PRINT)
ISBN 978-91-7833-531-2 (PDF)

http://hdl.handle.net/2077/60766

Printed in Gothenburg, Sweden 2019
Printed by BrandFactory

To my loving wife and family

ABSTRACT

Anxiety is a broad concept, difficult to detect and recognize. Expression may shift over the lifetime further complicating identification. Generalized Anxiety Disorder (GAD) is one of the most common anxiety disorders in older adults; however, the true nature remains unclear. Research on older populations is lacking, even though the proportion of older adults is growing larger. The aim of this thesis was to increase the understanding of anxiety symptoms and GAD, by exploring changes in the expression and consequences of anxiety among older adults.

The samples were derived from the Gothenburg H70-birth cohort studies. Participants completed a semi-structured psychiatric interview and a comprehensive battery of tests conducted by trained research nurses or medical doctors. Psychiatric diagnoses were mainly based on items from the Comprehensive Psychopathological Rating Scale (CPRS), according to current classification systems.

The main results were as follows. **Study I**: GAD was common in old age, around 4%. The prevalence was similar for both classification systems. However, diagnostic agreement was moderate and different classification systems only captured the same individuals in about half of the cases. Comorbidity with selected mental disorders was high, and highest in those with depression. **Study II**: The expression of anxiety changed with increasing age. Autonomic arousal and muscle tension decreased markedly, while symptoms of worry remained stable or increased. **Study III**: Midlife anxiety, but not worry, was shown to increase the risk of dementia in late life. The association was independent of depression, neuroticism, and stress level at baseline. Furthermore, our findings support the notion of qualitative differences between anxiety and worry.

The findings suggest that current classification systems for GAD, in many cases, capture different individuals. Emphasis, in upcoming revisions, should be directed at unifying criteria to avoid misclassification. Our results showed that exposure to anxiety increased the risk of incident dementia, suggesting that increased attention to identification and successful treatment of anxiety may be warranted in dementia prevention.

Keywords: Anxiety, Worry, GAD, Epidemiology

ISBN 978-91-7833-530-5 (PRINT)
ISBN 978-91-7833-531-2 (PDF)

SAMMANFATTNING PÅ SVENSKA

Ångest är ett brett och svårfångat koncept. Inte bara för lekmän utan också för kliniker. Vetenskapliga studier har tidigare visat att presentationen av ångest kan variera i olika åldrar vilket komplicerar identifieringen av drabbade personer. Generaliserad ångest (GAD) är ett av de vanligaste ångesttillstånden bland äldre, men det råder delade meningar kring hur man ska definiera syndromet. Tidigare studier har ofta fokuserat på yngre populationer, och då den äldre delen av befolkningen växer, så finns här en kunskapslucka att fylla. Målet med avhandlingen var att öka kunskapen kring ångest genom att undersöka förändringar och konsekvenser av ångest hos äldre.

Data till delarbetena har insamlats i Göteborg. Deltagarna har genomfört en semistrukturerad psykiatrisk intervju samt ett omfattande testbatteri, under översyn av kliniskt erfarna sjuksköterskor eller läkare. Psykiatriska diagnoser har i huvudsak baserats på CPRS, ett instrument utvecklat på 70-talet för att mäta förändringar i psykopatologi. Diagnoserna har ställts i enlighet med dagens klassifikations system.

De viktigaste resultaten var följande: Studie I: GAD var vanligt bland äldre, ca 4%. Även om prevalensen var likartad för de två vanligaste diagnossystemen så fångade man endast samma individer i ungefär hälften av fallen. Samsjukligheten var hög, i likhet med studier på yngre, och vanligast med depression. Studie II: Presentationen av ångest symtom skiljde sig åt med stigande ålder. Autonoma symtom (dvs. hjärtklappning, muntorrhet etc.) och muskelspänningar minskade markant, medan symtom associerade med oro/ängslan var oförändrade. Studie III: Ångest i medelåldern ökade risken för demens senare i livet, oberoende av depression, stress eller neurotiska personlighetsdrag. Resultaten visade också på kvalitativa skillnader mellan ångest och oro/ängslan.

Avhandlingens resultat tyder på att dagens klassifikationssystem delvis fångar olika individer. I framtida revisioner bör man fokusera på att hitta en samsyn kring GAD för att undvika underbehandling och feldiagnosticering. Fynden visade också att ångest ökade risken för demens senare i livet, vilket signalerar att man i arbetet med demensprevention bör spendera mer resurser för att identifiera och behandla ångest.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Nilsson J, Östling S, Waern M, Karlsson B, Sigstrom R, Guo X, Skoog I. (2012). The 1-Month Prevalence of Generalized Anxiety Disorder According to DSM-IV, DSM-V, and ICD-10 Among Non-demented 75-Year-Olds in Gothenburg, Sweden. *American Journal of Geriatric Psychiatry,* 20(11): 963-972

II. Nilsson J, Sigstrom R, Östling S, Waern M, Skoog I. (2018). Changes in the expression of worries, anxiety, and generalized anxiety disorder with increasing age: A population study of 70 to 85-year-olds. *International Journal of Geriatric Psychiatry,* 34(2): 249-257

III. Nilsson J, Najar J, Sundh V, Johansson L, Zettergren A, Östling S, Waern M, Skoog I. Midlife anxiety, but not worry, increases risk of late-life dementia: A 44-year follow-up of the Prospective Population Study of Women. *(Submitted manuscript)*

CONTENT

ABBREVIATIONS

AOO	Age of Onset
CPRS	The Comprehensive Psychopathological Rating Scale
DSM	Diagnostic and Statistical Manual of mental disorders
Free-floating anxiety	Anxiety when no dangers are present, and it seems to occur without anything triggering it
GAD	Generalized Anxiety Disorder
GAF	The Global Assessment of Functioning
GEE	Generalized Estimating Equation
ICD	International statistical Classification of Diseases and related health problems
MDD	Major Depressive Disorder
MINI	The Mini International Neuropsychiatric Interview
PD	Panic Disorder
QoL	Quality of Life
SCR	Skin Conductance Response
SF-36	The Short Form Health Survey. A 36-item, self-reported survey of patient health
WMH	World Mental Health survey initiative, a cross-cultural project by the World Health Organization

1 INTRODUCTION

The demographics of present day society are shifting. In western societies reduced birth rates and increased life expectancy have resulted in a larger proportion of older people. Although, older people are healthier and live longer than before, disease is highly prevalent. Anxiety disorders are common in older adults and generalized anxiety disorder (GAD) is one of the most common anxiety disorders in old age. Diagnosis is complicated by medical comorbidity, cognitive decline, differences in help-seeking behavior and age-dependent changes in the expression of disease, suggesting that a better understanding of the epidemiology, i.e. the distribution and determinants of health, of older populations is required to meet the challenge of the increasing personal and societal costs.

1.1 ANXIETY & WORRY

Anxiety is a broad concept and difficult to define. However, most people would agree that anxiety comprises multiple symptoms of autonomic hyperarousal, muscular tension, vigilance and scanning, and apprehensive expectations (worry). Several definitions have been presented with a common theme of focusing on future events and expectation of negative outcomes or circumstances. Freud defined it as 'something felt', a physical state to warn us of impending danger. A feeling of unpleasantness often difficult to pinpoint, but still 'felt' [1]. Anxious apprehension, referring to a future-oriented mood state in which one becomes ready or prepared to attempt to cope with upcoming negative events, has been suggested as a more appropriate description of anxiety [2].

Anxious apprehension has later been distinguished from anxious arousal, referring to the somatic symptoms of anxiety frequently found in 'panic attacks' [3]. Furthermore, evidence from test-anxiety studies suggests two major components of anxiety i.e. emotional or somatic anxiety and cognitive anxiety [4,5]. Emotionality refers to the subjective emotional experience and perception of anxiety i.e. the manifestation of sympathetic activation such as palpitations, dry mouth, muscular tension, etc. Cognitive anxiety refers to worrying i.e. the internal dialogue, contemplating consequences of failure or peers comparisons [6]. This division is similar to the definition in the Comprehensive Psychopathological Rating Scale (CPRS), a diagnostic instrument designed to assess changes in psychopathology [7], where anxiety has been divided into two parts: inner tension referring to the somatic symptoms of anxiety, and worry referring to the cognitive symptoms of anxiety.

Anxiety and worry are suggested to be two separate dimensional constructs [8,9], meaning that pathological symptoms is a matter of degree rather than kind [10]. Autonomic arousal symptoms or hyperarousal are the symptoms most clinicians associate with anxiety; they are easily observed (flushed skin, tremors, and sweating) and measured objectively, including pulse/heart rate (HR), bloodpressure, skin conductance response (SCR), and pupil dilation. These symptoms are caused by increased sympathetic activation of the autonomic nervous system (ANS), more commonly known as the "fight-or-flight" system, in response to danger [11]. Worry, on the other hand, is a cognitive process of thoughts and images, used to reduce emotional reactivity in the short term [12]. It has been suggested that semantic cognitive activity, as found in worry, has the effect of decreasing somatic activity resulting from

fearful imagery [13]. Thinking and verbal articulation of fearful circumstances produces significantly less physiological response than images of the same content [14]. However, such cognitive avoidant behavior serves to maintain anxiety and exacerbate negative affect through negative reinforcement. Moreover, the process of worry mainly involves cortical structures such as the prefrontal cortex (PFC) as opposed to anxiety that mainly engage subcortical structures in the limbic system such as hippocampus, and amygdala [15]. However, these constructs are overlapping and subjected to frequent conceptual confusion, among laymen and professionals, highlighted by the Swedish term "ångest" and the English "anxiety". Both terms are derived from the same root, yet the Swedish term is more closely associated with dread and the English more closely related to worrying [7].

In this thesis anxiety is defined in accordance with the CPRS [7] referring to inner tension or somatic anxiety, i.e. feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Worry is subsequently defined as worrying over trifles, representing a more cognitive process involving feelings of apprehension, and undue concern over trifles, which is difficult to stop and out of proportion to the circumstances.

1.1.1 MEASUREMENTS

The ambiguity in the definition of anxiety is reflected in anxiety measurement. Most instruments are designed as screening tools in order to identify people with high levels of distress, and comprise sum scores from different combinations of anxiety symptoms. Instruments can be either clinician-rated or self-reported depending on the intended purpose. A large variety of scales are used. However, most were developed for young adult populations [16]. A literature review of anxiety measures among older adults found 91 different scales from 213 articles. Out of these 91, 12 were commonly used and only three had sufficient psychometric properties to be used in older adults [17].

Another aspect in measuring symptoms of anxiety is the discordance between self-reported symptoms and the observed reaction. In test anxiety studies it is well established that subjective reports of arousal is distinct from the actual physiological reaction [4]. The reason for this phenomenon is largely unknown. However, the discordance is higher in chronic anxiety, e.g. GAD, compared to intermittent anxiety [18], suggesting a blunted or desensitized reaction.

A third aspect to consider in the study of anxiety is the existence of two complementary concepts: state or trait anxiety. State anxiety refers to the subjective and objective physiological responses to a perceived threat and trait anxiety refers to a personality trait, describing the individual's tendency to react with anxiety [19]. The rationale for these two concepts is to distinguish chronic anxiety from short transient episodes.

1.2 GENERALIZED ANXIETY DISORDER

"Last night we went to bed and my boyfriend had a sore throat. He soon fell asleep and I listened to him snoring, and that's when it started. I was thinking, what if he falls ill and can't go to work tomorrow. Then he'll have to call in sick. But what if his throat is so sore that he can't speak, then I'll have to make the call. But who do I call? Do I call the company he's deployed at now, or do I call the company he actually works for? And what if I call the wrong company? He might get fired. And my own contract will end in 2 months ... so what if they don't renew it ... then we'll end up with no money and won't be able to pay for this house anymore."

Clinical presentation of a GAD patient [20]

1.2.1 PHENOMENOLOGY

Generalized anxiety disorder (GAD) is characterized by excessive worry and excessive anxiety concerning everyday activities and events. Worries may revolve around several different domains like health-concerns, financial situation, family, school or work related issues [21]. Content may change over time and intensity may fluctuate. However, the disorder is chronic by nature.

Features separating those with GAD from non-pathological anxiety are; the worry/anxiety is difficult to control, even if more important matters arise; more pervasive, longer duration (6 months), and out of proportion to the perceived threat; more likely to be associated with physical symptoms [21]. Symptoms include restlessness or feeling keyed up or on edge, motor tension, mind going blank or difficulties concentrating, irritability, fatigue, difficulties falling asleep and fragmented sleep are common. A typical person with GAD worries about a number of minor every day events and often simultaneously; starting sentences with What if…? They are often convinced that something bad is going to happen and that they will not be prepared. The worries may be uncued or triggered by very subtle stimuli [22].

1.2.2 NOSOLOGY

1.2.2.1 A BRIEF HISTORY

Anxiety and GAD are recent constructs, only recognized as distinct disorders in 1980 with the introduction of DSM-III [23]. However, the Latin philosopher Cicero (106 BC to 43 BC) was the first to separate anxiety (angor) and worry (sollicitudo) classifying them as disorders [24]. Another Latin philosopher (Seneca) proposed to treat anxiety by focusing on the present instead of worrying about the future, which is recognized as a key feature of mindfulness in the present day treatment of GAD [25].

> *"There are more things to alarm us than to harm us, and we suffer more often in apprehension than reality"* Seneca, L.A., 41 AD

In the following centuries these distinct categories were lost and new terms and constructs were presented. Panophobia and related terms (pantaphobia, pantophobia, panphobia) was employed by physician Caelius Aurelianus (fifth century), alluding to patients who supposedly were afraid of everything [24]. This term was later subdivided. Panophobia hysterica alluded to the reaction of terror, accompanied by palpitations and pallor, in response to

being startled. Panophobia phrontis, alluded to patients who worried excessively and showed signs of avoidance behavior, complaining of pain and bodily tension [15].

In the late 19th century, Sigmund Freud provided the first comprehensive attempt to describe the topology of anxiety disorders. He separated the term, anxiety neurosis, from the contemporary definition of neurasthenia [26], which then comprised a broad range of symptoms. Freud included 4 major syndromes in his term anxiety neurosis; general irritability, chronic apprehension/anxious expectation, anxiety attacks and secondary avoidance, which constitutes the foundation for modern classification of anxiety disorders [1,27]. The concept of anxious expectation included nervousness, apprehension and free-floating anxiety and is the precursor to the current definition of GAD.

