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Mean Age and Gender Distribution of Patients with Mental Disorders in Randomized Controlled Studies

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Hiermit erkläre ich, die Dissertation mit dem Titel "Mean Age and Gender Distribution of Patients with Mental Disorders in Randomized Controlled Studies" eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

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Content

1. Introduction

Mental disorders are common and cause a high degree of disability and costs (Gustavsson et al. 2011; Wittchen 2004; Wittchen and Jacobi 2005; Wittchen et al. 2011). The treatment of mental disorders is a crucial public health problem. Mental disorders are among the most burdensome of all types of disease and represent some of the most impairing chronic diseases (Kessler et al. 2001b). For example, the World Health Organization (WHO) has ranked depression the fourth leading cause of disability worldwide (Murray and Lopez 1996) and the Global Burden of Disease (GBD) study found that major depressive disorder was the second leading cause of disability in 2010 (Vos et al. 2012). Thus, psychiatric epidemiologic research is increasingly clinically relevant.

1.1 Common mental disorders

Table 1 briefly summarizes the most common psychiatric disorders according to ICD-10 (International Classification of Diseases) and their treatment approach.

Table 1. Brief description and code of the most common psychiatric disorders according to ICD-10 and their treatment approach

Brief Description and Code of Psychiatric Disorders According to ICD-10	Treatment Approach
Alzheimer's Disease (F00)	
Dementia in Alzheimer's disease is a neurodegenerative disease with a decline of mental functioning. Impairments of cognitive function such as loss of memory and changes in language and behaviour occur. Subtypes are classified due to the age-of-onset.	Anti-dementia medication
Vascular Dementia (F01)	
Vascular dementia is caused by multiple infarcts of the brain due to cerebrovascular disease. The infarcts cumulate in effects over time and result in a decline of mental functioning.	Anti-dementia medication

Brief Description and Code of Psychiatric Disorders According to ICD-10	Treatment Approach
Alcohol Dependence Syndrome (F10.2)	
Alcohol dependence syndrome includes a persistent desire of alcohol use, difficulties in controlling consumption behaviour, continued use despite the knowledge of harmful consequences, increased tolerance, withdrawal symptoms, and reduced pursuits to other activities and obligations than alcohol use.	Relapse prevention, support groups, psychotherapy, different medications (e.g. naltrexone, nalmefene, acamprosate)
Schizophrenia (F20)	
The patient is suffering from a fundamental distortion of thinking, perception, and inappropriate affects. Positive symptoms such as a distorted self-experience, delusions, hallucinations, and thought disorders are typical features. Negative symptoms such as anhedonia, blunted affects, reduced speaking, and social isolation occur. Different subtypes can be classified.	Antipsychotics and other drugs
Schizoaffective Disorder (F25)	
Episodic disorder in which both affective and schizophrenic symptoms occur but which do not strictly meet diagnostic criteria for either schizophrenia or depressive/ manic episodes. Different subtypes can be classified.	Antipsychotics, mood stabilizers, antidepressants
Manic Episode (F30)	
Mood and energy level is highly elevated, resulting in overactive behaviour, pressured speech, and a decreased need for sleep. The patient gets distracted easily and cannot sustain attention. Grandiose ideas, overconfidence, tought disturbances, and loss of social inhibitions occur. Psychotic symptoms such as delusions and hallucinations may or may not occur.	Mood stabilizers, antipsychotics
Bipolar Affective Disorder (F31)	
A major affective disorder characterized by manic and depressive episodes, repeatedly appearing in remission and recurrence, and followed by symptom-free intervals.	Mood stabilizers, antipsychotics, antidepressants
Major Depressive Disorder (F32-33)	
In a depressive episode, the patient suffers from low mood, decreased energy, and reduction of activity. Enjoyment, interest, and concentration is reduced. Fatigue and sleep disturbances are common. A lowered self-esteem or self-confidence, ideas of guilt or worthlessness, and suicidal ideation can be present. Somatic symptoms such as loss of interest, anhedonia, waking early in the morning, psychomotor retardation or agitation, loss of appetite, weight and libido can occur. Severe episodes may be accompanied by psychotic symptoms.	Antidepressants, other drugs, psychotherapy

Brief Description and Code of Psychiatric Disorders According to ICD-10	Treatment Approach
Dysthymia (F34.1)	
A chronic form of depression, lasting at least two years, which is not sufficiently severe or prolonged to meet diagnosic criteria of a depressive disorder.	Antidepressants, other drugs, psychotherapy
Panic Disorder with Agoraphobia (F40.0) or without Agoraphobia (F41.0)	
Recurrent attacks of anxiety that are not related to any circumstances and therefore seem unpredictable. Somatic symptoms such as palpitations, chest pain, dizziness, and feelings of unreality, "derealization" and "depersonalization", arise. Often patients are afraid of dying, losing control, or going mad. Agoraphobia is characterized by avoiding phobic situations, e.g. leaving home and entering public places. Anxiety arises during confrontation and little or no symptoms are being experienced through avoidance.	Cognitive behavioural therapy, antidepressants and other medications
Social Phobia (F40.1)	
An anxiety disorder characterized by an intense fear of social interaction in which the individual believes to be scrutinized by others.	Cognitive behavioural therapy, antidepressants and other medications
Generalized Anxiety Disorder (F41.1)	
An anxiety disorder characterized by persistent free-floating fear and excessive worry, lasting at least six months, accompanied by somatic symptoms of anxiety and physiologic arousal.	Cognitive behavioural therapy, antidepressants and other medications
Obsessive-Compulsive Disorder (F42)	
Recurrent obsessional, stereotypical, and distressing thoughts or compulsive acts which do not lead to the completion of a useful task. The patient aims to prevent some unlikely incidence which he fears might otherwise occur. The most common compulsions include cleaning, repeating, and checking. The most common obsessions include contaminants and fear of harm to the self or to another. Repeated attempts to resist fail due to distressing anxiety. Thoughts are recognized as the patient's own thoughts.	Cognitive behavioural therapy, antidepressants and other medications
Posttraumatic Stress Disorder (F43.1)	
A protracted response to exposure of a trauma, being defined as an situation of exceptionally threatening or catastrophic nature, that would cause distress in almost anyone. Typical symptoms include intrusive memories ("flashbacks"), nightmares, emotional numbness and blunting, detachment from the social environment, hyperarousal, insomnia, unresponsiveness to the surrounding, anhedonia, and avoidance of triggering situations. The onset of the syndrome occurs a few weeks or months after the traumatic event.	Cognitive behavioural therapy, antidepressants and other medications

Brief Description and Code of Psychiatric Disorders According to ICD-10	Treatment Approach
Somatoform Disorders (F45)	
Repeated preoccupation with physical symptoms and requests for medical investigations in spite of negative findings and reassurances by physicians that the symptoms are not related to any physical disorder. If a somatic disease is present, it does not explain the extent of the symptoms.	Psychotherapy, antidepressants
Anorexia Nervosa (F50.0)	
An eating disorder mostly occurring in young women, characterized by self-induced underweight, self-perception as overweight, and fear of gaining weight. Patients induce loss of weight by restricted diet, excessive training, vomiting and purgation, and use of medication, e.g. diuretics. Undernutrition is leading to endocrine and metabolic complications.	Psychotherapy, medications
Bulimia Nervosa (F50.2)	
An eating disorder characterized by a recurrent episodes of compulsive overeating followed by purging. Similar to anorexia nervosa, a constant worry about controlling the body weight occurs. Patients tend to be of average weight. Repeated vomiting is leading to physical complications, e.g. electrolyte derangements.	Psychotherapy, medications
Binge Eating Disorder (F50.81)	
Recurrent episodes of rapidly eating large amounts of food even without being physically hungry. A lack of control during the episodes and a feeling of guilt afterwards is common.	Cognitive behavioural therapy, anti-obesity medication, bariatric surgery
Nonorganic Insomnia (F51.0)	
A sleep disturbance including difficulty falling asleep, difficulty staying asleep, or early final wakening. Nonorganic insomnia is not related to any mental and physical disorder.	Sedatives
Emotionally Unstable (Borderline) Personality Disorder (F60.3)	
Personality disorder characterized by difficulties in regulating emotions. The impulsive type is characterized by emotional instability and lack of impulse control. The borderline type is characterized by a distorted self-image, a feeling of emptiness, intense and unstable relationships, and a tendency to self-harming behaviour. The patient can hardly consider consequences of emotional or behavioural outbreaks.	Dialectical behavioural therapy

1.2 Previous epidemiological research

Some informative research has been published over the last decades focusing on psychiatric epidemiology. Epidemiological surveys have been conducted worldwide, estimating prevalence, lifetime risk, and gender distribution of national representative population segments.

For example, the mental health module in the German Health Interview and Examination Survey (DEGS1-MH) has been carried out in Germany, assessing a nationally representative sample aged 18–79 years of more than 5000 respondents in order to estimate prevalence and risk factors of mental disorders, and more than 4000 respondents to estimate morbidity, comorbidity, treatment/health care, impairment/disability, quality of life, cognitive impairment, mental health, and functioning of persons (Jacobi et al. 2014a).

The WHO's World Mental Health (WMH) household surveys are being carried out in regions and countries all over the world. A remarkable sample size of more than 85,000 respondents have been investigated to estimate 12-month and lifetime prevalence, projected lifetime risk, severity, gender, and age-of-onset distributions of mental disorders (Kessler et al. 2007b).

For a complete clinical benefit of psychiatric epidemiology, community and clinical epidemiology need to be further integrated. The WMH surveys only started the process of integration by measuring severity of mental disorders.

1.2.1 WMH household surveys

In the following, it is referred to the WMH household surveys to exemplify content and methods of epidemiological household studies. A brief overview of the WMH survey methods is provided. Table 2 gives an overview of the sample characteristics of the WMH surveys.

Table 2. Sample characteristics of the WMH Surveys, adapted and reprinted with permission (The World Mental Health Survey Initiative 2005)

Country	Survey[1]	Field Dates	Response Rate[2]	Age Range	Sample Size
Argentina	AMHES	2015	77.3 %		3927
Australia	SMHWB	2007	60.0 %		8841
Belgium	ESEMeD	2001–2002	50.6 %	18+	2419
Brazil	Sao Paulo Megacity	2005–2008	81.3 %		5037
Bulgaria	NSHS	2002–2006	72.0 %		5318
Colombia	NSMH	2003	87.7 %	18-65	4426
Colombia – Medellín	MMHHS	2011–2012	97.2 %		3261
France	ESEMeD	2001–2002	45.9 %	18+	2894
Germany	ESEMeD	2002–2003	57.8 %	18+	3555
Iraq	IMHS	2006–2007	95.2 %		4332
Israel	NHS	2003–2004	72.6 %	21+	4859
Italy	ESEMeD	2001–2002	71.3 %	18+	4712
Japan	WMHJ - Region 1	2002–2003	56.4 %	20+	1663
	WMHJ - Region 2	2003–2004	55.1 %		1323
	WMHJ - Regions 3- 5	2004–2006	42.6 %		1143
Lebanon	LEBANON	2002–2003	70.0 %	18+	2857
Mexico	M-NCS	2001–2002	76.6 %		5782
Netherlands	ESEMeD	2002–2003	56.4 %	18+	2372
New Zealand	NZMHS	2004–2005	73.3 %	16+	12992
Nigeria	NSMHW	2002–2004	79.3 %	18+	6752
Northern Ireland	NIMHS	2005–2008	68.4 %		4340
Peru	EMSMP	2004–2005	90.2 %		3930
Poland	EZOP	2010–2011	50.4 %		10081
Portugal	NMHS	2008–2009	57.3 %		3849
PRC[3] Beijing	B-WMH	2001–2003	74.8 %	18+	2633
PRC[3] Shanghai	S-WMH	2001–2003	74.6 %	18+	2568
PRC[3] Shenzhen	Shenzhen-WMH	2005–2007	80.0 %	18+	7134
Romania	RMHS	2005–2006	70.9 %		2357
South Africa	SASH	2002–2004	87.1 %	18+	4315
Spain	ESEMeD	2001–2002	78.6 %	18+	5473
Spain - Murcia	PEGASUS-Murcia	2010–2012	67.4 %		2621

Country	Survey[1]	Field Dates	Response Rate[2]	Age Range	Sample Size
Ukraine	CMDPSD	2002	78.3 %	18+	4725
United States	NCS-R	2001–2003	70.9 %	18+	9282

1 AMHES (Argentina Mental Health Epidemiologic Survey); SMHWB (National Survey of Mental Health and Wellbeing); ESEMeD (European Study Of The Epidemiology Of Mental Disorders); NSHS (Bulgaria National Survey of Health and Stress); NSMH (Colombian National Study of Mental Health); MMHHS (Medellín Mental Health Household Study); IMHS (Iraq Mental Health Survey); NHS (Israel National Health Survey); WMHJ (World Mental Health Japan Survey); LEBANON (Lebanese Evaluation of the Burden of Ailments and Needs Of the Nation); M-NCS (Mexico National Comorbidity Survey); NZMHS (New Zealand Mental Health Survey); NSMHW (Nigerian Survey of Mental Health and Wellbeing); NIMHS (Northern Ireland Mental Health Survey); EMSMP (La Encuesta Mundial de Salud Mental en el Peru); EZOP (Epidemiology of Mental Health and Access to Care Survey); NMHS (Portugal National Mental Health Survey); B-WMH (Beijing World Mental Health Survey); S-WMH (Shanghai World Mental Health Survey); RMHS (Romania Mental Health Survey); SASH (South Africa Health Survey); PEGASUS-Murcia (Psychiatric Enquiry to General Population in Southeast Spain-Murcia); CMDPSD (Comorbid Mental Disorders during Periods of Social Disruption); NCS-R (US National Comorbidity Survey Replication).

2 The response rate is defined by the percentage of persons asked to answer a survey who finally participate.

3 PRC - People's Republic of China

The WHO's WMH household surveys represent regions from all over the world. The surveys were conducted in Africa (Nigeria, South Africa), the Americas (Colombia, Mexico, United States), Asia and the Pacific (Japan, New Zealand, Beijing and Shanghai in the People's Republic of China - described as Metropolitan PRC), Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Ukraine), and the Middle East (Israel, Lebanon). The surveys were nationally representative except for China, Japan, and Nigeria. A total of 85,052 interviews have already been completed, the total eventual sample size will include 151,773 respondents. The weighted average response rate was 71.1 %. Estimates of prevalence, projected lifetime risk, severity, distribution, social burden, and patterns of treatment of mental disorders are being assessed. Diagnoses cover anxiety disorders, mood disorders, impulse-control disorders, eating disorders, and substance use disorders. Not all disorders were assessed in all countries. Diagnoses were based on the Composite International Diagnostic Interview (CIDI), which is a fully structured interview generating ICD-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)- IV diagnoses. Organic exclusion criteria were formulated in determining diagnoses. The surveys were performed by lay interviewers

operating with a computer-assisted personal interview (CAPI). The interviewers were coached during a one-week training course conducted by certified trainers from the WHO (Alonso et al. 2004). A subsample of respondents was re-interviewed by experienced clinicians in order to analyze consistency with the diagnoses based on the CIDI (Kessler et al. 2006).

1.3 Comparison of household surveys and clinical trials

Regarding characteristics and methods of epidemiological household surveys and randomized clinical trials (RCTs), major differences should be highlighted. Table 3 presents an comparison of characteristics of the WHO surveys, stated as an example for epidemiological community surveys, and RCTs.

Table 3. Characteristics of the WHO epidemiological surveys and RCTs

WHO Epidemiological Surveys	Analysis of Randomized Controlled Studies
Sample • national representative household surveys assessing population-segments • age range: 18+	**Sample** • RCTs assessing treatment-seeking patients with mental disorders • age range: 18+
Sample Size • number of surveys: 16 (eventual number of surveys: 28) • total sample size N=85,052 (eventual sample size N=151,773)	**Sample Size** • number of primary studies: 832 • total sample size N=151,336
Countries of Conduction • worldwide	**Countries of Conduction** • worldwide
Core Diagnoses • alcohol and drug abuse and dependence, nicotine • mania, bipolar affective disorder, dysthymia, major depressive disorder • agoraphobia, social phobia, specific phobia, panic disorder, generalized anxiety disorder,	**Core Diagnoses** • Alzheimer's disease, vascular dementia • alcohol dependence syndrome • schizoaffective disorder, schizophrenia • mania, bipolar affective disorder, major depressive disorder, dysthymia

WHO Epidemiological Surveys	Analysis of Randomized Controlled Studies
separation anxiety disorder, posttraumatic stress disorder, somatoform disorder, obsessive-compulsive disorder, neurasthenia • anorexia nervosa, bulimia nervosa, binge eating disorder • intermittent explosive disorder, pathological gambling • conduct disorder, adult persistence of attention-deficit disorder, oppositional defiant disorder • premenstrual tension syndrome *Not all disorders were assessed in all countries.*	• panic disorder with or without agoraphobia, social phobia, generalized anxiety disorder, posttraumatic stress disorder, somatoform disorder, obsessive-compulsive disorder • anorexia nervosa, bulimia nervosa, binge eating disorder • nonorganic insomnia • emotionally unstable personality disorder *Not all disorders were assessed in all countries.*
Diagnostic Assessment • trained lay interviewers without medical background • according to DSM-IV and ICD-10 criteria	**Diagnostic Assessment** • culturally competent and experienced psychiatrists • according to DSM-IV and ICD-10 criteria
Common Exclusionary Criteria • homeless people, hospitalized patients, and those in institutions; (2) severe comorbid physical illness *Information about further exclusionary criteria has not been provided.*	**Common Exclusionary Criteria** • (1) suicidal risk; (2) severe comorbid physical illness; (3) current co-occurring Axis I psychiatric disorder; (4) pregnant or lactating women and sexually active women of childbearing potential who are not using contraception; (5) history of substance dependence; (6) unstable medical condition; (7) cognitive impairment; (8) additional treatment during the study

Information on the age of patients with mental disorders in scientific articles and textbooks is often heterogeneous. It is mostly derived from epidemiological studies which are performed by lay interviewers assessing a sample of non-clinical subjects. Some of these surveys determine an age range but cannot provide information on the age in which a disorder is most common or most severe. Household surveys usually do not determine the severity of disorders by using disorder-specific rating scales. Thus, it seems probable that subthreshold

and mild cases are included. Some published data on age and gender distribution of mental disorders may have been based on samples of clinical patients diagnosed by psychiatrists, but estimates deriving from single studies seem less representative, as data is obtained from patients recruited from a single treatment centre, from a single country, or from a single ethnical group only. Moreover, the results may be biased, as household surveys do not represent several population segments, for example hospitalized patients. People with mental illness have been described to participate less likely than others in surveys, because of sample frame exclusions, differential mortality, or greater reluctance to participate (Allgulander 1989).

By pooling data from a large number of RCTs, more reliable information can be obtained. Only clinical patients fulfilling a minimum degree of severity are included in a RCT and diagnoses are reliable as they are assessed by specialist clinicians. Moreover, it can be assumed that the average patient tends to participate in a clinical trial when the degree of illness severity has reached its climax, because the patient is seeking help. Thus, the mean age of patients in RCTs is a good estimator for the age in which the disorder tends to show the highest degree of severity.

Relevant aspects of community epidemiology and clinical epidemiology will be discussed in detail hereafter.

1.3.1 Sample characteristics

National representative household surveys and clinical studies investigate different target populations.

In community surveys, population segments are being interviewed, in order to assess a representative sample. Household surveys do not represent several important population segments, e.g. homeless people, hospitalized patients, and those in institutions. Estimates of proportional treatment are likely to be downwardly biased due to the exclusion of hospitalized patients (Demyttenaere et al. 2004). Severe cases and certain disorders, such as depression, schizophrenia, or personality disorders, are likely to be downwardly biased because typical characteristics of these disorders, such as suicidal or hostile behaviour and social

isolation, require inpatient treatment and deductively might be underrepresented in household surveys. On the other hand, disorders such as anxiety disorders rarely require inpatient treatment and might be overrepresented in household surveys.

People with mental illness are less likely than others to participate in household surveys because of sample frame exclusions named above, differential mortality, or greater reluctance to participate (Allgulander 1989). The weighted average response rate of the WMH surveys was approximately 71 %. Deductively, nearly 30 % of the population segments are not represented in the sample. Previous research reported about selection bias in population-based surveys, resulting from selective participation of healthier persons (Allgulander 1989; Criqui et al. 1978; Eaton et al. 1992; Kessler et al. 1995a). People who did not participate in these surveys were found to have significantly higher rates and severity of mental illness than respondents (Allgulander 1989; Eaton et al. 1992; Kessler et al. 1994b). Deductively, prevalence and severity estimates of household surveys are most likely not reliable.

In comparison, RCTs investigate samples of treatment-seeking patients with a diagnosis of mental illness. Clinical trials recruiting inpatients and/or outpatients have been considered in this work. Respondents can be expected to be serious and engaged in the process of the trial, and they are more likely to provide accurate responses because they are seeking professional help (Kessler 2007).

