Affective and anxiety disorders in patients with different rare chronic diseases: a systematic review and meta-analysis

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Abstract

We aimed to identify the prevalence of affective and anxiety disorders across different rare disease and identify correlates of psychopathology. We performed a systematic review and meta-analysis. We systematically searched Medline, PSYNDEX, PsycINFO for observational studies examining clinically diagnosed affective and/or anxiety disorders in adults with rare chronic diseases. Two researchers reviewed titles and abstracts independently and, for eligible studies, independently extracted data. The prevalence rates were pooled using a random intercept logistic regression model. We published a review protocol (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018106614CRD42018106614). We identified and screened 34 402 records for eligibility and considered 39 studies in the qualitative and 37 studies in the quantitative analysis, including $N = 5951$ patients with 24 different rare diseases. Heterogeneity between studies was large. Prevalence rates ranged widely between studies, with pooled prevalence estimates of 13.1% (95% CI 9.6–17.7%; $I^2 = 87\%$, $p < 0.001$) for current and 39.3% (95% CI 31.7–47.4%; $I^2 = 84\%$, $p < 0.001$) for lifetime major depressive disorder, 21.2% (95% CI 15.4–28.6%; $I^2 = 90\%$, $p < 0.001$) for current and 46.1% (95% CI 35.8–56.8%; $I^2 = 90\%$, $p < 0.001$) for lifetime affective disorders, and 39.6% (95% CI 25.5–55.6%; $I^2 = 96\%$, $p < 0.001$) for current and 44.2% (95% CI 27.0–62.9%; $I^2 = 94\%$, $p < 0.001$) for lifetime anxiety disorders. Sensitivity analyses excluding studies of low quality revealed nearly the same results. We conducted the first systematic review examining affective and anxiety disorders in adults with different rare diseases and found high prevalence rates. Supporting patients in disease adjustment can be crucial for their overall health and well-being.

Introduction

There are around 7000 different rare diseases worldwide (prevalence <1:2000). The majority of these conditions have a genetic origin and a chronic and often progressive course. Valid information about rare diseases is scarce, diagnostic processes are difficult, and treatment options limited (Kole & Faurisson, 2009). On an individual level, the conditions cause constraints, psychological and interpersonal problems, and decreased quality of life (Cohen & Biesecker, 2010; von der Lippe, Diesen, & Feragen, 2017). In a cross-sectional online study we conducted including patients with different rare diseases, high percentages of patients showed increased depression and anxiety levels, assessed with standardized questionnaires (Uhlenbusch et al., 2019). Comorbid mental diseases in addition to a chronic condition can worsen the course of the disease (Lichtman et al., 2014; Watkins et al., 2013) and add to reduced quality of life (Cruz, de Almeida Fleck, & Polanczyk, 2010; Müller-Tasch et al., 2007). Since the majority of rare diseases are not curable, maintaining and enhancing quality of life is crucial.

The prevalence of affective and anxiety disorders in patients with rare diseases is unclear. Studies on psychopathology in specific rare diseases such as amyotrophic lateral sclerosis (ALS) (Chen et al., 2015) or systemic sclerosis (Baubet et al., 2011) exist but no study has systematically synthesized this evidence across rare diseases. Systematically summarizing evidence can help to better understand the burden of living with a rare disease and enables deriving implications for comprehensive patient care. This may be particularly relevant in the field of rare diseases, where the high number of different rare diseases and the rarity of each condition challenges research and healthcare (Eidt et al., 2009). The objective of this systematic review was to examine the prevalence of clinically relevant affective and anxiety disorders in patients with different rare chronic diseases. Moreover, we aimed at identifying aspects associated with increased psychopathology.

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Method

We performed a systematic review and meta-analysis following the PRISMA guidelines. We published a review protocol on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018106614).

Eligibility criteria

We included studies published in English or German with the primary aim of investigating the prevalence of affective and/or anxiety disorders, assessed with structured clinical interviews or clinical diagnoses. We included observational studies (cross-sectional studies, case-control studies, cohort studies) and excluded case studies, case series, randomized controlled trials, and grey literature. Included patients were adults with any rare chronic disease. If a study addressed children and adolescents, it was included if data for age-based subgroups were available. Rarity was defined as affecting less than one in 2000 individuals. We included diseases with a primarily genetic origin since we aimed at investigating chronic rather than acute conditions. Therefore, we excluded rare cancers, injuries, infections, complications after medical interventions and somatoform diseases. We further excluded studies assessing rare sub-forms of non-rare diseases (e.g. early-onset Parkinson disease) and gen-carriers without the clinical picture of the disease.

Search strategy

We discussed the search strategy with an independent librarian of the University of Hamburg beforehand. We systematically searched three electronic databases between May and June 2018: MEDLINE, PSYNDEX, PsycINFO. The search term included all rare diseases listed in the orpha.net registry of rare diseases [(RARE DISEASE) AND (DEPRESSION OR ANXIETY OR PSYCHOSOCIAL OR MENTAL HEALTH OR QUALITY OF LIFE OR PATIENT EXPERIENCES OR PSYCHOPATHOLOGY OR WELL-BEING)]. An excerpt of the search term is in the online Supplementary material. In addition, we hand-searched references and used the cited-by function for all articles meeting inclusion criteria. Last date of hand-search was 25 January 2020. We used Ovid for the database search and Endnote X7.3.1 to manage references during the screening process.

Study selection

We imported all studies detected during the database search into Endnote X7.3.1, where we screened for eligibility. During the initial screening process, one researcher assessed eligibility based on the titles, abstracts, and study types. Studies meeting any exclusion criteria were removed during the initial screening process. Potentially relevant studies or studies where eligibility remained unclear were further evaluated in the secondary screening. During the secondary screening process, two researches independently checked abstracts and full-texts. If full-texts were not available, we contacted corresponding authors. We documented all reasons for exclusion during the secondary screening. We discussed unclear cases and in case of disagreement, other co-authors were consulted.

Data extraction

We prepared a data extraction form based on the objectives of this review, which we piloted with a sample of studies and revised it until found adequate. We extracted the following data items: disease, sample size, study design, measures to assess psychopathology, comparison group (if applicable), frequency of current and lifetime major depressive disorder, current and lifetime affective disorders, current and lifetime anxiety disorders (assessed with clinical interview or clinical diagnoses), all reported correlates of depression and anxiety symptoms (assessed with clinical interviews as well as standardized questionnaires, if these were used additionally). Two researchers (NU, JS) independently read all studies meeting inclusion criteria, extracted relevant data, and compared the extracted information.

