**SUPPLEMENTARY MATERIAL**

**Excerpt of the search strategy**

((AA amyloidosis or AAA syndrome or AADC deficiency or AAE or AAE 2 or AAE II or Aagenaes syndrome or AAOR or AApoAI amyloidosis or AApoAII amyloidosis or AApoAIV amyloidosis or Aarskog-like syndrome or Aarskog-Ose-Pande syndrome or Aarskog-Scott syndrome or Aarskog syndrome or Aase-Smith II syndrome or Aase-Smith I syndrome or Aase-Smith syndrome or Aase syndrome or AAV or Abacavir toxicity or ABCB4 gene mutation-associated cholelithiasis or Abdominal muscle deficiency syndrome or Aberfeld syndrome or ABeta2M amyloidosis or ABeta2Mwt amyloidosis or ABetaA21G amyloidosis or ABetaA21G-related amyloidosis or ABeta amyloidosis, Arctic type or ABeta amyloidosis, Dutch type or ABeta amyloidosis, Flemish type or ABeta amyloidosis, Iowa type or ABeta amyloidosis, Italian type or ABeta amyloidosis, Piedmont type or ABetaD23N amyloidosis or ABetaE22G amyloidosis or ABetaE22K amyloidosis or ABetaE22Q amyloidosis or ABetaL34V amyloidosis or ABetaL34V-related amyloidosis or Abetalipoproteinemia or Ablepharon macrostomia syndrome or Abnormal eye movements or Abnormal number of coronary ostia or Abnormal origin of right left pulmonary artery from the aorta or Abnormal origin of the pulmonary artery or Abnormal origin aberrant course of coronary artery or ABPA or ABri amyloidosis or Abruzzo-Erickson syndrome or ABSD or Absence deformity of leg-cataract syndrome or Absence of brachiocephalic vein or Absence of dermatoglyphics-congenital milia syndrome or Absence of fingerprints-congenital milia syndrome or Absence of innominate vein or Absence of pulmonary valve-Fallot tetralogy-absence of ductus arteriosus syndrome or Absence of pulmonary valve-ventricular septal defect-persistent ductus arteriosus syndrome or Absence of the pulmonary artery or Absence of the superior caval vein or Absence of the superior vena cava or Absence of the SVC or Absent eyebrows eyelashes-intellectual disability syndrome or Absent patellae-scrotal hypoplasia-renal anomalies-facial dysmorphism-intellectual disability syndrome or Absent pulmonary valve syndrome or Absent radius-anogenital anomalies syndrome or Absent thumb-short stature-immunodeficiency syndrome or Absent tibia-polydactyly-arachnoid cyst syndrome or Absent tibia-polydactyly syndrome or ABSN or ACAD9 deficiency or ACADM deficiency or ACADS deficiency or Acalvaria or Acanthamoeba keratitis or Acanthokeratolytic verrucous nevus or Acanthoma of the nail matrix or Acanthosis nigricans-insulin resistance-muscle cramps-acral enlargement syndrome or Acatalasemia or ACC-abnormal genitalia syndrome or Accelerated skeletal maturation-facial dysmorphism-failure to thrive syndrome or Accessory breasts or Accessory mitral valve tissue or Accessory nostril or Accessory pancreas or Accessory tricuspid valve tissue or ACD-intellectual disability syndrome or ACDMPV or ACER3-related early childhood-onset progressive leukodystrophy or Aceruloplasminemia or Acetaminophen poisoning or Acetazolamide-responsive congenital myotonia or Acetazolamide-responsive myotonia or ACFS or Achalasia-addisonianism-alacrima syndrome or Achalasia cardia or Achalasia-microcephaly syndrome or Acheiria or Acheiropodia or Acheiropody or ACHM or Achondrogenesis or Achondroplasia or Achondroplasia-SCID syndrome or Achondroplasia-severe combined immunodeficiency syndrome or Achondroplasia-Swiss type agammaglobulinemia syndrome or Achromatopsia or Acid beta-glucosidase deficiency or Acid ceramidase deficiency or Acinar cell carcinoma of pancreas or Acitretin etretinate embryopathy or Ackerman dermatitis syndrome or Ackerman fused molar rooth syndrome or Ackerman syndrome or ACNES or Aconitase deficiency or Acoustic neurilemoma or Acoustic neurinoma or Acoustic neuroma or ACPS2 or ACPS4 or Acquired adult-onset immunodeficiency or Acquired alimentary behavior disorder of infancy or Acquired amyloid peripheral neuropathy or Acquired aneurysmal subarachnoid hemorrhage or Acquired angioedema or Acquired angioneurotic edema or Acquired anterior horn cell disease or Acquired ataxia) and (depression or anxiety or psychosocial or mental health or quality of life or patient experiences or psychopathology or well-being)).kp,sh,ti.