Altogether, estimates derived from data of clinical trials are most likely to be accurate and reliable. The sample of RCTs consists of clinical subjects, whereas in household surveys people with mental illness are likely to be underrepresented.

1.3.2 Reliability of diagnoses

Reliability of diagnoses can be expected to differ between household surveys and clinical trials due to various factors, for example methods of data collection, the background of the interviewer, and motivation of the respondents.

Representative population surveys show considerable variations in prevalence rates and diagnoses seem less reliable. This may be attributed to several aspects. Sample bias due to the selection of population segments has been described before. Furthermore, the fieldwork of

household trials usually is conducted by interviewers without medical background. Concerning the WHO surveys, lay interviewers were coached during a one-week training course for psychiatric interviews only (Alonso et al. 2004). Due to high costs and the difficulty of recruiting enough qualified specialists for the assessment of the large sample size of population surveys, only lay interviewers were hired. It is a disadvantage that in community surveys diagnoses are not assessed by experienced psychiatrists. Even for trained lay interviewers, it seems difficult to distinguish between subthreshold cases and more severe cases of mental disease on the basis of the CIDI. Additionally, some of the DSM and ICD criteria did not derive from field studies but were decided by committees and do not allow to identify clinical cases precisely. Even for qualified psychiatrists it may be challenging to distinguish between mild forms of social anxiety disorder and shyness or modesty, namely to distinguish between pathological and well-founded fear in general. For example, a lay interviewer could possibly diagnose generalized anxiety disorder of a healthy mother that would report to worry constantly about the physical well-being of her children. It has been criticized that the prevalence rates for some mental disorders obtained in community surveys seem to be exaggerated. For instance, according to the NCS (National Comorbidity Survey) study, every third woman suffers from an anxiety disorder once in her life. At the same time, interviewer error might have led to under-reporting of other mental disorders.

Discrepancies in the application of the diagnostic interview tools could have also lead to inaccurate estimates. Analysis of the CIDI diagnoses has shown acceptable reliability and validity (Kessler et al. 2003; Wittchen et al. 1991; Wittchen 1994), but considering the limitations named above, it is not surprising that diagnoses have shown variance compared to diagnoses that were assessed by clinicians (Haro et al. 2006).

The fully structured diagnostic interviews, such as the CIDI, use diagnostic criteria and operationalize them into questions that the average respondent will understand. It is a disadvantage that cultural aspects in conveying psychiatric symptoms have not been considered. Language differences or translating problems might occur. The terms and phrases to describe mental symptoms could be less consistent with cultural concepts of less developed countries compared to those of Western countries. It has been described that absence of free speech and public opinion surveying results in greater reluctance to admit emotional or substance-abuse problems in less developed countries than in developed Western countries. Therefore,

accuracy of diagnoses might vary across countries (Demyttenaere et al. 2004).

Interviewer error might also lead to inaccurate estimates. Clinical interviews to compare the CIDI diagnoses obtained by the lay interviewer with those obtained by the reappraisal clinician administering the axis I Structured Clinical Interview for DSM-IV (SCID) were carried out, but the clinical re-interviews took place mostly in Western countries, where cultural understanding of psychiatric disorders might be more consonant anyways, and have been conducted in total only 264 times for the ESEMeD surveys.

It is a disadvantage that some data of household surveys are based on recall (Wittchen et al. 1989). Epidemiologic research proposed that age-of-onset reports were a mean of approximately ten years before the interview regardless of the respondent's age (Simon and VonKorff 1995; Simon et al. 2005). Data might have been recalled incorrectly even though the WMH surveys used strategies to reduce bias. The age-of-onset of mental disorders was determined by syndrome onset and did not consider any prodromes at an earlier age. For example, estimates of the age-of-onset of psychosis were based on incident treatment. Epidemiological analysis of early indicators of incipient disorders would almost certainly lead to much earlier estimates of age-of-onset than those reported (Kessler et al. 2007a).

In comparison to the fieldwork of household surveys, the fieldwork of clinical studies is conducted by experienced clinicians and diagnoses are reliable and multiple confirmed by considering accurate documentary. Diagnoses of clinical trials assess mental disorders using the Structured Clinical Interview for the DSM-IV Axis I Disorders (Lobbestael et al. 2011). The criteria of the DSM and ICD classifications only represent on the surface of what psychiatrists presume to be the underlying disease construct, and usually categorize mental disorders by reducing the dimension of symptoms (Andrews 2000). Therefore, next to the classification scheme it seems important that diagnoses are assessed by experienced clinicians. For example, a psychiatrist who is seeing patients with generalized anxiety disorder on a regular base is able to take other signs and symptoms into account to distinguish between normal worries and pathological fear. However, studies conducted in psychiatric outpatient services or in primary care settings may also provide valuable information. Research indicated that if interviews are conducted by psychiatrists (Wittchen et al. 1992) or the study uses a general psychiatric outpatient sample (Lepine et al. 1989), clinical cases will probably

be identified more reliably.

Altogether, in clinical trials interviewer error appears less probable and diagnoses are likely to be highly accurate and reliable, whereas methods of population surveys do not allow to identify accurate diagnoses.

1.3.3 Assessment of disorder severity

Population surveys and RCTs use different methods and scales to measure severity of mental disorders. Definitions of disorder severity vary according to different criteria such as diagnosis, disability, and duration of mental illness. Also, accuracy of responses need to be considered and might vary between respondents of household surveys and RCTs.

The results of household surveys are limited by the possibility that people with a history of mental illness might under-report their disorders (Kessler et al. 2005b). One crucial factor is the well-known bias against reporting embarrassing behaviours (Cannell et al. 1977). Additionally, respondents in community epidemiological surveys can be expected to be less engaged in the process and more likely to provide inaccurate responses because they often do not rate their participation in the survey as something serious (Kessler 2007). Some studies showed the CIDI diagnoses of epidemiological surveys to have poor agreement with diagnoses based on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) clinical interview (Wing et al. 1990) in a community sample (Brugha et al. 2001), and others showing agreement to be good in a patient or primary care provider sample (Andrews et al. 1995; Jordanova et al. 2004). The variation in results, with much higher concordance in patient samples than community samples, raises the possibility that respondent motivation is more of an issue than problems with question wording (Kessler 2007). Selection bias resulting from selective participation of healthier persons in population-based surveys has been mentioned before (Allgulander 1989; Criqui et al. 1978; Eaton et al. 1992; Kessler et al. 1995a).

A detailed description of the severity classification, incorporating criteria such as suicidality, work disability, and specific diagnoses of mental disorders, is described elsewhere. WMH measures of disorder severity were applied to 12-month cases only, and results propose that the majority of cases were mild (Demyttenaere et al. 2004). Severity of lifetime cases have

not been estimated. Caution is needed in interpreting the results, as severity of some disorders might be underestimated due to a crude severity classification scheme in some of the WMH surveys. For example, the Western European surveys, which were fielded first, had much more item-missing data than later surveys, which led to underestimation of severity of some disorders because the Sheehan Disability Scales (SDS) were sometimes mistakenly skipped (Demyttenaere et al. 2004).

The majority of clinical surveys operate with fully structured versions of standard clinical severity measures for the specific mental disorders. The frequently used scales are listed elsewhere. Multiple studies proved that disorder severity is strongly related to treatment in all countries (Bijl et al. 2003; Demyttenaere et al. 2004; Kessler et al. 1997). It has been described that severe disorders will more typically come to clinical attention than less severe disorders (Kessler et al. 2007b). Responses of participants of clinical studies can be considered more accurate because respondents are more serious due to the fact that they are seeking professional help (Kessler 2007).

The method applied in this study was to analyze the mean age of patients being enrolled in RCTs in order to estimate the age in which the disorder tends to show the highest degree of severity.

To sum up, it can be expected that more severe cases will be represented in clinical studies and estimates of severity will be more reliable, whereas mild cases will be represented in population surveys as respondents will either underreport severity of their symptoms or not even participate in the process.

1.4 Age-of-onset distribution of mental disorders

Generally, many mental disorders are known to have onsets in childhood, adolescence, or early adulthood. Later onsets appear as secondary conditions in most cases. Early age-of-onset has been described to be associated with greater disorder severity (Kessler et al.

2001c), persistence (Clark et al. 2006), and lack of treatment response (Nierenberg et al. 2004). Unfortunately, little is known about treatment of cases with first-onset disorders during childhood and adolescence.

A brief overview about the age-of-onset distributions of major mental disorder is provided hereafter.

Age-of-onset distributions of anxiety disorders vary. Anxiety disorders start in childhood, adolescence, or early adulthood until they reach a peak in middle age (Bandelow and Michaelis 2015). The median age-of-onset for anxiety disorders is 11 years (Kessler et al. 2005a). Specific phobias and separation anxiety disorder start earliest, with a median age-of-onset ranging from age 7–14 (Kessler et al. 2007b; Sheehan et al. 1998), followed by agoraphobia without panic attacks (Jacobi et al. 2014b), and panic disorder (Sartorius et al. 1996). Generalized anxiety disorder and posttraumatic stress disorder have later age-of-onset distributions (median age 24–50) and have been described to vary widely between nations (Kessler et al. 2007b). Generalized anxiety disorder has the latest median age at onset (31 years). Age-of-onset distributions of posttraumatic stress disorder are expected to vary according to the trauma exposure occurring throughout the life course.

Obsessive-compulsive disorder often starts in childhood and adolescence. It is unusual for symptoms to begin after the early thirties. Age-of-onset curves vary according to gender. Males make up the majority of very early onset cases during childhood, whereas more females develop obsessive-compulsive disorder during adolescence (Ruscio et al. 2010).

The median age-of-onset of mood disorders ranges between 29–43 years, varying widely between countries (Kessler et al. 2007b). Results are quite similar to those for the later-onset anxiety disorders. Age-of-onset distributions of mood disorders increase through late middle age and decrease thereafter.

The majority of psychoses occur in the thirties with a median in the early twenties. Onset of psychotic disorders during childhood is not common. A marked increase in prevalence is shown among adolescents aged 15–17 (Thomsen 1996). Schizophrenic spectrum disorders make up the majority of psychotic disorders. Median age-of-onset for schizophrenia usually is described to be in the early twenties (Jones et al. 1994; Lauronen et al. 2007). It should be

mentioned that the distributions of median age-of-onset of schizophrenia vary according to gender. Both males and females are described to have age-of-onset distributions with peaks at the early twenties and mid or end thirties. Females have an additional peak at the early sixties (Castle et al. 1998). Schizoaffective disorders appears to have a broad age-of-onset in adults (del Rio Vega and Ayuso-Gutierrez 1990), patients develop the condition from prior to mid twenties until after mid thirties (Marneros et al. 1990).

Most of the substance use disorders begin in adolescence and early adulthood. Findings of the median range of age-of-onset distributions varies widely between countries (Kessler et al. 2007b).

Altogether, considerable consistency exists in findings of age-of-onset distributions in epidemiological surveys (Christie et al. 1988; Kessler et al. 2007b). Also, the WMH surveys did not detect a strong consistency in between-country differences in age-of-onset distributions across disorders. Between-country differences were not related to economic development, region of the world, or to other structural correlates (Kessler et al. 2007b).

Nevertheless, difficulties arise in measuring the age-of-onset of mental disorders and limitations should be considered. As mentioned before, in most community surveys estimates of age-of-onset distributions of mental disorders are based on retrospective reports. Therefore, data might have been recalled incorrectly. For example, age-of-onset results ignored any prodrome at earlier age, but focused on syndrome onset. In other cases, estimates were based on incident treatment. Epidemiologic research proposed that age-at-onset reports were a mean of approximately ten years before the interview regardless of the respondent's age (Simon and VonKorff 1995; Simon et al.). Epidemiological analysis of early indicators of incipient disorders would almost certainly lead to much earlier estimates of age-of-onset than those reported (Kessler et al. 2007a).

1.5 Gender distribution of mental disorders

Sex and gender differences in mental disorders belong to the most stable findings in psychiatry. A brief overview is presented hereafter.

Epidemiological surveys have consistently documented significantly higher rates of anxiety

and mood disorders among women than men (Kuehner 2003; Pigott 1999). Generally, an increased risk is proposed for women concerning affective disorders (Bebbington 1998; Gater et al. 1998; Jacobi et al. 2004; Kessler et al. 1994a; Weissman et al. 1993; Wittchen et al. 1998), anxiety disorders (Gater et al. 1998; Lewinsohn et al. 1998; Merikangas et al. 2002; Weissman et al. 1997; Wittchen et al. 1999; Yonkers et al. 1998), and somatoform disorders (Lieb et al. 2000; Piccinelli and Simon 1997; Smith et al. 2001). In contrast, significantly higher rates of externalizing, substance use disorders, and antisocial disorders have been documented among men (Arnold 1996; Bijl et al. 1998; Brady and Randall 1999; Gili et al. 1998; Keenan et al. 1999; Kessler et al. 1993; Nelson and Wittchen 1998; Spauwen et al. 2003). Males and females are about equally affected from obsessive-compulsive disorder (Kiejna et al. 2002).

Findings of gender differences in mental disorders are relatively consistent across cultures. Deductively, an association with biological or psychosocial factors that have similar effects across cultures seems plausible (Gater et al. 1998). Biological differences across races and ethnic groups and culturally determined psychosocial differences would be expected to vary between different societies (Gater et al. 1998).

Gender differences in mental disorders can be observed in prevalence rates of disorders, the timing of onset and diagnosis, course, and treatment of disease. Sociodemographic correlates of patterns of the female predominance in most mental disorders are still not being fully understood (Klose and Jacobi 2004). Risks are multiple and interconnected. For example, it is well known that the social gradient in health correlates with gender. More women than men are exposed to poverty, discrimination, and socioeconomic disadvantage. Gender is associated with mental health. Gender-based violence, social status, exposure to mental health risks, and access to resources and treatment need to be considered.

1.6 Lifetime prevalence of mental disorders

The lifetime prevalence is defined as the proportion of the population with a disorder at some point of life up to the age at which the assessment takes place.

The WMH survey estimates of lifetime prevalence of individuals suffering from one or more

mental disorder vary between the countries that have been investigated, namely from 47.4 % in the United States to 12.0 % in Nigeria (Kessler et al. 2007b). More than 30 % of respondents in Colombia, France, New Zealand, Ukraine, and the United States reported at least one lifetime mental disorder. Prevalence rates were more than 25 % in Belgium, Germany, Lebanon, Mexico, the Netherlands, and South Africa, and more than 16 % in Israel, Italy, Japan, and Spain. Metropolitan PRC and Nigeria had prevalence estimates of less than 14 %. Anxiety disorders and mood disorders were the most prevalent in most countries. Estimates vary between 4.8–31.0 % for anxiety disorders and 3.3–21.4 % for mood disorders. Impulse control disorders were the least prevalent in most countries (0.3–25.0 %), and substance use disorders were the least prevalent among all countries that have been investigated (1.3–15.0 %) (Kessler et al. 2007b).

The results show that lifetime disorder co-occurrence appears commonly. The sum of prevalence across anxiety disorders, mood disorders, impulse control disorders, and substance use disorders was even 30–50 % higher than the prevalence of any single disorder. Within-class co-occurrence can be observed more commonly than between-class co-occurrence (Kessler et al. 2007b).

1.7 Projected lifetime risk of mental disorders

The projected lifetime is defined as the estimated proportion of the population who will have the disorder by the end of their life, which is defined as the age of 75.

WHO estimates suggest that the projected lifetime risk varies among countries. According to the findings of WHO, 47–55 % of the population will eventually suffer from a mental disorder in Colombia, France, New Zealand, South Africa, Ukraine, and the United States; the projected lifetime risk is supposed to be as high as 30–43 % in Belgium, Germany, Israel, Lebanon, Mexico and the Netherlands, 24–29 % in Italy, Japan and Spain, and 18–19 % in Metropolitan PRC and Nigeria (Kessler et al. 2007b).

The projected lifetime risk of any disorder appeared higher than the estimated lifetime prevalence. For example, the WHO found the projected lifetime risk to be 17 % higher in the United States and 69 % higher in Israel than the estimated lifetime prevalence. There was a

high risk-to-prevalence ratio of 57–69 % in Israel, Nigeria, and South Africa. No strong difference between the risk and the prevalence ratio was described between developed and less developed countries. The highest class-specific proportional increase in projected life-time risk was reported for mood disorders (45–70 %), and the lowest for impulse control disorders (0–14 %). These findings are compatible with the late age-of-onset distribution of mood disorders and an early age-of-onset distribution of impulse control disorders (Kessler et al. 2007b).

1.8 Severity of mental illness

There is no internationally standardized definition of severe mental illness (Ruggeri et al. 2000). Definitions are inconsistent and comprise various criteria such as diagnosis, disability, and duration of mental illness.

This is reflected in inconsistent estimates of the severity of mental illness. In a US study, estimates of diagnoses of patients with serious mental illness varied between 4–88 % according to different definition of severity and persistence of mental illness (Schinnar et al. 1990).

A brief overview about definitions of severity of mental illness and frequently used scales is presented hereafter.

The US National Institute of Mental Health presents a definition of wide consensus, defining serious mental illness if individuals meet all of the following criteria:

- a diagnosis of non-organic psychosis or personality disorder
- a duration of prolonged illness (≥2 years) and long-term treatment (≥2 years)
- disability, defined as fulfilling criteria such as working abilities, reliance on public financial assistance, limited personal support system, basic living skills, and inappropriate social behaviour leading to intervention by the mental or judicial system (National Institute of Mental Health 1987)

Epidemiological studies such as the NCS-R (US National Comorbidity Survey Replication) surveys investigated serious mental illness of 12-month cases.

They were classified serious if fulfilling any of the following criteria:

- a serious suicide attempt within the past 12 months
- work disability or considerable impairment due to a mental disorder
- a diagnosis of non-affective psychosis, bipolar affective disorders, substance dependence with serious role impairment, or an impulse-control disorder with repeated serious violence
- a long duration of impairment, being defined as not being able to carry out normal daily activities in more than 30 days in the year due to a mental disorder.

Cases were defined moderate if fulfilling any of the following criteria:

- suicide gesture, plan or ideation
- substance dependence without serious role impairment
- at least moderate work limitation due to a mental disorder
- any disorder with at least moderate role impairment in the domains of the SDS, which is a self-report tool assessing disability in work, family life or home responsibilities, and social life (Leon et al. 1997)

The remaining cases were classified as mild.

The NCS-R results propose that many mental disorders are mild. Indeed, 40.4 % of the investigated NCS-R cases are being described as mild, whereas only 22.3 % are being described as serious (Kessler et al. 2005b). Analysis of CIDI surveys in Canada, Chile, Germany, the Netherlands, and the United States found similar rates of mild cases (Bijl et al. 2003). Further research indicated a correlation of treatment with severity and found serious cases generally to receive between three and five times more likely treatment than mild cases (Bijl et al. 2003). Still, between 30–60 % of serious cases in these surveys did not receive any treatment at all. Interestingly, in Germany the treatment rate of mild cases was the highest among the countries that have been investigated.

The majority of clinical surveys embed fully structured versions of standard clinical severity measures into the assessments of mental disorders. Some of the frequently used scales are listed below:

- the Clinical Global Impression-Severity Scale (CGI-S) is a 7-point scale rating the severity of the patient's illness in relation to patients with the same diagnosis (Guy 1976)
- the Quick Inventory of Depressive Symptoms Self-Report (QIDS-SR) (Rush et al. 2003) and Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979) and Beck Depression Inventory (BDI) (Beck et al. 1996) are being used to assess the severity of major depressive episodes
- a fully-structured version of the Young Mania Rating Scale (YMRS) is being used to measure the severity of manic episodes (Young et al. 1978)
- the Panic Disorder Severity Scale (PDSS) (Shear et al. 2001) and Panic and Agoraphobia Scale (PAS) (Bandelow 1995) are being used to assess the severity of panic disorder
- the Mini Mental State Examination (MMSE) is being used to measure cognitive impairment, it is commonly used to screen for dementia (Folstein et al. 1975)
- the Positive and Negative Symptoms Scale (PANSS) is a scale used for measuring symptom severity of patients with schizophrenia (Kay et al. 1987)
- the Yale Brown Obsessive Scale (Y-BOCS) is being used to assess the severity of obsessive compulsive disorder (Goodman et al. 1989)
- the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) objectifies alcohol withdrawal severity of individuals with alcohol dependence (Sullivan et al. 1989)
- the Hamilton Anxiety Rating Scale (HAM-A) is a questionnaire rating the severity of patient's anxiety (Hamilton 1959)

Altogether, measuring severity of mental disorders seems difficult and different approaches are being used. It has been previously described that treatment-seeking is related to severity. This approach will be the method applied in this study.

1.9 Mental health care use

Many individuals affected by psychiatric disorders remain untreated although there are effective treatment methods. A Dutch study found that only 33.9 % of those with a psychiatric disorder used primary or mental health care in a 12-month period (Bijl and Ravelli 2000). Studies reported about several variables associated with patterns of mental health care use.