Data analysis

Quality and risk assessment

We assessed the quality of individual studies using the STROBE checklist for reporting observational studies (https://www.strobe-statement.org/index.php?id=available-checklists). Based on the number of items in the checklist, a maximum of 34 points (sub items included) could be reached. If information was not reported, we rated it as not fulfilled. Some items are only applicable for certain study designs. We calculated the percentage of fulfilled items in relation to the number of applicable items for the study design with a possible range from 0% to 100%. Two researchers independently rated the studies and discussed disparities until reaching agreement. In vague cases, a third researcher was consulted. We calculated interrater reliability using κ.

Meta-analysis

Based on the outcomes assessed in each study, the prevalence rate of clinically diagnosed affective and anxiety disorders was calculated as the reported number of subjects with a clinical diagnosis divided by the total number of subjects of the study (one-arm study) and the considered study arm (two-arm study), respectively. The prevalence rates were transformed with a logit transformation and pooled using a random intercept logistic regression model. Ninety-five percent confidence intervals for the individual study results were calculated using Clopper-Pearson intervals. The results of the meta-analysis are presented using forest plots. Overall heterogeneity among studies was assessed using the I^2 and τ^2 statistics and heterogeneity tests. The reported p values are one-sided; p values less than 0.025 are considered statistically significant. Funnel plots were created to evaluate reporting bias. In a sensitivity analysis, the pooled estimates were stratified by the quality of the included studies distinguishing between low (<40%) and high quality (≥40%). All analyses and graphs were generated with the statistical software R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). The meta-analysis was performed using the command *metaprop* of the R-package meta (version 4.11–0).

Results

Search results and characteristics of included studies

We identified 41 146 records by database search and 671 studies by hand-search. After removing duplicates, we screened 34 402 titles/abstracts in the initial screening and full texts of 531 studies during the secondary screening. Due to the high number of potentially relevant studies, we excluded studies published before the year 2000 during the secondary screening. Finally, we included 39 studies in the qualitative analysis and 37 in the quantitative analysis (flowchart in Fig. 1). Sample sizes ranged between
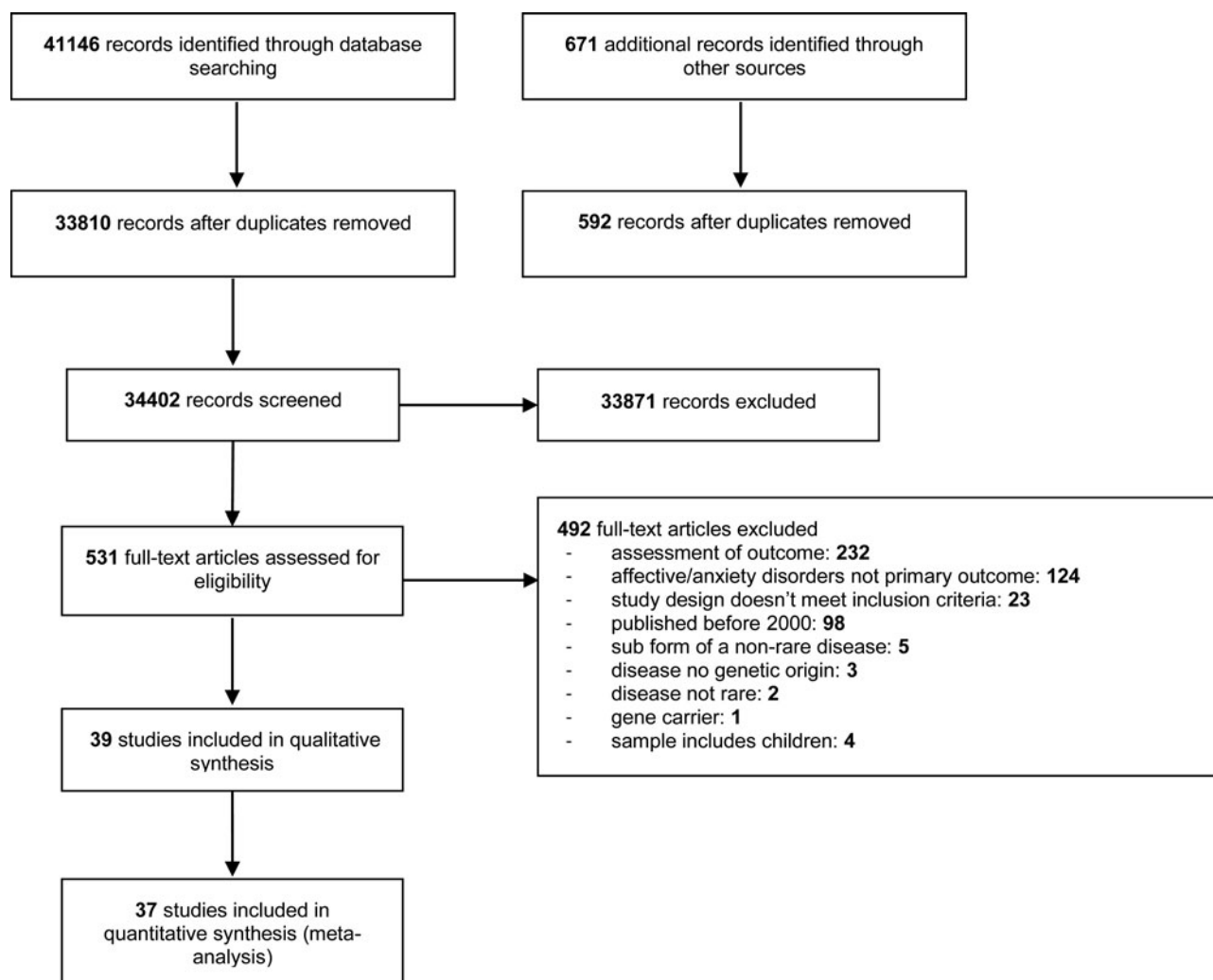
Fig. 1. Flowchart representing search results and selection process. *Notes*. Inclusion criteria were applied in the following order: (1) primary outcome, (2) assessment of outcome, (3) study design, (4) sample characteristics.
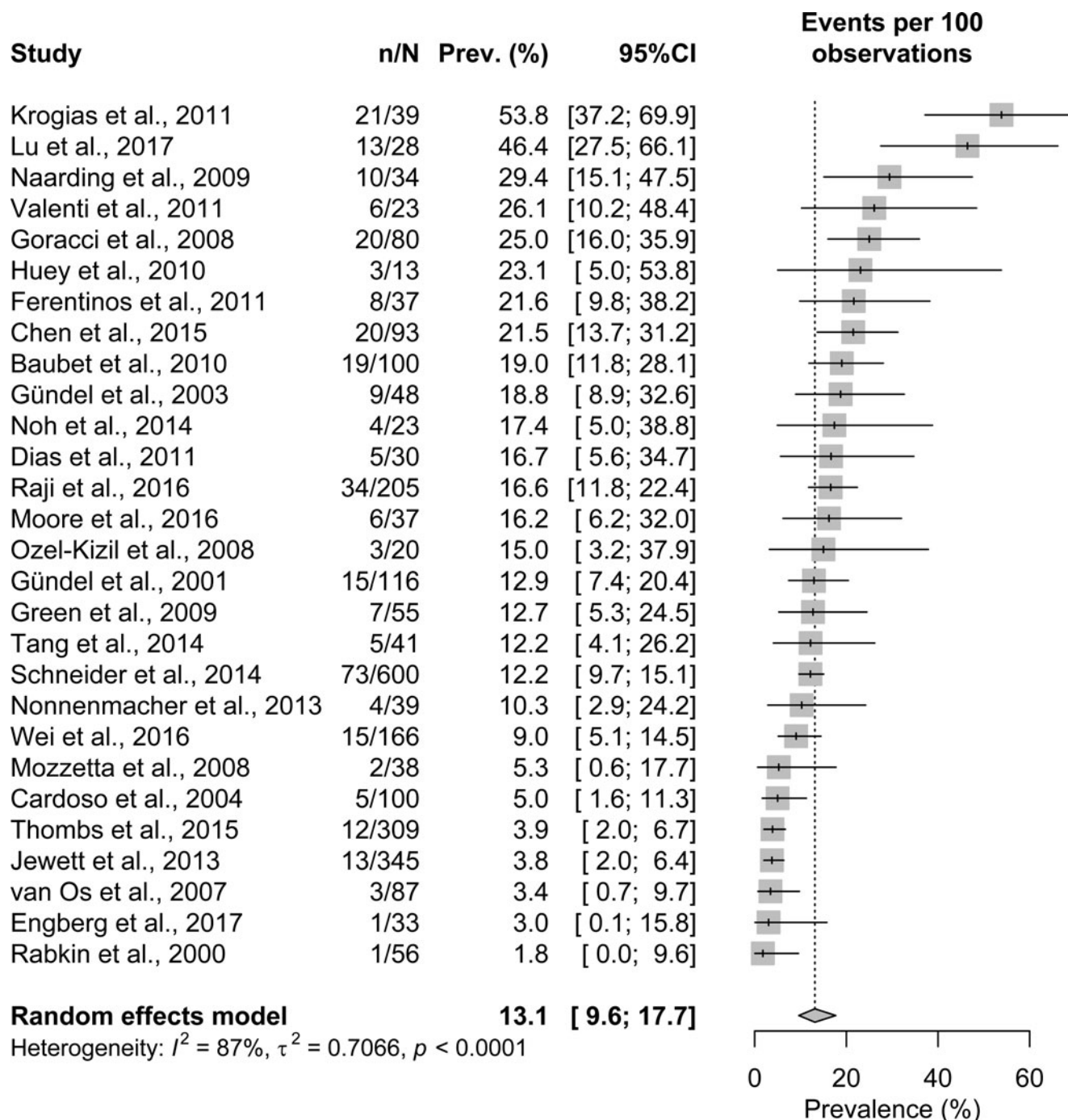
$N = 13$ and $N = 1752$. In total, $N = 5951$ patients with 24 different rare diseases were included (a list of all diseases and their prevalence rates is in online Supplementary Table S1). The largest group were patients with ALS (7 studies, $N = 2156$ patients). Thirty-four studies had a cross-sectional design, two studies were cohort studies, and one study was a combined case-control study and cohort study. Two studies had a longitudinal design with baseline and follow-up assessments. In these cases, we used the baseline data. Twenty-two studies assessed both affective disorders (or only MDD) and anxiety disorders, 17 studies only affective disorders (or only MDD), and no study examined only anxiety disorders. The quality of included studies ranged between 29.41% and 91.18% with a mean value of 57.91% (s.d. = 14.74%). Interrater reliability was good with $\kappa = 0.74$. Online Supplementary Table S2 provides an overview of the characteristics and main results of all included studies. The final quality rating for each study is in online Supplementary Table S3.