*Table 1*

|  |  |  |
| --- | --- | --- |
| **Disease** | **Prevalance** | **Studies** |
| 22q11.2 deletion syndrome | 1-5 : 10 000 | Green et al. (2009), Schneider et al. (2014), Tang et al. (2014) |
| ALS | 1-9 : 100 000 | Chen et al. (2015), Ferentinos et al. (2011), Huey et al. (2010), Nonnenmacher et al. (2013), Rabkin et al. (2000), Roos et al. (2016), Wei et al. (2016) |
| CADASIL | 1-9 : 100 000 | Noh et al. (2014), Valenti et al. (2011) |
| CAH | 1-9 : 100 000 | Jenkin-Jones et al. (2018), Morgan et al. (2005) |
| CAIS / GD | 1-9 : 1 000 000 /  1-9 : 100 000 | Engberg et al. (2017) |
| Cervical dystonia (Spasmodic torticollis) | 20-4100 : 1 000 0001 | Gündel et al. (2003), Gündel et al. (2001), Ozel-Kizil et al. (2008) |
| Darier disease | 1-9 : 100 000 | Gordon-Smith et al. (2010) |
| Huntington Disease | 1-9 : 100 000 | Krogias et al. (2011), Naarding et al. (2009) |
| Neuromyelitis optica | 1-9 : 100 000 | Moore et al. (2016) |
| PBC / PSC | 1-5 : 10 000 /  1-9 : 100 000 | van Os et al. (2007) |
| Phenylketonuria | 1-5 : 10 000 | Manti et al. (2016) |
| Prader-Willi syndrome | 1-9 : 100 000 | Hedgeman et al. (2017), Sinnema et al. (2011) |
| Primary focal dystonia | 1-5 : 10 0002 | Dias et al. (2011) |
| SAPHO syndrome | Unknown | Lu et al. (2017) |
| Sarcoidosis | 1-5 : 10 000 | Goracci et al. (2008) |
| Sickle cell disease | 1-5 : 10 000 | Raji et al. (2016) |
| Spinocerebellar ataxia | 1-9 : 100 0003 | Schmitz-Hübsch et al. (2011) |
| Stiff man syndrome | 1-9 : 1 000 000 | Henningsen et al. (2003) |
| Systemic sclerosis | 1-5 : 10 000 | Baubet et al. (2011), Jewett et al. (2013), Mozzetta et al. (2008), Thombs et al. (2015) |
| Tuberous sclerosis | 1 : 6 000 | Raznahan et al. (2006) |
| Turner syndrome | 1-5 : 10 000 | Cardoso et al. (2004) |
| Williams syndrome | 1 : 7 500 | Stinton et al. (2010) |
| *Notes.*Unless otherwise stated, prevalence rates are based on information from orpha.net. Other sources were used only when prevalence information was not available in orpha.net. 1Defazio, et al. (2013), doi: 10.7916/D80C4TGJ; 2Prevalance for the group of focal, segmental or multifocal dystonia, 3Prevalance for autosomal dominant spinocerebellar ataxia **Abbreviated diseases:** ALS: amyotrophic lateral sclerosis, CAH: Congenital Adrenal Hyperplasia, CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, CAIS: complete androgen insensitivity syndrome, GD: complete gonadal dysgenesis, PBC: Primary biliary cirrhosis, PSC: primary sclerosing cholangitis. | | |