Significant predisposing sociodemographic factors which determine the use of mental health care include female gender (Bland et al. 1997; Kessler et al. 2005b; Parslow and Jorm 2000; Wang et al. 2005), younger age (Kessler et al. 1998; Lewis et al. 2005), Caucasian race (Kessler et al. 2005b; Lewis et al. 2005; Wang et al. 2005), and higher education (Lewis et al. 2005; Parslow and Jorm 2000). Furthermore, persons who live alone, single parents, unemployed persons, and disabled persons are more likely to use mental health care (Bijl and Ravelli 2000; Bland et al. 1997; Crow et al. 1994; Lin et al. 1996; Olfson et al. 1998).

Mental health disability correlates with seeking care (Katz et al. 1997). Significant enabling factors for accessing health care use include urban residence (Wang et al. 2005), and health insurance coverage (Bruce et al. 2002). Significant illness variables for accessing mental health care include mood disorders (Lewis et al. 2005; Parslow and Jorm 2000), substance use disorders (Lewis et al. 2005; Parslow and Jorm 2000), and anxiety disorders (Greenberg et al. 1999; Lewis et al. 2005; Parslow and Jorm 2000). It has been described that patients with mood disorders are the most likely to seek professional care, whereas patients with alcohol- and drug-related disorders are less likely to do so (Bijl and Ravelli 2000). Patients affected by generalized anxiety disorder have been found to be frequent utilizers of primary care resources and have been associated with over-utilization of general health care resources (Maier et al. 2000; Roy-Byrne and Katon 1997; Wittchen et al. 2000; Wittchen et al. 2002).

Gender difference exists in patterns of seeking help. For example, women are more likely to reach out for primary health care while men are more likely to seek specialist mental health care and represent principal users of inpatient care.

Studies of initial contact with the treatment system show that individuals affected by early-onset disorders often need more than ten years until they manage to seek treatment, and

finally have developed seriously impairing disorders that might have had a better treatment outcome if they had received treatment at the beginning of their illness (Christiana et al. 2000; Olfson et al. 1998; Wang et al. 2007). Regardless of race or ethnicity, adults with serious mental illness were more likely than adults with any mental illness to report mental health service use in a 12-month period (Substance Abuse and Mental Health Services Administration 2015). Especially in developing countries, where there are financial and structural barriers to access mental health services, many lifetime cases sought treatment for their disorders (Saxena et al. 2003).

Further research proposed that the perceived need for treatment has stronger effects in treatment seeking than sociodemographic and access variables (Bland et al. 1997; Kessler et al. 2001a; Leaf et al. 1988; Rayburn et al. 2005). Research assessing respondents with serious mental illness participating in the NCS household surveys reported that next to situational barriers, financial barriers, and a perceived lack of effectiveness, the most commonly reported reason for failing to seek treatment and for treatment dropout was wanting to figure out the problem by themselves (Kessler et al. 2001a).

A change of financing mental health service is clearly needed. Moreover, the importance of patient-centered care and patient's acknowledgement of need for treatment becomes apparent (Kessler et al. 2001a).

1.10 Future prospects

Despite encouraging advances, much work still needs to be done until psychiatric epidemiology can unfold its full potential to improve the mental health of populations. In contrast to other branches of epidemiology, difficulties arise in psychiatric epidemiology to conceptualize and measure mental disorders. Findings report about a high lifetime prevalence of mental disorders, as high as 50 % in some countries (Kessler 2007), but little is known about disorder severity. The course of the majority of mental disorders is often chronic-recurrent and patients require lifelong treatment. Accordingly, clinical interest in research on the course of illness is inevitably increasing. Research up to now fails to provide an adequate picture about severity and the course of mental disorders.

Therefore, I used the approach to extract data of the mean age and gender distribution from a large number of RCTs in order to obtain reliable results. The mean age of patients participating in RCTs is a good estimator for the age in which the disorder tends to show the highest degree of severity.

Data which provide information about the age-related severity of mental disease lead to a further understanding of the course and prognosis of mental illness. These results can be used in scientific publications or educational materials and can help health care providers or researchers to plan treatment programs. Data might be relevant for the formulation of upcoming DSM and ICD diagnostic criteria. Patients can be informed about the natural course of the disorder. Gender differences and the mean age of patients with mental disorders who participate in a clinical trial are potentially relevant because they may guide clinicians in assessment and treatment. The age when participating in a clinical trial may suggest a specific disease entity and accordingly, management could be directed. Medical intervention could be optimized and adjusted to the age of patients, for example by considering medical interaction and somatic comorbidities, and finally target precise interventions. Clinical data of this sort can be helpful for learnings of medical students and physicians, and in a final step for policy planning. Furthermore, the data is helpful for an optimized planning of clinical trials and medical wards. For example, the age of patients might be established as a criterion for stating a trial as representative, detect outliers, and presume an accurate psychiatric diagnose and its prognosis of course due to its specific age.

Further investigations about the course and severity of psychiatric disorders are sorely needed. Data on the impact of previous treatment needs to be assessed. Also, the aetiology of mental disorders may be elucidated further by investigating the reasons why some disorders occur predominantly at a certain age or have an unbalanced gender distribution. For example, when a disorder has a highly-unbalanced gender distribution, sexual hormones or genetic causes may be involved. Underlying biological settings, for instance modulation of receptors and changes of neurotransmitters, might influence the course of a disease at a certain age, and have similar effects across cultures, either interacting or working alone.

1.11 Goal of the study

In the present work, I aimed to investigate the mean age and gender distribution of patients with the most common mental disorders who participated in randomized controlled studies. The goal of the study was to provide a table with the mean age and gender distributions of all major mental disorders.

Because these data are based on a large number of RCTs in which help-seeking individuals with a minimum severity score were diagnosed by experienced clinicians, they may be more reliable than other sources based on a non-systematic selection of studies. As treatment-seeking is related to severity of mental illness, it can be assumed that the average patient is included in an RCT when the degree of severity has reached a climax. Thus, the mean age of patients in RCTs is a good estimator for the age in which the disorder tends to show the highest degree of severity.

With this data, further conclusions about the course of psychiatric disorders can be drawn.

2. Design and methods

2.1 Selection of mental disorders

The following mental disorders diagnosed according to the criteria of the ICD-10 classification of mental and behavioural disorders have been investigated:

- **Organic, including symptomatic, mental disorders**:
  - Dementia in Alzheimer's Disease (F00)
  - Vascular Dementia (F01)
- **Mental and behavioural disorders due to psychoactive substance use:**
  - Alcohol Dependence Syndrome (F10.2)
- **Schizophrenia, schizotypal and delusional disorders:**
  - Schizophrenia (F20)
    (including paranoid, hebephrenic, catatonic, undifferentiated, residual, and unspecified schizophrenia; schizophreniform disorder)
  - Schizoaffective Disorders (F25)
    (including bipolar type, depressive type, mixed type, and unspecified schizoaffective disorder)
- **Mood (affective) disorders:**
  - Manic Episode (F30)
  - Bipolar Affective Disorder (F31)
  - Major Depressive Disorder (F32-F33)
  - Dysthymia (F34.1)
- **Neurotic, stress related and somatoform disorders:**
  - Panic Disorder with Agoraphobia (F.40.0) or without Agoraphobia (F41.0)
  - Social Phobia (F40.1)
  - Generalized Anxiety Disorder (F41.1)
  - Obsessive-Compulsive Disorder (F42)
  - Posttraumatic Stress Disorder (F43.1)

- Somatoform Disorders (F45)
  (including somatization disorder; undifferentiated, other, and unspecified somatoform disorder; hypochondriacal disorders; somatoform autonomic dysfunction; persistent somatoform pain disorder)

- **Eating disorders:**
  - Anorexia Nervosa (F50.0)
  - Bulimia Nervosa (F50.2)
  - Binge Eating Disorder (F50.81)
- **Nonorganic sleep disorders:**
  - Nonorganic Insomnia (F51.0)
- **Disorders of adult personality and behaviour:**
  - Emotionally Unstable (Borderline) Personality Disorder (F60.3)

The selection is representing the most common thus clinically most relevant mental disorders. These were the disorders most often investigated in clinical trials. Due to insufficient eligible data, clinical trials assessing patients with dissocial personality disorder and paedophilia have not been investigated.

2.2 Search methods

To identify relevant randomized clinical trials concerning the most relevant psychiatric disorders, a databased-driven literature research was performed using PubMed. Electronic databases of ResearchGate and Google Scholar were used to complement handsearch for literature research and to retrieve full-texts. The reference lists of reviews, meta-analyses, and guidelines were inspected for further relevant studies. Relevant randomized trials were identified by searching the electronic databases named above using the following terms: “randomized” [all fields] and the ICD name of the mental disorder, e.g. “alcohol dependence” [title]. Searching terms for “dysthymia” [title] have been complemented by using the terms “dysthymic disorder” [title] and “minor depression” [title]. Searching terms for “somatoform disorder” [title] have been complemented by using the term “somatization” [title]. The selection of mental disorder is stated above. I aimed to consider articles published in English.

Studies have been extracted according to the search algorithm of the PRISMA-Statement

(Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Table 4 provides detailed information. The first 50 consecutive studies for each of the mental disorders have been considered. The first 60 consecutive studies have been considered for anorexia nervosa, as the sample was subdivided into a sample of adults and adolescents. Due to insufficient eligible data, clinical trials assessing patients with dissocial personality disorder and paedophilia could not be investigated.

The electronic searches retrieved an original pool of 10.465 results and ended on the 20th of August 2017. A number of 1896 full-text articles were eligible and 375 additional records were identified through handsearch. After applying inclusion and exclusion criteria, a total of 1439 studies were excluded, leaving a total of 832 relevant randomized controlled trials.

Table 4. Search algorithm according to the PRISMA-Statement (Moher et al. 2009)

Timespan	1950–2017 (Database closed: August 20th, 2017)	
Identification	10.465 records identified in PUB MED	Search algorithm, exemplified: ("alcohol dependence" [Title] *and* "randomized" [All fields]). No language restrictions
	Total: 10.465 records	
Screening	2.654 records screened by title and abstract	
Eligibility	1896 full-text articles assessed for eligibility	1.439 excluded (double publications, eligibility or quality criteria not fulfilled) 375 additional records identified through hand search
Included	832 studies were included in qualitative synthesis	

2.3 Study selection

To be considered for inclusion studies had to fulfil the following criteria:

- published in English
- conducted in a randomized design
- report of treatment for a major mental disorder
- used DSM or ICD diagnoses assessed by using a standardized clinical interview; due to the lack of sufficient eligible studies, a minority of studies recruiting patients diagnosed with somatoform disorders were included though not assessing diagnoses according to DSM or ICD; patients diagnosed with probable or possible dementia diagnosed according to the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) have been included
- provided mean age, standard deviation (SD), and gender distribution of the sample; due to the lack of sufficient eligible studies, a minority of studies have been included though not providing gender distribution or standard deviation of the sample
- included consecutively enrolled patients
- 1. recruited a sample without any age restrictions; *and*

  2. among the studies that recruited samples with age restrictions, those studies that (a) have a minimum age of not more than 18 years, and (b) either do not have a maximum age or the maximum age is not less than 60 years; the majority of studies assessed patients aged 18–65 years; *and*

  3. in addition, considering the age-related prevalence of specific mental disorders and the diversity of age restrictions of clinical trials, studies using other age restrictions than those referred to under 2 above, including: (a) for patients diagnosed with anorexia nervosa and bulimia nervosa, studies with a minimum age of 16 years and a maximum age of 35 years; (b) for patients diagnosed with borderline personality disorder, studies with a maximum age of 40 years; (c) for patients diagnosed with schizophrenic spectrum disorders and panic disorder, studies with a maximum age of 50 years; (d) for patients diagnosed with binge eating disorder, studies with a maximum age of 55 years; (e) for patients diagnosed with dementia, studies with a minimum age of 60 years and a maximum age of 75 years; (f) due to the lack of sufficient eligible studies assessing primary insomnia and dysthymia, patients with a minimum age of 25 years; *and*

4. for adolescent patients, only patients diagnosed with anorexia nervosa were investigated; only studies with a minimum age of not less than 11 years and a maximum age of not more than 21 years were included; the majority of studies assessed patients aged 12–18 years

- assessed a sample of patients of both genders; however, considering the female predominance of eating disorders and borderline personality disorder, studies assessing female cohorts of these mental disorders have been included; studies assessing patients diagnosed with posttraumatic stress disorder have been included irrespective of gender restrictions

Criteria for exclusion of studies were:

- no indication of mean age and sample size
- restricted cohorts that would possibly influence the mean age or gender distribution of the sample; e.g. first onset of the disorder, patients with comorbidities only, treatment refractory patients, medically resistance of the disease, sample in a mild phase of the disorder, or women only; however, for eating disorders and borderline personality disorder clinical trials excluding male participants have been considered; for subgroup analysis in posttraumatic stress disorder, subgroups of samples, e.g. female sample, veterans, have been taken into account
- age restrictions other than named above
- no randomized design

There were no limitations with regard to the state of illness (acute or chronic), the intake of medication (stable, without any or taking specific medication), the method of recruitment, and the status of the patients (inpatient or outpatient). The clinical trials have been selected randomly, worldwide clinical trials have been assessed.

2.4 Analysis

I aimed to include 50 studies for each of the most common mental disorders, in order to base calculations on a robust number of studies to obtain reliable results. A total of 60 studies has been included assessing a sample of patients diagnosed with anorexia nervosa because the

sample was subdivided into adults and adolescents. For some disorders, however, it was not possible to retrieve 50 eligible studies, restricting the generalizability of findings. Due to insufficient eligible data, clinical trials assessing patients with dissocial personality disorder and paedophilia could not be investigated. If data of secondary analyses was provided, I aimed to retrieve the original full-text of the studies.

I aimed to retrieve studies recruiting a sample without age restrictions or aged 18–65 years. Due to the age-related prevalence of specific mental disorders and the diversity of age restrictions of clinical trials, some age restrictions have been adapted. To analyze gender distributions, studies recruiting a sample of both genders have been included. Exceptionally, considering the female predominance of eating disorders and borderline personality disorder, studies assessing female cohorts of these mental disorders have been included; studies assessing patients diagnosed with posttraumatic stress disorder have been included irrespective of gender restrictions.

Of the eligible studies, data of the sample size, mean age, SD, and gender distribution, specified as female (%), was extracted. Age restrictions and standard clinical severity measures were listed in detail. Some of the studies did not contain information about the standard deviation or gender distribution, this was considered in statistical evaluation. It was aimed to analyze the age range and distribution of inpatients and outpatients of the samples that have been recruited for the studies. However, it was not possible to retrieve sufficient data to obtain reliable results. Furthermore, it was not possible to retrieve sufficient data to analyze the date since trauma of posttraumatic stress disorder happened.

The majority of the trials consisted of several study arms, the weighted mean of the provided data of each of the study has then been calculated. The standard deviation of each of the eligible studies has been pooled. The standard error (SE) has been generated by the SD.

The weighted mean age and weighted gender distribution of the studies has been calculated. The weighted mean age and pooled SD was specified as “26.9 ±7.6” years. The age range of the studies with the lowest mean age and the highest mean age has been mentioned.

3. Results

Table 5 provides data on the mean age and gender distribution of patients with major mental disorders who participated in RCTs. A detailed list of the primary studies can be found in the appendix.

Table 5. Results of the data on mean age and gender distribution of patients with common mental disorders participating in randomized controlled studies.

Mental Disorder	Mean Age[1]	min[2]	max[2]	SE	Pooled SD	Female (%)[1]	min[3]	max[3]	Sample Size (N)	Number of Studies
Alzheimer's Disease	74.8	64.5	87.9	0.8	8.2	56.5	38.8	84.0	6252	33
Vascular Dementia	72.7	64.3	81.0	0.6	6.5	43.5	12.5	73.2	6578	23
Alcohol Dependence Syndrome	44.3	39.7	52.4	0.9	9.9	26.3	3.0	47.0	11190	50
Schizophrenia and Related Disorders	38.3	21.6	46.3	0.9	10.7	36.2	18.2	59.0	17838	50
• schizophrenia only	38.9	21.6	42.7	0.9	10.9	35.2	18.2	59.0	11927	29
Mania	38.3	24.0	46.3	1.4	9.0	49.8	30.4	77.8	8590	50
Bipolar Disorder	39.6	30.0	47.5	1.2	11.1	57.4	28.2	75.0	9014	50
Major Depressive Disorder	42.7	33.5	50.2	0.9	12.1	63.3	46.4	82.9	22278	50
Dysthymia	45.3	31.1	55.2	0.9	13.3	64.6	41.5	73.0	2308	13
Panic Disorder	37.2	30.7	42.8	1.3	9.6	65.7	40.0	90.5	6933	50
Social Anxiety Disorder	35.2	24.4	41.4	1.3	10.3	50.5	29.0	85.0	5842	50
Generalized Anxiety Disorder	40.7	31.0	53.4	1.2	11.5	63.0	50.8	83.5	11118	50
Obsessive-Compulsive Disorder	35.6	19.9	42.1	1.6	9.9	55.1	34.8	80.0	4336	50
Posttraumatic Stress Disorder	38.3	28.0	57.5	1.6	10.1	56.7	n.e.	n.e.	3972	50
• all genders	38.2	29.8	44.4	1.7	11.9	66.9	31.3	96.4	2102	29
• women	33.2	28.0	44.4	1.4	9.2	100.0	n.e.	n.e.	582	8
• veterans	42.6	36.4	57.5	1.6	7.2	4.9	n.e.	n.e.	677	9
Somatoform Disorder	45.4	37.1	53.6	1.3	12.7	70.9	49.5	93.5	3227	22

Mental Disorder	Mean Age[1]	min[2]	max[2]	SE	Pooled SD	Female (%)[1]	min[3]	max[3]	Sample Size (N)	Number of Studies
Anorexia Nervosa, adolescents	15.1	14.1	16.7	0.2	1.5	93.3	n.e.	n.e.	2162	22
• all gender	14.8	14.1	15.7	0.2	1.5	90.7	85.7	95.1	1541	14
• girls	15.8	15.1	16.7	0.2	1.4	100.0	n.e.	n.e.	621	8
Anorexia Nervosa, adults	25.3	21.7	34.0	1.1	7.1	97.5	n.e.	n.e.	2052	38
• all genders	26.3	22.7	34.0	1.4	8.1	93.9	89.0	98.0	392	8
• women	25.0	21.7	33.3	1.0	6.7	100.0	n.e.	n.e.	1520	26
Bulimia Nervosa	26.9	21.0	34.0	0.8	7.6	94.8	n.e.	n.e.	4925	50
• all genders	27.1	25.8	29.3	0.8	8.5	88.1	57.5	98.6	1181	12
• women	26.8	21.0	34.0	0.8	7.1	100.0	n.e.	n.e.	1542	25
Binge Eating Disorder	45.4	30.2	52.2	1.2	9.5	83.9	n.e.	n.e.	10069	50
• all genders	45.7	35.9	52.2	1.0	9.4	83.0	56.0	96.6	9062	39
• women	42.0	30.2	50.0	1.4	10.5	100.0	n.e.	n.e.	520	9
Primary Insomnia	45.3	34.6	63.8	1.2	10.9	62.5	12.5	76.7	8310	31
Borderline Personality Disorder	30.7	24.3	38.6	1.1	8.6	83.9	n.e.	n.e.	4342	50
• all genders	31.1	25.1	38.6	1.1	8.8	78.5	52.4	93.4	3255	31
• women	29.2	24.3	36.8	1.1	7.6	100.0	n.e.	n.e.	1087	19
							Total number		**151336**	**832**

1 weighted

2 min – study with the lowest mean age; max – study with the highest mean age

3 min – study with the lowest percentage of female respondents; max – study with the highest percentage of female respondents

4. Discussion

To my knowledge, the summarized data illustrate the first comprehensive and most recent overview of epidemiological information on mental disorders from a representative number of RCTs. The mean age and gender distribution of patients with mental disorders participating in more than 800 RCTs has been analyzed.

It can be assumed that the average patient is recruited for a RCT when the degree of severity of the mental illness has reached a peak level. Therefore, analyzing the mean age of patients being enrolled in RCTs is a good estimator for the age at which the disorder tends to show the highest degree of severity.

In contrast to previous findings of household surveys, several advantages of clinical trials can be observed. First, estimates and diagnoses are likely to be highly accurate and reliable. Diagnoses are assessed by psychiatrists and highly formalized diagnostic procedures and inclusion criteria are being used. Furthermore, a sample of treatment-seeking patients of inpatients and/or outpatients with a history of mental illness are being represented. RCTs identify patients with clinically relevant disorders fulfilling a minimum severity score of fully structured versions of standard clinical severity measures. Reporting bias of respondents does not seem probable. Data is not based on retrospective recall and it can be assumed that participants responses are more accurate due to the fact that they are seeking professional help (Kessler 2007). It has been previously mentioned that respondent motivation is more of an issue than problems with question wording (Kessler 2007). Moreover, large RCTs are often performed on an international basis. A sample of respondents from many different countries and ethnical groups improves the generalizability of the results. Large sample size allows powerful analyses.