In DSM III (1980)[23] the diagnostic approach shifted from psychoanalytical theory to a descriptive, criteria based approach. Several new diagnostic categories were created and anxiety neurosis was split into panic disorder (PD) and GAD, due to evidence suggesting qualitative differences in response to treatment with imipramine [28]. However, this notion was later disproved and other qualitative differences were established [29]. Three major changes to the diagnostic criteria have since been implemented. First, the duration requirement was extended from 1 month to 6 months to discriminate against major depression (MDD). Second, anxiety and worry were restricted to excessive symptoms and uncontrollability was added to criteria. Third, the number of associated symptoms (including autonomic arousal) was reduced, and in effect shifted the disorder towards a chronic worry disorder. These changes will be discussed in further detail below.

1.2.2.2 CURRENT DIAGNOSTIC CRITERIA

The American Psychiatric Association (APA) and the World Health Organization (WHO) published the current classification systems, DSM-5 [21] and ICD-11 [30], respectively. In this thesis, papers including GAD diagnosis have used DSM-IV/DSM-5 criteria (which are almost identical except for differences in hierarchical exclusion criteria) (table 1) and ICD-10 diagnostic criteria for research (ICD-10-DCR) (table 2).

Since the first appearance in 1980, several changes have been made in the criteria for GAD. Unfortunately, researchers have not been able to reach a consensus, which is reflected in significant differences between the current classification systems. One major difference is the mandatory inclusion of autonomic arousal symptoms in the ICD-10-DCR criteria and the absence of

Table 1. Generalized Anxiety Disorder according to DSM-5

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months): *Note: Only one item required in children.*
    1. Restlessness, feeling keyed up or on edge.
    2. Being easily fatigued.
    3. Difficulty concentrating or mind going blank.
    4. Irritability.
    5. Muscle tension.
    6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another medical disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

the same in more recent versions of DSM. In fact, in the description of GAD in DSM-5, it was stated that symptoms of autonomic hyperarousal are less prominent than in other anxiety disorders [21], highlighting the difference between DSM and ICD. Some of the controversies are examined below.

The excessive criterion was incorporated in order to discriminate people with GAD from normal worriers. However, more recent research has shown that it does not provide a meaningful distinction between GAD and Non-GAD [31]. Normal people may also worry excessively. Instead, worrying about minor events and more about interpersonal relations, may be a better discriminator of GAD [32]. The term has also been criticized to be ambiguous and one of the main reasons for reduced reliability in test-retest studies [31,33,34]. If removed, more people with milder symptoms would be identified and prevalence would increase, in some populations substantially [12].

In DSM-III, symptoms were required to present during the last month. A 6-month requirement was suggested to minimize over-diagnosing ordinary anxious reactions to life events [12]. Another reason was to discriminate GAD from MDD by letting the criteria reflect the chronic course of GAD. However, the association with depression remains and by reducing 6 months to one month, test retest reliability would increase from κ 0.45-0.72 [35]. Several groups of researchers have found the requirement not being meaningful as there is no qualitative difference in comorbidity, onset or familial risk [12,36]. It has been suggested that reducing the duration requirement to 3 months would still reflect the chronic nature and capture more people with significant distress [12].

Criterion B, “difficult to control worries”, has been proposed to be one of the key features of GAD; in one study it was suggested that worriers with GAD more often had negative beliefs about, and difficulties to control, their worry compared to normal high-worriers [37]. However, the distinction may not be specific to GAD [12]. Moreover, most of the discriminant validity may already be covered by the excessive criterion, suggesting limited impact [38].

Another controversial change in DSM-IV was removing hyperarousal symptoms from the diagnostic criteria. Two factors contributed to this development; first, the low diagnostic reliability of GAD, which was the lowest among anxiety disorders [39], second, the identification of apprehensive expectation, i.e. chronic worrying, as the main distinguishing characteristic of GAD [32]. In order to increase reliability, the number of associated symptoms was reduced, including hyperarousal symptoms [40]. This was supported by a previous finding suggesting lower rates of autonomic hyperarousal in

Table 2. Generalized Anxiety Disorder according to ICD-10 DCR

A. A period of at least six months with prominent tension, worry and feelings of apprehension, about every-day events and problems.
B. At least four symptoms out of the following list of items must be present, of which at least one from items (1) to (4).
    1) Palpitations or pounding heart, or accelerated heart rate.
    2) Sweating.
    3) Trembling or shaking.
    4) Dry mouth (not due to medication or dehydration).
    5) Difficulty breathing.
    6) Feeling of choking.
    7) Chest pain or discomfort.
    8) Nausea or abdominal distress (e.g. churning in stomach).
    9) Feeling dizzy, unsteady, faint or light-headed.
    10) Feelings that objects are unreal (derealization), or that one's self is distant or "not really here" (depersonalization).
    11) Fear of losing control, going crazy, or passing out.
    12) Fear of dying.
    13) Hot flushes or cold chills.
    14) Numbness or tingling sensations.
    15) Muscle tension or aches and pains.
    16) Restlessness and inability to relax.
    17) Feeling keyed up, or on edge, or of mental tension.
    18) A sensation of a lump in the throat, or difficulty with swallowing.
    19) Exaggerated response to minor surprises or being startled.
    20) Difficulty in concentrating, or mind going blank, because of worrying or anxiety.
    21) Persistent irritability.
    22) Difficulty getting to sleep because of worrying.
C. The disorder does not meet the criteria for panic disorder, phobic anxiety disorders, obsessive-compulsive disorder or hypochondriacal disorder.
D. Most commonly used exclusion criteria: not sustained by a physical disorder, such as hyperthyroidism, an organic mental disorder or psychoactive substance-related disorder, such as excess consumption of amphetamine-like substances, or withdrawal from benzodiazepines.

Table 3. Generalized Anxiety Disorder according to ICD-11

Generalized anxiety disorder is characterized by marked symptoms of anxiety that persist for at least several months, for more days than not, manifested by either general apprehension (i.e. 'free-floating anxiety') or excessive worry focused on multiple everyday events, most often concerning family, health, finances, and school or work, together with additional symptoms such as muscular tension or motor restlessness, sympathetic autonomic over-activity, subjective experience of nervousness, difficulty maintaining concentration, irritability, or sleep disturbance. The symptoms result in significant distress or significant impairment in personal, family, social, educational, occupational, or other important areas of functioning. The symptoms are not a manifestation of another health condition and are not due to the effects of a substance or medication on the central nervous system.

individuals with GAD compared to non-GAD [41]. However, by removing autonomic symptoms the discriminant validity to depression was reduced [42]. It has also been argued that the focus on worry will orphan a substantial group of people with significant distress from free-floating anxiety [27,36].

A recurrent debate in GAD nosology concerns the association with depression. Genetic pleiotropy, i.e. a single mutation giving rise to 'different' disorders, has been suggested as a potential reason for the close association [43]. However, most of the genetic variation may be explained by the genetic association to neuroticism, shared by other anxiety disorders [44]. Moreover, evidence shows that the diagnostic overlap between GAD and MDD, i.e. sleep disturbances, fatigue, concentration difficulties and irritability, may have artificially increased comorbidity [45]. Changes to DSM criteria, i.e. increasing duration, increasing severity (excessiveness) and reducing symptoms, have not had the intended effect and ironically evidence indicates that discriminant validity is worse since the removal of autonomic arousal symptoms. It has been argued that the debate is a remnant from the residual status of DSM-III GAD, and that trying to separate GAD and MDD actually obscures important clinical features of the comorbid condition [46].

The two most important differences between DSM and ICD are the excessiveness criteria and the inclusion of autonomic arousal [33]. In the beta version of DSM-5 it was suggested to further reduce the required associated symptoms but instead include maladaptive avoidance behaviors. Critics

argued that the proposed criteria in DSM-5 would not improve recognition, but significantly lower the threshold causing an artificial epidemic of GAD [47]. The changes would also have further increased the gap between DSM and ICD as ICD-11 retains the definition regarding free-floating anxiety with prominent autonomic arousal symptoms.

1.2.3 PREVALENCE

The general opinion is that the frequency of GAD increases with age until age 40-55 [48-51], and declines thereafter [52,53]. GAD is together with specific phobia the most common anxiety disorder in old age [48]. One month prevalence rates for older adults range from 0.8-7.3% [54,55]. Most studies diagnose GAD according to DSM. However, a few studies present prevalence rates of GAD according to ICD ranging from 1.7-3.8% [54,56]. Higher rates of GAD are also found in individuals of European descent compared to individuals from Asia or Africa, and more frequent in high-income countries compared to low-income countries [57].

The large disparity is most likely explained by differences in methodology. A key factor is case selection, as small differences in severity assessment may have substantial impact on prevalence rates due to the high proportion of anxiety symptoms. Moreover, lower figures are seen in studies that employ hierarchical rules and in those that use fully structured interviews compared to the semi-structured format [58]. Another common limitation in epidemiological studies is the exclusion of individuals in nursing homes and residential care. This group has a higher prevalence of anxiety disorders than the population, hence exclusion may lead to underestimation of disease [59]. However, cultural differences may also have influenced the prevalence rates. Current criteria were developed in western societies and may not capture anxiety in a different cultural context. GAD may be expressed differently, presenting with more somatic symptoms, as evidence shows in Asian populations [60]. Furthermore, low mental health literacy and stigma are barriers for seeking help and it is plausible that in certain cultures individuals are reluctant to admit having a mental disorder [61,62]. Finally, we cannot exclude the possibility that the disparity reflects real regional and cross-cultural differences in risk and resilience.

1.2.4 ONSET & COURSE

Compared to other anxiety disorders GAD has a late onset, with an estimated age of onset (AOO) of 35 years of age [63]. Few cases are diagnosed before age 25, which differs substantially from AOO of phobias that usually presents in childhood. Peak incidence is found in midlife and about 1% of cases debut after 74 years of age [64]. AOO of GAD is earlier in high-income countries, however, as most studies of AOO in low-income countries are retrospective this might reflect a recall bias [57,63]. It may also be that earlier onset in high-

income countries is due to the relative impact of common risk factors or differences in susceptibility.

According to the DSM, GAD is considered to be chronic. Symptoms may fluctuate between syndromal and subsyndromal levels but rates of full remission are low [21]. Higher rates of persistence are found in those with comorbid conditions (especially specific phobia) [65], in those with early onset [66], and in those living in low-income countries [57]. However, successful treatment may reduce symptomatology for both GAD and the comorbid condition [67]. Poorer prognosis is also suggested for those with more severe disability [68] and with treatment delay [69], suggesting that the amount of experienced distress is important.

1.2.5 ETIOLOGY

The cause of GAD is not fully understood [70]. However, it is generally agreed that several factors are involved. A biopsychosocial model has been proposed suggesting a genetic predisposition to develop GAD. Results from twin studies suggest a hereditability around 32% [71]. However, a substantial part is explained by associations with neuroticism [72,73]. Candidate gene studies have gathered considerable evidence regarding associations with serotonergic and catecholaminergic systems and neurotrophic signaling, however, replication of these results are still lacking [74,75]. It has also been suggested that genetic evidence lack specificity for GAD, yet some support has been given to the distinction of two types of anxiety, generalized and phobic [76].

It is well established that social and environmental factors are important [36]. Risk markers associated with GAD include, female sex, neuroticism, single/divorced/widowed, low income, low education, stressful life events, although these factors may not be specific for GAD [21,44].

Several psychological models are offered to theoretically conceptualize the development of GAD. Different perspectives on the theory and treatment of GAD are highlighted, such as the avoidance hypothesis [77], the positive beliefs about worrying [78], and the experiential avoidance [79]. Below are two different models described involving the concepts of intolerance of uncertainty and emotional hyperarousal.

1.2.5.1 INTOLERANCE OF UNCERTAINTY

The model comprises four parts (1) intolerance of uncertainty (IU), (2) positive beliefs about worry, (3) negative problem orientation, (4) cognitive avoidance [80]. The main feature of this theory is the belief among patients that uncertainty is stressful, unfair and upsetting. Worrying is seen, by the patient, as a way to reduce uncertainty by mentally or physically preparing for potential catastrophes, and in doing so protecting loved ones or stopping bad things from happening. The third feature is related to information processing regarding uncertain events and one's own problem solving ability. It is suggested that patients suffering from GAD perceive uncertain events more threatening compared to healthy controls [81]. The fourth feature is the identification of worry as a cognitive avoidant process. By engaging in active thought processes (worrying), patients may reduce mental imagery, and subsequently avoid the somatic anxiety symptoms stemming from phobic imagery [82]. Empirical studies show that changes in IU precedes changes in worry [83], and that IU is more related to GAD than to other anxiety disorders [84,85], thus making IU an appropriate target for interventions in GAD.

1.2.5.2 EMOTIONAL DYSREGULATION MODEL

The emotional dysregulation model (EDM) is an emotional/behavioral model also consisting of four parts (1) emotional hyperarousal, (2) poor understanding of emotions, (3) negative attitudes to emotions, (4) maladaptive emotion regulation or management strategies [86]. It is suggested that people with GAD experience more intense emotions, more negative than positive, compared to those without GAD. Difficulties to process intense emotions, and deficits in extracting useful information from them, is suggested to induce discomfort or anxiety when strong emotions occur [85]. Worry is then used as an ineffective strategy to cope with dysregulated emotions. Empirical studies have found that people with GAD experience more intense negative emotions [87], have increased difficulty identifying, describing, and understanding their emotions [86], and engage in more emotional coping strategies (i.e., excessive worry, emotional outbursts, emotional suppression) compared to individuals with depression and social anxiety [88]. However, there are some conflicting evidence suggesting that some parts of the model needs to be revised [81].

1.2.6 COMORBIDITY

Comorbidity with other psychiatric disorders is high in GAD, however, not more so than for other anxiety disorders [61]. The most common comorbid

disorders worldwide is mood disorders (MDD), other anxiety disorders, disruptive behavior disorders, and substance abuse disorders [57]. Comorbidity is associated with greater disability, and lower rates of remission [70]. Around 80-90% of those with a lifetime diagnosis of GAD have, or will have, experienced another psychiatric diagnosis in their lifetime [57,70].

GAD also frequently co-occurs with somatic symptoms and disease. Gastrointestinal symptoms and associations with irritable bowel syndrome (IBS) are frequently reported. About 50% with IBS also have GAD emphasizing the close link between the two disorders [89]. Other somatic disorders associated with GAD are asthma, coronary heart disease, diabetes, peptic ulcers, and chronic obstructive pulmonary disease [70,90,91].

1.2.7 SEX DIFFERENCES

That GAD is more common in women than in men is found in most population studies [50,51]. It has been suggested that this difference does not persist into old age, however, in the last decade several studies among older adults have confirmed previous findings in younger populations [92]. There are very few differences in men and women that develop the disorder but some differences in comorbidity patterns have been suggested. While women with GAD more often have a comorbid anxiety or mood disorder, men tend to show high rates of comorbid substance abuse disorders.

