Chapter 2

A cluster analysis of early onset in common anxiety disorders

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Abstract

Early onset is regarded as an important characteristic of anxiety disorders, associated with higher severity. However, previous findings diverge, as definitions of early onset vary and are often unsubstantiated. We objectively defined early onset in social phobia, panic disorder (with or without agoraphobia), agoraphobia (without panic), and generalised anxiety disorder, using cluster analysis with data gathered in the general population. Resulting cut-off ages for early onset were ≤22 for social phobia, ≤31 for panic disorder, ≤21 for agoraphobia, and ≤27 for generalised anxiety disorder. Comparison of psychiatric comorbidity and general wellbeing between subjects with early and late onset in the general population and an outpatient cohort, demonstrated that among outpatients anxiety comorbidity was more common in early onset agoraphobia, but also that anxiety- as well as mood comorbidity were more common in late onset social phobia. Our results encourage future studies into correlates of early onset of psychiatric disorders.

2.1. Introduction

Age of onset (AOO) is seen as an important clinical characteristic of psychiatric disorders (Kessler et al., 2007). Anxiety disorders form a class of disorders that, overall, are known to typically emerge early in life. Social phobia (SP) often has an onset in childhood or adolescence (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999; Scheibe & Albus, 1992). In panic disorder (with or without agoraphobia; PD), as well as agoraphobia (without panic; AP), onset usually occurs during adolescence through mid-adulthood (Beesdo et al., 2009; Kessler et al., 2007; Thyer et al., 1985; Craske, 1999). Finally, for generalised anxiety disorder (GAD), adolescent-/early adult- (Beesdo et al., 2009; Scheibe & Albus, 1992), as well as mid adult- (Kessler et al., 2007; Thyer et al., 1985), and late adult onset are common (Craske, 1999). Anxiety disorders that have an early onset are thought to represent a subtype that is generally thought to be more severe. Early onset has been associated with higher symptom severity in SP (Van Ameringen et al., 2004), PD (Segui et al., 2000; Tibi et al., 2013), and GAD (Le Roux et al., 2005). In addition, more psychiatric comorbidity was found in early onset PD (Goodwin et al., 2001; Goldstein et al., 1997; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013) and GAD (Le Roux et al., 2005; Campbell et al., 2003). Finally early onset was associated with more suicidality in PD (Iketani et al., 2004). It must be noted though, that these findings have been contradicted by studies reporting no association between early onset and symptom severity, comorbidity, or suicidality (Segui et al., 2000; Iketani et al., 2004; Segui et al., 1999; Le Roux et al., 2005).

These contradictory findings regarding correlates of early onset might be attributed to variations in definitions of early onset that were used in previous studies (Tibi et al., 2013). AOO has for example been approached as a continuous variable in SP (Van Ameringen et al., 2004), GAD (Campbell et al., 2003), and PD (Goodwin et al., 2001); but also through unsubstantiated cut-off ages, covering a wide age-range covering 9 (Van Ameringen et al., 2004) and 20 (Ramsawh et al., 2011) in SP; 18 (Segui et al., 1999), 20 (Goldstein et al., 1997; Ramsawh et al., 2011), 25 (Iketani et al., 2004), and 60 (Segui et al., 2000) in PD; and 20 (Ramsawh et al., 2011) and 50 (Le Roux et al., 2005) in GAD. The use of an objectively determined cut-off to define early onset could benefit the comparability of findings, as well as their translation to clinical practice. One method that has been suggested to empirically define age cut-offs for early- and late onset in various psychiatric disorders is model based clustering (Albert et al., 2015; Anholt et al., 2014; Bauer et al., 2010; Bellivier et al., 2001; Delorme et al., 2005; Hamshere et al., 2009; Ortiz et al., 2011; Panariello et al., 2010; Tibi et al., 2013; Tibi et al., 2015; Tozzi et al., 2011; Zhu et al., 2012). If early onset anxiety is a naturally occurring subtype within anxiety disorders, the distribution of age of onset of this subtype will be Gaussian (Delorme et al., 2005). Therefore, if we would describe the total AOO frequency

distribution of each disorder, separate normal distributions should be discernable. Description of the distinct normal distributions that can be detected in the AOO frequency distribution will allow the identification of early onset. Cut-points of the distributions can then be used to determine cut-offs for early onset. Cluster analysis can be used to define the number of distinct normal distributions, or clusters, that best fits the AOO frequency distribution. With regard to anxiety disorders, application of cluster analysis in previous studies has resulted in cut-offs of 27 years for PD (Tibi et al., 2013) and AP (Tibi et al., 2015). In these studies, both carried out in a sample containing a mix of treated as well as untreated subjects, early onset PD was associated with higher prevalence of AP and childhood trauma (Tibi et al., 2013). Early onset AP was associated with first-degree family history of anxiety disorders (Tibi et al., 2015). To date, to our knowledge, no attempt has been made to describe early onset of SP and GAD using cluster analysis.

In the present study we applied cluster analysis to age of onset data that were gathered in a large general population study to estimate early onset cut-offs for PD, AP, SP, and GAD. Subsequently, we compared psychiatric comorbidity as well as general wellbeing in subjects with early- and late onset PD, AP, SP, and GAD. In order to identify the relevance of early onset for clinical practice, the comparison of psychiatric comorbidity and wellbeing between early- and late onset anxiety was repeated in an outpatient sample. Based on previous studies (Van Ameringen et al., 2004; Campbell et al., 2003; Goodwin et al., 2001; Goldstein et al., 1997; Iketani et al., 2004; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999; Segui et al., 2000; Tibi et al., 2013; Tibi et al., 2015), we hypothesized that early onset would be associated with more psychiatric comorbidity and less wellbeing.

2.2. Materials and methods

2.2.1 Participants

AOO frequency data were collected in The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), a large epidemiologic survey in the Dutch general population ages 18-64. The first wave ran between November 2007 and July 2009. Structured interviews were conducted during house visits by trained- and supervised lay-interviewers. The response percentage was 65% and the sample adequately represented the Dutch population (de Graaf et al., 2010). Respondents provided written informed consent, and the study design was approved by the METIGG, a national mental healthcare ethics committee in The Netherlands. A more detailed description of the NEMESIS-2 design can be found in De Graaf et al. (2010). Although the NEMESIS-2 sample reflected the Dutch population well, younger subjects were

slightly under-represented; therefore, NEMESIS-2 data were weighted in analyses (de Graaf et al., 2010).