Overview of all included diseases, their prevalence and the respective studies

*Table 2*

Characteristics and results of included studies

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Disease** | **Design** | **Instru-ment** | ***N*** | **Prevalence of depression/ anxiety: Number (%)** | | | | | | **Comparison with control group** | **Study quality (in %)** |
| **MDD current** | **Aff D. current** | **MDD lifetime** | **Aff. D lifetime** | **AD current** | **AD lifetime** |
| Baubet et al. (2011) | Systemic sclerosis | Cross-sectional | MINI | 100 | 19 (19) | 34 (34) | 56 (56) | 64 (64) | 49 (49) | 64(64) | NA | 78.13 |
| Cardoso et al. (2004) | Turner syndrome | Cross-sectional | SCID | 100 | 5 (5) | 11 (11) | 36 (36) | 47 (47) | 11 (11) | 15 (15) | NA | 46.88 |
| Chen et al. (2015) | ALS | Cross-sectional | SCID | 93 | 20 (21.5) | 53 (57) | NA | NA | 63 (67.7) | NA | Affective/anxiety disorder rates higher compared to caregivers | 46.88 |
| Dias et al. (2011) | Primary focal dystonia | Cross-sectional | MINI+ | 30 | 5 (16.7) | 7 (23.3) | NA | NA | 29 (96.7) | NA | Affective/anxiety disorder rates higher in patients with Parkinson’s disease | 43.75 |
| Engberg et al. (2017) | CAIS/ GD | Cross-sectional | MINI+ | 33 | 1 (3) | 4 (12.12) | 22 (67) | 24 (72.7) | NA | 19 (58) | Affective/anxiety disorder rates higher than in age-matched healthy controls but similar as in ovarian insufficiency | 78.10 |
| Ferentinos et al. (2011) | ALS | Cross-sectional | SCID | 37 | 8 (21.6) | NA | 14 (37.8) | NA | NA | NA | NA | 53.13 |
| Goracci et al. (2008) | Sarcoidosis | Cross-sectional | MINI+ | 80 | NA (25) | NA | NA | NA | NA | NA | NA | 46.88 |
| Gordon-Smith et al. (2010) | Darier disease | Cross-sectional | SCAN | 100 | NA | NA | NA (30) | NA (50) | NA | NA (16) | NA | 50.00 |
| Green et al. (2009) | 22q11.2 deletion syndrome | Cross-sectional | SCID | 55 | 7 (12.72) | 13 (23.6) | NA | NA | 27 (49.1) | NA | NA | 56.25 |
| Gündel et al. (2003) | Spasmodic Torticollis | Cross-sectional | SCID | 48 | 9 (18.8) | 9 (18.8) | 19 (39.7) | 19 (39.7) | 33 (68.8) | 40 (83.3) | Affective/anxiety disorder rates higher than in alopecia areata and general population | 62.50 |
| Gündel et al. (2001) | Spasmodic torticollis | Cross-sectional | SCID | 116 | 15 (12.9) | 19 (16.4) | 53 (45.7) | 62 (53.4) | 58 (50) | 97 (83.6) | Affective/anxiety disorder rates higher than in general population | 50.00 |
| Hedgeman et al. (2017) | Prader-Willi syndrome | Cohort study | NPR | 155 | NA | NA | NA | NA | NA | NA | Risk for anxiety disorders higher in the patient group than in matched controls of the general population (risk ratio 2.8 (95% CI 1.0-7.5)) | 75.00 |
| Henningsen et al. (2003) | Stiff man syndrome | Cross-sectional | ADIS-R | 43 | NA | NA | NA | 5 (11.63) | NA | 28 (65.12) | NA | 41.18 |
| Huey et al. (2010) | ALS | Cross-sectional | SCID | 13 | 3 (23.1) | 6 (46.2) | 7 (53.8) | NA | 2 (15.4) | 2 (15.4) | Curent depressive disorder rates higher in ALS than in PLS patients by a non-significant trend. | 37.50 |
| Jenkin-Jones et al. (2018) | CAH | Cohort study | NPR | 307 | NA | NA | NA | 157 (51.1) | NA | NA | Higher risk for affective disorders than in matched controls without CAH | 91.18 |
| Jewett et al. (2013) | Systemic sclerosis | Cross-sectional | CIDI | 345 | 13 (3.8) | NA | 79 (22.9) | NA | NA | NA | NA | 62.50 |
| Krogias et al. (2011) | Huntington disease | Cross-sectional | Interview | 39 | 21 (53.8) | NA | NA | NA | NA | NA | NA | 58.82 |