Frequency of affective disorders

Of the 39 studies included in the qualitative analysis, all studies assessed affective disorders (or only MDD), with widely ranging

frequency rates. The prevalence of current MDD ranged between 2.0% (Rabkin, Wagner, & Del Bene, 2000) and 53.8% (Krogias et al., 2011). The pooled prevalence estimate was 13.1% (95%CI 9.6–17.7%) across 28 studies with significant heterogeneity ($I^2 = 87\%$, $p < 0.0001$). Visual inspection of the funnel plot showed no indications of reporting bias across studies. A sensitivity analysis excluding three studies with a quality of <40% revealed a pooled prevalence of 13.3% (95% CI 9.5–18.2%). The prevalence for lifetime MDD ranged between 11.1% (Morgan, Murphy, Lacey, & Conway, 2005) and 73.9% (Valenti et al., 2011). The pooled prevalence estimate was 39.3% (95% CI 31.7–47.4%) across 15 studies. Heterogeneity was significant with $I^2 = 84\%$ ($p < 0.0001$) and the funnel plot showed no asymmetry. After excluding two studies with a quality of <40%, the pooled prevalence was 40.2% (95% CI 32.7–48.3%). The forest plots for current and lifetime MDD are in Figs 2 and 3. All forest plots showing the sensitivity analyses and all funnel plots are in the online Supplementary material.

The frequency of any affective disorder ranged between 5.6% (Stinton, Elison, & Howlin, 2010) and 57.0% (Chen et al., 2015) for current diagnoses. The pooled prevalence estimate for any current affective disorder was 21.2% (95% CI 15.4–28.6) across 17 studies with significant heterogeneity ($I^2 = 90\%$, $p < 0.0001$). The

Study	n/N	Prev. (%)	95%CI	Events per 100 observations
Krogias et al., 2011	21/39	53.8	[37.2; 69.9]	
Lu et al., 2017	13/28	46.4	[27.5; 66.1]	
Naarding et al., 2009	10/34	29.4	[15.1; 47.5]	
Valenti et al., 2011	6/23	26.1	[10.2; 48.4]	
Goracci et al., 2008	20/80	25.0	[16.0; 35.9]	
Huey et al., 2010	3/13	23.1	[5.0; 53.8]	
Ferentinos et al., 2011	8/37	21.6	[9.8; 38.2]	
Chen et al., 2015	20/93	21.5	[13.7; 31.2]	
Baubet et al., 2010	19/100	19.0	[11.8; 28.1]	
Gündel et al., 2003	9/48	18.8	[8.9; 32.6]	
Noh et al., 2014	4/23	17.4	[5.0; 38.8]	
Dias et al., 2011	5/30	16.7	[5.6; 34.7]	
Raji et al., 2016	34/205	16.6	[11.8; 22.4]	
Moore et al., 2016	6/37	16.2	[6.2; 32.0]	
Ozel-Kizil et al., 2008	3/20	15.0	[3.2; 37.9]	
Gündel et al., 2001	15/116	12.9	[7.4; 20.4]	
Green et al., 2009	7/55	12.7	[5.3; 24.5]	
Tang et al., 2014	5/41	12.2	[4.1; 26.2]	
Schneider et al., 2014	73/600	12.2	[9.7; 15.1]	
Nonnenmacher et al., 2013	4/39	10.3	[2.9; 24.2]	
Wei et al., 2016	15/166	9.0	[5.1; 14.5]	
Mozzetta et al., 2008	2/38	5.3	[0.6; 17.7]	
Cardoso et al., 2004	5/100	5.0	[1.6; 11.3]	
Thombs et al., 2015	12/309	3.9	[2.0; 6.7]	
Jewett et al., 2013	13/345	3.8	[2.0; 6.4]	
van Os et al., 2007	3/87	3.4	[0.7; 9.7]	
Engberg et al., 2017	1/33	3.0	[0.1; 15.8]	
Rabkin et al., 2000	1/56	1.8	[0.0; 9.6]	
Random effects model		**13.1**	**[9.6; 17.7]**	