For the comparison of psychiatric comorbidity and general wellbeing between subjects with early- and late onset anxiety, in addition to the NEMESIS-2 general population sample, we used clinical data from the Leiden Routine Outcome Monitoring (ROM) Study. The Leiden ROM Study is a naturalistic study among outpatients at Rivierduinen, a regional mental healthcare provider, and at the department of psychiatry of the Leiden University Medical Centre in The Netherlands. Both centres treat patients who have been referred by their general practitioner for specialized treatment of mood-, somatoform- or anxiety disorders. As part of routine clinical practice, all patients between ages 18 and 65 were administered an extensive battery of diagnostic and psychometric measures by trained research nurses or through supervised computerized self-report. This procedure is known as ROM and is described in more detail by De Beurs et al. (2011). Inclusion during the study period January 2004 and September 2012 was estimated at 80% (van Noorden et al., 2011; Zitman, 2012). Data were anonymised and the ethical review board at the Leiden University Medical Centre approved their use in scientific research.

2.2.2 Measures

In the NEMESIS-2 sample, diagnostic information was collected using the Composite International Diagnostic Interview 3.0 (CIDI-3.0; Kessler & Ustun, 2004). The CIDI-3.0 has good validity (Haro et al., 2006). studies of earlier versions of the CIDI demonstrated good reliability with inter-rater reliabilities above 0.94 for anxiety disorders (Wittchen et al., 1991) and test-retest reliability above 0.57 for all anxiety disorders except GAD (κ=0.41) (Semler et al., 1987). In ROM, diagnostic information was collected with the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; van Vliet et al., 2000). The MINI-Plus also has good psychometric properties, with inter-rater reliability between 0.88 and 1.00; test-retest reliability between 0.76 and 0.93; and adequate validity compared to the CIDI-1.0 (Lecrubier et al., 1997). The CIDI-3.0 and MINI-Plus were used to ascertain current (12-month) and lifetime Diagnostic Statistical Manual fourth edition (DSM-IV; NEMESIS-2) and DSM-IV-text revision (DSM-IV-TR; ROM) anxiety disorders (including post-traumatic stress disorder, specific phobia, and obsessive compulsive disorder), comorbid depressive and dysthymic disorders, and alcohol- and drug abuse and dependence. As in both samples all diagnostic information was collected through diagnostic screening instruments, no distinctions between primary and secondary diagnoses could be made.

In both the CIDI-3.0 and the MINI-Plus, AOO of anxiety disorders was assessed. In the MINI-plus, after confirming (past or present) diagnosis, the patient was asked: "How old were

you when you first experienced these symptoms?" In the CIDI-3.0, after confirming (past or present) diagnosis, the subject was asked: "Can you remember your exact age the very first time you experienced these symptoms?" If the subject did not provide an exact age, he/she was asked to provide an estimate. If the answer remained inconclusive, the subject was asked whether this occurred before the first year of school (AOO=4), before puberty (AOO=12) or not before puberty (AOO=13). For subjects who could not provide an AOO or stated that the disorder had always been present, AOO was considered missing.

In both samples general wellbeing was examined using the subscale general health perception of the Dutch version of the Short Form-36 (SF-36; Aaronson et al., 1998), a 36-item self-report survey. Measurement scales vary, ranging from yes/no to answers on a 3-, 5- or 6-point Likert-scale. Raw scores are linearly converted to 0-100 subscales, with higher scores representing higher levels of wellbeing. The SF-36 general health perception scale has moderate to good psychometric properties (Cronbach's alphas between 0.76 and 0.78 (Aaronson et al., 1998)). To facilitate interpretation, we used reference cut-off values for the general population (Schulte-van Maaren et al., 2012), with scores below the cut-off of 45 indicating poor functioning, and scores above the cut-off being in the normal range.

2.2.3 Statistical analyses

We applied 'mclust module version 5.0.2 for R: normal mixture modelling for model-based clustering, classification and density estimation' (Fraley & Raftery, 2002; Fraley et al., 2012) to the AOO data of NEMESIS-2 subjects with lifetime SP, PD, AP, and/or GAD. Mclust assumes that data represent a mixture of normal distributions without making prior assumptions regarding their size, number, or shape (Fraley & Raftery, 2002). Selection of the optimal number of clusters was based on the Bayesian Information Criteria (BIC). Group-membership and cut-off age were determined by calculating individual posterior probabilities of belonging to the resulting clusters.

For each disorder, the resulting cut-off for early onset was then used to compare subjects with early- and late onset current PD, AP, SP, and/or GAD with regard to psychiatric comorbidity (multiple anxiety disorders, depressive/dysthymic disorder, alcohol abuse or -dependence, drug abuse or -dependence), and general wellbeing (SF-36 general health subscale). These comparisons were made in the general population (NEMESIS-2) as well as the clinical (ROM) sample. For each disorder, the early onset cut-off was used as a lower limit for inclusion of subjects. Associations with early onset were analysed with multivariable logistic regression, adjusting for confounding by age and gender. Categorical data are presented as number (percentage), continuous variables are presented as mean (M; ±standard deviation; SD), odds ratios (OR) with 95% confidence intervals (CI) are provided. All tests were two-tailed

with p<0.05 denoting statistical significance, and corrected for multiple testing using Bonferroni adjustment. We used R version 3.2.2 (R foundation for Statistical Computing) and SPSS 20.0 (IBM Corp., Armonk, NY, USA).

2.3 Results

2.3.1 Cut-off for early onset in general population lifetime anxiety disorders

A total of 618 participants in the NEMESIS-2 study met diagnostic criteria for lifetime SP. For 3 participants no AOO could be established, therefore they were excluded. Mean age of the lifetime SP sample was 40.27 and 58.2% was female. A total of 251 subjects had lifetime PD, their mean age was 43.67 (SD=11.53) and 62.4% were female; 59 subjects met criteria for lifetime AP, one participant was unable to report an AOO and therefore had to be excluded. The average age in the lifetime AP sample was 44.37 years (SD=10.81) and 76.5% were female. Finally, 298 subjects met criteria for lifetime GAD, for 3 subjects no AOO could be established so they had to be excluded. The mean age in the lifetime GAD sample was 41.43 (SD=12.80) and 59.0% was female.