| Lu et al. (2017) | SAPHO syndrome | Cross-sectional | MINI | 28 | 13 (46.4) | NA | NA | NA | NA | NA | MDD rate higher than in the age- and gender-matched healthy controls | 67.65 |
| Manti et al. (2016) | Phenylketonuria | Cross-sectional | Interview | 34 | NA | 4 (11.8) | NA | NA | 4 (11.8) | NA | Affective/anxiety disorder rates higher than in age-matched healthy controls | 52.94 |
| Moore et al. (2016) | Neuromyelitis optica | Cross-sectional | MINI | 37 | 6 (16) | NA | 17 (46) | NA | 14 (37.8) | 17 (45.9) | Recurrent MDD higher than in patients with MS but lifetime psychopathology similar | 61.76 |
| Morgan et al. (2005) | CAH | Cross-sectional | SCID | 18 | NA | NA | 2 (11.1) | NA | NA | 5 (27.77) | NA | 34.38 |
| Mozzetta et al. (2008) | Systemic sclerosis | Cross-sectional | Interview | 38 | 2 (6) | 21 (55.3) | NA | NA | 10 (25) | NA | Affective/anxiety disorder rates higher than in age-matched patients with melanocytic naevi or melanoma | 29.41 |
| Naarding et al. (2009) | Huntington Disease | Cross-sectional | MINI | 34 | 10 (29.4) | NA | NA | NA | NA | NA | NA | 43.75 |
| Noh et al. (2014) | CADASIL | Cross-sectional | MINI+ | 23 | 4 (17.4) | NA | NA | NA | NA | NA | NA | 68.75 |
| Nonnenmacher et al. (2013) | ALS | Cross-sectional | SCID | 39 | 4 (10.3) | 9 (23.1) | 10 (25.6) | NA | 8 (20.5) | 13 (33.33) | NA | 53.13 |
| Ozel-Kizil et al. (2008) | Cervical dystonia | Cross-sectional | SCID | 20 | 3 (15) | NA | NA | NA | 7 (35) | NA | No differences compared to patients with hemifacial spasm or with essential tremor | 34.38 |
| Rabkin et al. (2000) | ALS | Cross-sectional | SCID | 56 | 1 (2) | 7 (12.5) | NA | NA | NA | NA | Slightly higher depressive symptoms compared to caregivers. No differences in clinical diagnoses. | 40.63 |
| Raji et al. (2016) | Sickle cell disease | Cross-sectional | MINI | 205 | 34 (16.6) | NA | 61 (29.8) | NA | NA | NA | NA | 68.75 |
| Raznahan et al. (2006) | Tuberous sclerosis | Cross-sectional | SADS-L | 32 | NA | NA | 11 (33.4) | 15 (46.9) | NA | 3 (9.4) | NA | 71.88 |
| Roos et al. (2016) | ALS | Case-control study/ cohort study | NPR | 1752 | NA | NA | NA | NA | NA | NA | Higher depressive disorder risk after the ALS diagnosis than matched controls of the general population (Hazard ratio: 4.1 (95% CI 2.6-6.5) | 91.18 |
| Schmitz-Hübsch et al. (2011) | Spinocerebellar ataxia | Cross-sectional | Clinical evaluation | 526 | NA | NA (15.4) | NA | NA | NA | NA | NA | 50.00 |
| Schneider et al. (2014) | 22q11.2 deletion syndrome | Cross-sectional | Several | 600 | 73 (12.16) | 107 (17.83) | NA | NA | 143 (25.04) | NA | NA | 68.75 |
| Sinnema et al. (2011) | Prader-Willi syndrome | Cross-sectional | Clinical evaluation | 97 | NA | NA | NA | 29 (29.9) | NA | NA | NA | 56.25 |
| Stinton et al. (2010) | Williams syndrome | Cross-sectional | PAS-ADD | 92 | NA | 5 (5.6) | NA | NA | 13 (14.8) | NA | NA | 71.88 |
| Tang et al. (2014) | 22q11.2 deletion syndrome | Cross-sectional | SCID | 41 | 5 (12.2) | 11 (26.83) | NA | NA | 16 (39.02) | NA | NA | 65.63 |
| Thombs et al. (2015) | Systemic sclerosis | Longitudinal | CIDI | 309 | 12 (3.9) | NA | NA | NA | NA | NA | NA | 62.50 |
| Valenti et al. (2011) | CADASIL | Cross-sectional | SCID | 23 | 6 (26.1) | NA | 17 (73.9) | NA | NA | NA | NA | 59.38 |
| van Os et al. (2007) | PBC/PSC | Cross-sectional | SADS | 87 | 3 (3.5) | NA | NA | NA | NA | NA | NA | 62.50 |
| Wei et al. (2016) | ALS | Longitudinal | Clinical evaluation | 166 | 15 (9) | NA | NA | NA | NA | NA | NA | 68.75 |