Sex and gender differences have consistently been found in relation to anxiety and mood disorders across cultures, and it has been argued that women have an increased psychiatric vulnerability [93,94]. Possible explanations include psychosocial factors, which have been suggested to affect sex differences in GAD. However, the support is weak for other anxiety disorders [95]. Hormonal factors have also been suggested, as puberty, pregnancy and menopause are triggers for onset and exacerbation of affective disorders [93]. However, persisting differences in prevalence past menopause into old ages argues against hormonal factors as the sole explanation. Increased sensitivity to catecholamines in memory consolidation and that blood pressure and pulse are more reactive to anxiety in women could argue for a susceptibility for fear conditioning [96]. This is in line with previous findings that women have reported higher frequencies of autonomic arousal [97]. Another suggested explanation is the influence of social gender roles and the protective effect of masculinity [98], suggesting that lower levels of masculinity in females compared to males may partly account for the sex differences in anxiety. This

effect is attributed to men underreporting symptoms, but also to a gender socialization processes. In short, genetic vulnerabilities may gradually evolve into fully articulated anxiety traits through interactions with gender specific environmental factors, such as differences in confronting fears during childhood, division of work status, socioeconomic status and different types of environmental stressors [99].

1.2.8 IMPAIRMENT & HELP-SEEKING

It is well established that individuals with GAD suffer considerable impairment. GAD has been negatively associated with different domains of quality of Life (QoL), and life satisfaction according to measures of self-reported health [100]. Several objective measures such as increased functional limitations [101], restricted professional roles and reduced productivity have also been linked to the disorder [70]. Furthermore, it has been suggested that individuals with GAD are less likely to take part in physical and social activities [70].

According to the WMH survey initiative, the proportion of severe impairment among people with GAD is substantial (median 48,6%) across the globe. The proportion was higher in high-income countries, and in the Netherlands the proportion of severe impairment, among people with GAD, was 80% [57]. Noteworthy, the Netherlands has also recorded the highest prevalence rates (7.3%) for GAD [55]. On average across the globe >40 days/year were spent unable to work or carry out daily activities due to GAD [57].

It has been proposed that GAD is the anxiety disorder associated with most impairment, comparable to impairment levels for depression [20]. Both entities have independently been linked to similar rates of disability and impairment. One study even found that QoL scores, according to SF-36, were generally worse than for depression [102]. GAD is a severity marker in comorbid GAD/MDD with increased rates of suicide [70]. There is also an independent risk of suicide, however, significantly lower than for MDD [103].

Patients with GAD are primarily found in primary care, consuming large amounts of healthcare recourses [104]. Help-seeking behavior in pure GAD is very low [105]. However, GAD with comorbid mental disorders significantly exacerbates the functional impairment and help-seeking behavior [89]. Barriers to help-seeking include low perceived need, problem recognition, and attitudinal barriers such as stigma [62]. Problem recognition is higher among

older adults [106]. Furthermore, help-seeking is higher in high-income countries, in line with data on increased severity [57]. However, it may also explain some of the disparate prevalence rates found across the globe.

1.2.9 TREATMENT

In general the treatment gap for mental disorders is significant. Only about 60% of those diagnosed with GAD receive treatment [107]. Effective treatments for GAD are available and by attaining higher treatment coverage, personal and societal costs could be significant reduced [20]

However, recognition of GAD is complex, even more so among older adults. One study found that in a primary care setting only 34% of GAD patients were recognized, the others often being misdiagnosed with other mental disorder (Hoyer 2001)[20]. One reason for this may be that apprehension and GAD rarely is the primary complaint, and that GAD patients primarily present with somatic complaints, pain, sleep disturbances or depressive symptoms [108]. Thus, public awareness or mental health literacy for GAD may be lacking. Older adults have a higher frequency of comorbid conditions, suggesting that both clinicians and patients may have more difficulties recognizing GAD in this age-group.

In accordance with the statements above; National Institute for Health and Care Excellence (NICE) guidelines recommend stepped care: identification and information, low intensity psychological interventions (psychoeducation), high intensity interventions (CBT or SSRI), complex treatments (combinational therapy, in-patient care) [109]. Specific guidelines for older populations are lacking. Evidence suggests that CBT treatment in older adults may show reduced efficacy, possibly mediated by age-related cognitive decline in executive functions [110-112]. On the other hand, with age, medication could increase the risk of polypharmacy and adverse side effects. Combination treatment (CBT/SSRI) for older adults may improve effect sizes for CBT and allow reduced dosage [113]. However, studies with long-term follow-ups are still missing.

1.3 ANXIETY & AGING

Old age is associated with considerable distress and increased exposure to potential psychiatric triggers, e.g. loss of a loved one, loss of social status, and loss of function. Nevertheless, research indicates decreasing prevalence rates of anxiety disorders [64,92,114], decreasing severity of anxiety symptoms [115,116], decreasing frequency of worry [117,118] and less autonomic arousal [64,119] with increasing age. This apparent paradox has stimulated research interest of the aging process related to anxiety disorders in order to inform whether changes to diagnostic criteria should be recommended to better reflect anxiety in old age.

It has been argued that anxiety disorders are underdiagnosed in older populations [92,120-122]. Some age-specific methodological considerations will be reviewed below. Older adults have more physical comorbidities, which have been found to be the main source of diagnostic confusion in primary care settings [120]. Lower help-seeking behavior may also contribute to lower recognition among older adults [123]. Anxiety has been associated with higher all-cause mortality, thus survival bias may be a potential explanation for the reductions in anxiety and improved prognosis found among older adults [116,124,125]. Furthermore, higher levels of anxiety have been found in individuals with cognitive impairment and patients in institutions [59]. However, they are often excluded from epidemiological studies leading to selection bias. Evidence also shows that anxiety may be experienced differently with age [126,127], highlighting the need for age-appropriate criteria [128].

Empirical studies, examining age differences in negative affect, show that emotional control and self-regulation increases with age [129], resulting in reduced anxiety and reduced "reactivity" to negative emotions. This may be mediated by acceptance of negative emotional experiences motivated by the transience of life [130,131], i.e., that old age and less time to live make individuals more positive (about present matters) and less inclined to dwell on the future. Support for the positivity effect has been found in MRI studies showing that older, compared to younger, adults responded with less activity in amygdala when presented with negatively valenced pictures, while maintaining their reactivity to positive information [132]. It is suggested that emotional control/stability improves gradually during the life-course through increased activation of medial prefrontal areas [133,134]. These results also lend support to studies showing reduced severity of anxiety disorders [135]. Critics argue that a more nuanced picture is required and that the theory focuses too

much on global domains of negative and positive effect, neglecting to explain higher frequencies of sadness (negatively valenced) found in older adults [131].

Another explanation suggests that biological brain changes in older people prevent the expression of autonomic arousal. Evidence shows a progressive loss of neurons in the locus coeruleus (LC), responsible for arousal and autonomic function [119]. Also, in response to negative valenced pictures subjective ratings of emotion correlated with physiological responses (SCR) in younger, but not in older participants [136]. A similar result was found in a experimental study where exposure to CCK-4 induced fewer and less intense panic-like symptoms in older adults compared to younger individuals [137]. Fewer autonomic symptoms in older adults, irrespective of distress level, may decrease the perception of anxiety [138]. Thus, disrupting the feedback loop responsible for the most severe symptoms of panic attacks, excessive symptoms will be reduced while milder symptoms remain stable.

1.4 CONSEQUENCES OF ANXIETY

Anxiety has frequently been associated with somatic disease, such as irritable bowl syndrome (IBS), asthma, cardiovascular disease, chronic pain and dementia [91,139]. Even though evidence of causal associations is scarce it has been suggested that mental disorders, including anxiety, have detrimental effects on physical health [90]. Results regarding all-cause mortality are not consistent, with some reporting an increase in excess mortality [140,141], and others report no association or even beneficial effects [142,143]. Such effects have been suggested to be attributed to increased use of health care services [143]. The risk of cardiovascular disease and dementia are examined in more detail below.

1.4.1 CARDIOVASCULAR DISEASE

Anxiety among patients with cardiovascular disease (CVD) is highly prevalent [144,145]. Having an anxiety disorder is associated, with some exceptions, with worse prognosis and increased mortality in stable CVD patients [146]. Prospective evidence shows mixed results but a majority of studies suggest anxiety to be a risk factor for CVD. Anxiety has been associated with earlier onset of first myocardial infarction (MI) [147]. One prospective study with 20 years followed-up showed increased risk of MI in those with anxiety symptoms [148]. However, it has also been argued that confounding has not been sufficiently accounted for. Results have been attenuated after adjustments and it has been suggested that results may be biased from reverse causality i.e. undiagnosed disease causing the distress/anxiety [149]. Similar findings were found in recent meta-analyses with regard to depressive comorbidity [144]. Others have found that anxiety is an antecedent risk factor and may be driving established risk factors [140].

The proposed mechanism for increased risk of CVD in anxiety patients may be indirect through increasing established cardiovascular risk factors such as hypertension, low omega-3 fatty acids, smoking, physical inactivity, and low adherence to medication [147]. Another mechanism that has been suggested is increased HPA axis activity, resulting in release of catecholamines and subsequent damage to vascular endothelium [91]. Furthermore, many anxiety disorders including GAD have been associated with reduced heart rate variability, which is associated with adverse cardiovascular effects [150]. However, it remains to be seen if successful treatment of anxiety may alleviate some of the risk associated with anxiety.

1.4.2 DEMENTIA

Anxiety is a common symptom in individuals with dementia [151-153]. Several studies have found that increased levels of anxiety predicted dementia onset in both community and clinical samples [154,155], while others report no association [156-158]. Anxiety symptoms have also been associated with incident dementia in studies with longer follow-up (>10 years), suggesting a causal relationship [159-163].

Critiques argue that anxiety is a normal response to loss of function [164,165], and that anxiety prior to dementia diagnosis may reflect prodromal signs of disease [139,151,166]. It is suggested that the long prodromal phase in dementia requires studies with very long follow up (>20 years). Preclinical signs of cognitive decline may be seen already 18 years before dementia diagnosis [167], and pathological biomarkers are reported to occur 20-25 years before clinical symptoms [168,169].

There are several mechanisms by which anxiety may increase the risk of dementia. The most studied is the glucocorticoid cascade hypothesis [170], which suggests that prolonged exposure to stress and hypersecretion of glucocorticoids may lead to downregulation of receptors and neural degeneration in the brain. Anxiety may accelerate the aging process through further activating the HPA-axis in older adults [171]. In support of this, exposure to anxiety has been associated with gray matter atrophy in the hippocampus and the prefrontal cortex [172], which is also found in many dementia disorders, including AD. Others have suggested that the association between anxiety and dementia may be indirect, via reduced cognitive reserve [173] or increased cardiovascular risk [141].

2 AIMS

The overall aim of this thesis was to examine generalized anxiety disorder (GAD) and anxiety symptoms in old age. It is assumed that current classification systems of GAD focus on different expressions of the disease and may capture different people. It is also hypothesized that anxiety symptoms are expressed differently with increasing age and may impact the GAD criteria. Finally, the aim is to study the consequences resulting from exposure to different expressions of anxiety.

Specific Aims:

I. To examine the one month prevalence of GAD according to different classification systems and to study co-morbidity with other psychiatric disorders.
II. To examine the association between anxiety symptoms and age, and their impact on current classification systems among older adults.
III. To examine the association between anxiety symptoms and dementia development.

3 METHODS

The samples from Study I-III were derived from The Gothenburg H70-birth cohort study [174,175]. The studies include a longitudinal study of women, the Prospective Population Study of Women (PPSW) [176-178], and several studies of selected birth cohorts followed from 70 years of age. The psychiatric part of PPSW began in 1968 and is presently on-going. Studies I-II are based on data from 2000-2009 and include people born 1922/23 and 1930. Study III is based on longitudinal data from the PPSW between 1968-2012. The samples were systematically selected from the Swedish Population Register based on birth date, and include persons living in private households and in institutions. Examinations took place at an outpatient clinic of Sahlgrenska University Hospital in Gothenburg and those who declined were offered home visits. Participants in the longitudinal study who relocated from Gothenburg were also offered home visits in other places of Sweden.

3.1.1 STUDY I

The study used data collected in 2005 from the 1930 birth cohort (age 75). Among those selected (N=1363), 11 died before they could be examined, 18 could not be traced, 15 had emigrated outside Sweden and 32 could not speak Swedish, leaving an effective sample of 1287 individuals. Among these, 827 (321 men, 506 women) accepted to take part in the psychiatric examination (response rate 64.3%). Out of the 827, 49 were excluded because of dementia and one due to missing symptom ratings, leaving 777 individuals (299 men, 478 women) for the study. Non-participants had a higher three-year mortality rate compared to participants (14.3% versus 4.7%; $p<0.001$). There were no significant differences between the groups regarding gender, marital status, or in-patient care during the last year with psychiatric diagnoses (5.7% versus 4.2%; $p=0.251$), depression (3.0% versus 1.8%; $p=0.154$), anxiety disorders (1.5% versus 0.5; $p=0.053$), or dementia (4.1% versus 2.4%; $p=0.086$) according to the Swedish Hospital Discharge register.

3.1.2 STUDY II

The study used data collected between 2000-2009, and included two birth cohorts born 1930 and 1922/23 (figure 1, page 33). In 2000, 896 individuals born on pre-specified dates in 1930 and living in Gothenburg, Sweden on September 1 were selected for a study on 70-year olds. Among these, 28 persons died or had emigrated/relocated before the study started, and 23 could not take part for other reasons (e.g. language difficulties), leaving an effective sample of 845 individuals. Among these, 580 accepted participation

in a psychiatric examination (response rate 68.5 %). For this specific study, 16 were excluded due to dementia and two due to missing symptom ratings, leaving 562 individuals (224 men, 338 women). The participation rate did not differ between men and women, but due to oversampling of women (the merge of PPSW and H70 in 2000 meant that women born at additional dates were included), the sample had a higher proportion of women than the general population. Non-participants had a higher three year mortality rate compared to participants (5.6% versus 1.7%; p=.004). There were no significant differences between the groups regarding lifetime psychiatric diagnoses (6.0% versus 5.0%; p=.621), or in-patient care during the last year (13.5% versus 13.6%; p=1.00) according to the Swedish Hospital Discharge register.

During 2005 (at age 75), a second examination was conducted and the sample from 2000 was extended to include an extra 569 individuals. Among those selected (N=1437), 71 died or emigrated/relocated before they could be examined, 79 could not take part for other reasons, leaving an effective sample of 1287 individuals. Among those, 832 accepted to take part in the psychiatric examination (response rate 64.6%). For this specific study, 48 were excluded due to dementia and 14 due to missing symptom ratings, leaving 770 individuals (293 men, 477 women). There were no significant differences between the groups regarding sex. Non-participants had higher three year mortality rate than participants (13.7% versus 4.5%; p<.001). There were no significant differences between non-participants and participants regarding lifetime psychiatric diagnoses (7.6% versus 5.3%; p=.115), or in-patient care during the last year (18.5% versus 17.8%; p=.763) according to the Swedish Hospital Discharge register.

