Chapter 4

Predictors of outcome in outpatients with anxiety disorders: The Leiden Routine Outcome Monitoring Study

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Abstract

Little is known about the predictors of outcome in anxiety disorders in naturalistic outpatient settings. We analysed 2-year follow-up data collected through Routine Outcome Monitoring (ROM) in a naturalistic sample of 917 outpatients in psychiatric specialty care in order to identify factors predicting outcome. We included patients with panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, or generalised anxiety disorder. Main findings from Cox regression analyses demonstrated that several socio-demographic variables (having a non-Dutch ethnicity [HR = 0.71)], not having a daily occupation [HR = 0.76]) and clinical factors (having a diagnosis of agoraphobia [HR = 0.67], high affective lability [HR = 0.80] and behaviour problems [HR = 0.84]) decreased chances of response (defined as 50% reduction of anxiety severity) over the period of two years. Living with family had a protective predictive value [HR = 1.41]. These results may imply that factors that could be thought to limit societal participation are associated with elevated risk of poor outcome. A comprehensive ROM screening process at intake may aid clinicians in the identification of patients at risk of chronicity.

4.1. Introduction

Anxiety disorders are highly prevalent (Wittchen et al., 2011) and are associated with marked functional impairment, high disease burden, substantial costs (Gustavsson et al., 2010), and a chronic course (Angst & Vollrath, 1991; Baldwin et al., 2010; Penninx et al., 2011). The manifesto for a European anxiety disorders network (Baldwin et al., 2010) states that, although psychological and pharmacological treatment have been proven effective in (randomised) clinical trials (RCT), for a substantial number of patients in clinical practice they do not translate into good outcome. Therefore, studies on predictors of response in naturalistic settings need to be conducted (Baldwin et al., 2010; Rothwell, 2005).

Previous studies have focused on various socio-demographic predictors of outcome of anxiety disorders. Different studies failed to demonstrate an association with gender (Tyrer et al., 2004; Yonkers et al., 2003; Serretti et al., 2009). Older age was associated with longer time to remission in treated as well as untreated panic disorder with or without agoraphobia (PD/A), agoraphobia without panic (AP), social phobia (SP), generalised anxiety disorder (GAD) and/or depression (MDD) (Penninx et al., 2011). Conversely, older age was associated with lower severity at one-year follow-up and a steeper decline in anxiety over time in subjects with PD/A and GAD but not in SP (Ramsawh et al., 2009). Others found no predictive value of age (Chavira et al., 2009; Van Ameringen et al., 2004; Beutel et al., 2011; Beard et al., 2010; Serretti et al., 2009). Additional socio-demographic factors that have been linked to poor outcome in anxiety disorders are: lower education-level (Ramsawh et al., 2009), and being unemployed and having low socioeconomic status in PD/A (Roy-Byrne et al., 2003). Finally, although no association with ethnicity has been established, results do render further research necessary (Serretti et al., 2009).

Besides socio-demographic characteristics, several clinical factors have been studied in relation to outcome in anxiety disorders. First of all, in a sample diagnosed with GAD, SP and/or PD/A, patients with SP were least likely to have recovered at 12-year follow-up (Bruce et al., 2005). PD patients without agoraphobia were most likely to recover (Bruce et al., 2005; Roy-Byrne et al., 2003). In SP comorbid PD/A predicted poor outcome (Beard et al., 2010). In a sample of inpatients diagnosed with PD/A, AP, SP, GAD, posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD) and/or specific phobia (SPP), poor outcome was predicted by comorbid eating disorders and having multiple anxiety disorders (Beutel et al., 2011). The presence of comorbid MDD or alcohol abuse or dependence was associated with worse 12-year outcome in PD/A, SP and GAD (Bruce et al., 2005), although other studies showed no association with MDD (Roy-Byrne et al., 2003; Serretti et al., 2009; Beutel et al., 2011). Comorbid personality disorders or maladaptive personality traits have repeatedly been associated with poor outcome (Beutel et al., 2011; Ansell et al., 2011; Telch et al., 2011).