The implicit assumption of this approach, that mentally ill patients eventually come to clinical attention and participate in a clinical trial when the degree of severity of the mental illness has reached a peak level, has not been proven but makes clinical sense. The assumption is supported by findings of studies proving that disorder severity is strongly related to treatment (Bijl et al. 2003; Demyttenaere et al. 2004; Kessler et al. 1997).

Some patients though may have been recruited for a clinical trial at a less severe phase of their illness. For example, some symptoms of mental disorders may remit without treatment and patients may already show spontaneous remission when they had to wait to participate in the study. The influence of previous treatment to the course of symptoms has not been investigated.

Some mental disorders show a fluctuation in the persistence and stability of the diagnostic status and severity, in terms of remission and shifts from one syndrome and disorder to another. For instance, mental disorders such as panic disorder or depression are known to have a strong tendency to wax and wane over time. These patients can be expected to participate in a study when they are in a severe episode of their mental disease. Studies of panic disorder or obsessive-compulsive disorder found low probabilities of remission and high rates of relapse among those who remit (Eisen et al. 1999; Faravelli et al. 1995). In other disorders, severity is increasing during the course of the disease, for example the chronic progressive course of dementia.

It is important to bear in mind that the probability of participating in a clinical trial might depend on the diagnostic category. It has been reported that patients with mood disorders, substance use disorders, and anxiety disorders are more likely to seek help (Greenberg et al. 1999; Lewis et al. 2005; Parslow and Jorm 2000). Admission for a clinical trial depends on insight of the disease, psychological strain, and treatment adherence.

Unmet need for treatment among patients with the severe forms of mental illness is a major concern for researchers in psychiatric epidemiology. The most commonly reported reason both for failing to seek treatment and for treatment dropout was that patients wanted to deal with their problems on their own. Other findings suggest that a majority of those who received no treatment did not agree that their problems require any treatment (Kessler et al. 2001a). This seems probable e.g. for patients in a manic episode, with dissocial personality disorder, or being affected by anorexia nervosa. Certainly, the lack of demand for appropriate help when mental health services are available is relevant and requires further study. When the individual does not agree on the necessity for treatment though, symptoms of psychiatric disorders may bring the patient to the attention of others. For example, symptoms of

psychosis will most likely lead to inpatient treatment. When the patient does perceive a necessity for treatment, these factors become less important as the individual requires less external motivation to seek care. Of those patients recognizing the need for appropriate help, the most commonly reported reasons for not seeking treatment were situational barriers, financial barriers, and a perceived lack of effectiveness. A perceived lack of effectiveness of conventional therapy may contribute to a higher motivation for participation in a clinical trial.

It seems probable that the utilization of mental health service varies not only according to the presence of disorder but also according to availability of mental health service, i.e. by country. Further investigations on demographic barriers are needed. Nevertheless, previous research found that the perceived need for treatment has stronger effects in treatment seeking than sociodemographic and access variables.

Further research on the course of mental disorders, for example the impact of previous treatment, such as psychological treatment and the use of maintenance medication, is sorely needed. Sociodemographic and underlying biological settings, which might lead to a climax of a mental disease at a certain age, need to be further analyzed.

However, statistically, it seems probable that the average patient will participate in a clinical trial at the most severe stage of the mental disorder. Altogether, there is no possible bias that could affect the data in a way that the patients included in a study are not the worst cases. Therefore, it can be assumed that the age of highest severity of a mental disorder can be determined by the method applied in this study.

Altogether, results confirm that patients are being recruited for a clinical study at a similar age for each of the investigated mental disorders. The mean age at which patients were enrolled for a clinical trial varied among the specific mental disorders. The range between the study with the lowest and the one with the highest mean age differed among the mental disorders. A narrow range of the age ranges and gender distributions across various studies demonstrates that results are very homogenous across all countries with different cultures and ethnical groups. Deductively, a natural cause of disease, for example related to genetic factors, seems more probable than psychosocial causes.

Patients diagnosed with anorexia nervosa and bulimia nervosa had the lowest mean age among all respondents of RCTs. The mean age of patients diagnosed with bulimia nervosa and borderline personality disorder was similar. Patients suffering from anxiety disorders ranged in the mean age from 35–41 years. Among those, patients suffering from generalized anxiety disorder had the highest mean age. Patients diagnosed with schizophrenic spectrum disorder, mania and bipolar disorder had a similar mean age of 38–40 years. No significant age-related difference between patients diagnosed with schizophrenia only or any schizoaffective disorder could be found. The mean age of patients being recruited for a clinical trial and diagnosed with an affective disorder ranked from 38–45 years. Patients affected from depression and dysthymia were significantly older than patients suffering from mania or bipolar disorder. The mean age of Alzheimer's disease and vascular dementia, representing the highest mean age among all mental disorders, was similar.

Gender differences in rates and patterns of mental disorders belong to the most stable findings in psychiatry. For some mental disorders, distribution of rates of psychiatric disorder were almost balanced for men and women but remarkable gender differences have been found in the patterns of the diseases. For example, marked gender differences occur in age-of-onset of symptoms, frequency of symptoms, course of disease, social adjustment, and long term outcome. Psychosocial, genetic, and biological components have been discussed as possible determinants for the higher prevalence of mental disorders among women. Different treatment utilization and social behaviours could result in a sampling bias of gender distribution of patients with mental disorders participating in RCTs. More research on gender disparities in mental health is clearly needed.

Overall, most of the results of the gender distribution reconfirm previous findings of epidemiological psychiatry. Therefore it seems probable that the data is representative. Some disorders are known to have a highly unbalanced gender distribution of prevalence estimates in populations which seems to be reflected in the gender-related participation rate of RCTs. Eating disorders, including binge eating disorder, and borderline personality disorder are predominantly diagnosed in women and depict the majority of respondents of RCTs. Furthermore, findings of gender differences in respondents of RCTs occured particularly in the

rates of depression and dysthymia, anxiety and somatic complaints, except for social anxiety disorder, alcohol dependence, schizophrenia and related disorders, and primary insomnia. There were no marked gender differences in the rates of mania and social anxiety disorder.

Results of the mean age and gender distribution of patients being recruited into the investigated studies will be discussed in detail hereafter.

4.1 Mean age distribution in detail

Among the respondents with mental disorders that have been investigated, patients with the lowest mean age were those affected by anorexia nervosa (25.3 ±7.1, weighted mean age and pooled SD in years), and bulimia nervosa (26.9 ±7.6 yrs). The sample of adolescents diagnosed with anorexia nervosa were on average 15.1 ±1.5 years old. The sample of anorectic patients was subdivided into adults and adolescents, deductively the sample size of subgroups appeared relatively small. However, results still seem reliable, as the range between the study with the lowest and the one with the highest mean age was found to be quite narrow. No significant difference of mean age could be found according to gender of either anorexia nervosa or bulimia nervosa. The results make clinical sense, as it is well known that rates of anorexia nervosa and bulimia nervosa are highest among young women. By trend, patients affected by anorexia nervosa are younger than those affected by bulimia nervosa, which might be reflected in a higher mean age of patients with bulimia nervosa. A substantial degree of crossover from anorexia nervosa to bulimia nervosa has been described within the first years of the disease (Bulik et al. 1997; Eckert et al. 1995; Eddy et al. 2002; Strober et al. 1997; Tozzi et al. 2005).

The proximity of the mean age of patients diagnosed with bulimia nervosa and borderline personality disorder (30.7 ±8.6 yrs) supports the assumption of a nosological proximity of these disorders. Women diagnosed with borderline personality disorder had a lower mean age (29.2 ±7.6 yrs) than the cohort of both genders (31.1 ±8.8 yrs).

Among the eating disorders that have been investigated, respondents of RCTs who were diagnosed with binge eating disorder were on average approximately 20 years older than patients with anorexia nervosa (45.4 ±9.5 yrs). Women diagnosed with binge eating disorder

had a lower mean age (42.0 ±10.5 yrs) than the cohort of both genders (45.7 ±9.4 yrs). In clinical settings, patients with binge eating disorder frequently report a long history of their disease, presenting for treatment decades after onset of the syndrome (Mussell et al. 1995). The course of binge eating disorder is marked by spontaneous remission and resurgence of symptoms, possibly being reflected in a broader range between the study with the lowest and the one with the highest mean age.

Patients diagnosed with dementia who participated in clinical studies had the highest mean age among the mental disorders that have been investigated. Patients suffering from Alzheimer's disease were on average 74.8 ±8.2 years old, the mean age of patients with vascular dementia was 72.7 ±6.5 years. Alzheimer's disease and vascular dementia are the two most common causes of dementia in older people. Mixed dementia, in which both pathologies coexist in a patient, is rarely diagnosed in the clinic and often biased towards a diagnosis of Alzheimer's disease, though possibly comprising the majority of cases (Kalaria 2002). The majority of clinical studies did not exclude cases with mixed dementia, possibly due to a pressure to recruit. The proximity of the mean age of the two forms of dementia allows the assumption that mixed dementia might represent most of the cases in clinical studies. Though less than 50 studies were eligible for either studies assessing patients diagnosed with Alzheimer's disease or vascular dementia, analysis still seems powerful due to a large total sample size. The range between the study with the lowest and the one with the highest mean age was found to be relatively broad for Alzheimer's disease. Further research regarding this is needed. Inclusionary criteria for age restrictions of studies accessing patients with dementia were quite inhomogenous, possibly restricting generalizability of findings. Nevertheless, the age range for vascular dementia was found to be relatively narrow, supporting the assumption that results are reliable.

The mean age of patients suffering from anxiety disorders ranged from 35–41 years. Thereof, patients suffering from generalized anxiety disorder had the highest mean age (40.7 ±11.5 yrs). It has been previously described that generalized anxiety disorder has a later age-of-onset than other anxiety disorders, which will possibly be reflected in a later peak of severity and participation in clinical trials. The mean age of patients diagnosed with social phobia was 35.2 ±10.3 years, patients with panic disorder had a mean age of 37.2 ±9.6 years. The range between the study with the lowest and the one with the highest mean age

was found to be relatively narrow for panic disorder, for generalized anxiety disorder it was found to be relatively broad. Further research on this is needed. Anxiety disorders are known to follow a chronic course. It has been previously described that anxiety disorders start in childhood, adolescence, or early adulthood and reach a peak in middle age (Bandelow and Michaelis 2015), decreasing in prevalence rates with older age (Jacobi et al. 2014b), which might be reflected in participation of RCTs. Clinical reports suggest that it will take up to ten years until patients will be diagnosed and receive treatment (Ballenger et al. 2001; Kessler et al. 2001c; Rogers et al. 1999). Clinical studies found that generalized anxiety disorder often is seen in comorbid presentation with major depression. The mean age of major depressive disorder and generalized anxiety disorder are very similar, perhaps reflecting the high diagnostic overlap between these disorders.

Results of the mean age of patients diagnosed with posttraumatic stress disorder (38.3 ±10.1 yrs) need to be interpreted with caution due to a possible sample bias. The majority of studies investigated trauma-related subgroups, restricting generalizability of findings. However, analysis of cohorts in which gender bias was less probable, resulted in a similar mean age of 38.2 ±11.9 years. Overall, mean age seems to be strongly associated with gender and the type and date of trauma. For instance, the mean age of the cohort of veterans (42.6 ±7.2 yrs), being traumatized during adulthood and consisting of a predominantly male sample, was approximately 10 years older than the cohort of sexually assaulted women (33.2 ±9.2 yrs), where trauma happened predominantly during childhood. Findings of these cohorts are limited by a small number of eligible studies and a small sample size, restricting generalizability of findings. The range between the study with the lowest and the one with the highest mean age was found to be quite broad.

Generally, clinical studies found that traumatized patients have been exposed to several traumic events during lifetime (Carey et al. 2003). Studies suggest that the use of care by people who experienced trauma is a feasible approach to assess the severity of their disorder (Andrews et al. 2001), confirming the clinical sense of the method applied in this study. The course and severity of posttraumatic stress disorder is known to depend upon multiple factors, for example the traumatic event, perceived trauma intensity, gender, sociodemographic variables, and comorbidities. It has been suggested that some traumatic events, for example sexual abuse, cause posttraumatic stress disorder more often than others, and that perceived

trauma intensity could be an important factor influencing the development of posttraumatic stress disorder (Breslau et al. 1997). Still, correlates of posttraumatic stress disorder are not fully understood yet. Disorder symptoms occur with a latency of months or years after the experienced trauma. I aimed to analyze data on the latency of onset on the disease, but unfortunately information was not provided in most of the studies.

The mean age of patients being recruited for a clinical trial and diagnosed with an affective disorder ranked from 38–45 years. Patients diagnosed with mania (38.3 ±9.0 yrs) and bipolar disorder (39.6 ±11.1 yrs) had a similar mean age, probably because the majority of manic patients had a diagnosis of bipolar disorder. Patients with bipolar disorder have been recruited in a depressive, manic or mixed episode. The mean age of those patients was more similar to the mean age of patients diagnosed with depressive disorder. Patients affected from major depressive disorder (42.7 ±12.1 yrs) and dysthymia (45.3 ±13.3 yrs) were on average three to seven years older. Depressed patients might possibly wait longer for seeking treatment due to low impulsivity and a tendency to socially withdraw, whereas symptoms of psychosis or risky behaviour of patients in a manic episode may bring the patient to the attention of others, resulting in more immediate access to mental health care and clinical studies, even though treatment-seeking might require external motivation.

Results of studies assessing patients with dysthymia need to be regarded with caution due to a small sample size and few eligible studies. The range between the study with the lowest and the one with the highest mean age was found to be narrower for bipolar disorder than for mania. Further research on this is needed. The majority of RCTs investigating mania included patients with a score of YMRS ≥20, therefore, it is confirmed that severe cases have been represented.

Patients diagnosed with schizophrenic spectrum disorder, mania, and bipolar disorder had a similar mean age of 38–40 years. No significant age-related difference between patients diagnosed with schizophrenia (38.9 ±10.9 yrs) or any schizoaffective disorder (38.3 ±10.7 yrs) could be found. The range between the study with the lowest and the one with the highest mean age was found to be relatively broad for schizophrenic and related disorders. Generally, psychosis is substantial under-representated in community epidemiological studies (Perala et al. 2007), therefore analysis of treated cases in RCTs is a good approach for further

research.

Results of the mean age of patients diagnosed with somatoform disorders (45.4 ±12.7 yrs) might be less representative due to a small total sample size and few eligible studies. One probable reason for the paucity of studies assessing patients diagnosed with somatoform disorder might be that patients do not accept their diagnosis and therefore are reluctant to take part in a clinical study. One prominent feature of the disorder is that patients do often not agree that they have a mental disorder.

Still, the range between the study with the lowest and the one with the highest mean age was found to be relatively narrow.

4.2 Gender distribution in detail

Results of gender distribution reconfirm a female predominance of the majority of affective disorders (female respondents with major depressive disorder 63.3 %, dysthymia 64.6 %, bipolar disorder 57.4 %). There were no notable gender differences in the distribution rates of mania (49.8 % female).

Previous research suggested that women are more likely to evidence affective disorders (Bebbington 1998; Gater et al. 1998; Jacobi et al. 2004; Kessler et al. 1994a; Weissman et al. 1993; Wittchen et al. 1998). Depression has mostly been reported to appear twice as common in women compared with men across different cultures and social contexts. The gender difference in depressive symptoms has been described to emerge in early adolescence and remain throughout adulthood (Nolen-Hoeksema and Girgus 1994). Depression may be more persistent in women (Bracke 2000) and female gender has been described to be a significant predictor of relapse (Kuehner 1999). Traditional female gender role with components of submission and dependence, unpaid domestic work, and low status in society, increases susceptibility of depression. Conversely, improving the status of women should likely improve the mental health of women.

It has been suggested that prevalence rates of bipolar disorder are balanced between women and men, though studies suggested that mixed mania may occur more commonly in women than in men. Gender differences in the course of bipolar disorders have been described.

Women have a geater chance to develop the rapid cycling form of the illness, exhibit more comorbidity (Leibenluft 1997), and are more likely to receive inpatient treatment during the manic phase of the disorder (Hendrick et al. 2000). Women diagnosed with bipolar mania presented with specific patterns of psychotic symptoms that appeared to be associated with greater severity of the acute episode, more mixed states, and a more severe course of illness (Braunig et al. 2009).

Findings of this investigation corroborate a female predominance in generalized anxiety disorder (63.0 %) and panic disorder (65.7 %). No marked gender differences occurred in patients diagnosed with social phobia (50.5 %). An increased risk for women to develop anxiety disorders has been previously described (Gater et al. 1998; Lewinsohn et al. 1998; Merikangas et al. 2002; Weissman et al. 1997; Wittchen et al. 1999; Yonkers et al. 1998). Women had higher rates of lifetime diagnosis for anxiety disorders except for social anxiety disorder, where no gender difference in prevalence rates could be found (McLean et al. 2011). Findings might possibly be associated with evolutionary origins and functions of physiological anxiety. For example, physiological anxiety raises attention and functions as an evolutionary advantage for women in taking care of their offspring.

Results reconfirm that more women than men have posttraumatic stress disorder. Analysis of cohorts in which gender bias appeared less probable, resulted in a gender distribution of 66.9 % of female respondents. Results of all eligible studies (56.7 % female) need to be interpreted with caution due to a sample bias. For example, some studies recruited only female sexual assault victims, and most of the studies recruiting veterans included only male participants. It has been reported that combat experience is most commonly related to posttraumatic stress disorder in men, whereas in women sexual assaults appears as a stronger risk factor (Kessler et al. 1995b).

In general, several studies found that although men are more likely to experience trauma (Breslau and Anthony 2007; Tolin and Foa 2006), more women than men develop posttraumatic stress disorder (Breslau 2002; Breslau 2009; Darves-Bornoz et al. 2008; Frans et al. 2005; Freedman et al. 2002; Wittchen et al. 2009). Previous research suggested that females have an approximately twofold higher prevalence for developing posttraumatic stress disorder compared to males (Ditlevsen and Elklit 2010; Laufer and Solomon 2009; Stallard et al.

2004; Walker et al. 2004). Gender disparity persists in severity of symptoms of posttraumatic stress disorder (Ditlevsen and Elklit 2010; Irish et al. 2011). However, caution is required in drawing conclusions on the consequences of trauma in men because men tend to express their distress more often through behavioural than through affective disorders (Choquet et al. 1997; Darves-Bornoz et al. 1998). A predisposing factor for gender disparity in posttraumatic stress disorder might be the increased ratio of psychiatric disorders before the trauma, such as pre-existing affective or anxiety disorders, which are more common in women (Acierno et al. 1999; Breslau et al. 1991a; Breslau et al. 1997; Mayou et al. 2001; McFarlane 1989; Perkonigg et al. 2000). This may explain why posttraumatic stress disorder shows an age and gender distribution which is similar to the distributions found in major depressive disorder and generalized anxiety disorder. Also, a family history of psychiatric disorders seems to be a predisposing factor (Breslau et al. 1991b; Bromet et al. 1998; Koenen 2006).

Among the respondents diagnosed with somatoform disorders, 71.9 % of the participants were female. It is even mentioned in the classification of DSM that women are predominantly affected by somatoform disorders. Previous research proposed an increased risk for women to develop somatoform disorders (Lieb et al. 2000; Piccinelli and Simon 1997; Smith et al. 2001).

Among the eating disorders that have been investigated, the majority of studies assessed a female sample, therefore results need to be regarded with caution.

Among the studies recruiting both genders, 93.9 % of the respondents diagnosed with anorexia nervosa, 88.1 % of the bulimic participants, and 83.0 % of the sample diagnosed with binge eating disorder were female. It is well known that anorexia and bulimia nervosa are more likely to occur among females than males (Hoek 2006; Striegel-Moore and Bulik 2007). Bulimia nervosa is described to occur about nine times more likely in women than in men, anorexia nervosa is estimated to occur about ten times more commonly in females (Smink et al. 2012). Previous research found the pronounced gender bias typically not as large in binge eating disorder (Hudson et al. 2007; Striegel et al. 2012), varying from approximately a 2:1 to a 6:1 ratio (Agh et al. 2015). The female predominance may be explained by sociocultural and biologically-based factors. For instance, binge eating disorder occurred two to six times more often in female rats compared to male rats (Klump et al.

2013). The authors concluded that gonadal hormones may lead to an increased reward responsiveness to food in females, tending to override homeostatic mechanisms.