During 2009 (at age 79), a third examination was conducted. Among those selected (N=1360), 208 had died before they could be reexamined, 44 could not take part for other reasons, leaving an effective sample of 1108 individuals. Among those, 662 accepted to take part in the psychiatric examination (response rate 59.7%). For this specific study, 56 were excluded because of dementia and 3 due to missing symptom ratings, leaving 603 individuals (239 men, 364 women). There were no significant differences between the groups regarding sex. Non-participants had a higher three year mortality rate (11.7% versus 7.6%; p=.026), higher prevalence of lifetime psychiatric diagnoses (9.0% versus 5.6%; p=.040), and lower rates of in-patient care during the last year (9.9% versus 18.1%; p<.001), but longer mean hospital stay (14.8 versus 9.1 days) compared to participants according to the Swedish Hospital Discharge register.

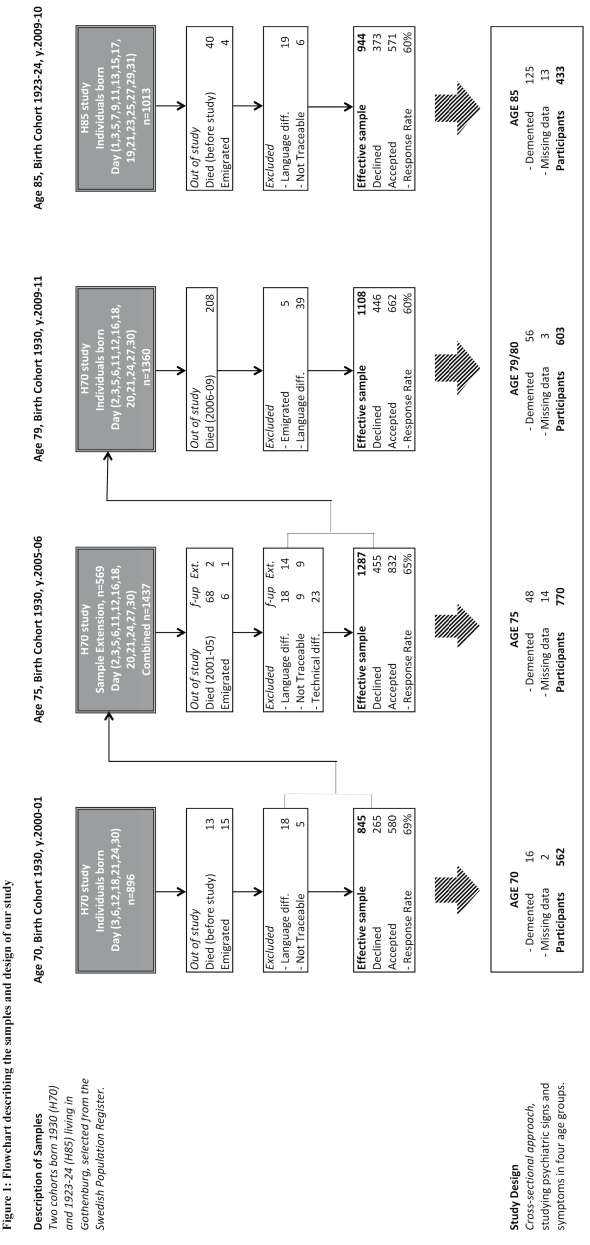

Figure 1. Flowchart describing study design and sample of study II

We also included a sample from the H85 study [179]. In 2009, 1013 85-year-olds born in 1923-24 and living in Gothenburg, were selected from the Swedish population register. Among those, 44 died or emigrated/relocated before they could be examined, and 25 could not take part for other reasons, leaving an effective sample of 944 individuals. Among those, 571 accepted to take part in the psychiatric examination (response rate 60.5%). For this specific study 125 were excluded due to dementia and 13 due to missing symptom ratings, leaving 433 individuals (169 men, 267 women). There were no significant differences between the groups regarding sex or three-year mortality rate. No data regarding lifetime psychiatric diagnoses and in patient care during the last year were available for non-participants.

3.1.3 STUDY III

The study used data collected between 1968-2012, and included women from the PPSW that took part in the psychiatric examination in 1968 (n=800, RR 91%). The women were born in 1914, 1918, 1922, and 1930. Follow-up examinations were performed in 1974 (n=677, 85% response rate), 1980–81 (n=629, 73% response rate), 1992–93 (n=371, 67% response rate), 2000–01 (n=363, 73% response rate), 2005–06 (n=299, 75% response rate), and 2009–10 (n=269, 67% response rate). A flowchart of study waves is provided in figure 2. In 1992, the youngest cohort born 1930 was not invited. Study participants were followed with regards to dementia occurrence until 2012 with information from the Swedish Hospital Discharge Registry and Swedish Death Registry.

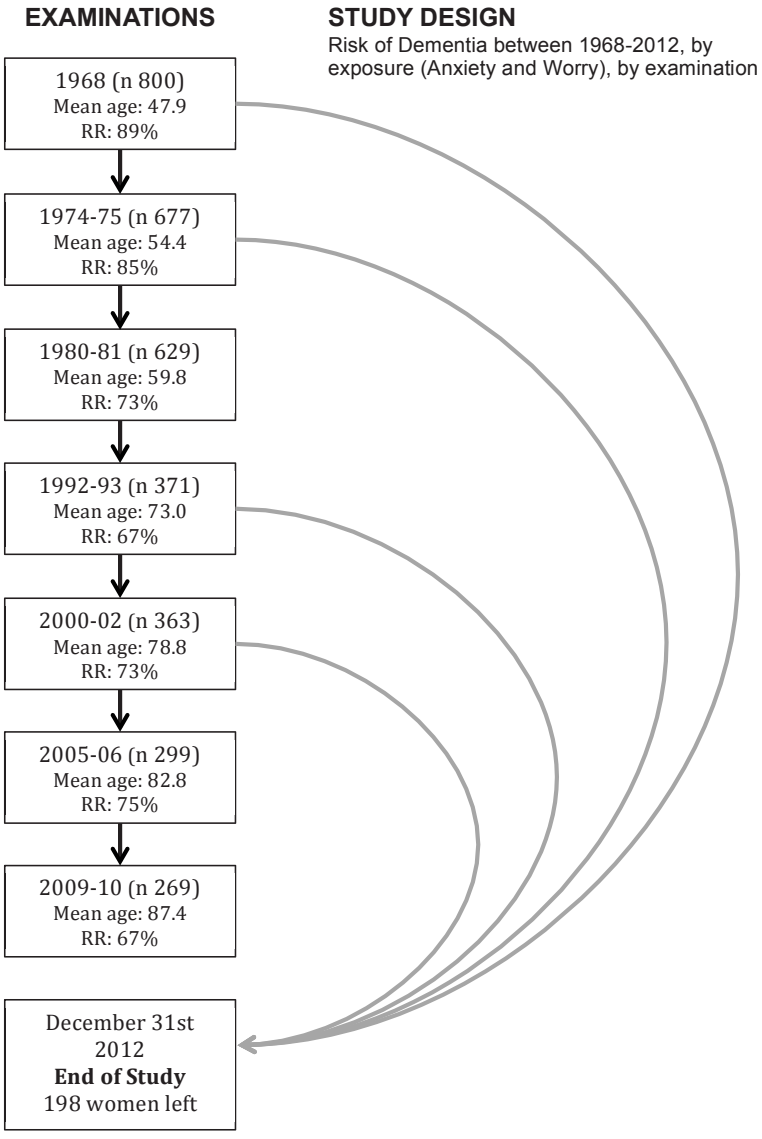

Figure 2. Flowchart describing sample selection in study III

3.2 ASSESSMENTS

All participants completed a psychiatric semi-structured interview at each examination; performed either by a psychiatrist or a trained research nurse with psychiatric experience. The interviewers assessed self-reported symptoms during the past month and observed signs during the interview. The instrument used was mainly based on the CPRS and the Mini International Neuropsychiatric Interview (MINI).

The CPRS [7] is a comprehensive 68-item scale designed specifically to measure change in psychopathology. The instrument is semi-structured, allowing for clarifying questions, and includes information on intensity, frequency, and duration of both reported symptoms and observed signs. The items are rated from 0-6 and are fitted with a characteristic description for each "scale step" in order to facilitate the distinction between different symptom levels and promote rater consistency. A rating of 2-3 indicates the presence of a symptom, however, it may or may not be pathological depending on context. A rating of 4-5 most often indicates pathology and a rating of 6 indicates very severe symptoms. The reliability is not influenced by aging or cognitive impairment and is validated for use in older populations [180].

The MINI is a short fully structured diagnostic interview, developed jointly by psychiatrists and clinicians in the US and Europe, for Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and International Classification of Diseases (ICD) 10th revision psychiatric disorders [181]. The instrument is binary and includes information on the presence of symptoms, but not severity. The psychiatric interview did not include items relevant to diagnose panic disorder (PD), agoraphobia, and post-traumatic stress disorder (PTSD).

The Global Assessment of Functioning (GAF) was used to assess functioning due to mental health problems [182]. Furthermore, specific assessments relevant for dementia diagnoses, such as recent and remote memory, semantic memory, concentration, judgment and abstract thinking were also included [183], as well as assessments from the Alzheimer's Disease Assessment Scale - Cognitive (ADAS-Cog)[184]. The Eysenck Personality Inventory (EPI) was used to assess neuroticism [185]. The neuropsychiatric examination also includes information on age, education, accommodation, hypertension, diabetes mellitus, cardiovascular disease (CVD), smoking, alcohol consumption, physical activity, body mass index (BMI), stress; used as covariates in the studies.

3.2.1 DEFINITIONS OF ANXIETY, WORRY, AND GAD

The definition of anxiety and worry in all three studies are based on items from the CPRS, with the exclusion of the first examination in study III in 1968. At this time the CPRS was not constructed and anxiety was instead defined as having vegetative anxiety attacks at least once per month. Worry was defined as often being overly anxious or often being worried for no apparent reason. Both were based solely on frequency items. We were thus not able to provide information on severity in 1968.

In study II and III (except in 1968) anxiety was defined as feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish (CPRS item 'inner tension'). Worry was defined as apprehension worry and undue concern over trifles, which is difficult to stop and out of proportion to the circumstances (CPRS item 'worrying over trifles'). The symptoms should have been present during the last month. Items were rated 0-1= No symptom present, 2-3= Mild symptoms, 4-6= Severe symptoms [7].

For the purpose of study III, we created dummy variables for midlife anxiety and midlife worry. A woman was considered to have midlife anxiety if she acknowledged anxiety symptoms in 1968, or received a rating ≥2 on the CPRS anxiety item in 1974. Conversely, a woman was considered to have midlife worry if she acknowledged worry symptoms in 1968, or received a rating ≥2 on the CPRS worry item in 1974.

Dual ratings by psychiatric research nurses and psychiatrists were conducted in 50 participants to assess inter-rater reliability. Inter-rater agreement for 'inner tension' was $\kappa = 0.94$, and 'worrying over trifles' was $\kappa = 0.90$.

In study I and II, GAD was diagnosed according to DSM-IV/5 [21] and the ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic criteria for research [186] using algorithms, constructed by the author under the supervision of three psychiatric specialists. Each symptom in the diagnostic manuals were identified and paired with the corresponding item in CPRS and MINI (figure 3-4). Cut-offs for CPRS items were based on expert opinion. Items from MINI were binary (Not present/Present) and were asked solely to those who endorsed a gateway question regarding anxiety or worry. For some items of MINI, raters were asked to distinguish between episodic and chronic anxiety. This specifier was included in the algorithm in study I, however, due to reliability concerns it was removed from the algorithm in study II. The ICD-10 symptom "dry mouth" is not covered by MINI or CPRS, but the question was included in the general examination. We had no questions regarding "exaggerated response to minor surprises", "feeling keyed up or on

edge", and "difficulty breathing" which are included in GAD according to ICD-10-DCR.

Inter-rater agreement for the signs and symptoms included in GAD diagnosis was high, with kappa values between 0.55 and 1.00.

Algorithm for DSM-5 Generalized Anxiety Disorder

Symptoms were assessed by ratings of the corresponding item in CPRS, from 0-6 with increasing severity. The cut-off of 4 out of 6 represents clinically relevant symptom levels. Items from MINI were rated present (1)/not present (0) after endorsing a gateway question of either anxiety or worry

Gateway criteria:
Excessive anxiety and worry (apprehensive expectation).
= Inner tension (separated from panic attacks) or Worrying over trifles

Associated symptoms: At least three or more of the following symptoms

1) Restlessness or feeling keyed up or on edge
   = Observed agitation (4-6) or Restlessness (1)

2) Being easily fatigued
   = Fatigue (4-6) or Easily exhausted (1)

3) Difficulty concentrating or mind going blank
   = Concentration difficulties (self-rated/observed) (4-6) or Concentration difficulties(1)

4) Irritability
   = Hostile feelings(self-rated/observed)(4-6) or Irritability(observed)(4-6) or Irritability(1)

5) Muscle tension
   = Muscular tension (self-rated/observed) (4-6) or Muscle tension (1)

6) Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)
   = Reduced sleep (4-6) or Sleep satisfaction† or Sleep disturbances (1)

† Item not included in CPRS, rated symptoms according to an ordinal scale of sleep satisfaction. Cut-off set at, not at all satisfactory, irrespective of hypnotic medication.

Figure 3. Diagnostic algorithm for GAD according to DSM-5

Algorithm for ICD-10 Generalized Anxiety Disorder

Symptoms were assessed by ratings of the corresponding item in CPRS, from 0-6 with increasing severity. The cut-off of 4 out of 6 represents clinically relevant symptom levels. Items from MINI were rated present (1)/not present (0) after endorsing a gateway question of either anxiety or worry.

Gateway criteria:

Prominent tension, worry and feelings of apprehension.
= Muscular tension (self-rated/observed) (4-6) or Muscle tension (1) or Inner tension (separated from panic attacks) (3-6) or Worrying over trifles (3-6)

Associated symptoms: At least four of the following symptoms of which one has to be from the first five items (1) to (5).