Heterogeneity: $I^2 = 87\%$, $\tau^2 = 0.7066$, $p < 0.0001$

Fig. 2. Forest plots with prevalence rates of original studies and pooled prevalence estimates (with 95% CI) for current major depressive disorder. *Notes.* n = affected cases, N = sample size; Prev. = prevalence.

funnel plot indicated no reporting bias across studies. A sensitivity analysis excluding two studies with a quality of <40% revealed a pooled prevalence of 18.8% (95% CI 13.8–25.2%). The prevalence of any lifetime affective disorder ranged between 11.6% (Henningsen & Meinck, 2003) and 72.7% (Engberg et al., 2017) with a pooled prevalence of 46.1% (95% CI 35.8–56.8%) across 10 studies. The model showed significant heterogeneity ($I^2 = 90\%$, $p < 0.0001$). Visual inspection of the funnel plot showed no evidence of reporting bias. No sensitivity analysis was performed since all studies had a quality of >40%. Figure 4 shows forest plots for current and lifetime affective disorders.

Frequency of anxiety disorders

Of the 39 studies included in the qualitative analysis, 22 studies assessed anxiety disorders. The frequency for any current anxiety disorder ranged between 11.0% (Cardoso et al., 2004) and 96.7% (Dias et al., 2011) with a pooled prevalence estimate of 39.6% (95% CI 25.5–55.6%) across 14 studies. Heterogeneity was significant with $I^2 = 96\%$ ($p < 0.0001$) and the funnel plot showed no asymmetry. A sensitivity analysis excluding one study with a quality of <40% revealed a pooled prevalence of 40.0% (95% CI 24.9–57.3%). The prevalence range for lifetime anxiety disorders was
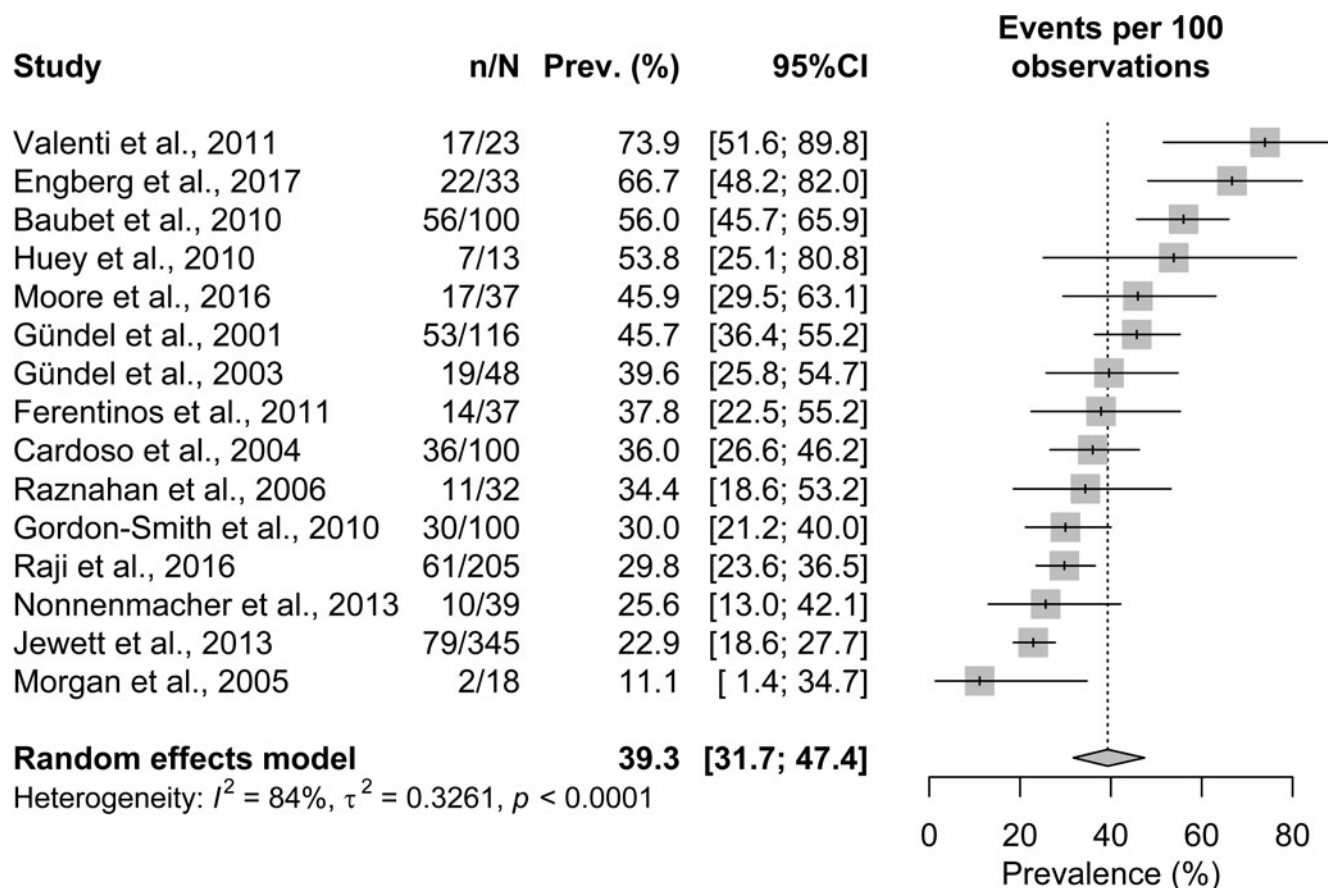
Fig. 3. Forest plots with prevalence rates of original studies and pooled prevalence estimates (with 95% CI) for lifetime major depressive disorder. *Notes.* n = affected cases, N = sample size; Prev. = prevalence.