*Notes.* NA=not applicable; indicated if corresponding data not available; **Abbreviated diseases:** ALS: amyotrophic lateral sclerosis, CAH: Congenital Adrenal Hyperplasia, CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, CAIS: complete androgen insensitivity syndrome, GD: complete gonadal dysgenesis, PBC: Primary biliary cirrhosis, PSC: primary sclerosing cholangitis**; Abbreviated outcomes:** MDD: major depressive disorder, Aff.D.: affective disorder, AD: anxiety disorder**; Abbreviated instruments:** ADIS-R: Anxiety Disorders Interview Schedule- Revised, CIDI: Composite International Diagnostic Interview, MINI: Mini-International Neuropsychiatric Interview, NPR: National Patient Registry, PAS-ADD: Psychiatric Assessment Schedules for Adults with Developmental Disabilities, SADS-(L): Schedule of Affective Disorders and Schizophrenia-(Lifetime), SCAN: Schedules for Clinical Assessment in Neuropsychiatry SCID: Structured Clinical Interview for DSM-IV. Quality ratings represent the percentage of fulfilled items in relation to the number of items fulfilled in the STROBE checklist with a possible range from 0% to 100%.

*Table 3*

Quality rating for every item of the STROBE checklist (<https://www.strobe-statement.org/index.php?id=available-checklists>)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study/Item** | **1a** | **1b** | **2** | **3** | **4** | **5** | **6a** | **6b** | **7** | **8** | **9** | **10** | **11** | **12a** | **12b** | **12c** | **12d** | **12e** | **13a** | **13b** | **13c** | **14a** | **14b** | **14c** | **15** | **16a** | **16b** | **16c** | **17** | **18** | **19** | **20** | **21** | **22** | **Final (%)** |
| Baubet et al. (2011) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 78.13 |
| Cardoso et al. (2014) | 0 | 1 | 1 | 1 | 0 | 0 | 1 | na | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | 46.88 |
| Chen et al. (2015) | 0 | 0 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 46.88 |
| Dias et al. (2011) | 0 | 0 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 43.75 |
| Engberg et al. (2017) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | na | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 78.10 |
| Ferentinos et al. (2011) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 53.13 |
| Goracci et al. (2008) | 0 | 1 | 1 | 1 | 1 | 1 | 0 | na | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 46.88 |
| Gordon-Smith et al. (2010) | 0 | 1 | 1 | 1 | 1 | 0 | 0 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 50.00 |
| Green et al. (2009) | 0 | 0 | 1 | 1 | 1 | 0 | 0 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 56.25 |
| Gündel et al. (2003) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 62.50 |
| Gündel et al. (2001) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 50.00 |
| Hedgeman et al. (2017) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 75.00 |
| Henningsen et al. (2003) | 0 | 1 | 1 | 1 | 1 | 1 | 0 | na | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 41.18 |
| Huey et al. (2010) | 0 | 0 | 1 | 1 | 1 | 0 | 0 | na | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 37.50 |
| Jenkin-Jones et al. (2018) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 91.18 |
| Jewett et al. (2013) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 62.50 |
| Krogias et al. (2011) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1 | na | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 58.82 |
| Lu et al. (2017) | 0 | 1 | 1 | 1 | 0 | 1 | 1 | na | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 67.65 |
| Manti et al. (2015) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 0 | 52.94 |
| Moore et al. (2016) | 0 | 0 | 1 | 1 | 1 | 0 | 1 | na | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 61.76 |
| Morgan et al. (2005) | 1 | 0 | 1 | 1 | 1 | 1 | 0 | na | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 34.38 |
| Mozzetta et al. (2008) | 0 | 0 | 1 | 1 | 1 | 0 | 0 | na | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 29.41 |
| Naarding et al. (2009) | 0 | 0 | 1 | 1 | 1 | 0 | 0 | na | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 43.75 |
| Noh et al. (2014) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | na | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 68.75 |
| Nonnenmacher et al. (2013) | 0 | 1 | 1 | 1 | 1 | 0 | 0 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 53.13 |
| Ozel-Kizil et al. (2008) | 0 | 0 | 1 | 1 | 1 | 1 | 0 | na | 1 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | na | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 34.38 |
| Rabkin et al. (2000) | 0 | 0 | 1 | 1 | 1 | 0 | 0 | na | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 40.63 |
| Raji et al. (2016) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | na | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 68.75 |
| Raznahan et al. (2006) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | 71.88 |
| Roos et al. (2016) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 91.18 |
| Schmitz-Hübsch et al. (2011) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 0 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 50.00 |
| Schneider et al. (2014) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 68.75 |
| Sinnema et al. (2011) | 0 | 1 | 1 | 1 | 1 | 0 | 0 | na | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | na | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 56.25 |
| Stinton et al. (2010) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 71.88 |
| Tang et al. (2014) | 1 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 65.63 |
| Thombs et al. (2015) | 0 | 1 | 1 | 1 | 1 | 1 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 62.50 |
| Valenti et al. (2011) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 59.38 |
| van Os et al. (2007) | 0 | 1 | 1 | 1 | 1 | 0 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 62.50 |
| Wei et al. (2016) | 0 | 1 | 1 | 1 | 1 | 1 | 0 | na | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | na | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 68.75 |