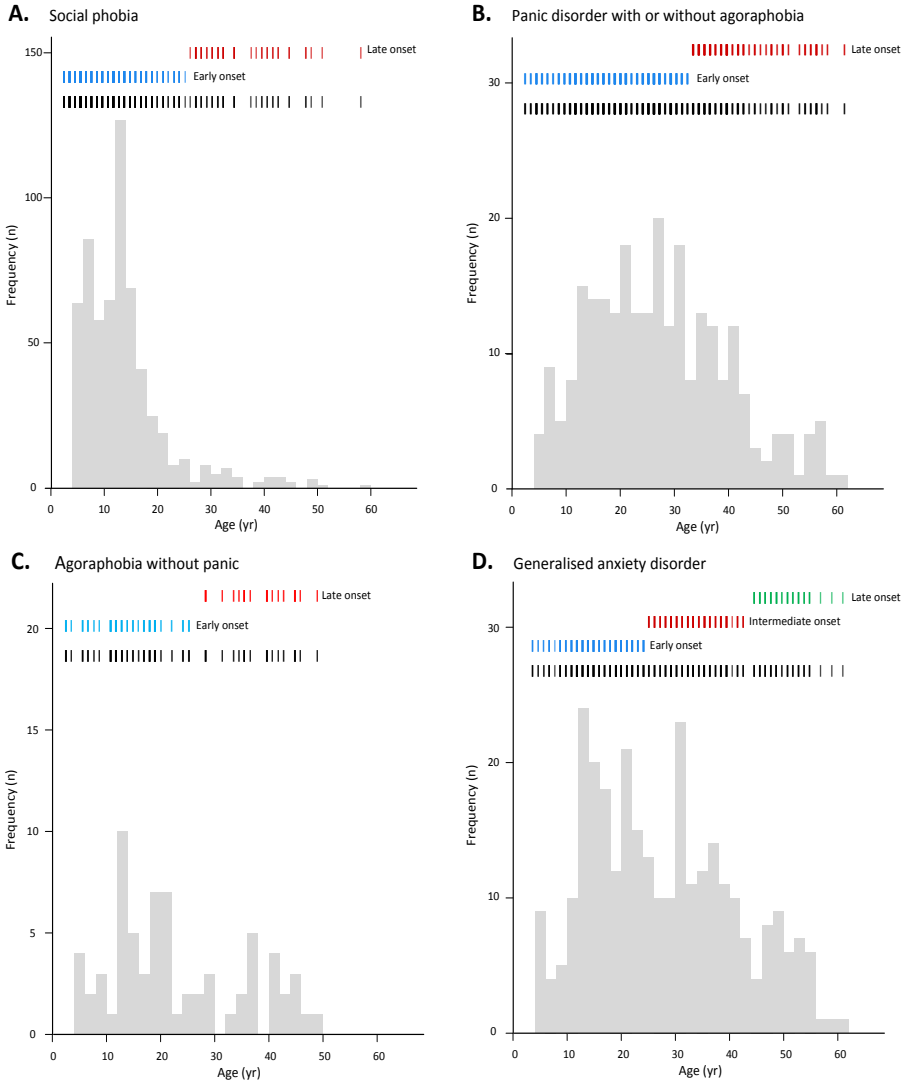
For SP, according to the BIC, model based cluster analysis yielded a best fitting model of two normally distributed clusters with equal variance. Based on the posterior probabilities, the early onset group ranged from AOO=4 to 22 (M=11.07; SD=4.28; n=575) and the late onset cluster ranged from AOO=23 to 58 (M=33.35; SD=8.48; n=40). Cluster analysis of the PD AOO data yielded a best fit with two normally distributed clusters with equal variance, with the early onset group ranging from AOO=4 to 31 (M=19.21; SD=7.05; n=174). Late onset ranged from AOO=32 to 61 (M=40.85; SD=7.12; n=77). The AP AOO distribution was best described by two normally distributed clusters with equal variance. The early onset group ranged from AOO=4 to 21 (M=14.01; SD=5.26; n=36); the late onset group ranged from AOO=23 to 49 (M=34.18, SD=7.54; n=22). Finally, the GAD AOO distribution was best described by three clusters with equal variances. The early onset cluster ranged from AOO=4 to 27 (M=15.95; SD=5.63; n=176), late onset could be divided in two groups: an intermediate group ranging from AOO=28 through 43 (M=34.42; SD=4.33; n=88) and a late onset group ranging from AOO=45 to 61 (M=50.84; SD=4.17; n=32). The results of the cluster analysis are shown in table 2.1 and figure 2.1.

Table 2.1 Classification of early onset in DSM-IV social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, and generalised anxiety disorder

	No. clusters	Log likelihood	BIC	Cut-off for early onset	Early onset		Late onset	
					n	Mean AOO(±SD)	n	Mean AOO (±SD)
Lifetime SP (n=615)	1	-424.8398	-4327.266					
	2	-397.0027	-4057.627	22	575	11.07 (4.28)	40	33.35 (8.48)
	3	-2016.052	-4070.479					
Lifetime PD (n=251)	1	-200.5739	-2075.300					
	2	-198.7438	-2073.651	31	174	19.21 (7.05)	77	40.85 (7.12)
	3	-197.7456	-2076.267					
Lifetime AP (n=58)	1	-78.38744	-550.9114					
	2	-76.27216	-537.2767	21	36	14.01 (5.26)	22	34.18 (7.54)
	3	-76.12158	-545.4261					
Lifetime GAD (n=295)	2	-235.9144	-2420.752					
	3	-233.1117	-2414.178	27	175	15.95 (5.63)	110	38.79 (8.45)
	4	-233.0287	-2424.901					

DSM-IV denotes Diagnostic Statistical Manual fourth edition; AOO denotes age of onset; SD denotes standard deviation; BIC denotes Bayesian Information Criterion; SP denotes social phobia; PD denotes panic disorder (with or without agoraphobia); AP denotes agoraphobia (without panic); GAD denotes generalised anxiety disorder; classification of early- and late onset is based on the results of cluster analysis using the mclust module version 5.0.2 for R.