Autonomic arousal symptoms

1) Palpitations or pounding heart, or accelerated heart rate (1)
2) Dry mouth (not due to medication or dehydration) (1)
3) Trembling or shaking (1)
4) Sweating (1)
5) Vegetative disturbances (observed) (4-6)

Symptoms concerning chest and abdomen

6) Chest pain or discomfort (1)
7) Nausea or abdominal distress (1)
8) Feeling of choking (1)

Symptoms concerning brain and mind

9) Derealisation or depersonalisation (1)
10) Feeling dizzy, unsteady, faint, or light-headed (1)
11) Fear of dying (1)
12) Feeling of losing control, "going crazy" (1)

General symptoms

13) Numbness or tingling sensations (1)
14) Hot flushes or cold chills (1)

Symptoms of tension

15) A sensation of a lump in the throat (1)
16) Restlessness and inability to relax
    = Observed agitation (4-6) or Restlessness (1)
17) Muscle tension or aches and pains
    = Muscular tension (self-rated) (4-6) or Aches and pains (self-rated) (4-6)

Other non-specific symptoms

18) Persistent irritability
    = Hostile feelings (self-rated/observed) (4-6)
19) Difficulty concentrating or mind going blank, because of worrying or anxiety
    = Concentration difficulties (self-rated/observed) (4-6) or Concentration difficulties(1)
20) Difficulties to sleep because of worrying
    = Sleep disturbances (1)

Figure 4. Diagnostic algorithm for GAD according to ICD-10-DCR

3.2.2 DEMENTIA

In study I and II, dementia was used only as an exclusion criteria. However, in study III, dementia and dementia subtypes were used as outcome variables. The diagnosis of dementia at each examination was based on the criteria in the DSM-III-R[187], using information from neuropsychiatric examinations and close informant interviews. Dementia diagnoses for individuals lost to follow-up were based on information from the Swedish Hospital Discharge Registry 1978-2012[188]. The diagnosis was made by consensus between, at least, two experienced psychiatrists.

Alzheimer's disease was diagnosed according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Vascular dementia was diagnosed similar to the criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherce et l'Enseignement en Neurosciences (NINDS-AIREN), as described previously [189]. Vascular dementia was diagnosed when there was a temporal relationship (within one year) between a history of acute focal neurological symptoms and signs (hemiparesis or motor aphasia) and the first symptoms of dementia. Mixed dementia was diagnosed when both Alzheimer's disease and cerebrovascular disease were judged to contribute to dementia.

Age of dementia onset was determined based on information from key informants, the hospital discharge register, and the examinations. If adequate information could not be obtained from these sources, age of onset was determined as the mid-point between the last examination free from dementia and the first with a dementia diagnosis.

3.2.3 DIAGNOSIS OF OTHER MENTAL DISORDERS

Social phobia, specific phobia, and obsessive-compulsive disorder were diagnosed according to DSM-IV criteria [182]. Items from CPRS, MINI, and the Y-BOCS were combined to follow diagnostic criteria as closely as possible. These diagnostic procedures have been described elsewhere in detail [190-192]. Major depression was diagnosed according to DSM 5 and minor depression was diagnosed according to DSM IV-TR criteria [193]. Inter-rater agreement for items used to diagnose depression varied between $\kappa = 0.62$ and $\kappa = 1.00$.

3.3 STATISTICS

All data analyses in Study I and II were made in SPSS versions 17-22 for Windows and MacOS respectively. In Study III all analysis were also made in Stata/SE 15 for Macintosh. Differences in proportion were tested with Pearson Chi-Square or Fisher's exact test. P-values were considered significant at a level of $p<0.05$ (two-tailed).

3.3.1 STUDY I AND II

The first study has a cross-sectional design. Analysis of variance (ANOVA) was used to test differences in means. Kappa (κ) value was used to measure level of agreement between different criteria for GAD.

The second study was also cross-sectional by design, including four age groups. The one-month prevalence of GAD associated symptoms according to ICD-10 and DSM-5 were measured, at age 70, 75, 79 and 85. To analyze the effect of age on a population level, we used generalized estimating equation models (GEE)[194], adjusting for repeated measurements with an exchangeable working correlation matrix structure and a robust estimator of the covariance matrix. For binary outcome variables, we used a logistic link function. All analyses were adjusted for sex.

To estimate the degree of functional disability we used GEE models with linear link functions, also with an exchangeable working correlation matrix structure and a robust estimator of the covariance matrix. The intercept was set at age 70. The models show associated functional disability for diagnoses of GAD (DSM-5 and ICD10), and for clinical and subclinical core symptoms of GAD. All analyses were adjusted for depression (major and minor), sex, age and medication with beta-blockers (which influences autonomic symptoms).

3.3.2 STUDY III

The third study has a longitudinal prospective study design, measuring exposure of anxiety and worry at baseline 1968 and at follow-ups. Participants were followed up with regard to incident dementia until the end of 2012. To assess the risk of dementia we used proportional hazard models (Cox). Kaplan-Meier (KM) plots did not reveal any overt violations of the proportional hazards assumption. Person time was measured from the baseline examination date to December 31, 2012. Individuals were censured when diagnosed with dementia, at the time of death, or at end of the study period. Model 1 adjusted for age. In Model 2, all analyses adjusted for age,

and major depression. Additional covariates were considered relevant at $p<0.3$ or after a significant Likelihood-ratio test. The final model for each analysis may be found in the caption below the corresponding table. The same sets of analyses were used to assess the risk for dementia and dementia subtypes.

In the analyses in relation to age of dementia onset, person time was redefined to begin at birth. Participants were stratified into age groups (38-64, 65-74, 75-84, 85-94, >95), based on when person time ended, i.e. until death, dementia diagnosis or December 31, 2012. The risk of dementia was assessed, for each age group, with a Cox regression.

We conducted two sensitivity analyses. In the first sensitivity analysis, participants born 1914 and 1918 were excluded in order to limit age range to 38-48 years at baseline, which gave a more strict definition of middle age. In the second sensitivity analysis, individuals diagnosed with dementia before 1999 were excluded, i.e. providing a sample with a minimum of 25 years between measurement of anxiety and dementia diagnosis. The cutoff was based on previous literature regarding the first presence of clinical biomarkers [169], which occurs already 22-25 years before diagnosis.

4 RESULTS & DISCUSSION

4.1.1 STUDY I

The aim of the study was to examine current classification systems of GAD in a cross-sectional sample of older adults. A review of the literature had revealed a lack of evidence concerning the characteristics of GAD in older Swedish populations. Evidence indicated substantial differences between current classification systems due to repeated alterations of the DSM, and in the advent of DSM-5 little was known of how this affected older populations. Special attention was given to prevalence, diagnostic overlap, and comorbidity.

The main findings concluded that GAD was common in old age. The prevalence was similar for all classification systems. However, rates were slightly increased for the proposed criteria for DSM-5. Diagnostic agreement was moderate, different classification systems only captured the same individuals in about half of the cases. Comorbidity with selected mental disorders was high, and highest in those with depression. According to both classification systems GAD was more common in women than in men.

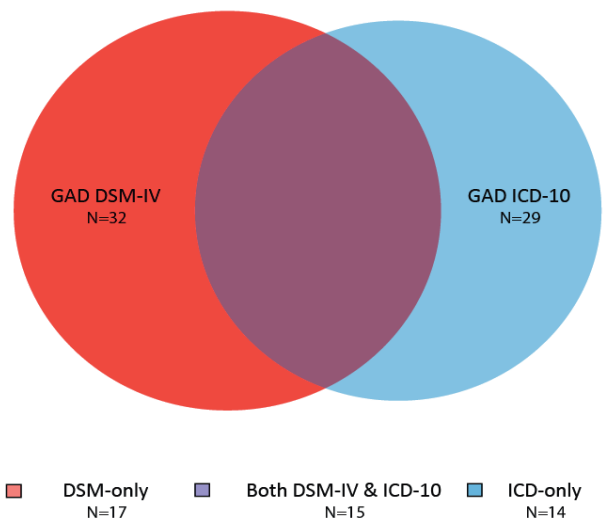

Figure 5. Venn diagram showing diagnostic overlap for Generalized Anxiety Disorder (GAD) according to DSM-IV and ICD-10-DCR

The results suggested that GAD is common, consistent with findings in younger populations. Our one-month prevalence rates around 4% were in line with other epidemiological studies among older adults [48,195,196]. Furthermore, our findings also confirmed sex differences and high comorbidity findings reported in younger populations. However, even though we found that GAD according to DSM-IV and ICD-10-DCR were similar in terms of prevalence, functional disability and patterns of comorbidity, diagnostic overlap was only moderate. Results suggested that a large group of people might be missed if either one of the diagnostic criteria were applied. It was also noted that the proposed criteria would further increase this disparity.

The most important limitation in study I is the size of our sample. GAD according to ICD-10-DCR includes 22 different symptoms, which is difficult to assess correctly without missing data in interviews. This was indicated by some symptoms being very rare. Furthermore, due to the overlap of the diagnostic criteria, comparisons were difficult as groups became small. A larger sample with more cases would have been preferred; hence some results should be interpreted with caution. Another consideration is the applicability of clinical criteria in a normal population, meaning that criteria may capture non-clinical cases if applied to the general population. This argument is supported by better agreement in clinical samples compared to epidemiological [33,197], however, those classified by both classification systems were not significantly more distressed arguing against this suggestion.

4.1.2 STUDY II

The aim of study II was to examine how the expression of anxiety and worry changes with increasing age. It was hypothesized that the prevalence of autonomic arousal and worry would decrease with age and that these differences would influence the diagnostic criteria for GAD according to DSM-5 and ICD-10-DCR. Results from study I indicated that autonomic arousal might cause GAD, according to ICD-10-DCR, to be less prevalent compared to DSM-5. A further review of the literature revealed that the expression of anxiety might change with age [127,198].

The main findings were in line with our hypothesis, symptoms associated with autonomic arousal and muscle tension decreased markedly with age. However, symptoms of worry remained stable or increased. The prevalence of GAD according to DSM-5 did not change with age, while the prevalence of GAD according to ICD-10-DCR tended to decrease. In addition, those with autonomic arousal and those diagnosed with GAD according to ICD10-

DCR had higher GAF scores with age, suggesting that these symptoms were associated with better functioning with increasing age.

The results from the second study suggest that the expression of anxiety and worry changes with age. We examined common anxiety symptoms in the general population between 70-85 and found that "fear"-related symptoms, i.e. symptoms related to free-floating anxiety and autonomic arousal, were less prominent and less intense in the older age-groups. This is in line with previous research [115,135]. However, cognitive symptoms remained or increased, suggesting different expressions of disease in old age.

Table 4. A GEE model, adjusted for sex, shows the effect of age on prevalence rates for GAD-associated symptoms in 70-85 year olds[199]

		Prevalence				Effect of Age		
		Age 70	Age 75	Age 79	Age 85	Generalized estimating equations		
		%	%	%	%			
GAD associated symptoms†	n	562	770	603	433	OR	(CI95%)	p-value
Anxiety	*Clinical*	2.5	2.6	1.7	0.2	0.91	(0.87-0.96)	<.001
	Subclinical	7.1	16.5	10.0	12.5	1.02	(1.00-1.04)	.129
Worry	*Clinical*	5.4	4.8	6.4	7.2	1.03	(0.99-1.06)	.139
	Subclinical	24.4	34.0	34.8	32.6	1.03	(1.01-1.04)	.004
Restlessness‡	*Clinical*	1.4	0.5	0.7	0.2	0.90	(0.80-1.00)	.056
	Subclinical	8.7	8.7	3.3	1.8	0.90	(0.87-0.93)	<.001
Being easily fatigued	*Clinical*	12.3	17.0	18.0	25.2	1.06	(1.03-1.08)	<.001
	Subclinical	26.0	44.5	53.6	47.6	1.07	(1.05-1.08)	<.001
Difficulties concentrating	*Clinical*	3.0	4.4	2.8	4.6	1.02	(0.98-1.06)	.431
	Subclinical	19.9	33.8	28.0	33.0	1.03	(1.02-1.05)	<.001
Irritability	*Clinical*	5.9	3.2	2.7	1.6	0.91	(0.87-0.96)	<.001
	Subclinical	23.5	27.1	30.7	29.8	1.03	(1.00-1.04)	.009
Muscle tension	*Clinical*	8.5	4.7	2.3	2.5	0.90	(0.86-0.94)	<.001
	Subclinical	30.8	35.6	28.4	17.8	0.96	(0.94-0.97)	<.001
Sleep disturbances	*Clinical*	24.4	29.4	24.8	29.0	1.01	(1.00-1.03)	.350
	Subclinical	22.2	32.5	44.1	40.4	1.06	(1.05-1.08)	<.001
Autonomic arousal	*Clinical*	5.5	3.5	2.2	2.1	0.92	(0.88-0.97)	.002
	Subclinical	29.9	22.7	11.4	14.5	0.92	(0.90-0.95)	<.001

† Symptoms derived from CPRS, based on self-reported and observed information
‡ Only information regarding observed restlessness were available

The implications of this change may be increased differences in prevalence in GAD according to DSM compared to ICD as autonomic symptoms are mandatory in GAD according to ICD-10-DCR while absent altogether in DSM. These results suggest that the emphasis, in upcoming revisions of current classification systems, should be directed at unifying criteria to avoid misclassification. If autonomic symptoms are reinstated, attention should be directed to designing age-appropriate criteria.

The main strength of this study lies in examining differences in diagnostic criteria for GAD and the influence of age on individual symptoms, with in the same study. The main limitations were that most anxiety items included in the diagnosis for GAD according to ICD-10-DCR lacked information regarding severity and only asked if participants endorsed the gateway symptoms anxiety or worry. Thus analysis of the influence of age on individual symptoms in the population was limited to items from CPRS. Furthermore, the GAD algorithm had to be changed, compared to study I, as it was realized that ratings for MINI anxiety symptoms had reliability concerns (discussed in section 3.2.1). This impacted the prevalence of the disorder positively making GAD according to ICD-10-DCR more prevalent than DSM-5, which is in line with other studies [33,54,200].

4.1.3 STUDY III

The aim of study III was to clarify temporal relationships and examine if anxiety and worry independently increases the risk of dementia or dementia subtypes. The association between anxiety and dementia is established, however, prospective findings of anxiety prior to dementia are somewhat debated [139,156]. A review of the literature revealed a lack of long follow-up studies able to exclude any effect of reverse causality [159]. Furthermore, anxiety assessment in most previous studies has relied on aggregated symptom scales that may obscure important characteristics of individual symptoms.

The main findings suggest that midlife anxiety, but not worry, may increase the risk of dementia in late life. The association was independent of depression, neuroticism, and stress level at baseline. Furthermore, anxiety closer to dementia onset did not increase the risk of dementia.

The results indicate that exposure to anxiety more than 25 years before dementia onset increased the risk of incident dementia. Our results expand findings from two long-term prospective studies (>10 years)[160,161], which had higher ages at baseline and employed self-reported scales to assess anxiety. Furthermore, the different association patterns with dementia for anxiety and

worry suggests qualitative differences between these constructs, and that results from anxiety scales may attenuate or obscure associations with dementia.