*Table 4*

Aspects associated with depression and anxiety

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient-related features** | | | |
|  | **Depression** | **Anxiety** | |
| **Sex** | no sex-related differences in six studies (Lu et al., 2017; Naarding et al., 2009; Raji et al., 2016; Raznahan et al., 2006; Roos et al., 2016; Wei et al., 2016) | no sex-related differences in three studies (Hedgeman et al., 2017; Henningsen & Meinck, 2003; Raznahan et al., 2006) | |
| association between female sex and depression in three studies (Nonnenmacher et al., 2013; Schmitz-Hübsch et al., 2011; Schneider et al., 2014) | association between female sex and anxiety in three studie s(Green et al., 2009; Schneider et al., 2014; Tang et al., 2014) | |
| higher prevalence for depression in females across all age groups, but a specifically high risk for men of 41 years and older when investigating subgroups (Jenkins-Jones et al., 2018) |
| **Age** | depression associated with older age in four studies (Baubet et al., 2011; Manti et al., 2016; Roos et al., 2016; Schneider et al., 2014) | anxiety disorders associated with younger age in four studies (Hedgeman et al., 2017; Manti et al., 2016; Ozel-Kizil et al., 2008; Schneider et al., 2014) | |
| no association between age and depression in five studies (Lu et al., 2017; Naarding et al., 2009; Raji et al., 2016; Schmitz-Hübsch et al., 2011; Wei et al., 2016) | no association between age and anxiety in three studies (Green et al., 2009; Henningsen & Meinck, 2003; Tang et al., 2014) | |
| highest prevalence of mood disorders in young adults (Green et al., 2009) |
| **Education/ income/ employment** | no association with any demographic variable or education in four studies (Jewett et al., 2013; Manti et al., 2016; Roos et al., 2016; Wei et al., 2016) | no association with any demographic variable or education in two studies Manti et al., 2016; Nonnenmacher et al., 2013) | |
| depression associated with lower education (Nonnenmacher et al., 2013; Raji et al., 2016), unemployment and low income (Raji et al., 2016) |
| **Other patient-related variables** | incriminating life event in the year before the initial manifestation of spasmodic torticollis associated with depression (Gündel et al., 2001) | incriminating life event in the year before the initial manifestation of spasmodic torticollis associated with anxiety (Gündel et al., 2001) | |
| **Disease-related and clinical features** | | | |
|  | **Depression** | | **Anxiety** |
| **Clinical symptoms/ disease course** | no association between clinical symptoms of the rare diseases and depression in eight studies (Baubet et al., 2011; Cardoso et al., 2004; Chen et al., 2015; Gordon-Smith et al., 2010; Gündel et al., 2001; Naarding et al., 2009; van Os et al., 2007; Wei et al., 2016) | | no association between clinical symptoms of the rare diseases and anxiety in five studies (Baubet et al., 2011; Cardoso et al., 2004; Chen et al., 2015; Gordon-Smith et al., 2010; Gündel et al., 2001) |
| associations with single symptoms in three studies: depression associated with more severe gastrointestinal track involvement in systemic sclerosis (Jewett et al., 2013), depression associated with less digestive symptoms in systemic sclerosis (Baubet et al., 2011), psychopathology associated with the presence of epilepsy in tuberous sclerosis (Raznahan et al., 2006) | | pain was positively associated with anxiety in one study (Rabkin et al., 2000) and negatively in another (Baubet et al., 2011). |
| pain was associated with depression in three studies (Baubet et al., 2011; Rabkin et al., 2000; Raji et al., 2016) | |
| presence and severity of depression did not correlate with disease progression (Wei et al., 2016) | |
| the presence of depression was unrelated to survival but the severity of depression was correlated with survival (Wei et al., 2016) | |
| association between depression and insomnia and fatigue (van Os et al., 2007) | |
| **Symptom severity** | no association between symptom severity and depression in four studies (Chen et al., 2015; Gündel et al., 2001; Krogias et al., 2011; Lu et al., 2017) | | no association between symptom severity and anxiety in two studies (Chen et al., 2015; Gündel et al., 2001) |
| positive association between depression and disease severity (Schmitz-Hübsch et al., 2011) | | positive association between disease severity and the development of phobia in individual cases (Henningsen & Meinck, 2003) |