Figure 2.1 Distribution and classification of age of onset of DSM-IV social phobia (A), panic disorder with or without agoraphobia (B), agoraphobia without panic (C), and generalised anxiety disorder (D).



DSM-IV denotes Diagnostic Statistical Manual fourth edition; Classification of early- and late onset is based on the results of cluster analysis using the mclust module version 5.0.2 for R.

Table 2.2 Associations with early onset of anxiety disorder in general population subjects (NEMESIS-2) with DSM-IV social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, or generalised anxiety disorder

	Early onset	Late onset	OR (95% CI)	p-value
Social phobia (n= 220)	***n=209 (95.0%)***	***n=11 (5.0%)***	***cut-off for early onset =22***	
Age (years) Mean (SD)	40.69 (10.51)	48.66 (9.88)		
Male gender n (%)	99 (47.5%)	5 (40.7%)		
Depressive/dysthymic	58 (27.8%)	5 (45.4%)	N.A.	N.A.
Alcohol abuse/dependence	29 (13.7%)	1 (10.2%)	N.A.	N.A.
Drug abuse/dependence	39 (18.8%)	2 (21.6%)	N.A.	N.A.
> 1 anxiety disorder	74 (35.7%)	6 (55.8%)	N.A.	N.A.
SF-36 general health below cut-off n (%)	56 (26.8%)	6 (49.7%)	N.A.	N.A.
Panic disorder (n=65)	***n=29 (44.6%)***	***n=36 (55.4%)***	***cut-off for early onset =31***	
Age (years) Mean (SD)	45.46 (7.53)	48.27 (8.68)		
Male gender n (%)	12 (40.6%)	21 (58.4%)		
Depressive/dysthymic	11 (38.2%)	9 (23.8%)	1.61 (0.53-4.93)	0.40
Alcohol abuse/dependence	4 (13.4%)	1 (3.8%)	5.02 (0.61-41.39)	0.13
Drug abuse/dependence	5 (18.4%)	2 (5.8%)	3.76 (0.66-21.37)	0.14
> 1 anxiety disorder	9 (31.3%)	6 (17.7%)	2.05 (0.62-6.81)	0.51
SF-36 general health below cut-off n (%)	11 (38.6%)	9 (24.2%)	0.45 (0.14-1.40)	0.17
Agoraphobia without panic (n= 25)	***n= 18 (72.0%)***	***n= 7 (28%)***	***cut-off for early onset =21***	
Age (years) Mean (SD)	43.32 (8.29)	45.60 (10.50)		
Male gender n (%)	5 (30.2%)	1 (13.5%)		
Depressive/dysthymic	8 (46.5%)	5 (69.8%)	N.A.	N.A.
Alcohol abuse/dependence	2 (10.4%)	0	N.A.	N.A.
Drug abuse/dependence	2 (10.4%)	0	N.A.	N.A.
> 1 anxiety disorder	14 (79.1%)	5 (68.2%)	N.A.	N.A.
SF-36 general health below cut-off n (%)	4 (53.5%)	9 (48.1%)	N.A.	N.A.

Generalised anxiety disorder (n=85)	*n=47 (55.3%)*	*n=38 (44.7%)*	*cut-off for early onset =27*	
Age (years) Mean (SD)	43.11 (11.00)	48.03 (9.00)		
Male gender n (%)	18 (38.4%)	11 (28.1%)		
Depressive/dysthymic	21 (44.7%)	16 (41.1%)	1.00 (0.41-2.47)	1.00
Alcohol abuse/dependence	5 (10.8%)	1 (2.2%)	4.76 (0.43-52.78)	0.20
Drug abuse/dependence	8 (16.5%)	2 (4.1%)	4.67 (0.75-29.06)	0.09
> 1 anxiety disorder	17 (37.0%)	6 (16.1%)	3.27 (1.11-9.67)	0.03
SF-36 general health below cut-off n (%)	21 (44.8%)	21 (54.4%)	1.33 (0.55-3.24)	0.53

*Odds Ratios (OR) are presented with 95% confidence interval (CI) and p-value obtained in logistic regression analysis adjusted for age and gender with early onset as the higher coded category; NEMESIS-2 denotes Netherlands Mental Health Survey and Incidence Study-2; DSM-IV denotes Diagnostic Statistical Manual fourth edition; AOO denotes age of onset; SD denotes standard deviation; SF-36 denotes short form 36; SF-36 reference value cut-offs are based on 95th percentile scores in the general population reference group from the NormQuest study (Schulte-van Maaren et al. 2012); N.A. indicates a reliable assessment was not attainable because of low cell count; * indicates significant difference post-hoc with Bonferroni correction for multiple testing.*

Table 2.3 Associations with early onset of anxiety disorder in outpatients (ROM) with DSM-IV-TR social phobia, panic disorder with or without agoraphobia, agoraphobia without panic, or generalised anxiety disorder

	Early onset	Late onset	OR (95% CI)	p-value
Social phobia (n=1080)	***n=841 (77.9%)***	***n=239 (22.1%)***	***cut-off for early onset =22***	
Age (years) Mean (SD)	35.46 (10.60)	41.14 (9.57)		
Male gender n (%)	375 (44.6%)	125 (52.3%)		
Depressive/dysthymic	408 (48.5%)	142 (59.2%)	0.72 (0.53-0.97)	0.03
Alcohol abuse/dependence	67 (8.0%)	24 (10.0%)	0.92 (0.55-1.53)	0.74
Drug abuse/dependence	51 (6.1%)	16 (6.7%)	0.77 (0.42-1.40)	0.39
> 1 anxiety disorder	275 (32.7%)	109 (45.6%)	0.61 (0.45-0.83)	.001*
SF-36 general health below cut-off n (%)	344 (40.9%)	124 (51.9%)	0.69 (0.52-0.93)	0.02
Panic disorder (n= 877)	***n=439 (50.1%)***	***n=438 (49.9%)***	***cut-off for early onset =31***	
Age (years) Mean (SD)	40.51 (8.24)	45.66 (7.71)		
Male gender n (%)	188 (42.8%)	160 (36.5%)		
Depressive/dysthymic	206 (46.9%)	258 (58.9%)	0.71 (0.54-0.95)	0.02
Alcohol abuse/dependence	35 (8.0%)	28 (6.4%)	1.25 (0.73-2.18)	0.41
Drug abuse/dependence	16 (3.6%)	12 (2.7%)	1.46 (0.64-3.35)	0.37
> 1 anxiety disorder	96 (21.9%)	74 (16.9%)	1.37 (0.96-1.96)	0.08
SF-36 general health below cut-off n (%)	227 (51.7%)	211 (48.2%)	1.16 (0.88-1.54)	0.27
Agoraphobia without panic (n= 871)	***n=303 (34.8%)***	***n=568 (65.2%)***	***cut-off for early onset =21***	
Age (years) Mean (SD)	36.9 (11.73)	42.64 (10.23)		
Male gender n (%)	94 (31.0%)	188 (33.1%)		
Depressive/dysthymic	129 (42.6%)	319 (56.2%)	0.59 (0.44-0.79)	<.001*
Alcohol abuse/dependence	26 (8.6%)	38 (6.7%)	1.36 (0.79-2.33)	0.27
Drug abuse/dependence	28 (9.2%)	23 (4.0%)	1.05 (1.13-3.71)	0.02
> 1 anxiety disorder	114 (37.6%)	127 (22.4%)	2.04 (1.49-2.78)	<.001*
SF-36 general health below cut-off n (%)	147 (48.5%)	305 (53.75)	0.83 (0.62-1.11)	0.21