9.4% (Raznahan, Joinson, O'Callaghan, Osborne, & Bolton, 2006) to 83.6% (Gündel, Wolf, Xidara, Busch, & Ceballos-Baumann, 2001). One study (Mozzetta et al., 2008) assessed only generalized anxiety disorders and reported that 25.0% had a current diagnosis. Another study (Huey, Koppel, Armstrong, Grafman, & Floeter, 2010) investigated only phobia and reported a prevalence of 15.4% both for current and lifetime phobic disorder. These studies were not included in the meta-analysis. The pooled prevalence rate for the remaining studies was 44.2% (95% CI 27.0–62.9%) across 11 studies with significant heterogeneity ($I^2 = 94\%$, $p < 0.0001$). Visual inspection of the funnel plot indicated no significant reporting bias. One study with a quality of <40% was excluded for the sensitivity analysis, which revealed a pooled prevalence of 45.9% (95% CI 27.3–65.8%). Figure 5 shows forest plots of the included studies and the overall effect estimates for current and lifetime anxiety disorders.

Comparisons with control groups

In 15 studies, the frequency of affective and anxiety disorders was compared with a control group (online Supplementary Table S2). All eight studies reporting comparisons with population-based samples found significant differences in terms of a higher psychopathological burden of patients with rare diseases (Engberg et al., 2017; Gündel et al., 2001, 2003; Hedgeman et al., 2017; Lu et al., 2017; Manti et al., 2016; Moore et al., 2016; Roos et al., 2016). In two studies (Chen et al., 2015; Rabkin et al., 2000), authors compared patients with their caregivers and one reported higher

frequencies of both depressive and anxiety disorders in patients (Chen et al., 2015). In four out of eight comparisons with patients with non-rare diseases, patients with rare diseases showed higher rates than controls (Gündel et al., 2003; Huey et al., 2010; Jenkins-Jones et al., 2018; Mozzetta et al., 2008), two studies found no differences (Engberg et al., 2017; Ozel-Kizil, Akbostanci, Ozguven, & Atbasoglu, 2008), and in two studies, the authors reported higher frequencies in the comparison group (Dias et al., 2011; Moore et al., 2016).

Correlates of psychopathology

Fifteen studies additionally investigated correlates of psychopathology. In one study, psychopathology was not related to any individual (e.g. age, IQ) or external (life events) variable (Stinton et al., 2010). In all other studies, authors found different associations with various patient-related, disease-related, or psychological features, partly with contradictory results. A detailed presentation of the observed correlates for all studies is in online Supplementary Table S4. In the following, we describe only major trends.

Patient-related features

Where sex differences were detected, most studies reported an association between female sex and both depression (Nonnenmacher, Hammer, Lule, Hautzinger, & Kuebler, 2013; Schmitz-Hübsch et al., 2011; Schneider et al., 2014) and anxiety
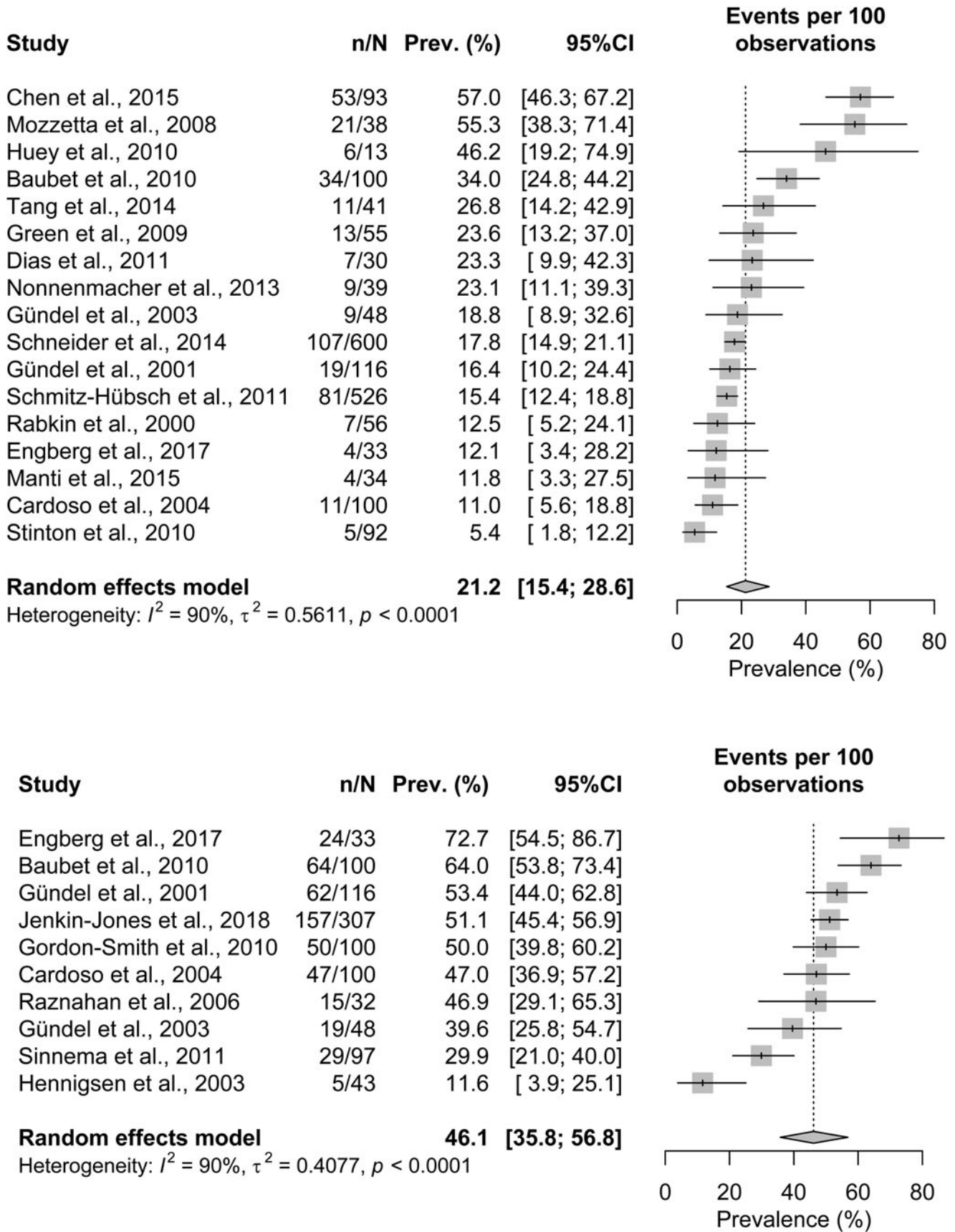
Study	n/N	Prev. (%)	95%CI	Events per 100 observations
Chen et al., 2015	53/93	57.0	[46.3; 67.2]	
Mozzetta et al., 2008	21/38	55.3	[38.3; 71.4]	
Huey et al., 2010	6/13	46.2	[19.2; 74.9]	
Baubet et al., 2010	34/100	34.0	[24.8; 44.2]	
Tang et al., 2014	11/41	26.8	[14.2; 42.9]	
Green et al., 2009	13/55	23.6	[13.2; 37.0]	
Dias et al., 2011	7/30	23.3	[9.9; 42.3]	
Nonnenmacher et al., 2013	9/39	23.1	[11.1; 39.3]	
Gündel et al., 2003	9/48	18.8	[8.9; 32.6]	
Schneider et al., 2014	107/600	17.8	[14.9; 21.1]	
Gündel et al., 2001	19/116	16.4	[10.2; 24.4]	
Schmitz-Hübsch et al., 2011	81/526	15.4	[12.4; 18.8]	
Rabkin et al., 2000	7/56	12.5	[5.2; 24.1]	
Engberg et al., 2017	4/33	12.1	[3.4; 28.2]	
Manti et al., 2015	4/34	11.8	[3.3; 27.5]	
Cardoso et al., 2004	11/100	11.0	[5.6; 18.8]	
Stinton et al., 2010	5/92	5.4	[1.8; 12.2]	
Random effects model		**21.2**	**[15.4; 28.6]**	