The strengths of this study include the representative and well-characterized population, the prospective longitudinal study design, the long observation period, comparably young age at baseline, multiple follow-up examinations with low attrition, structured assessments of anxiety and worry, and multiple sources of information used to detect and diagnose dementia.

The main limitation is the small sample size at later follow-ups, due to attrition and death, limiting statistical power. Another limitation is the infrequency of follow-ups. A third limitation is the use of different anxiety assessments 1968 and 1974 and onwards, this limited analyses on severity and direct comparisons. However, being able to show that separate measures of anxiety in midlife increased the risk of dementia strengthened the results.

5 GENERAL DISCUSSION

To summarize the findings of this thesis it is suggested that GAD is common in old age irrespective of diagnostic criteria. Current classification systems have evolved separately and may now capture different people in almost half the cases. Furthermore, age influences the core symptoms of GAD, anxiety and worry, differently and the expression of anxiety may, as a result, change with increasing age. Anxiety, but not worry, is suggested to be a potential modifiable risk factor for dementia, lending further support to the notion of qualitative differences between these constructs [10,201].

Among the strengths of this thesis are the population-based design and systematic sampling from the population register. Clinically experienced interviewers, using a semi-structured instrument allowing for clarifying questions, examined all participants. This method has been suggested to provide higher quality data compared to fully structured interviews [58].

There are also some methodological considerations that need to be considered. The comprehensive examinations limited the number of participants in our studies, hence some subgroups were small and results should be interpreted with caution. This was especially relevant when comparing overlapping symptom profiles for GAD according to DSM-5 and ICD-10-DCR. Mortality and psychiatric morbidity was higher in non-participants compared to participants, which may have led to an underestimation of results. Furthermore, due to the nature of our studies we did not include hierarchical exclusion criteria. This may have inflated prevalence rates; however, it was essential in order to conduct investigations on comorbid conditions. We also did not exclude substance abuse or medical conditions.

Some interesting issues were not adequately covered in my studies or should have been further explored. There are substantial cross-cultural differences in GAD across the globe, with higher rates of prevalence and associated disability in high-income countries compared to low-income countries [57]; however, lower rates of persistence are reported. The reason for this is not fully understood but several factors may be involved, i.e. awareness or mental health literacy, differences in treatment availability, genetic susceptibility or differences in environmental risk markers. Answering this question in full lies beyond the scope of my thesis; however, a study on prognosis and persistence of GAD in a Swedish population of older adults may have contributed important information to this topic, as no such study is

available. Furthermore, a follow-up study of older adults would also allow for analysis of persistence to the same classification system and also individual differences in functional disability.

Another finding not adequately covered was the hypothesis of two different types of anxiety [4,202]. In retrospect, further investigations on the factor analysis topic could have been conducted. We attempted a latent class analysis, however, due to very small numbers for selected items, results were underpowered and the analysis did not converge. Nevertheless, a further investigation using both exploratory and confirmatory factor analyses to visualize the two supposed factors in our sample would have been advantageous.

The field of anxiety and dementia also requires further exploration. Results in study III suggest that anxiety may lie on a causal pathway to dementia. Recent evidence from twin studies suggests that genetic factors may drive this association [160], possibly through a shared common biological pathway [203]. Several studies have attempted to establish an association with candidate genes such as brain derived neurotrophic factor (BDNF). However, in light of our findings, these associations may need to be examined at an earlier age than previously considered, as midlife and late-life anxiety may be differently associated with dementia. Furthermore, in addition to replication studies, further intervention studies, showing risk reduction in successfully treated patients with anxiety, are required to establish a causal relationship. Such studies should also be conducted at an early stage, as our results indicate that anxiety was present at least 25 years before dementia diagnosis.

5.1.1 FUTURE PERSPECTIVES

In this thesis, the recurrent topic has been the qualitative differences associated with anxiety and worry. Nonetheless, most studies use these constructs interchangeably, which may have attenuated or obscured important characteristics for each of the symptoms. Further exploration of the underpinnings is warranted. The genetic factors associated with anxiety and worry is largely unexplored, however, larger sample sizes, without compromising with the quality of data, are required to find these associations. This will require significant cooperation between research groups in consortiums such as the anxiety group in Psychiatric Genomics Consortium (PGC). Another recurrent topic in my work is autonomic arousal. Further exploration of autonomic dysfunction in GAD, dementia, old age and heart disease is needed to increase our understanding of the expression and consequences of anxiety.

6 ACKNOWLEDGEMENTS

I would like to acknowledge and extend my greatest appreciation to all that have contributed to this thesis. Including all participants and those who have contributed in data collection. Without the hard work and goodwill from you, I would not have been able to produce this work.

Ingmar Skoog, my main supervisor. I would like to thank you for the patience and sincere interest you have shown me and my research. You have been forthcoming and always ready to share your insights; may it be in your apartment, watching icehockey, or in your office. Your enthusiasm for research is inspiring.

Margda Waern, my co-supervisor. Structure, structure, structure! Always there with the red pen, yet never failing to encourage me. Thank you for interesting discussions and insightful comments. Thank you for being my sounding board when I needed it most.

Svante Östling, my co-supervisor. To the late Svante Östling, you will be dearly missed. You passed much to early; it came as a shock to me and, I am sure, to many others. Thank you for being there for me and helping me through these years.

Anna Zettergren, my co-supervisor. Thank you for your contributions to my work. Thank you for always keeping your door open, letting me speak and venting stupid, and not so stupid, ideas.

Robert Sigström, Jenna Najar, Lena Johansson, Björn Karlsson, Xinxin Guo, my other co-authors. Thank you for your important contributions and discussions.

Valter, Erik, Kristoffer, Nazib, Yadi. The process has been long, Erik and Kristoffer. However, the questions I had in the beginning were patiently explained time and again. I hope we can have more discussions in the future, but on more equal footing. Thank you, Valter, for all the help over the years. Thank you, Nazib, for your happy demeanor and all the help with MRI data, someday we will get there, and GO Liverpool! Yadi, we had very little time together but, all the same, I appreciated it.

Tina & Cecilia, administrative coordinators. Thank you for everything! Without you I would have been lost.

All my coworkers from Epinep and AgeCap. I will not mention you by name because you're just too many. Thank you all for making research fun. Thank you for all the discussions in the hallways and discussions over a drink. Thank you for all the lunches at OOTO, I bet that I'll never find such a place again, certainly not with the same company.

Finally, this thesis wouldn't have gotten ready in time if I hadn't had some help from my family. Thanks to my parents Jan-Erik and Susan. Thank you Bilgen, my loving wife, for supporting me, even though every extra hour I spent on the thesis was an hour less spare time for you. I will be sure to remember this…

I would also like to acknowledge our funding partners:

The Swedish Research Council (11267, 825-2007-7462, 825-2012-5041, RAM 2013-8717, 2015-02830, 2016-01590), Swedish Research Council for Health, Working Life and Wellfare (no 2001-2835, 2004-0145, 2006-0596, 2008-1111, 2010-0870, 2013-1202, 2013-2496, 2013-0475, AGECAP 2013-2300, Epilife 2006-1506, 2016-07097), Swedish Brain Power, Sahlgrenska University Hospital (ALF), The Alzheimer's Association Stephanie B. Overstreet Scholars (IIRG-00-2159), The Bank of Sweden Tercentenary Foundation, Sylvans stiftelse, Stiftelsen Söderström-Königska Sjukhemmet, Handlanden Hjalmar Svenssons Forskningsfond, Wilhelm och Martina Lundgrens Vetenskapsfond 2, Fredrik och Ingrid Thurings stiftelse, Gun och Bertil Stohnes stiftelse and Systrarna Greta Johansson och Brita Anderssons Minnesfond.

REFERENCES

1. Freud S, Strachey JE. The standard edition of the complete psychological works of Sigmund Freud. 1964.
2. Barlow DH. Disorders of emotion. *Psychological inquiry.* 1991;2(1):58-71.
3. Heller W, Nitschke JB, Etienne MA, Miller GA. Patterns of regional brain activity differentiate types of anxiety. *Journal of abnormal psychology.* 1997;106(3):376.
4. Schwarzer R. Worry and emotionality as separate components in test anxiety. 1980.
5. Deffenbacher JL. Cognitive and physiological components of test anxiety in real-life exams. *Cognitive Therapy and Research.* 1986;10(6):635-644.
6. Cassady JC, Johnson RE. Cognitive test anxiety and academic performance. *Contemporary educational psychology.* 2002;27(2):270-295.
7. Asberg M, Montgomery SA, Perris C, Schalling D, Sedvall G. A comprehensive psychopathological rating scale. *Acta Psychiatrica Scandinavica Suppl.* 1978(271):5-27.
8. Davey GC, Hampton J, Farrell J, Davidson S. Some characteristics of worrying: Evidence for worrying and anxiety as separate constructs. *Personality and Individual Differences.* 1992;13(2):133-147.
9. Olatunji BO, Broman-Fulks JJ, Bergman SM, Green BA, Zlomke KR. A taxometric investigation of the latent structure of worry: dimensionality and associations with depression, anxiety, and stress. *Behav Ther.* 2010;41(2):212-228.
10. Ruscio AM, Borkovec TD, Ruscio J. A taxometric investigation of the latent structure of worry. *J Abnorm Psychol.* 2001;110(3):413-422.
11. Jansen AS, Van Nguyen X, Karpitskiy V, Mettenleiter TC, Loewy AD. Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. *Science.* 1995;270(5236):644-646.
12. Andrews G, Hobbs MJ, Borkovec TD, et al. Generalized worry disorder: a review of DSM-IV generalized anxiety disorder and options for DSM-V. *Depress Anxiety.* 2010;27(2):134-147.
13. Borkovec TD, Lyonfields JD, Wiser SL, Deihl L. The role of worrisome thinking in the suppression of cardiovascular response to phobic imagery. *Behav Res Ther.* 1993;31(3):321-324.
14. Lang PJ. A bio-informational theory of emotional imagery. *Psychophysiology.* 1979;16(6):495-512.

15. Crocq M-A. The history of generalized anxiety disorder as a diagnostic category. *Dialogues in clinical neuroscience.* 2017;19(2):107.
16. Pachana NA, Byrne GJ, Siddle H, Koloski N, Harley E, Arnold E. Development and validation of the Geriatric Anxiety Inventory. *International psychogeriatrics.* 2007;19(1):103-114.
17. Therrien Z, Hunsley J. Assessment of anxiety in older adults: a systematic review of commonly used measures. *Aging & Mental Health.* 2012;16(1):1-16.
18. Lang PJ, McTeague LM. The anxiety disorder spectrum: Fear imagery, physiological reactivity, and differential diagnosis∗. *Anxiety, Stress, & Coping.* 2009;22(1):5-25.
19. Leal PC, Goes TC, da Silva LCF, Teixeira-Silva F. Trait vs. state anxiety in different threatening situations. *Trends in psychiatry and psychotherapy.* 2017;39(3):147-157.
20. van der Heiden C, Methorst G, Muris P, van der Molen HT. Generalized anxiety disorder: clinical presentation, diagnostic features, and guidelines for clinical practice. *J Clin Psychol.* 2011;67(1):58-73.
21. DSM-5. *Diagnostic and statistical manual of mental disorders.* 5th ed. Washington DC: American Psychiatric Association; 2013.
22. Craske MG, Rapee RM, Jackel L, Barlow DH. Qualitative dimensions of worry in DSM-III-R generalized anxiety disorder subjects and nonanxious controls. *Behaviour research and therapy.* 1989;27(4):397-402.
23. DSM-III. *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington DC: American Psychiatric Association; 1980.
24. Crocq M-A. A history of anxiety: from Hippocrates to DSM. *Dialogues in clinical neuroscience.* 2015;17(3):319.
25. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. *Journal of consulting and clinical psychology.* 2010;78(2):169.
26. Beard GM. A Practical Treatise on Nervous Exhaustion,(Neurasthenia;) Its Symptoms, Nature, Sequences, Treatment. *American Journal of Psychiatry.* 1880;36(4):521-a-526.
27. Rickels K, Rynn MA. What is generalized anxiety disorder? *J Clin Psychiatry.* 2001;62 Suppl 11:4-12; discussion 13-14.
28. Klein DF. Delineation of two drug-responsive anxiety syndromes. *Psychopharmacology.* 1964;5(6):397-408.
29. Anderson DJ, Noyes R, Crowe RR. A comparison of panic disorder and generalized anxiety disorder. *The American journal of psychiatry.* 1984.

30. ICD-11. *International statistical classification of diseases and related health problems.* 11th ed. Geneva: World Health Oranization; 2018.
31. Ruscio AM, Lane M, Roy-Byrne P, et al. Should excessive worry be required for a diagnosis of generalized anxiety disorder? Results from the US National Comorbidity Survey Replication. *Psychological Medicine.* 2005;35(12):1761-1772.
32. Sanderson WC, Barlow DH. A description of patients diagnosed with DSM-III—R generalized anxiety disorder. *Journal of Nervous and Mental Disease.* 1990.
33. Slade T, Andrews G. DSM-IV and ICD-10 generalized anxiety disorder: discrepant diagnoses and associated disability. *Social Psychiatry and Psychiatric Epidemiology.* 2001;36(1):45-51.
34. Wittchen HU, Kessler RC, Zhao S, Abelson J. Reliability and clinical validity of UM-CIDI DSM-III-R generalized anxiety disorder. *J Psychiatr Res.* 1995;29(2):95-110.
35. Wittchen H-U, Lachner G, Wunderlich U, Pfister H. Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Social psychiatry and psychiatric epidemiology.* 1998;33(11):568-578.
36. Bienvenu OJ, Nestadt G, Eaton WW. Characterizing generalized anxiety: temporal and symptomatic thresholds. *The Journal of nervous and mental disease.* 1998;186(1):51-56.
37. Ruscio AM, Borkovec T. Experience and appraisal of worry among high worriers with and without generalized anxiety disorder. *Behaviour research and therapy.* 2004;42(12):1469-1482.
38. Beesdo-Baum K, Winkel S, Pine DS, et al. The diagnostic threshold of generalized anxiety disorder in the community: A developmental perspective. *Journal of psychiatric research.* 2011;45(7):962-972.
39. Di Nardo PA, Moras K, Barlow DH, Rapee RM, Brown TA. Reliability of DSM-III-R anxiety disorder categories: using the Anxiety Disorders Interview Schedule—Revised (ADIS-R). *Archives of General Psychiatry.* 1993;50(4):251-256.
40. Marten PA, Brown TA, Barlow DH, Borkovec TD, Shear MK, Lydiard RB. Evaluation of the ratings comprising the associated symptom criterion of DSM-III—R generalized anxiety disorder. *Journal of Nervous and Mental Disease.* 1993.
41. Hoehn-Saric R, McLeod DR, Zimmerli WD. Somatic manifestations in women with generalized anxiety disorder: Psychophysiological responses to psychological stress. *Archives of General Psychiatry.* 1989;46(12):1113-1119.
42. Brown TA, Marten PA, Barlow DH. Discriminant validity of the symptoms constituting the DSM-III-R and DSM-IV associated symptom criterion of generalized anxiety disorder. *Journal of Anxiety Disorders.* 1995;9(4):317-328.