Generalised anxiety disorder (n=656)	*n=391 (59.6%)*	*n=265 (40.4%)*	*cut-off for early onset =27*	
Age (years) Mean (SD)	40.49 (9.97)	45.78 (9.11)		
Male gender n (%)	149 (38.1%)	133 (50.2%)		
Depressive/dysthymic	196 (50.1%)	135 (50.9%)	1.10 (0.79-1.52)	0.58
Alcohol abuse/dependence	28 (7.2%)	15 (5.7%)	1.51 (0.77-2.95)	0.23
Drug abuse/dependence	13 (3.3%)	6 (2.3%)	1.55 (0.56-4.31)	0.40
> 1 anxiety disorder	143 (36.6%)	70 (26.4%)	1.47 (1.03-2.08)	0.03
SF-36 general health below cut-off n (%)	168 (43.0%)	122 (46.0%)	0.90 (0.65-1.25)	0.53

*Odds Ratios (OR) are presented with 95% confidence interval (CI) and p-value obtained in logistic regression analysis adjusted for age and gender with early onset as the higher coded category; ROM denotes Routine Outcome Monitoring; DSM-IV-TR denotes Diagnostic Statistical Manual fourth edition, text revision; AOO denotes age of onset; SD denotes standard deviation; SF-36 denotes short form 36; SF-36 reference value cut-offs are based on 95th percentile scores in the general population reference group from the NormQuest study (Schulte-van Maaren et al., 2012); * indicates significant difference post-hoc with Bonferroni correction for multiple testing.*

2.3.2 Application of cut-offs for early onset in current anxiety samples

2.3.2.1 General population current anxiety sample

In order to test the hypothesis that early onset of anxiety disorders was associated with psychiatric comorbidity and wellbeing, we applied the cut-offs for early onset to subjects with current anxiety disorders in the general population (NEMESIS-2) as well as in an outpatient setting (ROM). After application of the early onset cut-offs as a lower limit for inclusion, the general population SP sample consisted of 220 subjects, 209 of whom could be categorised as having early onset, and 11 as having late onset SP. The current PD general population sample consisted of 65 subjects, 29 had early onset and 36 had late onset PD. The general population current AP sample consisted of 25 subjects, 18 of whom had early onset, whereas 7 had late onset. Finally, the general population GAD sample consisted of 85 subjects, 47 with early onset, and 38 with late onset. Age, gender, psychiatric comorbidity, and general wellbeing scores of the general population current anxiety sample are shown in table 2.2. Due to the small sample sizes no test results could be calculated for the SP and AP samples. In PD and GAD no significant associations emerged.

2.3.2.1 Outpatient current anxiety sample

Application of the cut-off for early onset SP in the outpatient sample resulted in a sample of 1080 outpatients, 841 of whom had early onset and 239 had late onset. The current PD sample consisted of 877 patients, 439 of whom had early onset and 438 had late onset. The current AP sample consisted of 871 subjects, 303 could be classified as having early onset, and 568 had late onset AP. A total of 656 outpatients met diagnostic criteria for GAD, 391 had early onset and 265 had late onset. Associations between early onset and psychiatric comorbidity and wellbeing in the outpatient sample are shown in table 2.3. Among those with early onset SP, anxiety comorbidity was less common (32.7%) than in patients with late onset SP (59.2%; OR= 0.61; 95% CI=0.45-0.83; p=0.001). In AP, patients with early onset significantly less often had comorbid depressive or dysthymic disorder (42.6%) than patients with late onset (56.2%; OR=0.59; 95% CI=0.44-0.79; p<0.001). In addition, patients with early onset AP were more likely to have anxiety disorder comorbidity (37.6%) than those with late onset AP (22.4%; OR=2.04; 95% CI=1.49-2.78; p<0.001). In PD and GAD no significant associations between early onset psychiatric comorbidity or general wellbeing emerged.

2.4 Discussion

To our knowledge, this has been the first study to empirically define early onset in SP and GAD. In addition, we have attempted to replicate previously found cut-offs in PD and AP (Tibi et al., 2013; Tibi et al., 2015). We found that the AOO distribution of SP, PD, and AP has a bimodal fit. The cut-off age for SP was 22 (with early onset when AOO≤22; and late onset when AOO>22). The cut-off for PD was 31 (with early onset when AOO≤31; and late onset when AOO> 31), and the cut cut-off for AP was 21 (with early onset when AOO≤21; and late onset when AOO>21). The distribution of AOO in GAD was best described by three clusters with a cut-off for early onset at 27 (with early onset when AOO≤27; and late onset when AOO>27). Few associations between early onset and psychiatric comorbidity and general wellbeing emerged: we found anxiety comorbidity was more common in late onset SP, more depressive comorbidity in late onset AP, and more anxiety comorbidity in early onset AP. These associations only emerged in the outpatient samples and not in the general population samples, although this may be attributable to the small sizes of the current anxiety general population samples. Previous reports of higher prevalence of psychiatric comorbidity in PD (Goodwin et al., 2001; Goldstein et al., 1997; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013), and GAD (Campbell et al., 2003; Le Roux et al., 2005) were not confirmed.