Heterogeneity: I^2 = 90%, τ^2 = 0.5611, p < 0.0001

Study	n/N	Prev. (%)	95%CI	Events per 100 observations
Engberg et al., 2017	24/33	72.7	[54.5; 86.7]	
Baubet et al., 2010	64/100	64.0	[53.8; 73.4]	
Gündel et al., 2001	62/116	53.4	[44.0; 62.8]	
Jenkin-Jones et al., 2018	157/307	51.1	[45.4; 56.9]	
Gordon-Smith et al., 2010	50/100	50.0	[39.8; 60.2]	
Cardoso et al., 2004	47/100	47.0	[36.9; 57.2]	
Raznahan et al., 2006	15/32	46.9	[29.1; 65.3]	
Gündel et al., 2003	19/48	39.6	[25.8; 54.7]	
Sinnema et al., 2011	29/97	29.9	[21.0; 40.0]	
Hennigsen et al., 2003	5/43	11.6	[3.9; 25.1]	
Random effects model		**46.1**	**[35.8; 56.8]**	

Heterogeneity: I^2 = 90%, τ^2 = 0.4077, p < 0.0001

Fig. 4. Forest plots with prevalence rates of original studies and pooled prevalence estimates (with 95% CI) for current and lifetime affective disorder. *Notes.* n = affected cases, N = sample size; Prev. = prevalence.
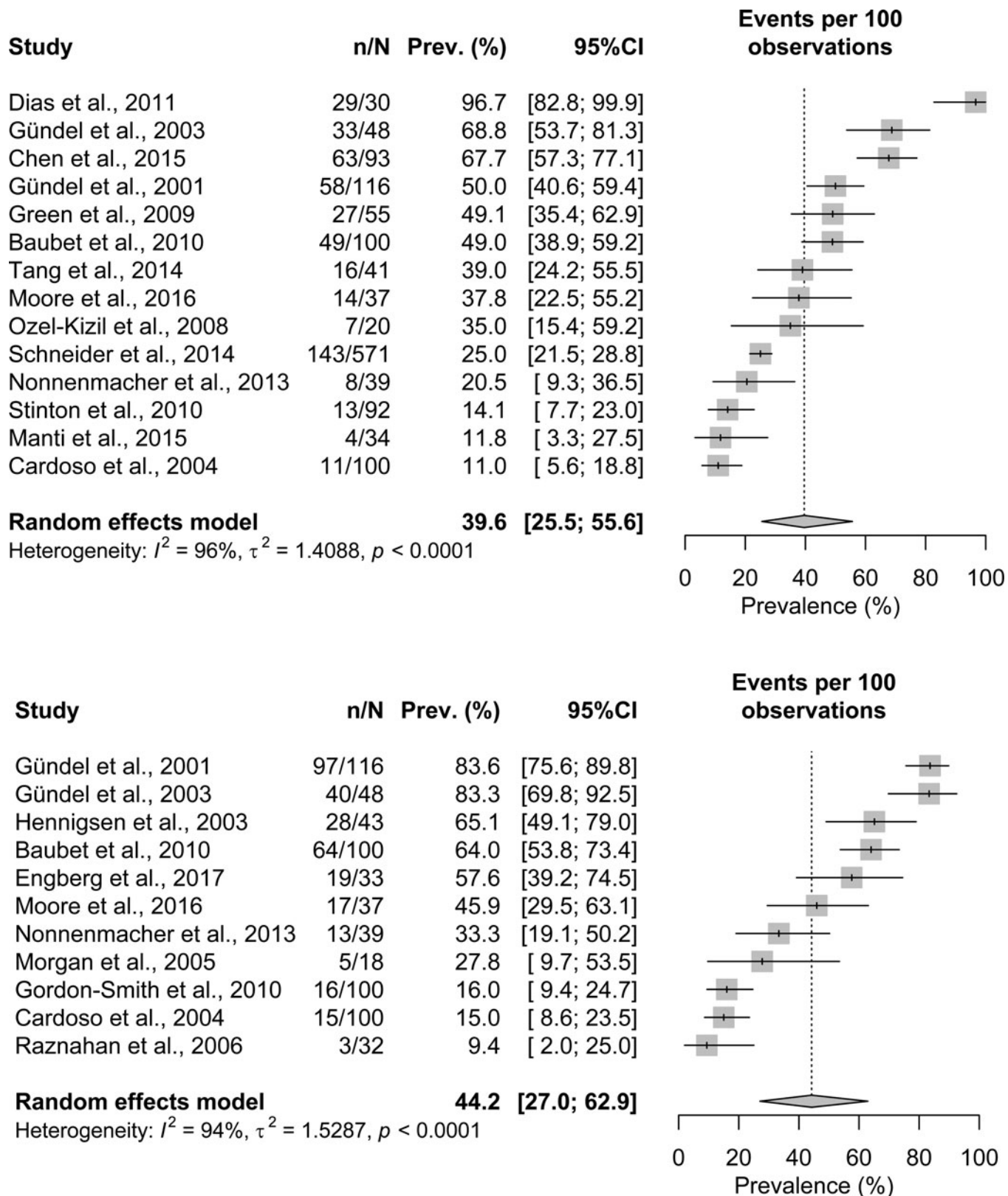
Study	n/N	Prev. (%)	95%CI	Events per 100 observations
Dias et al., 2011	29/30	96.7	[82.8; 99.9]	
Gündel et al., 2003	33/48	68.8	[53.7; 81.3]	
Chen et al., 2015	63/93	67.7	[57.3; 77.1]	
Gündel et al., 2001	58/116	50.0	[40.6; 59.4]	
Green et al., 2009	27/55	49.1	[35.4; 62.9]	
Baubet et al., 2010	49/100	49.0	[38.9; 59.2]	
Tang et al., 2014	16/41	39.0	[24.2; 55.5]	
Moore et al., 2016	14/37	37.8	[22.5; 55.2]	
Ozel-Kizil et al., 2008	7/20	35.0	[15.4; 59.2]	
Schneider et al., 2014	143/571	25.0	[21.5; 28.8]	
Nonnenmacher et al., 2013	8/39	20.5	[9.3; 36.5]	
Stinton et al., 2010	13/92	14.1	[7.7; 23.0]	
Manti et al., 2015	4/34	11.8	[3.3; 27.5]	
Cardoso et al., 2004	11/100	11.0	[5.6; 18.8]	
Random effects model		**39.6**	**[25.5; 55.6]**	