Finally, early age of onset of the anxiety disorder predicted remission in treated as well as untreated PD/A, AP, SP, GAD and/or MDD (Penninx et al., 2011) and in SP in a Sertraline RCT (Van Ameringen et al., 2004). Although in PD/A, SP and GAD, early onset did not predict recovery while it did predict relapse in PD/A (Ramsawh et al., 2011).

However, generalizability of research findings to patients seen in everyday clinical practice is often limited (Hoertel et al., 2012). This lack of generalizability could result from the use of strict in and exclusion criteria (Tyrer et al., 2004; Chavira et al., 2009; Roy-Byrne et al., 2003; Roy-Byrne et al., 2006; Van Ameringen et al., 2004), the focus on a single treatment modality (Telch et al., 2011; Van Ameringen et al., 2004; Serretti et al., 2009) and the focus on a narrowly defined patient group (Beutel et al., 2011; Chavira et al., 2009; Roy-Byrne et al., 2003; Roy-Byrne et al., 2006; Telch et al., 2011; Beard et al., 2010; Van Ameringen et al., 2004). Also, in observational cohort studies, high selectiveness may result from patients' motivation to participate in long-term follow-up studies stretching over a decade (Yonkers et al., 2003; Bruce et al., 2005; Ramsawh et al., 2009; Ramsawh et al., 2011; Beard et al., 2010).

Therefore, the present study aimed at establishing predictors of outcome in a large naturalistic cohort of outpatients suffering from anxiety disorders with a follow-up of up to 2 years. We used a broad range of patient characteristics that have been gathered as part of standard clinical procedure as potential predictors, avoiding the previously discussed limitations to generalizability. Although in the Diagnostic and Statistical Manual of Mental Disorders fourth edition-text revision (DSM-IV-TR), the category of anxiety disorders comprises PD/A, AP, SP, GAD, PTSD, SPP, OCD and acute stress disorder; marked differences exist with regard to aetiology, expression and clinical course between PD/A, AP, SP and GAD on the one hand, and PTSD, SPP, OCD and acute stress disorder on the other (Friedman et al., 2011; Stein et al., 2010; Lebeau et al., 2010). Therefore, following a common approach (Penninx et al., 2011; Bruce et al., 2005; Ramsawh et al., 2009; Ramsawh et al., 2011), this study focused primarily on predictors of outcome in patients diagnosed with PD/A, AP, SP and/or GAD.

4.2. Method

4.2.1. Routine outcome monitoring

As part of routine practice at the facilities involved in this study, all patients were administered an extensive battery of self-report and observer-rated measures at intake and at follow-up, every 3-4 months of treatment. This procedure is known as Routine Outcome Monitoring (ROM) and it continues for as long as the patient is being treated. Therefore the total number of assessments per patient varies as it depends on the duration of treatment. A more extensive description can be found in De Beurs et al. (2011). Both generic and disorder-specific

questionnaires were administered by formally trained psychiatric nurses and through computerized self-report, supervised by trained psychiatric nurses. This computerized administration prevents missing data within questionnaires as item-completion is necessary for progression to the next item (De Beurs et al., 2011). Inter-rater reliability in a small sample of research nurses on several questionnaires has been tested and was within acceptable range (Cohen's κ= 0.55-0.73; De Beurs et al., 2011). The primary goal of this data-collection is to inform both clinicians and patients. An estimated average of 80% of all patients is assessed at intake (van Noorden et al., 2012; Zitman, 2012). Data were anonymised and their use in scientific research was approved by the Ethical Review Board at the Leiden University Medical Centre (LUMC).