When comparing the cut-offs found in this study for SP and GAD with the (unsubstantiated) cut-offs that were used to distinguish early onset and late onset SP and GAD in previous studies, it appears that some were comparable (20 in SP (Ramsawh et al., 2011)), but others differed markedly (9 in SP (Van Ameringen et al., 2004), and 20 (Ramsawh et al., 2011) and 50 (Le Roux et al., 2005) in GAD). Our cut-off for early onset AP at 21 differs from the cut-off of 27 that was found previously in a similar study (Tibi et al., 2015). This is not surprising however, as Tibi et al. (2015) studied agoraphobia with or without panic, whereas our study focused on agoraphobia without panic disorder. The difference in the resulting cut-offs suggests that AP without PD may have an earlier onset than the comorbid state. Early onset PD was previously defined using cluster analysis at 27 (Tibi et al., 2013), our cut-off at 31 is somewhat later. However, it is clear that based on our and Tibi's (Tibi et al., 2013) results, the cut-off for early onset PD most likely lies around the late twenties/early thirties. This implies that previously used cut-offs of 18 (Segui et al., 1999), 20 (Goldstein et al., 1997; Ramsawh et al., 2011), and 60 (Segui et al., 2000), are likely to have been inappropriate for distinguishing early- and late onset PD.

Possibly, the difference between our cut off for early onset PD (31) and that found by Tibi et al. (27) (Tibi et al., 2013) stems from methodological differences. In the previous study AOO data were assessed in a sample that was gathered in the general population, primary care, and mental healthcare facilities (Penninx et al., 2008), whereas in the present study AOO

frequency data were gathered in a general population sample. This may be relevant, as in the sample used by Tibi et al. (Tibi et al., 2013; Tibi et al., 2015), subjects who sought help (in primary care or mental healthcare) were overrepresented relative to the general population. This help-seeking behaviour might be taken as an indication of higher severity or more impaired wellbeing, as it has been estimated that only 26.1% of those in the general population who meet diagnostic criteria for anxiety disorders actually seek help (Wittchen & Jacobi, 2005) As onset has been suggested to be associated with severity of the disorder, using a sample that over represents more severe cases, might distort the AOO distribution and the resulting cut-off. Our application of cluster analysis to data gathered in the general population might therefore have yielded different results. Another consideration is the use of current versus lifetime diagnoses. In the present study, the AOO frequency data of lifetime disorders were used, conversely, the studies by Tibi et al. (Tibi et al., 2013; Tibi et al., 2015) used AOO data of current cases. Including only those who currently meet diagnostic criteria for an anxiety disorder may also have implications for the distribution of AOO that is sampled. When including only current diagnoses, the sample will consist of younger as well as older subjects who have just experienced their first onset anxiety disorder, and of older subjects who have experienced early onset of an anxiety disorder that has become chronic or recurrent. However, as anxiety disorders can and do remit across the lifespan (Beesdo et al., 2009), the current anxiety sample will not contain the onsets of older subjects who had an early onset anxiety disorder that has remitted. Thus, sampling only current cases may negate part of the AOO distribution and, as such, influence the cut-off resulting from cluster analysis of that distribution. Consequently, our sampling the onset of lifetime anxiety disorders may have yielded different results. Further studies using cluster analysis are needed to replicate these findings.

Late onset SP was atypical in both our general population and our clinical sample. The finding of higher prevalence of anxiety comorbidity among outpatients with late onset SP, as well as the higher prevalence of mood disorders among those with late onset AP, could be hypothesized to reflect secondary onsets of these disorders. The late onset SP cases may have initially developed another disorder, to which the development of a social phobia came secondary. Although late onset AP was more common in our clinical sample, the higher prevalence of depression amongst late onset agoraphobics might similarly reflect elevated avoidance in chronic depression, leading to a secondary onset of AP in chronic depression. However, as our data are cross sectional and no information on primary or secondary diagnoses was available, these interpretations remain speculative. While findings of more psychiatric comorbidity in early onset PD and GAD, which had repeatedly been reported (Campbell et al., 2003; Goldstein et al., 1997; Goodwin et al., 2001; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999; Tibi et al., 2013) did not emerge, we did find more

anxiety comorbidity in early onset AP. Possibly, this erratic pattern of findings regarding comorbidity in early onset across studies, with repeated but not consistent reports of more comorbidity in early onset in various disorders, reflects a general element of chronicity in earlier onset cases. Perhaps the early onset cases are more likely to suffer from multiple disorders as a consequence of longer disease duration (Tibi et al., 2013). This would imply early onset as a subtype might be of less significance than disease duration (defined as total period of time during which the disorder was present). Unfortunately we did not have information on disease duration; therefore disease duration could not be included in analyses.

In addition to using general population data and lifetime diagnoses, our study is the first to describe cluster analysis of AOO data in SP and GAD. Further strong points are the use of a general population- as well as an outpatient sample when comparing psychiatric comorbidity and general wellbeing between those with early and late onset anxiety disorders. Our study does however also have some potential limitations. The size of the general population current anxiety disorder samples was small, especially for SP and AP. This did not allow for statistical analyses regarding psychiatric comorbidity and general wellbeing. In addition, as the primary aim of our study was the definition of early onset, a relatively small number of patient characteristics was incorporated (psychiatric comorbidity and general wellbeing) future studies could use the cut-offs for early onset to further explore associations between patient characteristics and early onset to replicate previous associations with suicidality, childhood trauma, and family history of anxiety disorders. A methodological consideration that could be noted is the fact that the current age of our cluster analysis sample (18-65) may have influenced the AOO frequency distribution: while all subjects would have had the chance to have experienced an AOO of 18, only those who had reached the age of 65 had been at risk for an AOO of 65. This may have skewed the AOO frequency distributions towards an overrepresentation of younger AOO's. Using lifetime anxiety data from a large older cohort might have yielded different results. Furthermore, the AOO of anxiety disorders was assessed retrospectively, which may have led to inaccurate reports (Simon & Vonkorff, 1995). However, this limitation holds for all previous studies using cluster analysis to determine a cut-off for early onset (Albert et al., 2015; Anholt et al., 2014; Bauer et al., 2010; Bellivier et al., 2001; Delorme et al., 2005; Hamshere et al., 2009; Ortiz et al., 2011; Panariello et al., 2010; Tibi et al., 2013; Tibi et al., 2015; Tozzi et al., 2011; Zhu et al., 2012). Retrospectively reported AOO has also been the norm in studies describing correlates of AOO in anxiety disorders (Goldstein et al., 1997; Goodwin et al., 2001; Iketani et al., 2004; Le Roux et al., 2005; Ramsawh et al., 2011; Segui et al., 1999; Segui et al., 2000; Van Ameringen et al., 2004) and studies describing AOO-distributions (Beesdo et al., 2009; Kessler et al., 2007; Scheibe & Albus, 1992; Thyer et al., 1985). However, a study by Kessler and Ustun (2004) on age of onset in psychiatric disorders did apply an adapted methodology, by asking a series of more elaborate questions geared