| **Illness duration** | no association between depression and illness duration in five studies (Gündel et al., 2001; Krogias et al., 2011; Lu et al., 2017; Nonnenmacher et al., 2013; Wei et al., 2016) | | no association between anxiety and illness duration in three studies, (Gündel et al., 2001; Henningsen & Meinck, 2003; Nonnenmacher et al., 2013) |
| higher rates of affective disorders early in the disease course/early after diagnosis (Roos et al., 2016) | | higher anxiety early in the disease course/early after diagnosis (Moore et al., 2016) |
| association between longer disease duration and depression (Schmitz-Hübsch et al., 2011) | |
| **Age at onset** | association between younger age at onset and an increased risk of depression in one study (Schmitz-Hübsch et al., 2011) | | NA |
| no association between age at onset and depression (Wei et al., 2016) | |
| **Functionality** | depression associated with decreased physical functioning in two studies (Rabkin et al., 2000; Wei et al., 2016) | | no association between anxiety and physical functioning (Nonnenmacher et al., 2013) |
| no association with physical functioning in three studies (Lu et al., 2017; Naarding et al., 2009; Nonnenmacher et al., 2013) | |
| **Weight** | no association between depression and body-mass-index in two studies (Raji et al., 2016; Wei et al., 2016) | | obesity associated with a higher risk for anxiety disorders (Hedgeman et al., 2017) |
| depression associated with weight loss (van Os et al., 2007) | |
| **Neurological features/ cognitive functions** | pathologic raphe echogenicity was detected significantly more often in patients with depression (Krogias et al., 2011) | | no association between neurological disability and cognitive performance and anxiety (Moore et al., 2016) |
| depression associated with abnormal brain activities (decreased ALFF in the bilateral VLPFC and right DLPFC, and disrupted functional connectivity in the default mode network (Lu et al., 2017) | | no associations between most of the assessed neurological features and anxiety disorders (Henningsen & Meinck, 2003) |
| association between greater neurological disability and poorer cognitive performance and depression (Moore et al., 2016) | |
| association between number of microbleeds and location (thalamic or cortical) and depressive emotional disturbance (Noh et al., 2014) | |
| cognitive impairment associated with a higher risk of depressive symptoms (Schmitz-Hübsch et al., 2011) | |
| positive association between depression and loss of concentration (van Os et al., 2007) | |
| no association between depression and cognitive functioning expect worse performance on the Stroop test (Valenti et al., 2011) | |
| no association between cognitive function and depression (Naarding et al., 2009) | |
| **Healthcare aspects** | diagnostic delay regarding the rare disease was not associated with depression (Wei et al., 2016) | | NA |
| no association between depression and treatment complications, adherence, past psychiatric history and healthcare services utilization (Raji et al., 2016) | |
| **Psychosocial features** | | | |
|  | **Depression** | | **Anxiety** |
|  | psychological variables (e.g. illness perception, coping) explained psychopathology better than clinical features such as illness severity and duration (Gündel et al., 2001) | | psychological variables (e.g. illness perception, coping) explained psychopathology better than clinical features such as illness severity and duration (Gündel et al., 2001) |
| depressive coping (instead of, for instance, problem-focused coping) was identified as a strong predictor of psychopathology (Gündel et al., 2001; Gündel et al., 2003) | | depressive coping (instead of, for instance, problem-focused coping) was identified as a strong predictor of psychopathology (Gündel et al., 2001; Gündel et al., 2003) |
| depression associated with reduced quality of life (Baubet et al., 2011; Rabkin et al., 2000) and more psychological and physical distress (Rabkin et al., 2000) | | the extent of body image dissatisfaction was a strong predictor for the diagnosis of social phobia (Gündel et al., 2001) |
| 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) | | anxiety associated with reduced quality of life (Baubet et al., 2011; Rabkin et al., 2000) and more psychological and physical distress (Rabkin et al., 2000) |
| depression associated with less enjoyment and satisfaction in different life areas (Goracci et al., 2008) | | anxiety associated with lower social functioning (Baubet et al., 2011) |

*Notes.* NA=not applicable; indicated if corresponding data not available.