Heterogeneity: $I^2 = 96\%$, $\tau^2 = 1.4088$, $p < 0.0001$

Prevalence (%) 0 20 40 60 80 100

Study	n/N	Prev. (%)	95%CI	Events per 100 observations
Gündel et al., 2001	97/116	83.6	[75.6; 89.8]	
Gündel et al., 2003	40/48	83.3	[69.8; 92.5]	
Hennigsen et al., 2003	28/43	65.1	[49.1; 79.0]	
Baubet et al., 2010	64/100	64.0	[53.8; 73.4]	
Engberg et al., 2017	19/33	57.6	[39.2; 74.5]	
Moore et al., 2016	17/37	45.9	[29.5; 63.1]	
Nonnenmacher et al., 2013	13/39	33.3	[19.1; 50.2]	
Morgan et al., 2005	5/18	27.8	[9.7; 53.5]	
Gordon-Smith et al., 2010	16/100	16.0	[9.4; 24.7]	
Cardoso et al., 2004	15/100	15.0	[8.6; 23.5]	
Raznahan et al., 2006	3/32	9.4	[2.0; 25.0]	
Random effects model		**44.2**	**[27.0; 62.9]**	

Heterogeneity: $I^2 = 94\%$, $\tau^2 = 1.5287$, $p < 0.0001$

Prevalence (%) 0 20 40 60 80 100

Fig. 5. Forest plots with prevalence rates of original studies and pooled prevalence estimates (with 95% CI) for current and lifetime anxiety disorder. *Notes.* n = affected cases, N = sample size; Prev. = prevalence.

(Green et al., 2009; Schneider et al., 2014; Tang et al., 2014). In studies that found age-related differences, depression was mostly associated with older age (Baubet et al., 2011; Manti et al., 2016; Roos et al., 2016; Schneider et al., 2014), while anxiety disorders occurred more frequently in younger individuals (Hedgeman et al., 2017; Manti et al., 2016; Ozel-Kizil et al., 2008; Schneider

et al., 2014). Most studies found no association with other demographic variables or education (Jewett, Razykov, Hudson, Baron, & Thombs, 2013; Manti et al., 2016; Roos et al., 2016; Wei et al., 2016). Contrarily, two studies (Nonnenmacher et al., 2013; Raji, Lawani, & James, 2016) found that depression was associated with lower education, unemployment, and low income.

Disease-related and clinical features

The majority of studies examining the relation between clinical symptoms of the rare diseases and psychopathology found no associations (Baubet et al., 2011; Cardoso et al., 2004; Chen et al., 2015; Gordon-Smith et al., 2010; Gündel et al., 2001; Naarding, Janzing, Eling, van der Werf, & Kremer, 2009; van Os et al., 2007; Wei et al., 2016) or only with single symptoms (Baubet et al., 2011; Jewett et al., 2013; Raznahan et al., 2006). Three studies reported an association between pain and depression or anxiety (Baubet et al., 2011; Rabkin et al., 2000; Raji et al., 2016). Illness duration showed no association with depression or anxiety in six studies (Gündel et al., 2001; Henningsen & Meinck, 2003; Krogias et al., 2011; Lu et al., 2017; Nonnenmacher et al., 2013; Wei et al., 2016), two studies found higher psychopathology early in the disease course or early after diagnosis for anxiety (Moore et al., 2016) and affective disorders (Roos et al., 2016). One study found a relation between longer disease duration and younger age of onset and depression (Schmitz-Hübsch et al., 2011). Another study found no association with age of onset (Wei et al., 2016). A variety of studies found associations between depression and different neurological features and/or cognitive abilities (Krogias et al., 2011; Lu et al., 2017; Moore et al., 2016; Noh et al., 2014; Schmitz-Hübsch et al., 2011; Valenti et al., 2011; van Os et al., 2007). Depression was further associated with decreased physical functioning in two studies (Rabkin et al., 2000; Wei et al., 2016), while three studies found no association (Lu et al., 2017; Naarding et al., 2009; Nonnenmacher et al., 2013).

Psychosocial features

Few studies examined psychological features such as illness perceptions. Gündel et al. (2001) observed that psychological variables explained depression and anxiety better than clinical features. Depressive coping (instead of, for instance, problem-focused coping) was identified as a strong predictor of depression and anxiety (Gündel et al., 2001, 2003). Depression and/or anxiety were further associated with reduced quality of life and poorer social functioning (Baubet et al., 2011), less enjoyment and satisfaction in different life areas (Goracci et al., 2008; Rabkin et al., 2000), and more psychological and physical distress (Rabkin et al., 2000). In patients with spasmodic torticollis, the extent of body image dissatisfaction was a strong predictor for the diagnosis of social phobia (Gündel et al., 2001). One study found no association between depression and meaning of health but a negative correlation between depression and the number of perceived positive amplifiers in the patient's life (Nonnenmacher et al., 2013).

Discussion

This is the first systematic review and meta-analysis on affective and anxiety disorders in patients with different rare chronic diseases. Prevalence rates ranged widely between studies, with pooled prevalence estimates of up to 46.1%, for instance for lifetime affective disorders. Heterogeneity between studies was high, which is reflected in large confidence intervals of the pooled

prevalence rates. The large variation between diseases may reflect the clinical heterogeneity of different rare diseases. However, even among studies investigating the same disease, results varied widely (e.g. current anxiety disorder in ALS 20.5–67.7%). Other methodological sources of heterogeneity could be different sampling strategies, study designs, or assessments of psychopathology although we tried to limit the latter by only including studies using clinical diagnoses. The pooled prevalence rates should be interpreted in a way considering the lower and upper bounds of the confidence interval as compatible with the overall estimate. However, even if conservatively referring to the lower bound, the pooled prevalence estimates we found are higher than in the general population (Jacobi et al., 2014). This is in line with studies on depressive and anxiety disorders in patients with more common chronic conditions. Mental diseases in addition to a somatic disorder can negatively affect the course of the somatic disease and reduce quality of life (Cruz et al., 2010; Lichtman et al., 2014; Müller-Tasch et al., 2007; Watkins et al., 2013). Therefore, detecting and treating mental disorders in patients with rare chronic diseases is crucial to improve overall health and well-being.