4.2.2. Patients and procedure

Subjects were outpatients referred to Rivierduinen, a regional mental healthcare provider, or the psychiatry department of the LUMC between March 2004 and November 2009. To allow two years of follow-up for all patients, follow-up data were collected until the end of November 2011. Inclusion criteria held that patients must be aged between 18 and 65, have adequate command of the Dutch language and meet DSM-IV-TR diagnostic criteria for one or more of the following disorders: PD/A, AP, SP or GAD. The patient population from which we drew our sample contained patients diagnosed with mood- and somatoform- as well as anxiety disorders; therefore, a risk of over-diagnosing has been suggested when using a semi-structured interview in a clinical sample (Zimmerman & Chelminski, 2003). Also, our dataset did not include clinical diagnoses (i.e. diagnoses made by treating psychiatrist). We therefore filtered out patients who did meet the criteria for anxiety diagnosis but were unlikely to have been treated for anxiety, by setting a criterion of moderate to severe baseline anxiety scores. Moderate to severe baseline severity was defined as 10.38 on the Brief Anxiety Scale (BAS; Tyrer et al., 1984), equalling the average BAS score in a group of general practice patients diagnosed with anxiety disorders (Tyrer et al., 1984), and 6 on the Brief Symptom Inventory-12 item version (BSI-12), with scores <6 signifying no to mild anxiety (Roy-Byrne et al., 2010). All patients received standard outpatient care, consisting of psychotherapy, pharmacotherapy or combination therapy, based on a stepped care model and in concordance with Dutch evidence-based treatment guidelines (van Fenema et al., 2012). Absence of follow-up assessments and missing data (resulting from the incidental failure to administer complete questionnaires), served as exclusion criteria.

4.3. Measures

4.3.1. Predictors of 2-year outcome

Besides patients' age and gender, a wide range of demographic variables was ascertained. Marital status was categorized as 'married or cohabiting' versus 'being unmarried and living without a partner.' Dutch ethnicity was assumed when both the patient and the patient's parents were born in the Netherlands (excluding former Dutch colonies). Education was divided into three levels, 'low education' (no education, primary school until approximately 10th grade), 'medium education' (ranging from 11th grade through high school and community college) and 'high education' (college undergraduate/graduate and higher). Patients were asked about their daily routine, patients who were employed full-time or part-time, were taking care of children, or were receiving education, were classified as 'having a daily occupation'. Patients who were unemployed, retired or on sick leave (without having any care giving responsibilities or receiving education), were classified as 'having no daily occupation'. Living situation was categorized as 'living independently with a partner and/or children', 'living independently alone', and 'living with family'.

DSM-IV-TR diagnostic information was assessed by trained psychiatric nurses using the Dutch version of the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; Van Vliet & De Beurs, 2007). The MINI-Plus has good psychometric properties, with good sensitivity and specificity for all diagnoses except AP, GAD and bulimia, and adequate validity compared to the Composite International Diagnostic Interview, with inter-rater reliability between 0.88 and 1.00 and test-retest reliability between 0.76 and 0.93 (Lecrubier et al., 1997). The MINI-Plus was used to ascertain the presence of anxiety disorders and comorbid depressive or dysthymic disorders, somatoform disorders (hypochondriasis, pain disorder, body dysmorphic disorder, somatization disorder or undifferentiated somatoform disorder), alcohol abuse or dependence and drug abuse or dependence. The number of comorbid anxiety disorders, including comorbid PTSD and OCD (not primary focus in this study) was dichotomized into "single anxiety disorder" versus "multiple anxiety disorders". Age of onset of anxiety disorder was defined as the age at which the disorder (not comprising PTSD or OCD) first manifested, based on the question: "What age were you when these symptoms first emerged?" Age of onset was classified into pre-adult onset (<18 years) and adult onset (≥18 years; van Noorden et al., 2011).