**Figure S1. Forest plot showing the sensitivity analysis for current major depressive disorder (excluding studies with a quality of <40%).**

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**Figure S2. Forest plot showing the sensitivity analysis for lifetime major depressive disorder (excluding studies with a quality of <40%).**

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**Figure S3. Forest plot showing the sensitivity analysis for current affective disorder (excluding studies with a quality of <40%).**

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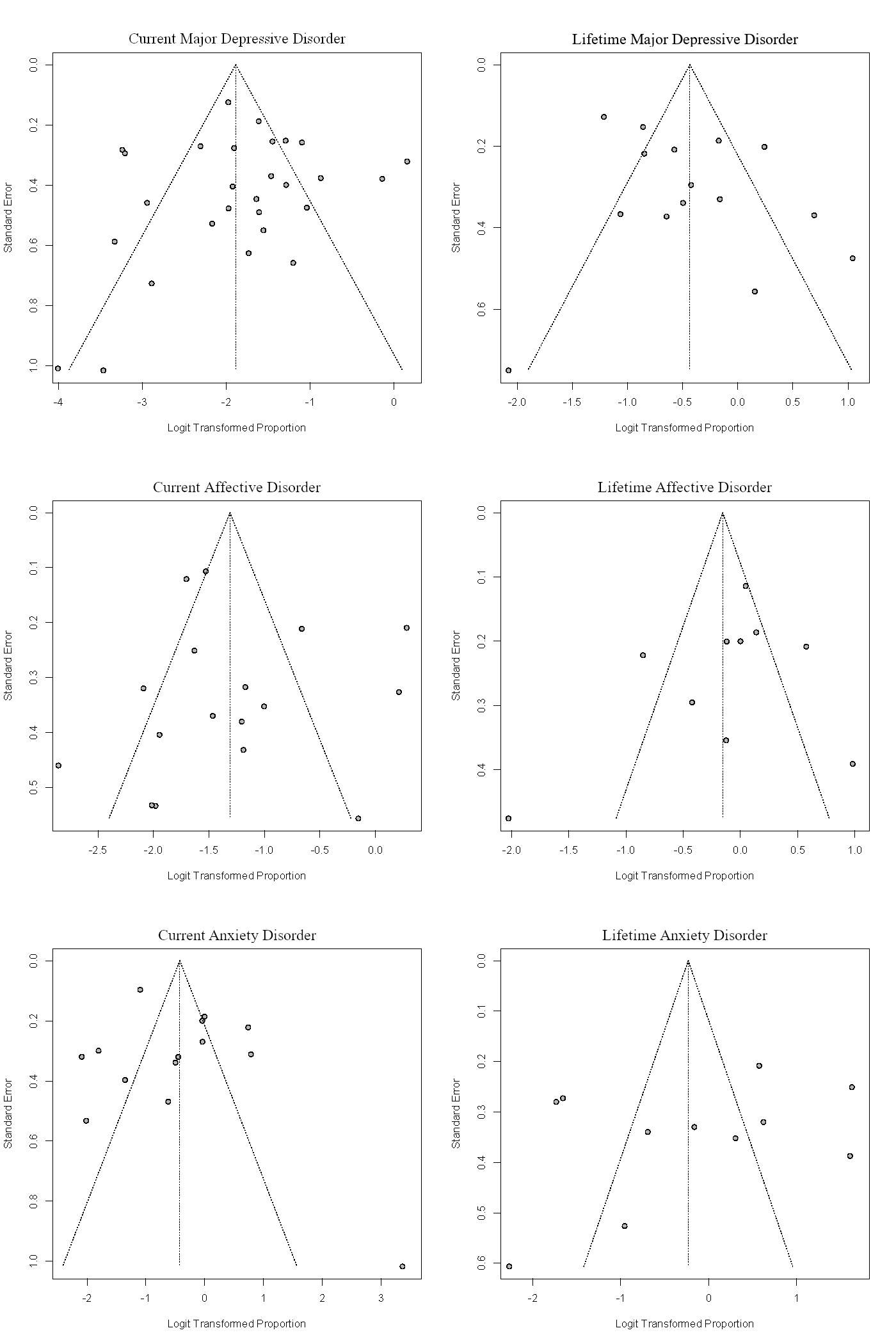
**Figure S4. Forest plot showing the sensitivity analysis for current anxiety disorder (excluding studies with a quality of <40%).**

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**Figure S5. Forest plot showing the sensitivity analysis for lifetime anxiety disorder (excluding studies with a quality of <40%).**

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**Figure S6. Funnel plots.**

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