Results of this investigation show that only 26.3 % of the respondents diagnosed with alcohol dependence were female. It is well known that significantly higher rates of alcohol dependence can be found among men (Brady and Randall 1999). Population based studies reported that the lifetime prevalence rate for alcohol dependence is more than twice as high in men than women. Generally, men tend to express their distress through behavioural disorders. However, depression and anxiety appear as frequent co-occuring diagnoses, illustrating the need for gender awareness to reduce gender stereotypes and assess accurate diagnosis of both affective disorders and alcohol dependence in men and women, if they are present. In comparison to mood disorders, rates of alcohol dependence among women are quite low. It does not seem probable that these disorders correlate directly with each other, because in that case prevalence rates of alcohol abuse should be higher among women and not the other way around.

A male predominance of respondents diagnosed with schizophrenia spectrum disorder could be observed (36.2 % female). No significant difference to patients diagnosed with schizophrenia only (35.2 %) was found. Estimates of gender distribution of schizophrenia related disorders are not stable in psychiatric epidemiology. It is though generally accepted that schizophrenia typically appears earlier, anywhere between 3–10 years, in men than in women (Hafner et al. 1992; Hafner et al. 1994; Hafner and an der Heiden 1999; Hambrecht et al. 1992; Hambrecht et al. 1994). Assuming that a greater severity of illness is associated with an early age-of-onset of the illness, men would develop relatively severe episodes of the disorder early and milder forms at older ages (Hafner 2003). In contrast, young women present milder cases (Hafner 2003), and show a post-menopausal peak with a higher incidence and more severe episodes of the disease. Theories that may explain this gender difference include the protective effect of estrogen until menopause, as estradiol has been found to be effective in treating schizophrenia when added to antipsychotic therapy (Kulkarni et al. 2001). Despite later outbreak of the disease, some studies report that women experience hallucinations more frequently and generally show more positive psychotic symptoms than men (Lindamer et al. 1999). However, sex differences in illness behaviour presumably influence the social course and outcome of the disorder (Hafner 2003). Men show socially

unfavorable illness behaviour more likely than women, which might contribute to their poorer social course and outcome (Hafner 2003), and bring them to the attention of others. Women tend to show prosocial behaviour, for example cooperating and showing a better therapy compliance, possibly leading to a better outcome of the disease.

More women than men diagnosed with Alzheimer's disease participated in RCTs (56.5 %), whereas a male predominance of patients diagnosed with vascular dementia could be observed (43.5 % female). Previous research of the age-specific incidence of Alzheimer's disease (Bachman et al. 1993; Barnes et al. 2003; Evans et al. 2003; Hebert et al. 2001; Kukull et al. 2002; Miech et al. 2002; Rocca et al. 1998) or any form of dementia (Bachman et al. 1993; Fillenbaum et al. 1998; Fitzpatrick et al. 2004; Kukull et al. 2002; Rocca et al. 1998) found no significant difference by gender. On average women live longer than men, accordingly, more women will be diagnosed with any form of dementia (Hebert et al. 2001; Seshadri et al. 1997).

Results depicting a predominance of 78.5 % female participants of RCTs diagnosed with borderline personality disorder reconfirm an unbalanced gender proportion that has been described in previous studies and DSM. Some studies though reported about equal prevalence among men and women, and assume that gender bias affects gender distribution in diagnosing mental disease (Bjorklund 2006; Grant et al. 2008). Certainly, there appear to be notable gender differences with regard to personality traits, comorbidity, and treatment utilization, leading to an overrepresentation of women in mental health service (Sansone and Sansone 2011). In contrast, men with borderline personality disorder tend to show substance abuse and would be overrepresented in substance abuse treatment programs (Sansone and Sansone 2011).

5. Limitations

The findings need to be interpreted within the context of the study limitations.

The assumption that the average patient participates in a clinical trial when psychiatric symptoms have reached a high degree of severity, is difficult to prove. The design of the present investigation cannot resolve this issue and further analyses should elaborate in greater detail about access and patterns of participation in clinical trials and the use of mental health care in general. Various factors might influence the admission for a clinical trial at certain age. For instance, participation in a clinical trial might depend on the diagnostic category and according to variables such as insight of the disease, psychological strain, and treatment adherence.

One is also to analyze the impact of previous treatment to the course of mental illness, e.g. psychological treatment and the use of maintenance medication. Monetary motives can be regarded as insignificant because few trials offer allowance to participants due to ethical and scientific considerations.

Not all different severity levels of disorders are being represented in the clinical trials because of sample frame exclusions. Sample frame exclusions such as age restrictions further restrict generalizibility of research findings. Those who do not seek help cannot be represented. It needs to be questioned whether the cross-national data can be regarded as representative, as demographic correlates have not been investigated. Further and more detailed analyses that would allow us to evaluate the reporting bias are not possible with the present data set. Further research regarding this is clearly needed.

Due to the large sample size and a high number of included studies, the results can be regarded as highly reliable. Every effort was taken to exclude studies which assessed a sample that could lead to a possible bias (e.g. studies including only young patients, patients in a mild phase of their disease, or only women). Age-restricted cohorts were included but restrictions attributed to these conditions did not affect the mean age of the sample.

I am not aware of any reasonable systematic bias that could lead to a distortion in the way that that the mean age of patients at a severe phase of their disease significantly differs from

the average age determined in randomized controlled studies, with one possible exception. An important potential limitation might be the fact that certain high-risk groups might not be appropriately covered, such as patients with a poor physical health status, severe comorbidities, or suicidal intention. Sample selection bias could be caused by early mortality or sufficient morbidity related to a history of mental disorders, which makes it impossible to participate in a survey or leads to an exclusion from the sample. Especially elderly patients tend to show high rates of somatic comorbidities and are therefore more likely to be excluded from participation in a clinical trial.

Admission for a RCT may be less representative for gender distribution of certain disorders. For example, obesity may be more problematic for women than for men, thus, more women than men could seek help for treatment, explaining a female predominance of participation rates in studies for binge eating disorder.

The study investigated the most common and thus most relevant mental disorders. A standard limitation of studies of that sort is that not all randomized clinical trials could be included due to missing data and limited access to full-texts. Despite systematic and thoroughly research, not enough eligible study material could be found for studies assessing individuals diagnosed with antisocial personality disorder and paedophilia. Some of the available studies were excluded, e.g. investigation of patients diagnosed with comorbid substance abuse. Analyses of subgroups and some mental disorders, e.g. dementia, dysthymia, and somatoform disorders, might be less representative because less than 50 eligible studies were found. Partly, data was not indicated for the drop out sample.

Considering the limitations named above, the data set provided represents a good estimator for analyzing the mean age and gender distribution.

6. Conclusion

Based on the assumption that patients are most probably enrolled in a clinical trial when they suffer the most from their disease, the data of the mean age and gender distribution of respondents of more than 800 clinical trials provide information of the age-related severity of mental disease. Results confirm that patients have been recruited for a clinical study at a similar age for each of the investigated mental disorders. The specific mental disorders varied for the mean age at which individuals were enrolled for a clinical trial. Results of gender distribution predominantly reconfirm findings of previous epidemiological investigations.

These results lead to important conclusions. A better understanding of the course and prognosis of mental illness may help to explore the nature and impact of mental disorders in general. Patients can be provided with information about the prognosis of the natural course of their disorder, as the mean age at which symptoms of a mental disorder reach a climax and decrease afterwards might be predicted. Moreover, data of this sort can be helpful for further investigations, learning and teaching of medical students and physicians, and in a final step for policy planning. The results can be used in articles or textbooks and can help health care providers or researchers to plan treatment programs. Information about the particular age of the most severe phase of the mental disease might be relevant for the formulation of DSM and ICD diagnostic criteria.

Data might help to presume accurate diagnoses and direct management accordingly. For instance, a patient with 55 years of age will unlikely suffer from a severe phase of borderline personality disorder, or, if difficulties in distinguishing panic disorder and depression in a patient with 65 years of age arise, it would be helpful to know that panic disorder is more common among younger patients, thus, major depression is the more likely diagnosis.

Medical intervention could be optimized, allowing to target precise interventions adjusted to the age of patients.

The data could contribute to an optimized planning and management of clinical trials, medical wards and rest homes, and in a final step for policy planning. For example, the average age of patients derived from many studies might be established as anchor point to state a trial as representative and detect outliers. Moreover, due to the shifting age structure of the

population and the age-related course of mental illness, it might be predicted that certain mental disorders will demand more attention in future times, whereas other mental disorders appear less frequent.

Further scientific research should elucidate the aetiology of the age-related course and gender distribution of major mental disorders. By determining the correlations of a peak of severity and unbalanced gender distribution of some mental disorders, conclusions regarding underlying factors of mental disorders can be drawn. For example, severity of symptoms of panic disorder peak at around 37 years of age and then tend to decrease. Thus, it can be presumed that the disorder is not based on a neurodegenerative process but rather on some kind hyperactivity of neuronal systems that tends to wane with increasing age.

Also, the data illustrate a narrow range of the age ranges and gender distributions across the investigated studies, demonstrating that the results are very homogenous across all countries with different cultures and ethnical groups. For instance, despite diverse cultural roles of women in society, the majority of studies investigating panic disorder found that approximately 66 % of the participants were women, irrespective of the country of conduction of the study. Thus, natural causes, e.g. genetic or hormonal factors, seem more plausible than psychosocial causes of the mental disorders, as the latter would be expected to vary between cultures and different countries.

7. Summary

The mean age and gender distribution of a total sample size of 151,336 consecutively enrolled respondents with mental disorders participating in 832 RCTs has been analyzed. It was assumed that the average patient is recruited for a randomized clinical study when the degree of severity of the mental illness has reached a peak level. Therefore, by extracting the mean age of patients from a large number of RCTs, reliable data for estimates of the age in which the disorder tends to show the highest degree of severity are being obtained. Results depict a major step in the investigation of course and severity of mental disorders. The results can be used in scientific articles or educational materials and can help health care providers or researchers to plan treatment programs. Patients can be informed about the prognosis of the course of their disorder. Information might be relevant for the formulation of coming-up versions of DSM and ICD diagnostic criteria and help to presume accurate diagnoses. By investigating the correlation of age-related severity and unbalanced gender distribution of some mental disorders, the aetiology of these disorders may be elucidated further.

Altogether, results confirm that patients are being recruited for a clinical study at a similar age for each of the investigated mental disorders. The age at which patients were enrolled for a clinical trial varied among the specific mental disorders. Patients with the lowest mean age were respondents of RCTs diagnosed with anorexia nervosa and bulimia nervosa. The mean age of patients diagnosed with bulimia nervosa and borderline personality disorder was similar, supporting the assumption of a nosological proximity of these disorders. Patients suffering from anxiety disorders ranged in the mean age from 35–41 years. Among those, patients suffering from generalized anxiety disorder had the highest mean age, possibly reflecting the later age-of-onset of the disease. Results of the mean age of PTSD need to be interpreted with caution because of a possible sample bias, still mean age seemed to be strongly associated with gender and the type of trauma. Patients diagnosed with schizophrenic spectrum disorder, mania, and bipolar disorder had a similar mean age of 38–40 years. No significant age-related difference could be found between patients diagnosed with schizophrenia or any schizoaffective disorder. The mean age of patients diagnosed with an affective disorder ranked from 38–45 years. Patients affected by depression and dysthymia

were significantly older than patients suffering from mania or bipolar disorder. The proximity of the mean age of Alzheimer's and vascular dementia, representing the highest mean age among all mental disorders, allows the assumption that mixed dementia might represent most of the cases.

Results show that the range between the study with the lowest and the one with the highest mean age varied among the mental disorders. A narrow range of the age ranges and gender distributions across various studies demonstrates that results are very homogenous across all countries with different cultures and ethnical groups.

Overall, results of gender distribution predominantly reconfirm findings of epidemiological psychiatry. In most of the cases, a female predominance could be found. Eating disorders, including binge eating disorder, and borderline personality disorder are predominantly diagnosed in women and depict the majority of respondents of RCTs. Further gender differences with a female predominance occured in the participation rates of depression and dysthymia, anxiety and somatic complaints (except for social anxiety disorder), obsessive-compulsive disorder, posttraumatic stress disorder, and primary insomnia. More women with bipolar disorder than with mania were recruited. In contrast, the majority of patients diagnosed with schizophrenic spectrum disorders and alcohol dependence syndrome were male. More men than women diagnosed with vascular dementia were recruited, whereas patients with Alzheimer's disease showed a female predominance. There were no marked gender differences in the rates of mania and social anxiety disorder.

An important potential limitation of this study might be the fact that certain high-risk groups might not be appropriately covered, such as patients with a poor physical health status, severe comorbidities, or suicidal intentions. Also, the assumption that the age at which the average patient gets enrolled for a clinical trial is related to a high degree of severity of psychiatric symptoms cannot be proven. Various factors might influence the admission for a clinical trial at a certain age. Health care utilization and participation in a study might depend on the diagnostic category and according to gender. However, statistically, it seems probable that the average patient registers for a clinical trial at the most severe stage of the mental disorder. Altogether, there is no possible bias that could affect the data in a way that the patients included in a study are not the worst cases.

8. Appendix

8.1 Abbreviations

Table 6 Abbreviations

CIDI	Composite International Diagnostic Interview
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESEMeD	European Study of the Epidemiology of Mental Disorders
ICD	International Classification of Diseases
NCS	National Comorbidity Survey
NCS-R	US National Comorbidity Survey Replication
PRC	People's Republic of China
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized clinical trial
SD	standard deviation
SDS	Sheehan Disability Scales
SE	standard error
WHO	World Health Organization
WMH	World Mental Health
YMRS	Young Mania Rating Scale

8.2 Tabulation of the investigated studies

Alcohol Dependence Syndrome	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Addolorato et al. 2002)	45.8	10.6	1.7	?	39	18-70
(Addolorato et al. 2011)	43.9	13.0	2.0	24.0	42	18-60
(Aguiar et al. 2012)	41.0	?	?	16.0	209	?
(Anton et al. 2006)	44.5	10.2	0.3	30.9	1383	?
(Anton et al. 2009)	46.3	10.5	1.3	24.5	60	18-70
(Anton et al. 2011)	44.7	9.6	0.8	18.3	147	?
(Arias et al. 2010)	49.1	10.5	1.7	42.5	40	18-65
(Blondell et al. 2011)	45.3	11.0	0.9	34.7	150	>18
(Brown et al. 2014)	44.4	10.8	1.5	45.0	49	18-65
(Chick et al. 2000)	43.5	9.0	0.7	25.1	175	18-65
(De Sousa et al. 2008)	43.3	?	?	?	100	18-65
(Doyle and Donovan 2009)	40.3	11.0	0.3	25.0	1666	?
(Drummond et al. 2017)	43.0	9.6	1.0	39	94	>18
(Dundon et al. 2008)	43.7	10.9	0.8	25.8	194	>18
(Eberl et al. 2013)	46.0	9.0	0.4	?	509	?
(Farren et al. 2009)	43.2	9.6	0.9	18.0	111	?
(Garbutt et al. 2010)	48.9	7.4	0.8	45.0	80	18-60
(Garland et al. 2010)	40.3	9.4	1.3	20.8	53	>18
(Gual and Lehert 2001)	41.0	9.2	0.5	20.5	288	18-65
(Heffner et al. 2010)	47.4	8.7	0.8	37.3	121	21-65
(Higuchi and Japanese Acamprosate Study 2015)	52.4	12.3	0.7	12.5	327	?
(Johnson et al. 2007)	47.3	9.0	0.5	26.9	364	18-65
(Jung et al. 2011)	48.0	6.9	1.1	26.8	41	?
(Kampman et al. 2009)	48.2	10.6	1.2	18.0	74	18-70
(Kiefer et al. 2011)	44.9	8.6	0.4	?	374	?
(Kiritze-Topor et al. 2004)	47.1	11.3	0.6	27.0	422	>18
(Klauss et al. 2014)	43.3	8.4	1.5	3.0	33	18-75
(Kranzler et al. 2000)	40.9	8.5	0.6	22.4	183	18-60
(Kranzler et al. 2011)	47.5	9.8	0.8	19.4	134	18-65
(Kwako et al. 2015)	43.6	9.4	1.3	10.9	55	21-65
(Laaksonen et al. 2008)	43.1	8.6	0.6	29.2	243	?
(Latt et al. 2002)	44.8	?	?	30.8	107	18-70
(Litt et al. 2009)	48.8	12.3	1.2	42.0	110	>18
(Litt et al. 2015)	45.0	11.4	0.8	41.9	210	>18
(Litten et al. 2013)	45.5	11.7	0.8	29.3	198	>18
(Manzardo et al. 2013)	47.5	7.9	0.7	19.0	120	18-60
(Mason et al. 2009)	39.7	11.9	2.1	21.2	33	?
(Mason et al. 2014)	44.5	10.9	0.9	46.2	150	>18
(McKay et al. 2011)	43.0	7.4	0.5	35.7	252	18-65

Alcohol Dependence Syndrome	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Morley et al. 2014)	46.9	?	?	36.0	42	18-60
(Neto et al. 2008)	41.6	8.2	0.6	16.0	209	?
(Pelc et al. 2005)	43.3	8.0	0.8	12.0	100	18-65
(Penzlin et al. 2015)	42.0	7.5	1.1	29.2	48	>18
(Plebani et al. 2010)	43.7	10.7	0.7	27.1	212	?
(Rose et al. 2015)	48.7	10.0	0.8	47.0	158	>18
(Schacht et al. 2011)	46.3	10.4	1.3	23.3	60	18-70
(Soyka et al. 2008)	44.8	8.8	0.5	19.4	258	18-65
(Tempesta et al. 2000)	45.9	11.2	0.6	11.3	330	18-65
(van den Brink et al. 2014)	44.3	11.4	0.4	23.0	675	>18
(Van Horn et al. 2014)	43.0	7.4	0.5	35.7	252	18-65

Alzheimer's Disease	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Aisen et al. 2008)	76.3	8.0	0.4	56.0	409	>50
(Black et al. 2010)	72.7	8.4	1.5	46.7	30	50-85
(Brodaty et al. 2009)	73.8	7.5	0.6	43.9	155	?
(Butchart et al. 2015)	72.5	2.2	0.3	38.8	41	>55
(Chatellier and Lacomblez 1990)	66.0	7.3	0.9	64.2	67	?
(Filip and Kolibas 1999)	83.0	?	?	?	173	>60
(Fleisher et al. 2008)	69.4	9.2	1.3	49.1	51	>50
(Fleisher et al. 2011)	74.6	8.5	0.9	50.6	89	>55
(Galasko et al. 2012)	72.8	9.0	1.0	46.0	78	50-85
(Galasko et al. 2014)	72.9	9.1	0.5	57.0	399	>50
(Gehrman et al. 2009)	82.9	7.0	1.1	68.3	41	?
(Guo et al. 2013b)	74.7	8.1	0.8	43.1	109	?
(Hussey et al. 2012)	77.5	6.3	1.6	60.0	15	?
(Ihl et al. 2012)	64.5	9.1	0.5	66.1	333	>50
(Li et al. 2013)	75.0	7.8	1.1	60.0	50	?
(Logue et al. 2011)	74.2	8.7	0.3	62.0	655	?
(Mishima et al. 1998)	78.0	?	?	60.0	10	?
(Nordberg et al. 2009)	74.9	7.9	1.0	69.9	63	50-85
(Palmer et al. 2013)	74.8	9.8	1.1	49.4	77	?
(Porsteinsson et al. 2014)	78.0	8.0	0.6	46.0	186	?
(Portelius et al. 2010)	70.4	8.6	1.5	54.3	35	>50
(Quinn et al. 2010)	76.0	8.7	0.4	52.2	402	?
(Raman et al. 2009)	76.0	8.3	0.3	55.2	715	?
(Roach et al. 2011)	87.9	6.1	0.6	?	105	?
(Rubright et al. 2010)	75.5	8.1	0.9	50.5	80	?
(Sabbagh et al. 2011)	75.4	8.3	1.0	61.2	67	>50
(Sano et al. 2011a)	74.6	9.3	0.5	59.4	406	>50
(Sano et al. 2011b)	73.8	8.0	0.8	56.0	111	?