As part of the standard ROM procedure, several additional scales were administered at baseline. Maladaptive personality traits were assessed using the Dimensional Assessment of Personality Pathology short form (DAPP-SF; van Kampen et al., 2008), a short version of the DAPP-BQ (Livesley et al., 1998). The DAPP-SF consists of 136 items on a 5-point Likert scale. 18

Subscales are computed by taking the average of the subscale items (range 1-5); higher scores are associated with pathology, whereas lower scores indicate normality. It has good internal consistency, with Cronbach's alphas ranging from 0.78 to 0.89 across subscales (van Kampen et al., 2008). The 25-item abbreviated Comprehensive Psychopathological Rating Scale (CPRS), besides measuring anxiety on the BAS, also measures psychomotor inhibition (Inh) with 5 items and depressive symptoms (Montgomery-Åsberg Depression Rating Scale [MADRS]) with 10 items. Items for both scales are measured on a 7-point Likert scale (0-6) and add up to a total score (range Inh 0-30; MADRS 0-60), with higher scores indicating more severe symptoms. The MADRS has good internal consistency with Cronbach's alpha equalling 0.86 (Montgomery and Åsberg, 1979). Generic health status was examined using the Dutch version of the Short Form-36 (SF-36; Ware & Sherbourne, 1992; Aaronson et al., 1998) a 36-item self-report survey, screening eight domains of general health: physical functioning, social functioning, role limitations due to physical health problems, role limitations due to emotional problems, general mental health perception, vitality, bodily pain, and general health perception. Measurement scales vary per subscale, ranging from yes/no to answers on a 3-, 5- or 6-point Likert scale. All raw scores are linearly converted to 0-100 subscales, with higher scores representing higher levels of functioning or wellbeing. The subscales of the SF-36 have moderate to good psychometric properties, with Cronbach's alphas between 0.66 and 0.93 (Aaronson et al., 1998).

4.3.2. Outcome measures

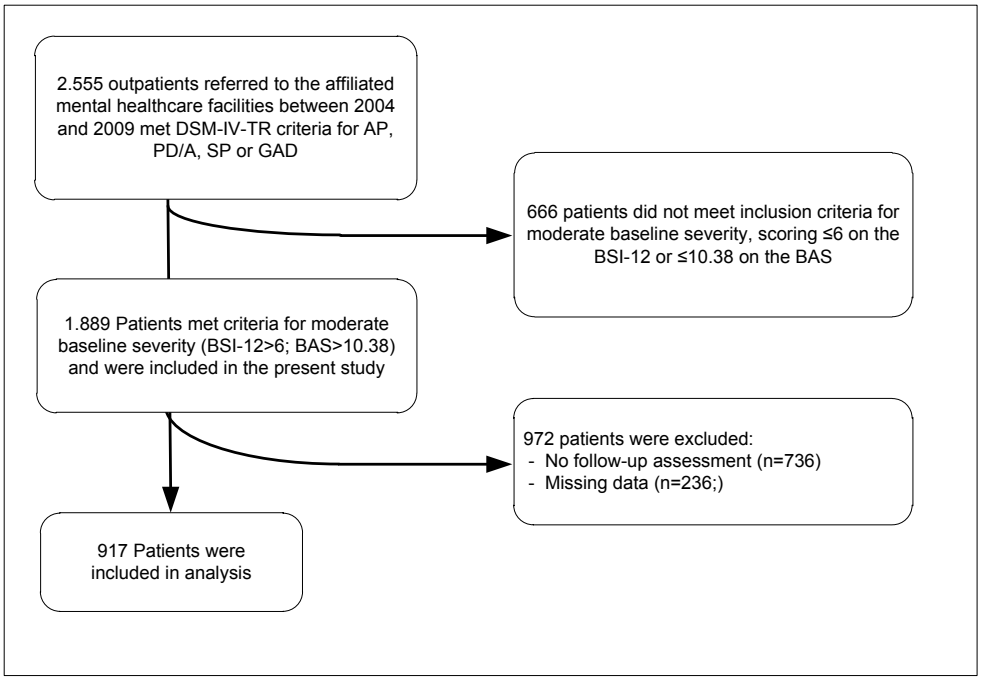
Primary outcome in this study was severity of anxiety symptomatology, which was assessed at baseline and follow-up using a self-report as well as an observational measure: the Dutch versions of the BSI-12 (De Beurs & Zitman, 2006; Roy-Byrne et al., 2010) and the BAS (Tyrer et al., 1984). The BSI-12 is a self-report measure comprising items of the anxiety and somatization subscales of the Brief Symptom Inventory 18-item version (Zabora et al., 2001), which is in turn derived from the Brief Symptom Inventory (Derogatis & Melisaratos, 1983), and has good internal consistency with Cronbach's alphas between 0.79 and 0.84 (Franke et al., 2011) and 0.86 in our cohort. The total score equals the sum score of 12 items on a 5-point Likert scale (0-4; range 0e48). The BAS is a 10-item observer-rated scale derived from the CPRS (Åsberg et al., 1978; Goekoop et al., 1992). The total score equals the sum-score of all 10 items on a 7-point Likert scale (0-6; range 0-60). It has adequate internal consistency with Cronbach's alpha of 0.43 in our cohort. Both scales assess the main components of all anxiety disorders, covering psychic and somatic components, and on both scales a higher score corresponds to more severe anxiety. Response was defined as at least 50% improvement on both the BSI-12 and the BAS (van Noorden et al., 2012; Roy-Byrne et al., 2010).