43. Gorwood P. Generalized anxiety disorder and major depressive disorder comorbidity: an example of genetic pleiotropy? *Eur Psychiatry.* 2004;19(1):27-33.
44. Hettema JM. The nosologic relationship between generalized anxiety disorder and major depression. *Depress Anxiety.* 2008;25(4):300-316.
45. Zbozinek TD, Rose RD, Wolitzky-Taylor KB, et al. Diagnostic overlap of generalized anxiety disorder and major depressive disorder in a primary care sample. *Depress Anxiety.* 2012;29(12):1065-1071.
46. Lawrence AE, Liverant GI, Rosellini AJ, Brown TA. Generalized anxiety disorder within the course of major depressive disorder: examining the utility of the DSM-IV hierarchy rule. *Depression and anxiety.* 2009;26(10):909-916.
47. Starcevic V, Portman ME, Beck AT. Generalized anxiety disorder: between neglect and an epidemic. *The Journal of nervous and mental disease.* 2012;200(8):664-667.
48. Krasucki C, Howard R, Mann A. The relationship between anxiety disorders and age. *International Journal of Geriatric Psychiatry.* 1998;13(2):79-99.
49. Angst J, Gamma A, Baldwin DS, Ajdacic-Gross V, Rossler W. The generalized anxiety spectrum: prevalence, onset, course and outcome. *European Archives of Psychiatry and Clinical Neuroscience.* 2009;259(1):37-45.
50. Carter RM, Wittchen HU, Pfister H, Kessler RC. One-year prevalence of subthreshold and threshold DSM-IV generalized anxiety disorder in a nationally representative sample. *Depression and Anxiety.* 2001;13(2):78-88.
51. Wittchen HU, Hoyer J. Generalized anxiety disorder: nature and course. *Journal of Clinical Psychiatry.* 2001;62 Suppl 11:15-19; discussion 20-11.
52. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Archives of General Psychiatry.* 2010;67(5):489-496.
53. Reynolds K, Pietrzak RH, El-Gabalawy R, Mackenzie CS, Sareen J. Prevalence of psychiatric disorders in US older adults: findings from a nationally representative survey. *World Psychiatry.* 2015;14(1):74-81.
54. Trollor JN, Anderson TM, Sachdev PS, Brodaty H, Andrews G. Prevalence of mental disorders in the elderly: the Australian National Mental Health and Well-Being Survey. *The American Journal of Geriatric Psychiatry.* 2007;15(6):455-466.
55. Beekman AT, Bremmer MA, Deeg DJ, et al. Anxiety disorders in later life: a report from the Longitudinal Aging Study Amsterdam. *International Journal of Geriatric Psychiatry.* 1998;13(10):717-726.

56. Costa E, Barreto SM, Uchoa E, Firmo JO, Lima-Costa MF, Prince M. Prevalence of International Classification of Diseases, 10th Revision common mental disorders in the elderly in a Brazilian community: The Bambui Health Ageing Study. *The American Journal of Geriatric Psychiatry* 2007;15(1):17-27.
57. Ruscio AM, Hallion LS, Lim CC, et al. Cross-sectional comparison of the epidemiology of DSM-5 generalized anxiety disorder across the globe. *JAMA psychiatry.* 2017;74(5):465-475.
58. Brugha TS, Bebbington PE, Jenkins R. A difference that matters: comparisons of structured and semi-structured psychiatric diagnostic interviews in the general population. *Psychological Medicine.* 1999;29(5):1013-1020.
59. Creighton AS, Davison TE, Kissane DW. The prevalence of anxiety among older adults in nursing homes and other residential aged care facilities: a systematic review. *International Journal of Geriatric Psychiatry.* 2016;31(6):555-566.
60. Khambaty M, Parikh RM. Cultural aspects of anxiety disorders in India. *Dialogues Clin Neurosci.* 2017;19(2):117-126.
61. Stein DJ, Scott KM, de Jonge P, Kessler RC. Epidemiology of anxiety disorders: from surveys to nosology and back. *Dialogues Clin Neurosci.* 2017;19(2):127-136.
62. Andrade LH, Alonso J, Mneimneh Z, et al. Barriers to mental health treatment: results from the WHO World Mental Health surveys. *Psychological medicine.* 2014;44(6):1303-1317.
63. Lijster JM, Dierckx B, Utens EM, et al. The Age of Onset of Anxiety Disorders. *Can J Psychiatry.* 2017;62(4):237-246.
64. Wolitzky-Taylor KB, Castriotta N, Lenze EJ, Stanley MA, Craske MG. Anxiety disorders in older adults: a comprehensive review. *Depression and Anxiety.* 2010;27(2):190-211.
65. Kessler RC, Andrade L, Bijl R, Offord D, Demler O, Stein D. The effects of co-morbidity on the onset and persistence of generalized anxiety disorder in the ICPE surveys. *Psychological Medicine.* 2002;32(7):1213-1225.
66. Le Roux H, Gatz M, Wetherell JL. Age at onset of generalized anxiety disorder in older adults. *American Journal of Geriatric Psych.* 2005;13(1):23-30.
67. Newman MG, Przeworski A, Fisher AJ, Borkovec TD. Diagnostic comorbidity in adults with generalized anxiety disorder: Impact of comorbidity on psychotherapy outcome and impact of psychotherapy on comorbid diagnoses. *Behavior Therapy.* 2010;41(1):59-72.
68. Rodriguez BF, Weisberg RB, Pagano ME, et al. Characteristics and predictors of full and partial recovery from generalized anxiety disorder in primary care patients. *The Journal of nervous and mental disease.* 2006;194(2):91.

69. Altamura AC, Dell'Osso B, D'Urso N, Russo M, Fumagalli S, Mundo E. Duration of untreated illness as a predictor of treatment response and clinical course in generalized anxiety disorder. *CNS spectrums.* 2008;13(5):415-422.
70. Parmentier H, Garcia-Campayo J, Prieto R. Comprehensive review of generalized anxiety disorder in primary care in Europe. *Curr Med Res Opin.* 2013;29(4):355-367.
71. Shimada-Sugimoto M, Otowa T, Hettema JM. Genetics of anxiety disorders: Genetic epidemiological and molecular studies in humans. *Psychiatry and clinical neurosciences.* 2015;69(7):388-401.
72. Mackintosh M-A, Gatz M, Wetherell JL, Pedersen NL. A twin study of lifetime generalized anxiety disorder (GAD) in older adults: genetic and environmental influences shared by neuroticism and GAD. *Twin research and human genetics.* 2006;9(1):30-37.
73. De Beurs E, Beekman A, Deeg D, Van Dyck R, Van Tilburg W. Predictors of change in anxiety symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. *Psychological Medicine.* 2000;30(3):515-527.
74. Gottschalk MG, Domschke K. Genetics of generalized anxiety disorder and related traits. *Dialogues in clinical neuroscience.* 2017;19(2):159.
75. Maron E, Nutt D. Biological markers of generalized anxiety disorder. *Dialogues Clin Neurosci.* 2017;19(2):147-158.
76. Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The structure of genetic and environmental risk factors for anxiety disorders in men and women. *Archives of general psychiatry.* 2005;62(2):182-189.
77. Borkovec T. The nature, functions, and origins of worry. 1994.
78. Wells A. A cognitive model of generalized anxiety disorder. *Behavior modification.* 1999;23(4):526-555.
79. Roemer L, Orsillo SM. Expanding our conceptualization of and treatment for generalized anxiety disorder: Integrating mindfulness/acceptance-based approaches with existing cognitive-behavioral models. *Clinical Psychology: Science and Practice.* 2002;9(1):54-68.
80. Dugas MJ, Gagnon F, Ladouceur R, Freeston MH. Generalized anxiety disorder: A preliminary test of a conceptual model. *Behaviour research and therapy.* 1998;36(2):215-226.
81. Fisher PL, Wells A. Conceptual models of generalized anxiety disorder. *Psychiatric Annals.* 2011;41(2):127-132.
82. Borkovec T, Inz J. The nature of worry in generalized anxiety disorder: A predominance of thought activity. *Behaviour research and therapy.* 1990;28(2):153-158.
83. Portman ME. *Generalized anxiety disorder across the lifespan: An integrative approach.* Springer Science & Business Media; 2009.

84. Ladouceur R, Dugas MJ, Freeston MH, et al. Specificity of generalized anxiety disorder symptoms and processes. *Behavior Therapy.* 1999;30(2):191-207.
85. Behar E, DiMarco ID, Hekler EB, Mohlman J, Staples AM. Current theoretical models of generalized anxiety disorder (GAD): conceptual review and treatment implications. *J Anxiety Disord.* 2009;23(8):1011-1023.
86. Mennin DS, Heimberg RG, Turk CL, Fresco DM. Applying an emotion regulation framework to integrative approaches to generalized anxiety disorder. *Clinical Psychology: Science and Practice.* 2002;9(1):85-90.
87. Turk CL, Heimberg RG, Luterek JA, Mennin DS, Fresco DM. Emotion dysregulation in generalized anxiety disorder: A comparison with social anxiety disorder. *Cognitive Therapy and Research.* 2005;29(1):89-106.
88. Mennin DS, Holaway RM, Fresco DM, Moore MT, Heimberg RG. Delineating components of emotion and its dysregulation in anxiety and mood psychopathology. *Behavior therapy.* 2007;38(3):284-302.
89. Ballenger JC, Davidson JR, Lecrubier Y, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. *The Journal of clinical psychiatry.* 2001.
90. Scott KM, Lim C, Al-Hamzawi A, et al. Association of mental disorders with subsequent chronic physical conditions: world mental health surveys from 17 countries. *JAMA psychiatry.* 2016;73(2):150-158.
91. Roy-Byrne PP, Davidson KW, Kessler RC, et al. Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry.* 2008;30(3):208-225.
92. Gum AM, King-Kallimanis B, Kohn R. Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication. *The American Journal of Geriatric Psychiatry.* 2009;17(9):769-781.
93. Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. *Frontiers in neuroendocrinology.* 2014;35(3):320-330.
94. Kessler RC. Epidemiology of women and depression. *Journal of affective disorders.* 2003;74(1):5-13.
95. Gater R, Tansella M, Korten A, Tiemens BG, Mavreas VG, Olatawura MO. Sex differences in the prevalence and detection of depressive and anxiety disorders in general health care settings: report from the World Health Organization Collaborative Study on Psychological Problems in General Health Care. *Archives of general psychiatry.* 1998;55(5):405-413.

96. Altemus M. Sex differences in depression and anxiety disorders: potential biological determinants. *Hormones and behavior.* 2006;50(4):534-538.
97. Vesga-Lopez O, Schneier FR, Wang S, et al. Gender differences in generalized anxiety disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry.* 2008;69(10):1606-1616.
98. Moscovitch DA, Hofmann SG, Litz BT. The impact of self-construals on social anxiety: A gender-specific interaction. *Personality and Individual Differences.* 2005;38(3):659-672.
99. McLean CP, Anderson ER. Brave men and timid women? A review of the gender differences in fear and anxiety. *Clinical psychology review.* 2009;29(6):496-505.
100. Lieb R, Becker E, Altamura C. The epidemiology of generalized anxiety disorder in Europe. *European Neuropsychopharmacology.* 2005;15(4):445-452.
101. Goncalves DC, Pachana NA, Byrne GJ. Prevalence and correlates of generalized anxiety disorder among older adults in the Australian National Survey of Mental Health and Well-Being. *J Affect Disord.* 2011;132(1-2):223-230.
102. Hoffman DL, Dukes EM, Wittchen HU. Human and economic burden of generalized anxiety disorder. *Depression and anxiety.* 2008;25(1):72-90.
103. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. *Journal of affective disorders.* 2002;68(2-3):183-190.
104. Porensky EK, Dew MA, Karp JF, et al. The burden of late-life generalized anxiety disorder: effects on disability, health-related quality of life, and healthcare utilization. *The American Journal of Geriatric Psychiatry* 2009;17(6):473-482.
105. Paulus DJ, Wadsworth LP, Hayes-Skelton SA. Mental health literacy for anxiety disorders: how perceptions of symptom severity might relate to recognition of psychological distress. *Journal of public mental health.* 2015;14(2):94-106.
106. Thompson A, Issakidis C, Hunt C. Delay to seek treatment for anxiety and mood disorders in an Australian clinical sample. *Behaviour Change.* 2008;25(2):71-84.
107. Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bull World Health Organ.* 2004;82(11):858-866.
108. Wittchen H-U, Kessler RC, Beesdo K, Krause P, Höfler M, Hoyer J. Generalized anxiety and depression in primary care: prevalence, recognition, and management. *The Journal of clinical psychiatry.* 2002.
109. Health NIf, Excellence C. Generalised anxiety disorder and panic disorder in adults: management. NICE London; 2011.

110. Gould RL, Coulson MC, Howard RJ. Efficacy of cognitive behavioral therapy for anxiety disorders in older people: A meta-analysis and meta-regression of randomized controlled trials. *Journal of the American Geriatrics Society.* 2012;60(2):218-229.
111. Stavestrand SH, Sirevåg K, Nordhus IH, et al. Physical exercise augmented cognitive behaviour therapy for older adults with generalised anxiety disorder (PEXACOG): study protocol for a randomized controlled trial. *Trials.* 2019;20(1):174.
112. Kishita N, Laidlaw K. Cognitive behaviour therapy for generalized anxiety disorder: Is CBT equally efficacious in adults of working age and older adults? *Clinical psychology review.* 2017;52:124-136.
113. Wetherell JL, Petkus AJ, White KS, et al. Antidepressant medication augmented with cognitive-behavioral therapy for generalized anxiety disorder in older adults. *American Journal of Psychiatry.* 2013;170(7):782-789.
114. Blay SL, Marinho V. Anxiety disorders in old age. *Curr Opin Psychiatry.* 2012;25(6):462-467.
115. Tuohy A, Knussen C, Wrennall MJ. Effects of age on symptoms of anxiety and depression in a sample of retired police officers. *Psychology and Aging.* 2005;20(2):202-210.
116. Ramsawh H, Raffa S, Edelen MO, Rende R, Keller M. Anxiety in middle adulthood: effects of age and time on the 14-year course of panic disorder, social phobia and generalized anxiety disorder. *Psychological medicine.* 2009;39(4):615-624.
117. Basevitz P, Pushkar D, Chaikelson J, Conway M, Dalton C. Age-related differences in worry and related processes. *International Journal of Aging & Human Development.* 2008;66(4):283-305.
118. Gould CE, Edelstein BA. Worry, emotion control, and anxiety control in older and young adults. *Journal of Anxiety Disorders.* 2010;24(7):759-766.
119. Samuels ER, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. *Current Neuropharmacology.* 2008;6(3):254-285.
120. Jeste DV, Blazer DG, First M. Aging-related diagnostic variations: need for diagnostic criteria appropriate for elderly psychiatric patients. *Biological Psychiatry.* 2005;58(4):265-271.
121. Bryant C, Mohlman J, Gum A, et al. Anxiety disorders in older adults: looking to DSM5 and beyond. *Am J Geriatr Psychiatry.* 2013;21(9):872-876.
122. Miloyan B, Byrne GJ, Pachana NA. Threshold and subthreshold generalized anxiety disorder in later life. *The American Journal of Geriatric Psychiatry* 2015;23(6):633-641.