towards triggering autobiographical memory in order to improve accuracy (Knauper et al., 1999). Future studies could be improved through the use of this methodology. Finally, and perhaps most importantly, like many studies on the topic of AOO in anxiety disorders, our study did not take into account that anxiety disorders are often comorbid with other anxiety disorders and with other psychiatric disorders. It has been demonstrated that while anxiety disorders can occur in isolation, they can also be preceded by other anxiety disorders (broad homotypic continuity) and by other psychiatric disorders such as externalising disorders (heterotypic continuity; Beesdo et al., 2009). In this light, it might be thought valuable to study the onset of psychiatric morbidity in general over the lifespan of the individual, rather than classifying the onset of an isolated disorder as early or late.

2.5. Conclusion

In conclusion, we have empirically defined early onset of SP (AOO≤22), PD (AOO ≤31), AP (AOO ≤21), and GAD (AOO ≤27). Future studies of early onset in anxiety disorders should use empirically defined age cut-offs to further explore associations with early onset (Anholt et al., 2014; Tibi et al., 2013), and take into account psychiatric history. Although we found some evidence of higher prevalence of anxiety comorbidity in early onset AP, and late onset SP, as well as more mood comorbidity in late onset AP, in general, with regard to the four commonly occurring anxiety disorders in this study, our results did not show more psychiatric comorbidity or less wellbeing in early onset.

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Reference List

Albert, U., Manchia, M., Tortorella, A., Volpe, U., Rosso, G., Carpiniello, B. et al. (2015). Admixture analysis of age at symptom onset and age at disorder onset in a large sample of patients with obsessive-compulsive disorder. Journal of affective disorders, 187, 188-196.

Aaronson, N. K., Muller, M., Cohen, P. D. A., Essink-Bot, M. L., Fekkes, M., Sanderman, R. et al. (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. Journal of Clinical Epidemiology, 51, 1055-1068.

Anholt, G. E., Aderka, I. M., van Balkom, A. J. L. M., Smit, J. H., Schruers, K., van der Wee, N. J. A. et al. (2014). Age of onset in obsessive-compulsive disorder: admixture analysis with a large sample. Psychological Medicine, 44, 185-194.

Bauer, M., Glenn, T., Rasgon, N., Marsh, W., Sagduyu, K., Munoz, R. et al. (2010). Association between age of onset and mood in bipolar disorder: Comparison of subgroups identified by cluster analysis and clinical observation. Journal of Psychiatric Research, 44, 1170-1175.

Beesdo, K., Knappe, S., & Pine, D. S. (2009). Anxiety and Anxiety Disorders in Children and Adolescents: Developmental Issues and Implications for DSM-V. Psychiatric Clinics of North America, 32, 483-524.

Bellivier, F., Golmard, J. L., Henry, C., Leboyer, M., & Schurhoff, F. (2001). Admixture analysis of age at onset in bipolar I affective disorder. Archives of General Psychiatry, 58, 510-512.

Campbell, L. A., Brown, N. A., & Grisham, J. R. (2003). The relevance of age of onset to the psychopathology of generalised anxiety disorder. Behavior Therapy, 34, 31-48.

Craske, M. G. (1999). Anxiety disorders psychological approaches to theory and treatment. Oxford: Westview Press.

de Graaf, R., ten Have, M., & van Dorsselaer, S. (2010). The Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2): design and methods. International Journal of Methods in Psychiatric Research, 19, 125-141.

Delorme, R., Golmard, J. L., Chabane, N., Millet, B., Krebs, M. O., Mouren-Simeoni, M. C. et al. (2005). Admixture analysis of age at onset in obsessive-compulsive disorder. Psychological Medicine, 35, 237-243.

Fraley, C., Raftery, A. E., Murphy, T. B., & Scrucca L. (2012). Mclust Version 4 for R: Normal Mixture Modeling for Model-Based Clustering, Classification, and Density Estimation Technical Report No. 597, Department of Statistics, University of Washington.

Fraley C. & Raftery A. E. (2002). Model-based Clustering, Discriminant Analysis and Density Estimation. Journal of the American Statistical Association, 97, 611-631.

Goldstein, R. B., Wickramaratne, P. J., Horwath, E., & Weissman, M. M. (1997). Familial aggregation and phenomenology of 'early'-onset (at or before age 20 years) panic disorder. Archives of General Psychiatry, 54, 271-278.

Goodwin, R., Lipsitz, J. D., Chapman, T. F., Mannuzza, S., & Fyer, A. J. (2001). Obsessive-compulsive disorder and separation anxiety co-morbidity in early onset panic disorder. Psychological Medicine, 31, 1307-1310.

Hamshere, M. L., Gordon-Smith, K., Forty, L., Jones, L., Caesar, S., Fraser, C. et al. (2009). Age-at-onset in bipolar-I disorder: Mixture analysis of 1369 cases identifies three distinct clinical sub-groups. Journal of Affective Disorders, 116, 23-29.

Haro, J. M., Arbabzadeh-Bouchez, S., Brugha, T. S., De Girolamo, G., Guyer, M. E., Jin, R. et al. (2006). Concordance of the composite international diagnostic interview version 3.0 (CIDI 3.0) with standardized clinical assessments in the WHO World Mental Health Surveys. International Journal of Methods in Psychiatric Research, 15, 167-180.