4.3.3. Statistical analyses

Baseline categorical characteristics are presented as number (percentage); continuous variables are presented as mean (standard deviation; SD) with interquartile range (IQR). Comparisons of demographics between included and excluded patients were made using χ^2 and independent samples t-tests for categorical and continuous variables respectively. Follow-up was censored at 24 months. Associations between time to response and social demographic and clinical factors were examined with Cox proportional hazards analysis. As the precise point in time at which response was achieved was not known, interval censoring was applied by defining the moment of response as the midpoint between the last and penultimate assessment (Hosmer et al., 2008). The percentage of cumulative response in the total sample was calculated using Kaplan-Meier analysis. Univariable Hazard Ratios (HR) and 95% confidence intervals (CI) were calculated for response. To facilitate comparability of effect sizes between continuous predictors, scores were standardized by calculating *Z*-scores for use in analyses. In addition, as higher scores on the SF-36 correspond with better functioning, whereas in all other instruments used in this study a higher score corresponds with greater severity, original SF-36 scores were inverted (i.e. subtracted from 100).

Following the first two steps of the purposeful selection method (Hosmer et al., 2008), all candidate predictor variables that achieved significance levels of 0.10 in univariable analysis were entered in multivariable analysis. Failure to achieve significance at p 0.10 in the resulting multivariable model resulted in removal except for age, gender and the four dichotomized main diagnostic categories in this study (i.e., PD/A, AP, SP and GAD), which were forced into the model (i.e. step 1). Backward stepwise removal of covariates was checked using the p-values of the Wald test and the partial likelihood ratio test, with values >0.05 demonstrating that removal was justified (i.e. step 2). Post-hoc interaction analyses using dummy variables were performed if considered relevant. Two measures of model performance were calculated: the measure of explained randomness $R^{2p,e}$ (O'Quigley et al., 2005); and $R^{2p,v}$ (Royston, 2006); which more closely resembles the measure of explained variation in linear regression (Hosmer et al., 2008). Kaplan-Meier survival curves were constructed for all variables in the final model. Sensitivity analyses were performed using a less strict response criterion of 40% improvement as well as a more strict definition of 60% improvement on BAS and BSI-12. All tests were two-tailed with $p < 0.05$ denoting statistical significance. IBM SPSS for Windows 20.0 was used for data analysis (IBM Corp., Armonk, NY, USA).

Figure 4.1 Flowchart of inclusion and exclusion



The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. AP denotes agoraphobia without panic; BAS, Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; GAD, generalised anxiety disorder; PD/A, panic disorder with or without agoraphobia; ROM, routine outcome monitoring; SP, social phobia.