123. Mackenzie CS, Reynolds K, Chou KL, Pagura J, Sareen J. Prevalence and correlates of generalized anxiety disorder in a national sample of older adults. *Am J Geriatr Psychiatry*. 2011;19(4):305-315.
124. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease:The Heart and Soul Study. *Arch Gen Psychiatry*. 2010;67(7):750-758.
125. Brenes GA, Kritchevsky SB, Mehta KM, et al. Scared to death: results from the Health, Aging, and Body Composition study. *The American journal of geriatric psychiatry*. 2007;15(3):262-265.
126. Flint AJ. Anxiety and its disorders in late life: moving the field forward. *Am J Geriatr Psychiatry*. 2005;13(1):3-6.
127. Miloyan B, Byrne GJ, Pachana NA. Age-related changes in generalized anxiety disorder symptoms. *International Psychogeriatrics*. 2014;26(4):565-572.
128. Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: methodological issues and a review of the literature. *J Affect Disord*. 2008;109(3):233-250.
129. Lawton MP, Kleban MH, Rajagopal D, Dean J. Dimensions of affective experience in three age groups. *Psychology and Aging*. 1992;7(2):171-184.
130. Shallcross AJ, Ford BQ, Floerke VA, Mauss IB. Getting better with age: The relationship between age, acceptance, and negative affect. *Journal of Personality and Social Psychology*. 2013;104(4):734-749.
131. Isaacowitz DM, Livingstone KM, Castro VL. Aging and emotions: experience, regulation, and perception. *Current opinion in psychology*. 2017;17:79-83.
132. Mather M, Canli T, English T, et al. Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science*. 2004;15(4):259-263.
133. Williams LM, Brown KJ, Palmer D, et al. The mellow years?: neural basis of improving emotional stability over age. *The Journal of Neuroscience*. 2006;26(24):6422-6430.
134. Gunning-Dixon FM, Gur RC, Perkins AC, et al. Aged-related differences in brain activation during emotional face processing. *Neurobiology of Aging; Neurobiology of Aging*. 2003.
135. Sheikh JI, Swales PJ, Carlson EB, Lindley SE. Aging and panic disorder: phenomenology, comorbidity, and risk factors. *The American Journal of Geriatric Psychiatry* 2004;12(1):102-109.
136. Neiss MB, Leigland LA, Carlson NE, Janowsky JS. Age differences in perception and awareness of emotion. *Neurobiology of Aging*. 2009;30(8):1305-1313.

137. Flint AJ, Koszycki D, Vaccarino FJ, Cadieux A, Boulenger JP, Bradwejn J. Effect of aging on cholecystokinin-induced panic. *American Journal of Psychiatry.* 1998;155(2):283-285.
138. Clark DM. A cognitive approach to panic. *Behaviour Research and Therapy.* 1986;24(4):461-470.
139. Gulpers B, Ramakers I, Hamel R, Kohler S, Oude Voshaar R, Verhey F. Anxiety as a Predictor for Cognitive Decline and Dementia: A Systematic Review and Meta-Analysis. *Am J Geriatr Psychiatry.* 2016;24(10):823-842.
140. Allgulander C. Anxiety as a risk factor in cardiovascular disease. *Curr Opin Psychiatry.* 2016;29(1):13-17.
141. Batelaan NM, Seldenrijk A, Bot M, Van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. *The British journal of psychiatry.* 2016;208(3):223-231.
142. Mykletun A, Bjerkeset O, Dewey M, Prince M, Overland S, Stewart R. Anxiety, depression, and cause-specific mortality: the HUNT study. *Psychosom Med.* 2007;69(4):323-331.
143. Colman I, Kingsbury M, Sucha E, Horton NJ, Murphy JM, Gilman SE. Depressive and anxious symptoms and 20-year mortality: Evidence from the Stirling County study. *Depress Anxiety.* 2018;35(7):638-647.
144. Celano CM, Millstein RA, Bedoya CA, Healy BC, Roest AM, Huffman JC. Association between anxiety and mortality in patients with coronary artery disease: A meta-analysis. *Am Heart J.* 2015;170(6):1105-1115.
145. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. *J Am Coll Cardiol.* 2010;56(1):38-46.
146. Batelaan NM, ten Have M, van Balkom AJ, Tuithof M, de Graaf R. Anxiety disorders and onset of cardiovascular disease: the differential impact of panic, phobias and worry. *J Anxiety Disord.* 2014;28(2):252-258.
147. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and Cardiovascular Disease Risk: a Review. *Curr Cardiol Rep.* 2016;18(12):120.
148. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. *American journal of epidemiology.* 1992;135(8):854-864.
149. Welsh J, Korda RJ, Joshy G, Butterworth P, Brown A, Banks E. Psychological distress and ischaemic heart disease: cause or consequence? Evidence from a large prospective cohort study. *J Epidemiol Community Health.* 2017;71(11):1084-1089.

150. Chalmers JA, Quintana DS, Abbott MJ, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Frontiers in psychiatry.* 2014;5:80.
151. Gallagher D, Coen R, Kilroy D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. *Int J Geriatr Psychiatry.* 2011;26(2):166-172.
152. Spalletta G, Musicco M, Padovani A, et al. Neuropsychiatric symptoms and syndromes in a large cohort of newly diagnosed, untreated patients with Alzheimer disease. *Am J Geriatr Psychiatry.* 2010;18(11):1026-1035.
153. Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Dement.* 2011;7(5):532-539.
154. Acosta I, Borges G, Aguirre-Hernandez R, Sosa AL, Prince M. Neuropsychiatric symptoms as risk factors of dementia in a Mexican population: A 10/66 Dementia Research Group study. *Alzheimers Dement.* 2018;14(3):271-279.
155. Santabarbara J, Lopez-Anton R, de la Camara C, et al. Clinically significant anxiety as a risk factor for dementia in the elderly community. *Acta Psychiatr Scand.* 2018.
156. de Bruijn RF, Direk N, Mirza SS, et al. Anxiety is not associated with the risk of dementia or cognitive decline: the Rotterdam Study. *Am J Geriatr Psychiatry.* 2014;22(12):1382-1390.
157. Potvin O, Bergua V, Meillon C, et al. State Anxiety and Cognitive Functioning in Older Adults. *American Journal of Geriatric Psych.* 2012.
158. Palmer K, Berger AK, Monastero R, Winblad B, Backman L, Fratiglioni L. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology.* 2007;68(19):1596-1602.
159. Gimson A, Schlosser M, Huntley JD, Marchant NL. Support for midlife anxiety diagnosis as an independent risk factor for dementia: a systematic review. *BMJ Open.* 2018;8(4):e019399.
160. Petkus AJ, Reynolds CA, Wetherell JL, Kremen WS, Pedersen NL, Gatz M. Anxiety is associated with increased risk of dementia in older Swedish twins. *Alzheimers Dement.* 2016;12(4):399-406.
161. Gallacher J, Bayer A, Fish M, et al. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. *Psychosom Med.* 2009;71(6):659-666.
162. Becker E, Orellana Rios CL, Lahmann C, Rucker G, Bauer J, Boeker M. Anxiety as a risk factor of Alzheimer's disease and vascular dementia. *Br J Psychiatry.* 2018;213(5):654-660.
163. Mortamais M, Abdennour M, Bergua V, et al. Anxiety and 10-Year Risk of Incident Dementia-An Association Shaped by Depressive

Symptoms: Results of the Prospective Three-City Study. *Front Neurosci.* 2018;12:248.
164. Sinoff G, Werner P. Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. *Int J Geriatr Psychiatry.* 2003;18(10):951-959.
165. Bunce D, Batterham PJ, Mackinnon AJ, Christensen H. Depression, anxiety and cognition in community-dwelling adults aged 70 years and over. *J Psychiatr Res.* 2012;46(12):1662-1666.
166. Wilson RS, Begeny CT, Boyle PA, Schneider JA, Bennett DA. Vulnerability to stress, anxiety, and development of dementia in old age. *Am J Geriatr Psychiatry.* 2011;19(4):327-334.
167. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. *Neurology.* 2015;85(10):898-904.
168. Jack CR, Jr., Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol.* 2010;9(1):119-128.
169. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med.* 2012;367(9):795-804.
170. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocr Rev.* 1986;7(3):284-301.
171. Prenderville JA, Kennedy PJ, Dinan TG, Cryan JF. Adding fuel to the fire: the impact of stress on the ageing brain. *Trends Neurosci.* 2015;38(1):13-25.
172. Mah L, Szabuniewicz C, Fiocco AJ. Can anxiety damage the brain? *Curr Opin Psychiatry.* 2016;29(1):56-63.
173. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *The Lancet Neurology.* 2012;11(11):1006-1012.
174. Sterner TR, Ahlner F, Blennow K, et al. The Gothenburg H70 Birth cohort study 2014–16: design, methods and study population. *European journal of epidemiology.* 2019;34(2):191-209.
175. Skoog I. Psychiatric epidemiology of old age: the H70 study–the NAPE lecture 2003. *Acta Psychiatrica Scandinavica.* 2004;109(1):4-18.
176. Bengtsson C, Blohme G, Hallberg L, et al. The study of women in Gothenburg 1968-1969--a population study. General design, purpose and sampling results. *Acta Med Scand.* 1973;193(4):311-318.
177. Bengtsson C, Hallberg L, Hallstrom T, et al. The population study of women in Goteborg 1974--1975--the second phase of a longitudinal study. General design, purpose and sampling results. *Scand J Soc Med.* 1978;6(2):49-54.
178. Lissner L, Skoog I, Andersson K, et al. Participation bias in longitudinal studies: experience from the Population Study of

Women in Gothenburg, Sweden. *Scand J Prim Health Care.* 2003;21(4):242-247.
179. Skoog I, Borjesson-Hanson A, Kern S, et al. Decreasing prevalence of dementia in 85-year olds examined 22 years apart: the influence of education and stroke. *Scientific Reports.* 2017;7(1):6136.
180. van der Laan NC, Schimmel A, Heeren TJ. The applicability and the inter-rater reliability of the Comprehensive Psychopathological Rating Scale in an elderly clinical population. *International journal of geriatric psychiatry.* 2005;20(1):35-40.
181. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry.* 1998;59 Suppl 20:22-33;quiz 34-57.
182. DSM-IV. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington DC: American Psychiatric Association; 1994.
183. Skoog I, Nilsson L, Palmertz B, Andreasson LA, Svanborg A. A population-based study of dementia in 85-year-olds. *The New England Journal of Medicine.* 1993;328(3):153-158.
184. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry.* 1984;141(11):1356-1364.
185. Eysenck HJ, Sybil B. An improved short questionnaire for the measurement of extraversion and neuroticism. *Life sciences.* 1964.
186. ICD-10-DCR. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic criteria for research.* Geneva: World Health Organization; 1993.
187. DSM-III-R. *Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington DC: American Psychiatric Association; 1987.
188. Guo X, Waern M, Sjogren K, et al. Midlife respiratory function and Incidence of Alzheimer's disease: a 29-year longitudinal study in women. *Neurobiol Aging.* 2007;28(3):343-350.
189. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies: report of the NINDS-AIREN International Workshop. *Neurology.* 1993;43(2):250-250.
190. Karlsson B, Klenfeldt IF, Sigstrom R, et al. Prevalence of social phobia in non-demented elderly from a swedish population study. *Am J Geriatr Psychiatry.* 2009;17(2):127-135.
191. Klenfeldt IF, Karlsson B, Sigström R, et al. Prevalence of obsessive-compulsive disorder in relation to depression and cognition in an elderly population. *The American Journal of Geriatric Psychiatry.* 2014;22(3):301-308.
192. Sigström R, Östling S, Karlsson B, Waern M, Gustafson D, Skoog I. A population-based study on phobic fears and DSM-IV specific phobia in 70-year olds. *Journal of anxiety disorders.* 2011;25(1):148-153.

193. DSM-IV-TR. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington DC: American Psychiatric Association; 2000.
194. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121-130.
195. Ritchie K, Artero S, Beluche I, et al. Prevalence of DSM-IV psychiatric disorder in the French elderly population. *Br J Psychiatry*. 2004;184:147-152.
196. Schoevers RA, Deeg DJ, van Tilburg W, Beekman AT. Depression and generalized anxiety disorder: co-occurrence and longitudinal patterns in elderly patients. *Am J Geriatr Psychiatry*. 2005;13(1):31-39.
197. Starcevic V, Bogojevic G. The concept of generalized anxiety disorder: between the too narrow and too wide diagnostic criteria. *Psychopathology*. 1999;32(1):5-11.
198. Flint AJ. Generalised anxiety disorder in elderly patients : epidemiology, diagnosis and treatment options. *Drugs Aging*. 2005;22(2):101-114.
199. Nilsson J, Sigstrom R, Ostling S, Waern M, Skoog I. Changes in the expression of worries, anxiety and Generalized anxiety disorder with increasing age: A population study of 70-85 year-olds. *Int J Geriatr Psychiatry*. 2018.
200. Andrews G, Slade T, Peters L, Beard J. Generalized anxiety disorder, obsessive-compulsive disorder and social phobia: sources of dissonance between ICD-10 and DSM-IV. *International Journal of Methods in Psychiatric Research*. 1998;7:110-115.
201. Barlow DH. Unraveling the mysteries of anxiety and its disorders from the perspective of emotion theory. *American psychologist*. 2000;55(11):1247.
202. Murphy JM, Leighton AH. Anxiety: its role in the history of psychiatric epidemiology. *Psychological Medicine*. 2009;39(7):1055-1064.
203. Raber J. Role of apolipoprotein E in anxiety. *Neural Plast*. 2007;2007:91236.