Iketani, T., Kiriike, N., Stein, M. B., Nagao, K., Minamikawa, N., Shidao, A. et al. (2004). Patterns of axis II comorbidity in early-onset versus late-onset panic disorder in Japan. Comprehensive Psychiatry, 45, 114-120.

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustun, T. B. (2007). Age of onset of mental disorders: a review of recent literature. Current Opinion in Psychiatry, 20, 359-364.

Kessler, R. C. & Ustun, T. B. (2004). The World Mental Health (WMH) Survey Initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). International Journal of Methods in Psychiatric Research, 13, 93-121.

Knauper, B., Cannel, C. F., Schwarz, N., Bruce, M. L., & Kessler, R. C. (1999). Improving accuracy of major depression age-of-onset reports in the US National Comorbidity Survey. International Journal of Methods in Psychiatric Research, 8, 39-48.

Le Roux, H., Gatz, M., & Wetherell, J. L. (2005). Age at onset of generalised anxiety disorder in older adults. American Journal of Geriatric Psychiatry, 13, 23-30.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H. et al. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. European Psychiatry, 12, 224-231.

Ortiz, A., Bradler, K., Slaney, C., Garnham, J., Ruzickova, M., O'Donovan, C. et al. (2011). An admixture analysis of the age at index episodes in bipolar disorder. Psychiatry Research, 188, 34-39.

Panariello, F., O'Driscoll, L., de Souza, R. P., Tiwari, A., Manchia, M., Kennedy, J. et al. (2010). Age at onset in Canadian Schizophrenia patients: Admixture analysis. Schizophrenia Research, 122, 278-279.

Penninx, B. W. J. H., Beekman, A. T. F., Smit, J. H., Zitman, F. G., Nolen, W. A., Spinhoven, P. et al. (2008). The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. International Journal of Methods in Psychiatric Research, 17, 121-140.

Ramsawh, H. J., Weisberg, R. B., Dyck, I., Stout, R., & Keller, M. B. (2011). Age of onset, clinical characteristics, and 15-year course of anxiety disorders in a prospective, longitudinal, observational study. Journal of Affective Disorders, 132, 260-264.

Scheibe, G. & Albus, M. (1992). Age at Onset, Precipitating Events, Sex Distribution, and Cooccurrence of Anxiety Disorders. Psychopathology, 25, 11-18.

Schulte-van Maaren, Y. W. M., Carlier, I. V. E., Zitman, F. G., van Hemert, A. M., de Waal, M. W. M., van Noorden, M. S. et al. (2012). Reference values for generic instruments used in routine outcome monitoring: the leiden routine outcome monitoring study. Bmc Psychiatry, 12.

Segui, J., Marquez, M., Garcia, L., Canet, J., Salvador-Carulla, L., & Ortiz, M. (1999). Differential clinical features of early-onset panic disorder. Journal of Affective Disorders, 54, 109-117.

Segui, J., Salvador-Carulla, L., Marquez, M., Garcia, L., Canet, J., & Ortiz, M. (2000). Differential clinical features of late-onset panic disorder. Journal of Affective Disorders, 57, 115-124.

Semler, G., Wittchen, H. U., Joschke, K., Zaudig, M., Vongeiso, T., Kaiser, S. et al. (1987). Test-Retest Reliability of A Standardized Psychiatric Interview (Dis/Cidi). European Archives of Psychiatry and Clinical Neuroscience, 236, 214-222.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. et al. (1998). The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry, 59, 22-33.

Simon, G. E. & Vonkorff, M. (1995). Recall of Psychiatric History in Cross-Sectional Surveys - Implications for Epidemiologic Research. Epidemiological Reviews, 17, 221-227.

Thyer, B. A., Parrish, R. T., Curtis, G. C., Nesse, R. M., & Cameron, O. G. (1985). Ages of Onset of Dsm-III Anxiety Disorders. Comprehensive Psychiatry, 26, 113-122.

Tibi, L., van Oppen, P., Aderka, I. M., van Balkom, A. J. L. M., Batelaan, N. M., Spinhoven, P. et al. (2013). Examining determinants of early and late age at onset in panic disorder: An admixture analysis. Journal of Psychiatric Research, 47, 1870-1875.

Tibi, L., van Oppen, P., Aderka, I. M., van Balkom, A. J. L. M., Batelaan, N. M., Spinhoven, P. et al. (2015). An admixture analysis of age of onset in agoraphobia. Journal of affective disorders, 180, 112-115.

Tozzi, F., Manchia, M., Galwey, N. W., Severino, G., Del Zompo, M., Day, R. et al. (2011). Admixture analysis of age at onset in bipolar disorder. Psychiatry Research, 185, 27-32.

Van Ameringen, M., Oakman, J., Mancini, C., Pipe, B., & Chung, H. (2004). Predictors of response in generalised social phobia: Effect of age of onset. Journal of Clinical Psychopharmacology, 24, 42-48.

van Noorden, M. S., Minkenberg, S. E., Giltay, E. J., den Hollander-Gijsman, M. E., van Rood, Y. R., van der Wee, N. J. et al. (2011). Pre-adult versus adult onset major depressive disorder in a naturalistic patient sample: the Leiden Routine Outcome Monitoring Study. Psychological Medicine, 41, 1407-1417.

van Vliet, I. M., Leroy, H., & van Megen, H. J. G. M. (2000). MINI internationaal neuropsychiatrisch interview nederlandse versie 5.0.0. (5 ed.) Utrecht.

Wittchen, H. U. & Jacobi, F. (2005). Size and burden of mental disorders in Europe - a critical review and appraisal of 27 studies. European Neuropsychopharmacology, 15, 357-376.

Wittchen, H. U., Robins, L. N., Cottler, L. B., Sartorius, N., Burke, J. D., & Regier, D. (1991). Cross-Cultural Feasibility, Reliability and Sources of Variance of the Composite International Diagnostic Interview (Cidi). British Journal of Psychiatry, 159, 645-653.

Zhu, T. N., De Luca, V., Gallaugher, L. A., Woldeyohannes, H. O., Soczynska, J. K., Szymkowicz, S. et al. (2012). Admixture analysis of age at onset in major depressive disorder. General Hospital Psychiatry, 34, 686-691.

Zitman, F. G. (2012). [ROM in mood, anxiety and somatoform disorders: a promising technique with pleasing results]. Tijdschr.Psychiatr., 54, 173-177.