4.4. Results

4.4.1. Sample characteristics

Between 2004 and 2009, a total of 1.889 patients met the diagnostic criteria for PD/A, AP, SP and/or GAD, with at least moderate baseline severity as measured on the BSI-12 and the BAS according to the previously specified criteria. Figure 4.1 presents a flowchart of inclusion, 736 cases did not have follow-up, 153 cases had to be excluded as entire questionnaires (DEMOG, DAPP-SF and SF-36) had not been administered at baseline. From a further 7 patients, no age of onset of anxiety disorder could be obtained. For some patients, baseline measurements had taken place over several assessment sessions with different time intervals, in 76 cases these intervals exceeded 3 weeks, which was deemed unacceptable. This resulted in the exclusion of 972 patients, leaving a sample of 917 patients. Baseline sample characteristics are presented in table 4.1. The occurrence of anxiety disorders is presented in figure 4.2, showing PD/A was

most prevalent at 43%, followed by SP (29%), GAD (23%) and AP (22%). In total, 31% of patients presented with comorbid anxiety disorders (including OCD and PTSD). Comorbid mood disorder occurred in 52% of patients, 14% of patients presented with a comorbid somatoform disorder, 4% suffered from comorbid alcohol abuse or dependence and 4% presented with comorbid drug abuse or dependence.

The 917 patients who were included for analyses did not differ from the 972 excluded patients with regard to age or gender. Inclusion was associated with Dutch ethnicity (83% vs. 75% in the excluded group; χ^2 (1, 1679) = 13.180, p < 0.001, phi = 0.090), with higher prevalence of high education-level (19% vs. 14% in the excluded group; χ^2 (2, 1679) = 11.581, p = 0.003, phi =0.08) and with a diagnosis of comorbid depressive disorder (52% vs. 66% in the excluded group; χ^2 (1, 1889) = 4.162, p = 0.04, phi = 0.05). Included patients had significantly lower BSI-12 scores than excluded patients (M = 19.9, SD = 9.0 vs. M = 21.5, SD = 9.6; t (1886.95) = 3.88, p < 0.001), eta squared = 0.008, Cohen's d = 0.26. Similar differences, with slightly higher scores in the excluded group, existed on several DAPP-SF scales, the MADRS, Inh and SF-36 (data not shown).

4.4.2. Univariable predictors of response

Over the 2-year follow-up period, the cumulative proportion responding was 63.6%. The median follow-up was 308 days (IQR = 114-620). At 2 years, 856 patients (93%) had reached an endpoint, 61 patients (7%) still continued treatment. Univariable categorical predictors of response are shown in Table 4.2. Response over 2-year follow-up at p 0.10 was predicted by having non- Dutch ethnicity as opposed to Dutch ethnicity, living independently with a partner and/or children as opposed to residing with family, low as opposed to high education-level, having no daily occupation, suffering from multiple simultaneously occurring anxiety disorders, comorbid mood disorder, comorbid alcohol abuse or dependence, a diagnosis of AP or the absence of a diagnosis of PD/A. Univariable continuous predictors of response are presented in Table 4.3, showing associations with poor response forage, a range of DAPP-SF personality traits and the SF-36 scales measuring general health and bodily pain.

4.4.3. Multivariable predictors of response

Survival was best predicted by a set of thirteen covariates, $R^{2p,e}$ = 0.18 (O'Quigley et al., 2005); $R^{2p,v}$ = 0.12 (Royston, 2006). Table 4.4 shows HR's with CI and p-values for each of the covariates. All covariates except age, gender, PD/A, SP and GAD reliably predicted time to response at p 0.10. Patients suffering from AP had a 33% decreased chance of response. Patients with non-Dutch ethnicity had 29% less chance of responding within 2 years. Not