Alzheimer's Disease	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Street et al. 2000)	82.8	6.6	0.5	61.2	206	?
(Tappen et al. 2000)	86.7	?	?	84.0	65	?
(Turner et al. 2015)	71.3	7.9	0.7	57.1	119	>49
(van Dyck et al. 2000)	72.9	8.1	0.3	54.7	850	>45
(Xu et al. 1999)	71.5	8.0	1.0	61.7	60	50-80

Anorexia Nervosa, Adolescents	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Accurso et al. 2014)	14.4	1.6	0.1	90.9	121	12-18
(Accurso et al. 2015b)	14.9	1.8	0.3	87.8	32	12-18
(Agras et al. 2014)	15.3	1.8	0.3	89.2	158	12-18
(Brownstone et al. 2012)	14.4	1.6	0.3	91.7	121	12-18
(Byrne et al. 2015)	14.5	1.6	0.2	89.3	108	?
(DiVasta et al. 2017)	16.3	1.9	0.3	100.0	41	13-21
(Eisler et al. 2016)	15.7	1.7	0.1	91.0	169	13-20
(Faje et al. 2013)	16.7	0.2	0.0	100.0	44	13-18
(Godart et al. 2012)	16.6	1.6	0.2	100.0	60	13-21
(Gowers et al. 2007)	14.1	?	?	92.0	167	12-18
(Hagman et al. 2011)	16.0	2.4	0.5	100.0	40	12-21
(Herpertz-Dahlmann et al. 2014)	15.3	1.5	0.1	100.0	172	11-18
(Le Grange et al. 2011)	15.2	1.6	0.2	89.9	79	12-18
(Le Grange et al. 2012)	14.4	1.6	0.1	91.0	121	12-18
(Le Grange et al. 2016)	15.5	1.5	0.1	87.7	106	12-18
(Lock et al. 2010)	14.4	1.6	0.1	91.0	121	12-18
(Lock et al. 2015)	14.6	1.4	0.2	85.7	35	12-18
(Madden et al. 2015)	14.9	1.5	0.2	95.1	82	12-18
(Misra et al. 2011)	16.5	0.2	0.0	100.0	110	12-18
(Rienecke et al. 2016)	14.4	1.6	0.1	91.8	121	12-18
(Rosling et al. 2016)	15.1	2.0	0.1	100.0	31	<18
(Strokosch et al. 2006)	15.2	1.3	0.1	100.0	123	?

Anorexia Nervosa, Adults	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Andony et al. 2015)	26.7	10.2	1.3	?	64	>18
(Andries et al. 2015)	33.3	12.7	2.6	100.0	24	>18
(Attia et al. 1998)	26.0	?	?	100.0	31	?
(Attia et al. 2011)	27.7	9.1	1.9	95.7	23	>16
(Barbarich et al. 2004)	23.0	6.3	1.2	?	26	?
(Bissada et al. 2008)	26.8	?	?	100.0	34	>18
(Brambilla et al. 2007a)	25.0	6.7	1.2	100.0	30	>18
(Brambilla et al. 2007b)	23.0	4.8	1.1	100.0	20	?
(Channon et al. 1989)	23.8	6.3	1.3	100.0	24	?

Anorexia Nervosa, Adults	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Conceicao et al. 2013)	25.4	8.4	0.7	100.0	137	18-58
(Crisp et al. 1991)	21.7	4.3	0.5	100.0	90	?
(Dare et al. 2001)	26.3	6.7	0.7	98.0	84	>18
(Fassino et al. 2002)	24.8	7.0	1.0	100.0	52	16-35
(Fazeli et al. 2010)	28.6	2.4	0.5	100.0	21	18-45
(Fichter et al. 2013)	24.1	6.1	0.4	100.0	210	>16
(Kaplan et al. 2009)	23.3	4.6	0.5	100.0	93	16-45
(Kaye et al. 2001)	22.5	7.4	1.2	100.0	35	?
(Kim et al. 2014)	23.1	9.4	1.7	100.0	31	>18
(Klein et al. 2010)	25.2	1.1	0.2	100.0	24	16-40
(Lock et al. 2013)	22.7	5.9	0.9	89.0	46	>16
(Marzola et al. 2015)	25.4	9.4	1.1	90.7	75	?
(McClelland et al. 2016)	26.7	8.6	1.2	100.0	49	>18
(Miller et al. 2011)	26.1	6.7	0.8	100.0	77	?
(Mondraty et al. 2005)	25.3	7.4	1.9	?	15	>18
(Nakahara et al. 2006)	26.2	8.5	1.3	100.0	41	?
(Parling et al. 2016)	25.7	7.5	1.1	97.7	43	>18
(Powers et al. 2012)	34.0	13.5	2.9	95.2	21	18-65
(Ruggiero et al. 2001)	24.1	5.1	0.9	?	35	>17
(Schmidt et al. 2012)	26.6	7.9	0.9	92.9	70	>18
(Stacher et al. 1986)	23.1	1.2	0.2	100.0	30	?
(Stacher et al. 1991)	22.0	?	?	100.0	13	18-39
(Steinglass et al. 2007)	27.0	7.4	2.2	100.0	11	18-45
(Steinglass et al. 2014)	28.0	8.0	1.5	93.0	30	16-45
(Trombetti et al. 2016)	22.5	0.5	0.1	100.0	62	18-40
(Vandereycken 1984)	23.5	?	?	100.0	18	?
(Walsh et al. 2006a)	23.3	4.5	0.5	100.0	93	16-45
(Wildes et al. 2012)	32.4	11.4	2.2	100.0	28	>18
(Zipfel et al. 2014)	26.8	8.2	0.5	100.0	242	>18

Binge Eating Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Agras et al. 1995)	47.6	10.1	1.4	86.0	50	?
(Alfonsson et al. 2015)	44.3	10.7	1.1	93.8	96	?
(Appolinario et al. 2003)	35.9	9.6	1.2	88.5	60	18-60
(Balodis et al. 2013)	41.0	10.1	1.6	63.2	38	19-64
(Brambilla et al. 2009)	46.0	9.0	1.6	100.0	30	?
(Brownley et al. 2013)	36.6	10.6	2.2	83.3	24	18-60
(Cambridge et al. 2013)	41.5	10.0	1.3	56.0	63	18-60
(Carter and Fairburn 1998)	39.7	10.0	1.2	100.0	72	18-65
(Cassin et al. 2008)	42.5	12.7	1.2	100.0	108	?
(Castelnuovo et al. 2011)	46.1	10.5	1.4	100.0	60	18-65

Binge Eating Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Claudino et al. 2007)	38.3	10.3	1.2	95.9	73	18-60
(Conceicao et al. 2013)	46.9	10.2	0.6	96.6	259	>18
(Devlin et al. 2005)	43.3	11.9	1.1	78.0	116	18-70
(Dingemans et al. 2009)	39.0	9.6	1.2	100.0	66	18-60
(Eldredge et al. 1997)	45.2	9.8	1.4	95.7	46	?
(Franko et al. 2012)	46.2	10.7	0.3	84.8	1325	?
(Geliebter et al. 2005)	30.2	8.6	1.4	100.0	37	?
(Golay et al. 2005)	40.9	6.2	0.7	91.0	89	18-65
(Grilo et al. 2011)	44.8	9.4	0.8	67.0	125	18-60
(Grilo et al. 2012)	44.0	8.6	0.8	78.0	108	18-60
(Grilo et al. 2013)	45.8	11.0	1.6	79.0	48	18-65
(Grilo et al. 2014)	43.9	11.2	1.1	70.2	104	18-65
(Hilbert et al. 2012)	44.9	10.2	1.1	78.9	90	?
(Hudson et al. 1998)	42.6	9.7	1.1	90.5	85	18-60
(Hudson et al. 2017)	38.7	10.0	0.6	87.6	267	18-55
(Jacobs-Pilipski et al. 2007)	41.8	9.6	0.5	90.3	451	18-65
(Leombruni et al. 2008)	39.6	8.5	1.3	100.0	42	18-65
(Linde et al. 2004)	50.7	?	?	71.8	1632	>18
(Masheb and Grilo 2008)	46.0	9.1	1.1	81.0	75	18-60
(Masheb et al. 2011)	45.8	7.6	1.1	76.0	50	?
(McElroy et al. 2003)	40.8	8.7	1.1	86.9	61	18-60
(McElroy et al. 2013)	45.2	11.3	1.4	90.0	62	>18
(McElroy et al. 2015)	41.3	12.0	1.5	85.0	60	18-65
(McElroy et al. 2016)	38.0	10.2	0.4	85.9	745	18-55
(Mitchell et al. 2003)	42.0	10.9	4.1	85.7	7	>18
(Peterson et al. 2009)	47.1	10.4	0.7	87.6	227	>18
(Peterson et al. 2013)	46.9	10.3	0.6	87.6	259	>18
(Puhl et al. 2011)	45.7	8.2	1.3	?	40	21-65
(Robinson and Safer 2012)	52.2	10.6	1.1	85.0	101	>18
(Robinson et al. 2015)	47.0	15.3	2.3	86.0	43	>18
(Safer et al. 2010)	52.2	10.6	1.1	85.0	101	>18
(Shingleton et al. 2015)	46.6	10.8	0.3	84.3	1325	?
(Sysko et al. 2010a)	48.5	12.0	0.8	85.3	205	?
(Telch et al. 2001)	50.0	9.1	1.4	100.0	44	18-65
(Utzinger et al. 2015)	46.7	10.2	0.7	90.0	189	?
(White and Grilo 2013)	44.1	12.5	1.6	100.0	61	18-65
(Wilfley et al. 2002)	45.3	9.6	0.8	82.7	162	18-65
(Wilfley et al. 2008)	42.0	9.8	0.6	90.0	304	18-65
(Wilson et al. 2010)	48.4	11.9	0.8	85.3	205	>18
(Zunker et al. 2010)	46.5	10.2	0.8	?	179	>18

Bipolar Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Amsterdam and Shults 2005)	38.0	14.2	4.1	75.0	12	>18
(Ball et al. 2006)	42.1	14.6	2.0	57.7	52	>18
(Bauer et al. 2016)	45.5	12.0	2.4	48.0	25	18-65
(Bobo et al. 2011)	40.5	9.5	1.3	67.0	50	18-64
(Bobo et al. 2014)	38.9	12.1	0.6	58.7	482	18-68
(Bowden et al. 2000)	39.2	11.8	0.6	51.0	369	18-75
(Bowden et al. 2008)	43.6	12.5	0.7	54.0	298	18-75
(Brown et al. 2009a)	37.0	11.1	0.5	60.0	410	18-60
(Calabrese et al. 2005)	36.8	9.7	0.5	61.6	314	>18
(Costa et al. 2011)	40.2	11.2	1.8	61.5	39	18-60
(de la Cruz et al. 2013)	42.0	11.3	0.6	66.7	384	>18
(Depp et al. 2015)	47.5	12.8	1.4	58.5	82	>18
(Durgam et al. 2015b)	38.4	10.7	0.7	33.5	236	18-65
(Frank et al. 2008)	35.4	10.5	0.9	59.2	125	18-60
(Ghanizadeh et al. 2014)	30.0	9.5	1.3	52.0	50	>18
(Hammersley et al. 2003)	40.5	10.4	1.1	66.6	96	>16
(Husain et al. 2017)	34.5	?	?	61.8	34	18-65
(Jones et al. 2015)	39.1	11.6	1.4	70.2	67	18-65
(Lam et al. 2003)	43.9	11.4	1.1	56.3	103	18-70
(Lam et al. 2005)	44.0	11.5	1.1	53.8	103	?
(Lee et al. 2013)	31.6	11.2	1.0	47.4	135	?
(Lee et al. 2014)	31.8	11.6	0.8	49.1	232	?
(Macfadden et al. 2009)	38.9	11.9	1.1	28.2	124	18-70
(Meyer and Hautzinger 2012)	44.0	11.9	1.4	50.0	76	18-65
(Miklowitz et al. 2003)	35.6	10.2	1.0	63.0	101	18-65
(Miller et al. 2008)	39.5	11.3	1.2	42.9	91	18-75
(Muzina et al. 2008)	38.2	12.2	2.3	67.9	28	?
(Nugent et al. 2014)	46.0	12.0	2.6	71.4	21	18-65
(Perlick et al. 2010)	34.7	15.0	2.4	62.5	40	18-65
(Perry et al. 1999)	44.5	12.0	1.4	68.0	69	18-75
(Peters et al. 2014)	40.0	11.8	0.8	60.0	205	?
(Prien et al. 1984)	38.1	12.4	0.8	58.0	216	21-60
(Quiroz et al. 2010)	39.0	12.1	0.7	48.5	303	18-65
(Quitkin et al. 1981)	36.8	13.1	1.5	52.0	75	?
(Simon et al. 2005)	44.2	12.9	0.6	68.5	441	>18
(Simon and Rutter 2008)	44.0	?	?	68.0	441	?
(Stange et al. 2013)	39.9	11.8	1.1	61.0	105	>18
(Sylvia et al. 2014a)	39.1	12.3	0.7	57.0	283	?
(Sylvia et al. 2014b)	39.9	12.1	0.9	59.0	200	>18
(Szegedi et al. 2012)	39.3	11.9	0.7	42.3	324	>18
(Thomas et al. 2008)	43.5	12.6	1.2	59.2	120	18-65
(Tohen et al. 2009)	39.2	11.9	0.4	57.7	731	>18
(van der Voort et al. 2015)	45.6	10.7	0.9	64.1	138	18-65

Bipolar Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Vieta et al. 2008)	43.5	11.9	1.6	65.5	55	>18
(Vieta et al. 2012)	35.6	11.0	0.6	52.4	398	18-65
(Vieta et al. 2007)	35.5	?	?	62.1	108	18-65
(Waxmonsky et al. 2014)	42.0	?	?	67.0	384	?
(Weisler et al. 2008)	37.0	11.3	1.1	62.2	111	>18
(Yatham et al. 2007a)	40.9	12.8	1.8	51.2	49	18-65
(Zaretsky et al. 2008)	40.7	12.0	1.4	?	79	18-60

Borderline Personality Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Bateman and Fonagy 2013)	31.1	7.7	0.7	80.0	134	18-65
(Bedics et al. 2012)	29.3	7.5	0.7	100.0	101	?
(Berking et al. 2009)	28.9	7.5	0.8	100.0	81	?
(Black et al. 2014)	29.5	8.3	0.8	70.9	95	18-45
(Black et al. 2016)	31.7	8.4	1.2	88.0	49	>18
(Blum et al. 2008)	31.5	9.5	0.9	83.0	124	>18
(Bogenschutz and George Nurnberg 2004)	32.6	10.3	1.6	62.5	40	?
(Borschmann et al. 2013)	35.8	11.6	1.2	80.7	88	>18
(Bos et al. 2010)	32.4	?	?	86.1	79	?
(Brown et al. 2009b)	30.0	7.3	0.8	100.0	77	18-45
(Brune et al. 2015)	27.5	7.3	1.9	66.7	15	?
(Carter et al. 2010)	24.5	6.1	0.7	100.0	70	18-65
(Clarkin et al. 2007)	30.9	7.9	0.8	92.2	90	18-50
(Cottraux et al. 2009)	33.5	9.3	1.1	76.9	65	18-60
(Davidson et al. 2006)	31.0	9.1	0.9	84.0	106	18-65
(Davidson et al. 2010)	32.0	?	?	84.0	106	?
(de la Fuente and Lotstra 1994)	32.7	?	?	70.0	20	?
(Doering et al. 2010)	27.3	7.2	0.7	100.0	104	18-45
(Farrell et al. 2009)	35.6	8.7	1.5	100.0	32	18-65
(Fertuck et al. 2012)	29.5	8.3	1.5	87.1	31	?
(Fleischer et al. 2015)	24.8	5.8	1.0	100.0	37	18-65
(Giesen-Bloo et al. 2006)	30.6	7.7	0.8	93.0	86	18-60
(Gratz et al. 2014b)	33.2	11.0	1.4	100.0	61	18-60
(Gratz et al. 2014a)	32.5	10.9	1.5	100.0	51	18-60
(Hollander et al. 2001)	38.6	10.4	2.3	52.4	21	?
(Kramer et al. 2011)	30.8	10.1	2.0	71.0	25	18-60
(Linehan et al. 2008)	36.8	9.0	1.8	100.0	24	18-60
(Loew et al. 2006)	25.3	5.5	0.7	100.0	56	?
(McMain et al. 2009)	30.4	9.9	0.7	86.1	180	18-60
(Neacsiu et al. 2010)	31.4	7.4	0.7	100.0	108	?
(Neacsiu et al. 2014)	29.3	7.5	0.7	100.0	101	18-45
(Nurnberg 2011)	33.0	10.8	0.5	73.6	451	18-65

Borderline Personality Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Pascual et al. 2008)	29.2	?	?	81.7	60	?
(Pascual et al. 2015)	32.6	7.4	0.9	74.3	70	18-45
(Pfohl et al. 2009)	29.0	7.5	0.6	85.0	164	>18
(Reich et al. 2009)	31.2	?	?	88.9	27	?
(Rinne et al. 2002)	29.2	7.6	1.2	100.0	38	18-50
(Salzman et al. 1995)	36.4	?	?	63.6	22	?
(Sauer and Baer 2012)	27.0	?	?	90.0	40	>18
(Schmahl et al. 2012)	28.8	8.5	1.7	100.0	25	18-50
(Schulz et al. 2008)	31.8	9.6	0.5	71.0	314	18-65
(Simpson et al. 2004a)	36.1	10.3	2.1	100.0	25	?
(Soler et al. 2005)	27.0	5.9	0.8	86.7	60	18-45
(Soler et al. 2016)	32.4	7.5	1.7	93.4	44	18-45
(Soloff et al. 1989)	25.1	?	?	75.6	90	?
(Soloff et al. 1993)	26.7	7.2	0.7	75.9	108	?
(Wingenfeld et al. 2014)	24.3	5.7	0.9	100.0	38	?
(Zanarini and Frankenburg 2001)	27.0	6.7	1.3	100.0	28	?
(Zanarini and Frankenburg 2003)	26.3	6.2	1.1	100.0	30	18-40
(Zanarini et al. 2011)	33.0	10.8	0.5	73.6	451	?

Bulimia Nervosa	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Accurso et al. 2015a)	27.3	9.6	1.1	72.9	80	>18
(Agras et al. 2000)	28.1	7.2	0.5	?	220	?
(Bachar et al. 1999)	24.1	3.3	0.7	100.0	25	?
(Bailer et al. 2004)	23.8	4.5	0.5	?	81	>17
(Bello et al. 2010)	23.8	4.6	1.5	100.0	10	18-42
(Blouin et al. 1988)	25.4	6.2	1.3	100.0	22	?
(Blouin et al. 1993)	26.0	1.9	0.4	100.0	19	?
(Burton and Stice 2006)	21.0	5.3	0.6	100.0	85	18-55
(Carter et al. 2003)	27.0	8.0	0.9	100.0	85	>17
(Conceicao et al. 2013)	26.1	8.3	0.5	96.6	255	18-61
(Crow et al. 2009)	29.0	10.7	0.9	100.0	128	?
(Crow et al. 2013)	29.7	8.9	0.5	100.0	293	>18
(Daniel et al. 2016)	25.8	4.9	0.6	98.6	70	>18
(Devlin et al. 2012)	24.0	3.0	0.5	100.0	32	18-45
(Durand and King 2003)	26.4	5.9	0.7	100.0	68	>18
(Ellison et al. 2016)	27.3	9.6	1.1	90.0	80	>18
(Ertelt et al. 2011)	29.3	11.0	1.0	57.5	116	>18
(Esplen et al. 1998)	26.6	6.0	0.9	?	50	?
(Fairburn et al. 1986)	22.9	4.4	0.9	?	24	>17
(Fassino et al. 2004)	27.1	6.7	1.3	100.0	28	?
(Freeman et al. 1988)	24.2	5.6	0.5	100.0	112	>18

Bulimia Nervosa	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Garner et al. 1993)	24.2	4.2	0.6	100.0	50	18-35
(Grob et al. 2012)	25.2	3.5	0.8	100.0	19	?
(Hsu et al. 1991)	25.4	7.0	0.8	100.0	68	?
(Katzman et al. 2010)	29.3	7.5	0.5	?	225	?
(Klein et al. 2009)	24.5	1.6	0.5	100.0	11	18-40
(Lavender et al. 2012)	27.7	7.5	0.9	92.7	70	18-60
(Lavender et al. 2014)	27.3	9.6	1.1	90.0	80	?
(Mitchell et al. 2008)	29.0	10.7	0.9	98.5	128	>18
(Mitchell et al. 2011)	29.7	8.9	0.5	?	293	>18
(Nickel et al. 2005)	21.3	2.9	0.4	100.0	60	>18
(Poulsen et al. 2014)	25.8	4.9	0.6	98.6	70	>18
(Robinson et al. 1985)	25.0	?	?	100.0	15	?
(Sabine et al. 1983)	24.0	?	?	100.0	50	16-65
(Safer et al. 2001)	34.0	11.0	2.0	100.0	31	18-65
(Schmidt et al. 2006)	28.9	8.4	1.1	?	60	?
(Schmidt et al. 2008)	27.1	7.6	0.8	96.9	97	?
(Schutzmann et al. 2010)	23.8	3.6	0.5	100.0	47	?
(Smitka et al. 2011)	24.3	1.4	0.5	100.0	8	>18
(Steele and Wade 2008)	26.0	5.8	0.8	97.9	48	>16
(Steele et al. 2011)	26.0	6.3	0.7	97.7	87	>16
(Stice et al. 2008)	21.0	5.3	0.6	?	85	18-55
(Sysko et al. 2010b)	28.0	7.8	0.3	?	785	>18
(Thiels et al. 1998)	28.1	8.0	1.0	?	62	>15
(Treasure et al. 1994)	25.9	6.2	0.7	?	81	?
(Treasure et al. 1996)	25.8	5.9	0.6	?	110	?
(von Wietersheim et al. 2008)	30.5	8.6	0.9	100.0	93	>18
(Wagner et al. 2013)	24.6	4.2	0.4	?	126	16-35
(Walsh et al. 1997)	26.7	4.9	0.5	100.0	92	18-45
(Walsh et al. 2004)	30.6	7.8	0.8	100.0	91	18-60

Dysthymia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Amore et al. 2001)	47.1	13.8	0.8	67.9	324	18-75
(Ebrahimi et al. 2013)	31.1	9.7	1.2	55.0	62	20-65
(Hegerl et al. 2010)	46.4	14.6	0.8	68.2	368	>18
(Hellerstein et al. 2001)	45.1	9.8	1.5	50.0	40	21-65
(Helmreich et al. 2012)	46.5	15.3	0.9	67.2	287	>18
(Hermens et al. 2007)	46.0	16.0	1.2	73.0	181	>18
(Judd et al. 2004)	43.5	11.7	0.9	59.3	162	>18
(Oxman et al. 2008)	55.2	16.0	1.3	58.2	141	>18
(Posner et al. 2013)	37.8	9.0	1.4	41.5	41	?
(Rapaport et al. 2011)	49.1	14.6	1.9	50.7	59	?