To better understand which aspects may lead to increased psychopathology rates, we further investigated correlates of depression and anxiety. Different and partly contradictory patient-related, clinical, and psychosocial features were associated with increased psychopathology. Regarding some of the clinical correlates such as cognitive impairments or fatigue, it is unclear whether these are symptoms of the somatic disease that are associated with depression or rather symptoms of a depressive disorder itself. Due to the cross-sectional design of most studies, the direction of these relationships remains unclear. Moreover, some of the conditions included in this review may have a pathophysiological predisposition for affective or anxiety disorders. For instance, Huntington's disease causes degenerative cerebral changes, which can contribute to the development of depressive disorder (Naarding et al., 2009) and in spasmodic torticollis, a functional disturbance of the basal ganglia affects the limbic loop, likely resulting in mood disorders (Gündel et al., 2003). In these cases, it can be difficult to differentiate whether the somatic predisposition or problems in adjusting to the disease cause psychopathological symptoms. Moreover, medication for the somatic disease can cause psychiatric symptoms as a side effect, e.g. steroids in sarcoidosis (Goracci et al., 2008). Overall, in some cases, it can be difficult to distinguish between somatic symptoms, side effects of medications and symptoms, or consequences of comorbid mental diseases. For healthcare providers, these distinctions may be difficult as well. Symptoms of mental disorders may be mistaken for physical symptoms, which could lead to an underestimation of psychological burden. To detect mental disorders in somatically ill patients, interdisciplinary cooperation, for example, through consultative services, or a systematic use of standardized screening instruments could be helpful. In three studies, the prevalence of affective or anxiety disorders was particularly high in early stages of the disease. This is in line with a qualitative study from our team, where patients described receiving the diagnosis as a life changing experience (Uhlenbusch, Löwe, & Depping, 2019) and indicates, that the time right after diagnosis may be a particularly critical phase in which patients need particular support in adjusting to their disease.

In many studies, clinical symptoms were not associated with depression or anxiety. Besides clinical features, psychological processes can play a role in the development of mental disorders. One study showed that psychological features such as illness

perceptions were better predictors of psychopathology than clinical features (Gündel et al., 2001). This is in line with a cross-sectional study we conducted on depression and anxiety symptoms in patients with rare diseases, where disease-related aspects did not contribute to explained variation of depression and anxiety, while psychological features played a substantial role (Uhlenbusch et al., 2019). This indicates that when addressing psychopathology, it may be adequate to provide healthcare, which is not tailored to the specific disease. This information is particularly useful in the field of rare diseases, where disease-specific support offers are hardly feasible due to the high number of different conditions.

Despite the rarity of the conditions, some authors succeeded at reaching large sample sizes. Most of these studies were cohort studies retrieving data from patient registries (Hedgeman et al., 2017; Jenkins-Jones et al., 2018; Roos et al., 2016), where medical information is organized and stored systematically. For instance, Denmark, Sweden, and other Nordic countries have nationwide registries with similar structures and personal identification numbers, which enable researchers to perform large cohort studies. This may be particularly useful in the field of rare diseases, where conducting adequately powered studies is challenging (Pai et al., 2019). In two other studies (Schmitz-Hübsch et al., 2011; Schneider et al., 2014), the authors attained large sample sizes by cooperating globally. Schneider et al. (2014) recruited patients across 15 different centers, all part of the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome (http://www.22q11-ibbc.org). Although collaborations of this form increase heterogeneity due to cultural variation or sampling differences, they could be a promising approach to strengthen evidence in the field of rare diseases.

A major strength of this study is the broad search considering all rare diseases listed in the orpha.net registry of rare diseases. A total of 34 402 studies were screened. However, due to the high number of records, many studies were excluded during the initial screening based on the information given in the title and abstract. This procedure enabled us to screen the high number of studies but we may have excluded potentially relevant studies for which the information in the abstract is inaccurate or incomplete. For the same reason, we did not update the database search, which is recommended in order to detect studies published during the time of data analysis (Eden, Levit, Berg, & Morton, 2011). The resulting time gap between the end of the search and the publication must be noted as a limitation. The quality of assessed studies ranged widely and some studies fulfilled less than half of the criteria in the STROBE checklist. This is a potential source of bias and may affect the reliability of individual study results. However, a sensitivity analysis excluding studies with a quality of <40% scarcely changed the pooled prevalence estimates. Moreover, the STROBE checklist is a guideline for reporting observational studies and it is not always clear whether an aspect was not reported or not performed. Some items further addressed specific analyses (e.g. sub-group or sensitivity analyses), which may have been beyond the scope of some studies. We rated 'not fulfilled' in all of these cases, which may result in a stricter assessment and an underestimation of the studies' quality. The current study aimed at complementing survey-based research on symptom burden in patients with rare diseases. Hence, we only included studies that used clinical diagnoses or structured clinical interviews. This allowed us to investigate clinically relevant affective and anxiety disorders and aimed to reduce heterogeneity. However, as we excluded studies solely based on questionnaires, the results do not provide a comprehensive representation of all research on psychopathology in rare diseases. Considering studies using self-report questionnaires may have resulted in a broader range of different rare diseases. Large studies on depression and anxiety used standardized questionnaires, for instance the International Depression Epidemiological Study by Quittner et al. (2014), who included more than 6000 patients with the rare disease cystic fibrosis across nine countries. More recent surveys investigated depression and anxiety in samples of patients with differing rare diseases in Germany (Uhlenbusch et al., 2019) and the USA (Bogart & Dermody, 2020). A further limitation lies in the fact that most of the included studies had a non-experimental, cross-sectional design and no conclusions can be drawn about causal relationships. Finally, the heterogeneity between but also within diseases is high and should be considered when interpreting the results.

In conclusion, this is the first systematic review on clinically diagnosed affective and anxiety disorders in patients with different rare diseases. We synthesized data on prevalence and correlates of psychopathology and found widely ranging prevalence rates and different, partly contradictory features to be associated with depression and anxiety. Disregarding the heterogeneity of different studies, pooled prevalence estimates showed that high percentages of patients across different rare diseases are affected by affective and anxiety disorders. Considering that the majority of rare diseases are not curable, early detecting and treating mental disorders can be critical in order to maintain and improve general health and well-being in patients with rare diseases.

Despite our broad search strategy considering all rare diseases listed in the orpha.net registry of rare diseases, only 24 different conditions were included, representing only a fraction of the estimated 7000 different rare diseases worldwide. This indicates that evidence on this topic still lacks a vast majority of rare diseases. Conducting studies in this area could be facilitated by building networks and research collaborations across sites.

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