Dysthymia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Ravindran et al. 2013)	41.5	11.5	1.8	47.5	40	18-60
(Shelton et al. 1997)	41.7	9.1	0.4	64.9	410	25-65
(Zanardi and Smeraldi 2006)	45.0	12.0	0.9	68.4	193	18-60

Generalized Anxiety Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Amsterdam et al. 2009)	45.7	12.7	1.7	59.6	57	>18
(Andersson et al. 2012c)	40.1	12.1	1.3	76.5	81	>18
(Andreatini et al. 2002)	53.4	8.4	1.4	52.8	36	?
(Arntz 2003)	35.9	?	?	66.7	45	18-69
(Ball et al. 2013)	38.4	12.0	0.9	51.8	168	>18
(Bose et al. 2008)	37.0	13.0	1.1	61.0	143	>18
(Coric et al. 2010)	38.9	?	?	?	260	18-65
(Crits-Christoph et al. 2011)	46.3	16.5	1.5	67.6	117	>18
(Czobor et al. 2010)	44.8	10.4	1.3	65.1	60	18-60
(Dahl et al. 2005)	41.4	11.3	0.6	55.0	373	>18
(Dahlin et al. 2016)	39.5	10.7	1.1	83.5	103	>18
(Davidson et al. 2004a)	39.5	12.6	0.7	52.7	315	18-80
(Dear et al. 2015)	43.8	11.3	0.6	76.0	338	18-64
(Dugas et al. 2010)	38.5	12.0	1.5	66.1	65	18-64
(Dunayevich et al. 2008)	46.2	15.9	2.4	61.4	44	>18
(Durgam et al. 2016)	40.0	13.1	0.7	65.4	404	18-70
(Durham et al. 1997)	39.0	?	?	67.0	110	18-65
(Eagleson et al. 2016)	31.0	11.3	1.4	?	70	18-65
(Feltner et al. 2003)	37.8	11.1	0.7	52.7	271	>18
(Feltner et al. 2008)	37.2	?	?	58.0	624	>18
(Feltner et al. 2009)	38.8	12.1	0.6	62.6	422	18-65
(Fluckiger et al. 2016)	43.9	12.1	1.6	75.4	57	>18
(Gelenberg et al. 2000)	39.5	11.5	0.7	59.0	238	>18
(Gommoll et al. 2015b)	40.3	13.1	0.7	69.4	398	18-70
(Gommoll et al. 2015a)	40.2	13.6	0.5	64.5	673	18-70
(Goodman et al. 2005)	40.5	13.5	0.9	61.5	252	>18
(Hartford et al. 2007)	40.8	13.7	0.6	62.6	487	>18
(Hayes-Skelton et al. 2013)	32.9	12.2	1.4	65.4	81	>18
(Hoge et al. 2013)	39.2	8.2	0.9	50.8	89	>18
(Holzel et al. 2013)	37.9	12.2	2.4	53.8	26	?
(Hoyer et al. 2009)	45.4	12.5	2.1	52.7	36	18-70
(Jonsson and Kjellgren 2016)	43.0	13.4	1.9	70.0	50	18-65
(Kasper et al. 2009)	40.8	11.9	0.6	61.0	374	18-65
(Katzman et al. 2011)	42.4	12.2	0.3	63.8	1224	18-65
(Kim et al. 2006)	44.4	8.5	1.3	60.9	46	18-65
(Koponen et al. 2007)	43.8	13.0	0.6	67.8	513	>18

Generalized Anxiety Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Koszycki et al. 2010)	43.5	13.8	2.9	59.1	22	?
(Koszycki et al. 2014)	42.4	16.7	3.5	65.3	23	>18
(Millstein et al. 2015)	32.9	?	?	65.4	81	>18
(Newman et al. 2011)	37.0	?	?	75.0	83	18-65
(Nicolini et al. 2009)	42.8	?	?	57.1	581	>18
(Paxling et al. 2011)	39.3	10.8	1.1	79.8	89	>18
(Power et al. 1990)	40.4	?	?	71.3	101	18-65
(Rapaport et al. 2006)	41.8	12.4	1.1	71.3	129	>18
(Rickels et al. 2005)	39.2	11.6	0.5	63.8	454	>18
(Rickels et al. 2010)	46.3	16.4	0.9	62.9	334	>18
(Robinson et al. 2010)	47.0	12.7	1.1	68.3	145	>18
(Roemer et al. 2008)	33.6	11.7	2.1	71.0	31	>18
(Rynn et al. 2008)	41.6	14.1	0.8	61.8	327	>18
(Sherman et al. 2010)	43.0	11.3	1.4	76.1	68	18-70

Mania	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Allen et al. 2006b)	39.2	11.6	0.6	45.4	374	?
(Amrollahi et al. 2011)	30.7	9.2	1.4	37.5	40	?
(Bahk et al. 2005)	37.6	?	?	49.9	74	18-65
(Baker et al. 2002)	38.6	9.7	0.9	50.4	115	18-70
(Baldessarini et al. 2003)	39.1	10.7	0.7	49.2	254	18-70
(Barbini et al. 1997)	36.6	10.0	1.9	63.0	27	?
(Behzadi et al. 2009)	35.0	8.4	0.9	?	88	?
(Berk et al. 1999)	30.7	?	?	76.0	30	18-65
(Bersudsky et al. 2010)	43.3	11.6	1.8	48.8	41	18-65
(Berwaerts et al. 2011)	40.0	11.0	0.6	36.0	300	18-65
(Bourin et al. 2014)	38.3	12.4	0.7	37.6	356	18-65
(Bowden et al. 2005a)	39.2	11.8	0.6	51.3	369	18-75
(Bowden et al. 2005b)	39.3	?	?	42.3	300	>18
(Bowden et al. 2010)	38.5	12.6	0.8	58.8	257	18-75
(Cazorla et al. 2013)	38.9	11.7	0.4	44.7	960	18-65
(Chen et al. 2013)	34.2	13.4	2.5	40.0	30	18-65
(Chengappa et al. 2010)	39.7	10.1	1.5	71.0	48	>18
(Dauphinais et al. 2011)	41.2	10.9	1.1	53.0	100	18-65
(El Mallakh et al. 2010)	40.5	1.0	0.0	51.7	401	>18
(Feifel et al. 2011)	39.5	?	?	42.9	28	18-65
(Gaudiano et al. 2007)	39.0	11.0	1.3	61.0	74	18-75
(Henriksen et al. 2016)	46.3	12.3	2.6	30.4	23	18-70
(Ichim et al. 2000)	32.8	?	?	46.7	30	18-65
(Jahangard et al. 2014)	34.4	11.5	1.5	38.6	57	?
(Janicak et al. 1988)	35.0	13.4	2.5	51.7	29	>18

Mania	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Janicak et al. 1989)	32.0	11.0	2.4	76.2	21	?
(Janicak et al. 1998)	36.2	10.6	1.9	40.6	32	?
(Jeong et al. 2012)	36.8	14.1	2.2	64.3	42	>18
(Kanba et al. 2014)	37.7	12.6	3.4	58.7	14	18-64
(Keck et al. 2003a)	40.5	12.2	3.3	56.0	14	>18
(Keck et al. 2003b)	38.3	10.5	0.7	39.0	197	>18
(Keck et al. 2009)	39.7	10.8	1.7	48.0	42	18-65
(Khanna et al. 2005)	34.8	?	?	33.1	160	>18
(Lipkovich et al. 2008)	41.2	12.0	0.8	58.2	222	?
(Machado-Vieira et al. 2008)	28.5	8.9	0.7	57.3	141	18-65
(Mirsepassi et al. 2013)	38.0	8.1	1.2	47.8	46	18-65
(Mokhber et al. 2008)	28.5	9.2	1.3	54.9	51	?
(Moreno et al. 2007)	38.9	13.0	3.7	75.0	12	?
(Sachs et al. 2006)	38.8	?	?	51.0	272	>18
(Sachs et al. 2015)	36.2	11.6	0.7	35.9	312	18-65
(Scarna et al. 2003)	40.8	12.4	2.5	40.0	25	?
(Segal et al. 1998)	33.6	?	?	77.8	45	?
(Sekhar et al. 2010)	24.5	2.5	0.5	36.7	30	18-60
(Thomas et al. 2008)	43.6	12.7	1.2	59.2	120	18-65
(Tohen et al. 2003)	40.5	13.0	0.6	58.7	453	>18
(Vieta et al. 2005)	41.8	0.6	0.6	62.0	347	18-65
(Vieta et al. 2011)	24.0	8.8	0.4	?	401	>18
(Yatham et al. 2007b)	39.5	?	?	50.0	200	>18
(Young et al. 2009)	40.8	?	?	55.9	970	>18
(Zarate et al. 2007)	35.4	7.8	2.0	87.5	16	18-65

Major Depressive Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Alam et al. 2014)	45.5	12.8	0.4	63.0	836	?
(Alvarez et al. 2012)	43.3	11.4	0.6	62.7	426	18-65
(Asnis et al. 2013)	41.1	12.3	0.5	62.7	713	18-65
(Bakish et al. 2014)	42.8	13.1	0.6	63.5	562	18-75
(Berk et al. 2014)	50.2	12.7	0.8	63.1	252	>18
(Boulenger et al. 2014)	46.8	13.7	0.6	65.6	607	18-75
(Brunoni et al. 2013)	42.3	12.6	1.2	68.3	120	18-65
(Chan et al. 2013)	46.5	8.1	1.1	80.0	50	?
(Citrome et al. 2015)	40.1	13.0	0.6	53.9	505	18-70
(Corruble et al. 2013)	43.2	12.4	0.7	71.0	324	18-70
(Croft et al. 2014)	40.2	13.0	0.6	53.7	518	18-70
(David et al. 2008)	37.0	8.3	0.6	66.5	170	?
(DeRubeis et al. 2005)	40.0	12.0	0.8	59.0	240	18-70
(Dimidjian et al. 2006)	39.9	11.0	0.7	66.0	241	18-60

Major Depressive Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Garlow et al. 2012)	42.4	11.0	0.9	62.1	153	18-60
(Gommoll et al. 2014)	43.3	13.1	0.7	60.2	357	18-80
(Hegerl et al. 2010)	46.4	14.6	0.8	68.2	368	>18
(Henigsberg et al. 2012)	46.4	12.1	0.5	62.7	560	18-75
(Hosenfeld et al. 2015)	43.4	11.5	0.9	68.0	178	?
(IsHak et al. 2015)	42.6	13.0	0.3	62.8	2280	18-75
(Jacobsen et al. 2015)	42.8	12.2	0.6	72.5	462	18-75
(Jain et al. 2013)	42.5	12.9	0.5	57.4	600	18-75
(Kato et al. 2015)	46.3	14.8	1.1	46.4	168	?
(Korgaonkar et al. 2014)	33.8	13.1	1.5	50.0	80	18-65
(Koshino et al. 2013)	37.1	10.8	0.5	54.0	564	18-65
(Lee et al. 2015)	40.2	15.2	2.4	82.9	41	?
(Leykin et al. 2007)	40.0	11.6	0.9	58.3	180	18-70
(Liebowitz et al. 2013)	42.0	13.7	0.5	60.7	673	>18
(Mahableshwarkar et al. 2015a)	45.1	12.4	0.6	70.2	469	18-75
(Mahableshwarkar et al. 2015b)	45.0	11.9	0.5	65.1	602	18-65
(Mathews et al. 2015)	41.8	12.9	0.4	57.4	1138	18-70
(McCall 2015)	42.1	12.4	1.6	67.0	58	18-70
(McIntyre et al. 2014)	45.7	12.0	0.5	66.2	598	18-65
(Montgomery et al. 2013)	44.5	?	?	66.5	553	18-70
(Mynors-Wallis et al. 2000)	35.0	?	?	76.2	151	18-65
(Papakostas et al. 2015)	44.5	12.9	1.1	70.5	139	18-65
(Rapaport et al. 2016)	46.1	12.6	1.0	58.7	148	18-80
(Sahraian et al. 2015)	33.5	9.4	1.4	74.4	43	18-65
(Sambunaris et al. 2014)	45.0	?	?	65.0	442	18-80
(Shachar-Malach et al. 2015)	43.3	16.1	4.6	75.0	12	18-80
(Shallcross et al. 2015)	34.9	11.2	1.2	76.0	92	18-65
(Shams Alizadeh et al. 2015)	34.7	11.5	1.8	69.0	42	18-65
(Sheehan et al. 2016)	43.6	12.2	0.3	67.6	2193	?
(Shiovitz et al. 2014)	43.3	12.2	0.7	58.0	345	18-65
(Thase et al. 2006)	37.3	11.9	0.6	60.1	342	>18
(Trivedi et al. 2013)	41.2	11.7	0.3	62.0	1752	18-65
(Vittengl et al. 2015)	42.7	11.8	0.8	67.0	241	18-70
(Wang et al. 2014)	40.0	11.7	0.5	71.5	459	18-65
(Zhu et al. 2013)	41.9	12.2	1.4	69.5	75	18-65
(Zilcha-Mano and Barber 2014)	37.5	12.2	1.0	59.0	156	?

Obsessive-Compulsive Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Albert et al. 2002)	29.7	8.3	1.0	52.1	73	>18
(Alonso et al. 2001)	35.2	11.4	2.7	66.7	18	?
(Anderson and Rees 2007)	33.8	11.6	1.6	?	51	18-75

Obsessive-Compulsive Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Andersson et al. 2012a)	34.0	13.0	1.3	66.0	101	>18
(Andersson et al. 2015)	34.8	12.3	1.1	58.0	128	>18
(Cottraux et al. 2001)	35.8	10.6	1.3	74.2	62	18-65
(Delorme et al. 2004)	19.9	11.4	2.6	36.8	19	?
(Denys et al. 2003)	35.0	11.5	0.9	62.0	150	18-65
(Emamzadehfard et al. 2016)	34.9	10.3	1.4	70.0	50	18-60
(Foa et al. 2005)	34.8	10.9	1.0	48.0	122	>18
(Freeston et al. 1997)	35.8	?	?	44.8	29	?
(Fux et al. 1999)	30.3	9.0	2.8	80.0	10	?
(Gomes et al. 2012)	36.4	6.8	1.5	59.1	22	18-60
(Greist et al. 1995a)	38.7	12.8	0.7	52.2	325	>18
(Greist et al. 1995b)	38.6	?	?	41.2	325	>18
(Hawken et al. 2016)	33.5	12.0	2.6	50.0	22	18-65
(Hiss et al. 1994)	31.0	?	?	40.0	20	?
(Hoexter et al. 2012)	31.5	10.2	1.7	60.5	38	18-65
(Humble et al. 2001)	42.1	13.4	2.0	46.8	47	18-75
(Huppert et al. 2009)	37.9	10.2	1.4	53.0	51	>18
(Jaurrieta et al. 2008)	31.1	8.7	1.4	36.8	38	?
(Jenike et al. 1997)	35.1	12.0	1.5	43.8	64	>18
(Kobak et al. 2005a)	33.7	11.2	1.4	45.0	60	18-65
(Koprivova et al. 2011)	29.2	5.0	0.7	60.0	50	?
(Landeros-Weisenberger et al. 2010)	35.9	11.0	0.9	58.2	165	>18
(Lindsay et al. 1997)	32.8	9.1	2.1	66.7	18	>18
(Lopez-Ibor et al. 1996)	34.0	11.9	1.6	61.8	55	>18
(Lovell et al. 2017)	32.7	?	?	60.3	473	>18
(Ma et al. 2014b)	28.3	9.2	1.4	34.8	46	18-60
(McLean et al. 2001)	35.0	?	?	47.6	63	18-65
(Montgomery et al. 2001)	37.5	11.5	0.6	61.5	401	18-65
(Nakatani et al. 2005)	33.7	8.5	1.6	67.9	28	18-65
(O'Connor et al. 2006)	37.7	11.8	1.8	65.1	43	?
(Olbrich et al. 2013)	34.6	11.9	2.2	56.7	30	?
(Prasko et al. 2006)	30.5	7.8	1.3	38.2	34	?
(Rodriguez et al. 2013)	34.2	9.0	2.3	44.0	15	18-55
(Rufer et al. 2005)	32.4	9.2	1.7	60.0	30	?
(Sarris et al. 2015)	37.0	12.1	1.8	45.5	44	18-70
(Simpson et al. 2004b)	33.4	11.0	1.6	56.5	46	18-70
(Simpson et al. 2008)	39.2	13.9	1.3	43.0	108	18-70
(Simpson et al. 2010)	39.9	13.4	2.4	47.0	30	18-70
(Simpson et al. 2013)	33.9	11.4	1.1	48.0	100	18-70
(Stein et al. 2007)	37.8	11.8	0.6	57.0	458	18-65
(Thompson-Hollands et al. 2015)	35.4	8.2	1.9	67.0	18	>18
(Twohig et al. 2010)	37.0	?	?	66.0	79	>18

Obsessive-Compulsive Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Vallejo et al. 1992)	32.0	11.0	2.2	53.8	26	18-65
(van Oppen et al. 1995)	34.7	10.4	1.4	53.0	57	18-65
(Volavka et al. 1985)	29.9	?	?	64.6	23	18-65
(Voon et al. 2017)	41.8	7.9	2.3	66.7	12	?
(Whittal et al. 2005)	35.0	?	?	62.7	59	18-65

Panic Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Andersch et al. 1991)	31.0	9.3	0.8	61.0	123	?
(Azhar 2000)	31.5	7.9	1.1	?	51	18-50
(Barlow et al. 2000)	36.1	10.7	0.6	62.5	312	?
(Bergstrom et al. 2010)	34.2	9.7	1.0	61.4	104	>18
(Bradwejn et al. 2005)	38.9	12.3	0.7	60.5	328	>18
(Broocks et al. 2002)	32.6	13.4	2.1	65.5	39	18-50
(Chavira et al. 2009)	41.2	?	?	?	232	18-70
(de Beurs et al. 1995)	38.8	9.8	1.0	75.0	96	18-65
(El Alaoui et al. 2013)	34.2	9.4	0.9	62.0	104	>18
(Gallagher et al. 2013)	37.1	11.7	0.6	64.7	361	?
(Hovland et al. 2013)	37.9	8.6	1.4	80.6	36	18-50
(Ito et al. 2001)	37.0	11.0	1.3	64.0	70	18-65
(Jacobs et al. 1997)	37.2	11.4	0.6	?	359	?
(Katzelnick et al. 2006)	39.1	12.2	0.8	79.6	245	>18
(Kenardy et al. 2003)	36.8	10.0	1.0	75.5	93	18-60
(King et al. 2011)	39.1	11.2	1.6	78.0	50	>18
(Klass et al. 2009)	33.0	9.1	1.3	69.0	49	18-55
(Marchand et al. 2008)	36.5	8.8	0.8	66.0	137	18-55
(Marks et al. 1993)	35.0	?	?	81.0	144	18-65
(Martinez et al. 2015)	39.4	12.9	3.3	40.0	15	?
(Meuret et al. 2008)	41.0	8.9	1.5	64.9	37	?
(Meuret et al. 2010)	33.2	9.8	1.5	82.9	41	>18
(Michelson et al. 1998)	37.1	10.7	0.7	69.5	243	?
(Michelson et al. 2001)	35.7	10.1	0.7	55.5	180	>18
(Otto et al. 2010)	35.0	11.0	2.1	50.0	28	18-65
(Pohl et al. 1989)	30.7	2.2	0.3	47.0	60	>18
(Pollack et al. 2007)	37.3	11.0	0.4	67.3	634	>18
(Ribeiro et al. 2001)	36.2	10.5	2.0	77.1	27	>18
(Richards et al. 2003)	42.8	14.9	3.3	90.5	21	?
(Roy-Byrne et al. 2005)	41.2	?	?	67.0	232	18-70
(Sandmann et al. 1998)	34.0	8.0	1.2	65.2	46	18-65
(Schmidt et al. 2000)	37.8	11.1	1.3	69.0	77	?
(Schweizer et al. 1988)	34.5	?	?	60.0	67	?
(Schweizer et al. 1993)	35.0	8.4	0.8	60.0	104	18-65

Panic Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Sharp et al. 1997)	37.6	?	?	77.2	149	18-70
(Sharp et al. 2000)	38.3	?	?	?	91	18-70
(Sheehan et al. 1993)	36.7	9.7	1.0	73.7	92	>18
(Sheehan et al. 2005)	37.7	10.4	0.3	60.0	889	18-65
(Simon et al. 2009)	37.7	11.2	1.7	57.1	42	18-65
(Stahl et al. 2003)	37.7	?	?	58.1	351	18-80
(Swinson et al. 1995)	40.5	10.8	1.7	88.1	42	?
(Telch et al. 1993)	34.6	10.3	1.3	73.1	67	18-65
(Uhlenhuth et al. 1989)	31.5	7.1	1.1	58.0	41	?
(Valenca et al. 2000)	37.0	6.9	1.4	58.3	24	18-55
(Valenca et al. 2002)	36.9	8.7	2.3	64.3	14	18-55
(Valenca et al. 2003)	36.9	8.8	1.5	55.9	34	18-55
(Van Dyck and Spinhoven 1997)	34.3	?	?	76.0	64	18-65
(Wardle et al. 1994)	42.5	13.0	1.4	82.5	91	?
(White et al. 2013)	37.8	11.9	0.9	66.8	157	>18
(Wiborg and Dahl 1996)	31.7	7.3	1.1	57.5	40	18-50

Posttraumatic Stress Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Baker et al. 2014)	40.8	13.3	2.1	63.0	40	>18
(Beck et al. 2009)	43.3	12.8	1.9	81.8	44	?
(Bomyea et al. 2015)[1]	28.0	5.9	0.9	100.0	42	18-65
(Brom et al. 1989)	42.0	14.3	1.4	78.6	112	?
(Bryant et al. 2003)	35.2	10.4	1.4	51.7	58	17-60
(Bryant et al. 2011)	43.0	8.7	1.6	96.4	28	17-70
(Carlson et al. 1998)[2]	48.0	5.1	0.9	0.0	35	?
(Chard 2005)[1]	32.8	8.9	1.1	100.0	71	?
(Cloitre et al. 2010)[1]	36.4	?	?	100.0	104	18-65
(Devilly and Spence 1999)	38.0	12.8	2.7	65.2	23	>18
(Dunne et al. 2012)	32.5	7.1	1.4	50.0	26	?
(Ehlers et al. 2005)	34.4	12.8	2.9	50.0	20	?
(Ehlers et al. 2014)	39.0	11.1	1.0	58.7	121	18-65
(Engel et al. 2015)[2]	36.4	8.7	1.6	19.0	80	?
(Forbes et al. 2012)[2]	53.4	13.7	1.8	3.4	59	?
(Galovski et al. 2012)	39.8	11.7	1.2	69.0	100	>18
(Gersons et al. 2000)	36.4	6.5	1.0	11.9	42	?
(Golier et al. 2012)[2]	48.9	12.7	4.5	0.0	8	?
(Hollifield et al. 2007)	42.2	13.1	1.4	67.9	84	?
(Jiang et al. 2014)	29.8	13.5	1.9	68.7	49	>18
(Jun et al. 2013)	37.4	11.3	0.8	75.5	200	18-65
(Kearney et al. 2013)[2]	52.0	12.6	1.8	21.3	47	?
(Lang et al. 2012)	44.4	13.6	1.0	76.8	181	?
(Le et al. 2013)	37.5	11.3	0.8	76.0	200	18-65

Posttraumatic Stress Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Lee et al. 2002)	35.3	?	?	45.8	24	?
(Lindauer et al. 2005)	39.0	9.6	2.8	54.2	12	?
(Macdonald et al. 2016)	37.1	11.3	1.8	75.0	40	?
(Maercker et al. 2006)	40.3	11.1	1.7	76.2	42	?
(Markowitz et al. 2015)	40.1	11.6	1.1	70.0	110	18-65
(Martin et al. 2015)[1]	44.4	12.4	2.0	100.0	38	18-65
(McDonagh et al. 2005)[1]	40.4	9.8	1.1	100.0	74	?
(Monson et al. 2006)[2]	54.0	6.3	0.8	10.0	60	?
(Monson et al. 2012)	37.1	10.9	1.7	75.0	40	18-70
(Neuner et al. 2004)	33.2	7.2	1.1	60.6	43	?
(Neuner et al. 2008)	35.0	12.8	0.8	51.3	277	?
(Neuner et al. 2010)	31.4	7.8	1.4	31.3	32	?
(Nijdam et al. 2012)	37.8	11.4	1.0	56.4	140	18-65
(Pacella et al. 2014)	36.2	11.2	2.1	72.4	29	18-65
(Powers et al. 2015)	34.0	11.8	3.9	88.9	9	18-65
(Ready et al. 2010)[2]	57.5	3.0	0.9	0.0	11	?
(Reist et al. 2001)[2]	50.5	8.0	1.9	0.0	17	?
(Resick et al. 2002)[1]	32.0	9.9	0.8	100.0	171	?
(Rothbaum 1997)[1]	34.2	10.4	2.4	100.0	18	>18
(Schneier et al. 2015)	40.0	12.5	2.1	63.9	36	18-75
(Schnurr et al. 2003)[2]	37.5	3.7	0.2	0.0	360	?
(Schnurr et al. 2013)	45.2	?	?	8.7	195	?
(Stecker et al. 2014)	29.4	6.2	0.4	51.0	274	?
(Taylor et al. 2003)	37.5	10.0	1.3	75.0	60	>18
(Zalta et al. 2014)[1]	39.1	12.6	1.6	100.0	64	?
(Zang et al. 2013)	37.5	11.9	2.5	77.3	22	>18

[1] female, [2] combats

Primary Insomnia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Almeida Montes et al. 2003)	50.0	12.7	4.0	40.0	10	?
(Connor et al. 2016)	46.9	10.9	0.4	62.6	633	18-65
(Cortoos et al. 2010)	42.6	?	?	35.3	17	18-60
(Deacon et al. 2007)	34.6	10.8	2.1	73.0	26	18-65
(Drake et al. 2000)	40.1	10.2	1.1	45.8	83	21-60
(Edinger et al. 2009)	56.0	16.1	2.5	12.5	40	>18
(Erman et al. 2008)	40.6	?	?	?	63	21-61
(Gross et al. 2011)	49.2	?	?	73.3	30	18-65
(Guo et al. 2013a)	48.9	13.6	1.8	67.8	60	25-75
(Hajak et al. 1996)	41.3	9.5	3.0	30.0	10	?
(Huang et al. 2011)	39.9	11.3	1.6	69.0	48	20-65
(Krystal et al. 2008)	45.7	11.0	0.3	61.2	1018	18-64
(Krystal et al. 2011)	44.5	11.3	0.8	73.0	221	18-64

Primary Insomnia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Lankford et al. 2008)	43.9	11.0	0.5	66.2	458	18-64
(Ma et al. 2014a)	45.0	?	?	59.0	229	?
(Mayer et al. 2009)	46.2	14.8	0.7	63.2	451	>18
(Ratti et al. 2013)	45.0	?	?	55.0	161	18-64
(Riemann et al. 2002)	47.0	10.9	1.5	41.8	55	18-70
(Roehrs et al. 2011)	49.5	?	?	58.8	95	21-70
(Rosenberg et al. 2008)	45.1	11.8	0.9	61.3	173	18-64
(Roth et al. 2006)	44.3	3.0	0.2	58.0	212	18-64
(Roth et al. 2007)	42.4	12.0	1.5	70.0	66	18-64
(Roth et al. 2010)	43.9	11.7	0.3	62.1	1532	18-65
(Scharf et al. 2007)	45.9	11.7	0.4	61.0	702	21-64
(Tsutsui and Zolipidem Study 2001)	42.2	12.7	0.6	65.0	428	?
(Wade et al. 2010)	63.8	9.3	0.7	74.4	172	18-80
(Walsh et al. 2000)	44.1	0.9	0.1	70.6	163	21-65
(Walsh et al. 2006b)	44.3	?	?	69.0	232	18-64
(Walsh et al. 2007)	45.6	11.8	0.4	61.0	828	21-64
(Yeung et al. 2009)	48.0	9.0	1.2	76.7	60	18-65
(Zick et al. 2011)	41.5	14.4	2.5	74.0	34	18-65

Schizophrenia and Related Disorders	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Ascher-Svanum et al. 2014)[1]	40.9	10.9	0.5	32.8	524	18-65
(Chien et al. 2016)	28.7	9.6	0.8	47.0	134	18-64
(Citrome et al. 2016)[1]	36.9	10.5	0.3	30.9	1466	18-60
(Daniel et al. 1999)	36.6	?	?	28.9	302	>18
(Del-Monte et al. 2014)[1]	34.4	10.6	1.6	35.6	45	?
(Downing et al. 2014)[1]	40.0	11.5	0.4	35.9	1009	18-65
(Durgam et al. 2015a)[1]	38.5	10.8	0.4	36.8	617	18-60
(Fu et al. 2015)	38.6	?	?	49.4	334	>18
(Gaebel et al. 2010)	41.6	12.8	0.7	42.0	666	>18
(Gomar et al. 2015)	46.1	10.0	0.9	31.5	130	18-65
(Hasan et al. 2015)	40.8	8.2	0.7	30.6	121	>18
(Hong et al. 2011)	42.8	?	?	34.4	64	18-60
(Ji et al. 2016)[1]	36.5	8.5	1.9	40.0	20	?
(Kane et al. 2014)[1]	42.4	11.0	0.6	21.0	340	18-65
(Keefe et al. 2008)	40.3	9.4	0.6	29.5	245	18-55
(Keefe et al. 2015)	38.5	10.0	0.6	32.2	317	18-55
(Keks et al. 2007)	35.2	11.9	0.5	42.9	547	>18
(Kimhy et al. 2015)[1]	36.9	10.1	1.8	36.0	33	18-55
(Kindler et al. 2015)	37.6	7.6	1.7	36.8	19	>18
(Kumari et al. 2015)[1]	40.2	14.2	2.3	39.5	38	18-61
(Laties et al. 2015)	40.4	10.8	0.3	41.2	1098	18-65
(Loh et al. 2015)[1]	21.6	10.2	1.0	28.8	104	18-65

Schizophrenia and Related Disorders	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Martin et al. 2016)	39.8	10.2	1.2	47.0	68	14-65
(McEvoy et al. 2013)	43.9	10.9	0.7	35.0	240	>18
(Meltzer et al. 2015)[1]	39.7	11.0	0.4	32.1	623	18-70
(Minzenberg et al. 2014)[1]	23.9	9.5	2.0	22.0	23	18-50
(Mueller et al. 2015)	34.2	8.6	0.7	30.8	156	18-50
(Nasrallah et al. 2015)[1]	38.3	10.8	0.3	27.5	1330	18-75
(Nasrallah et al. 2016)[1]	39.7	11.0	0.4	32.1	623	18-70
(Nikbakhat et al. 2016)[1]	34.1	5.9	0.7	32.8	64	18-50
(Peters-Strickland et al. 2015)[1]	41.2	10.6	0.3	40.6	1081	18-65
(Popova et al. 2014)[1]	37.2	9.0	1.2	33.3	57	?
(Potkin et al. 2015)[1]	41.2	10.0	0.5	25.8	353	18-64
(Sailer et al. 2015)	30.9	11.4	1.9	30.6	36	?
(Savitz et al. 2016)[1]	33.3	11.9	0.3	45.0	1429	18-70
(Silva et al. 2015)[1]	33.3	6.2	1.1	?	34	18-50
(Silverstein et al. 2014)	44.4	11.6	1.7	27.7	123	18-55
(Stauffer et al. 2010)	39.9	10.4	0.3	31.9	974	?
(Stauffer et al. 2014)[1]	42.7	11.4	1.1	27.2	103	18-65
(Strzelecki et al. 2015)[1]	38.3	?	?	52.0	50	18-60
(Svatkova et al. 2015)[1]	30.1	7.8	1.4	18.2	33	?
(Tandon et al. 2016)[1]	42.7	11.8	0.7	37.5	285	18-75
(Tomasik et al. 2015)	46.3	10.4	2.0	34.5	58	?
(Turkoz et al. 2015)	37.5	9.8	0.5	45.5	332	>18
(Weickert et al. 2015)	35.7	7.8	0.9	38.0	79	?
(Weiden et al. 2016)[1]	39.2	11.3	0.4	38.4	938	18-65
(Woolley et al. 2015)	44.0	9.7	1.7	19.4	31	?
(Zhang et al. 2015)[1]	38.9	10.2	0.7	48.1	235	18-60
(Zhang et al. 2016)[1]	30.7	10.5	1.0	59.0	106	>18
(Zhou and Gu 2014)[1]	35.0	9.8	0.7	47.3	201	18-60

[1] Schizophrenia only

Social Phobia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Alden et al. 2004)	33.6	10.4	1.8	60.6	33	?
(Amir et al. 2009)	29.4	10.8	1.6	59.1	44	?
(Amir et al. 2011)	30.7	11.1	1.0	51.0	112	?
(Andersson et al. 2012b)	38.3	11.1	0.8	68.8	204	>18
(Baldwin et al. 1999)	36.1	11.5	0.7	54.2	290	>18
(Beard et al. 2011)	37.4	15.8	2.8	75.1	32	18-79
(Beidel et al. 2014)	36.4	14.0	1.4	51.9	106	>18
(Berger et al. 2011)	37.2	11.2	1.2	53.1	81	>18
(Blanco et al. 2010)	32.5	9.0	0.8	40.6	128	18-65
(Blomhoff et al. 2001)	40.4	10.4	0.5	60.5	387	18-65
(Borgeat et al. 2009)	40.0	9.8	1.9	48.1	27	18-65

Social Phobia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Bunnell et al. 2013)	24.4	7.1	0.6	39.2	141	>18
(Caldirola et al. 1997)	30.7	9.6	2.4	31.0	16	?
(Carlbring et al. 2007)	32.7	9.2	1.2	65.1	57	>18
(Carlbring et al. 2012)	36.5	12.7	1.4	68.4	79	>18
(Cottraux et al. 2000)	33.7	10.4	1.3	58.7	63	18-60
(Craske et al. 2014)	28.4	6.8	0.7	46.0	87	?
(Davidson et al. 1993)	37.2	8.4	1.0	42.6	75	?
(Davidson et al. 2004b)	37.2	10.3	0.6	46.5	295	18-65
(de Oliveira et al. 2012)	34.4	11.8	2.0	75.0	36	?
(Furmark et al. 2002)	35.2	7.3	1.7	44.4	18	?
(Hackmann et al. 2000)	30.6	13.3	2.8	45.5	22	?
(Hedman et al. 2011)	35.4	11.4	1.0	35.7	126	?
(Hedman et al. 2013)	33.5	9.1	1.1	64.2	67	18-65
(Heimberg et al. 1998)	34.9	9.6	0.8	49.6	133	18-65
(Hofmann 2004)	32.0	9.5	1.0	36.0	90	?
(Hofmann et al. 2006b)	32.5	9.9	1.0	41.1	107	?
(Hofmann et al. 2006a)	33.7	10.0	1.9	40.7	27	>18
(Hofmann et al. 2013)	32.6	?	?	43.2	169	>18
(Jazaieri et al. 2012)	32.8	8.4	1.1	52.0	56	>18
(Kasper et al. 2005)	38.0	11.0	0.6	45.0	358	18-65
(Knijnik et al. 2008)	33.4	10.2	1.4	51.6	57	18-65
(Kobak et al. 2005b)	37.5	13.2	1.9	52.5	49	18-65
(Liebowitz et al. 2005)	36.3	11.5	0.6	46.5	413	>18
(Mansson et al. 2016)	32.3	9.7	1.9	85.0	26	?
(Morgan and Raffle 1999)	32.4	7.7	1.4	46.7	30	?
(Mortberg et al. 2007)	34.6	9.1	0.9	63.0	100	18-65
(Mortberg et al. 2015)	35.9	9.6	1.8	69.0	29	18-65
(Neubauer et al. 2013)	39.5	11.2	1.5	66.1	56	18-65
(Niles et al. 2013)	28.4	6.5	0.6	42.1	124	?
(Niles et al. 2014)	28.4	6.5	0.9	43.0	50	>18
(Price et al. 2011)	41.4	11.3	2.3	29.0	24	?
(Price and Anderson 2011)	39.1	11.2	1.2	61.0	91	?
(Smits et al. 2013)	32.5	10.5	0.9	41.8	145	>18
(Stangier et al. 2011)	35.6	11.8	1.1	55.5	117	18-65
(Stein et al. 1998)	36.3	?	?	56.7	187	>18
(Stein et al. 2002)	38.2	11.5	0.6	60.4	323	>18
(Stein et al. 2014)	35.0	13.3	0.7	34.0	346	>18
(Thyer 1999)	35.0	?	?	50.0	133	>18
(Tulbure et al. 2015)	28.8	8.0	0.9	40.8	76	>18

Somatoform Disorder	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Allen et al. 2006a)	46.6	9.7	1.1	89.4	84	18-70
(Aragona et al. 2005)	53.6	15.8	2.7	72.4	35	>18
(Bleichhardt et al. 2004)	43.9	10.4	0.8	73.3	191	?
(Dickinson et al. 2003)	47.1	14.1	0.7	93.5	382	?
(Eberhard et al. 1988)	50.3	12.6	1.5	72.9	70	?
(Han et al. 2008b)	45.2	12.6	1.3	61.0	95	>18
(Han et al. 2008a)	37.6	29.2	4.3	57.7	45	>18
(Hanel et al. 2009)	43.9	13.3	0.7	59.4	323	18-65
(Luo et al. 2009)	41.0	12.7	1.4	57.5	80	18-65
(McLeod et al. 1997)	39.4	9.4	1.0	73.6	96	?
(Melzer et al. 2009)	41.6	14.8	1.1	57.5	182	>18
(Moreno et al. 2013)	45.7	10.5	0.8	86.3	168	18-65
(Muller et al. 2004)	47.7	11.4	0.9	57.5	173	18-65
(Muller et al. 2008)	39.6	9.8	1.4	57.5	51	?
(Sattel et al. 2012)	48.0	11.6	0.8	66.0	211	18-77
(Schaefert et al. 2013)	48.9	12.4	0.7	75.0	304	18-70
(Smith et al. 2009)	52.5	?	?	83.3	30	>18
(Speckens et al. 1995)	37.1	12.6	1.4	49.5	79	18-64
(van Ravesteijn et al. 2013)	47.1	11.5	1.1	74.3	117	18-70
(Volz et al. 2000)	45.6	13.0	0.9	63.5	200	18-76
(Volz et al. 2002)	47.7	12.0	1.0	62.0	149	18-65
(Zonneveld et al. 2012)	42.4	11.1	0.9	80.9	162	18-65

Vascular Dementia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Auchus et al. 2007)	72.3	8.9	0.3	36.0	786	?
(Ballard et al. 2008)	72.8	8.0	0.3	38.0	710	50-85
(Bastos Leite et al. 2004)	71.0	?	?	?	73	?
(Black et al. 2003)	73.9	0.3	0.0	44.8	603	>40
(Chen et al. 2011)	68.2	6.4	0.5	12.5	168	?
(Cohen et al. 2003)	77.9	4.7	0.8	48.7	39	>55
(Di Perri et al. 1991)	70.4	?	0.7	40.8	120	50-80
(Guekht et al. 2011)	67.3	8.0	0.5	62.5	232	50-85
(Gunstad et al. 2005)	77.9	5.4	1.1	47.0	25	>55
(Ihl et al. 2012)	66.1	10.3	1.2	73.2	71	>50
(Liu et al. 2014)	67.1	8.5	1.2	46.0	50	45-80
(Logue et al. 2011)	73.5	9.1	0.3	60.0	826	?
(Mishima et al. 1998)	81.0	?	?	58.3	12	?
(Mok et al. 2007)	74.9	5.9	0.9	60.0	40	40-90
(Moretti et al. 2005)	71.0	1.5	0.2	57.5	40	60-75
(Muresanu et al. 2008)	70.7	1.6	0.2	51.2	41	?
(Pantoni et al. 2005)	75.3	6.1	0.4	40.6	230	55-87

Vascular Dementia	Mean Age (yrs)	SD	SE	Female (%)	Sample Size (N)	Age Inclusion
(Parnetti et al. 1997)	75.0	5.0	0.5	60.2	93	?
(Roman et al. 2010)	73.0	0.4	0.0	41.1	974	35-94
(Shi et al. 2015)	64.3	10.1	1.3	54.0	63	?
(Staekenborg et al. 2008)	73.0	8.0	0.3	38.0	706	?
(Wilkinson et al. 2003)	75.0	?	0.3	40.1	616	>40
(Yu et al. 2006)	66.7	10.5	1.4	25.0	60	>45

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