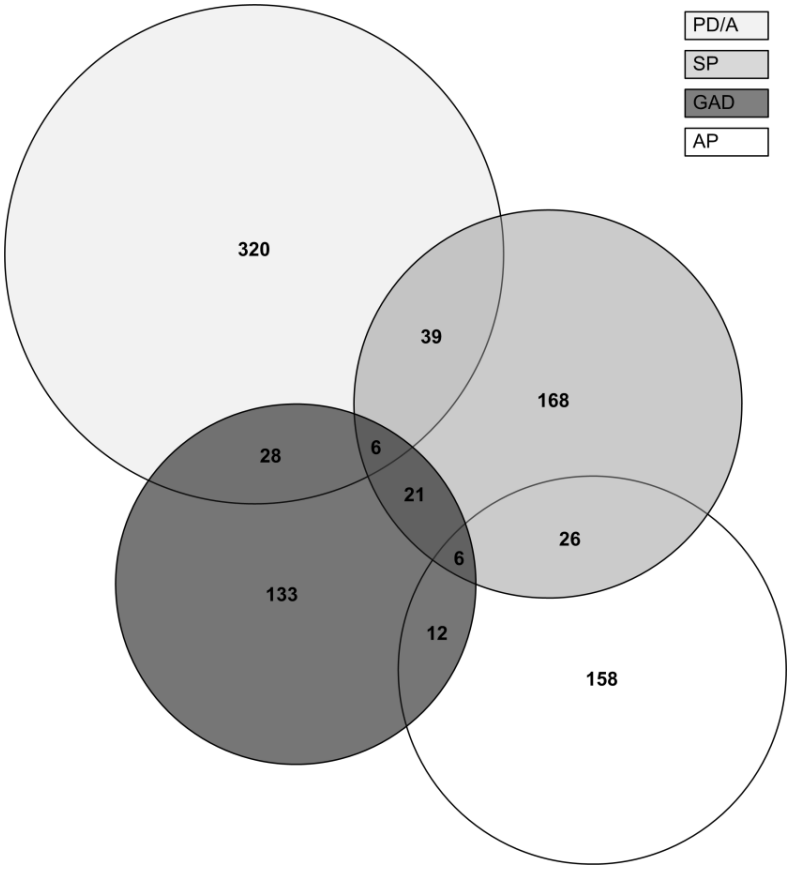
having a daily occupation decreased chances of response with 24%. A low education-level decreased chances of response with 24% although findings were non-significant. Living with family increased chances of response with 41%. Alcohol abuse or dependence decreased chances of response by 46% although findings were non-significant. A single SD increase on DAPP-SF subscales affective lability or conduct problems resulted in a respective 20% and 16% reduction of chances of response within two years. Figure 3 shows the Kaplan-Meier survival curves of naturalistic treatment response over the 2-year follow-up period.

Finally, the concurrence of multiple anxiety disorders versus single anxiety disorder, although univariably significant, did not independently predict outcome. Depressive or dysthymic comorbidity, somatoform comorbidity, marital status, drug abuse or dependence, pre-adult onset and severity of depressive symptoms as measured with the MADRS, all failed to achieve both univariable and multivariable significance. Sensitivity analyses, as described in the method section, confirmed findings for all covariates except for the associations with alcohol and ethnicity, which were less robust (data not shown).

4.5. Discussion

This study aimed at identifying predictors of 2-year outcome in a broad range of anxiety disorders in a naturalistic outpatient psychiatric specialty care setting. Eight independent socio-demographic and clinical predictors of response in PD/A, AP, SP and GAD emerged. With respect to socio-demographic factors, non-Dutch ethnicity, no daily occupation and low education-level (although non-significant) decreased chances of response, while living with family was protective. Regarding clinical factors, a diagnosis of AP, comorbid alcohol abuse or dependence (although non-significant), high scores on DAPP-SF affective lability and behaviour problems all decreased chances of response. These results largely confirm and contribute to earlier findings. First, findings of poor response in non-Dutch patients have not been previously reported. Although this might be explained by cultural differences or social barriers, or by members from ethnic minority groups receiving less adequate care (Lagomasino et al., 2011; Weisberg et al., 2007), it must be stressed that no information on the cultural background of the non-Dutch patients in our sample was available, therefore, these interpretations remain speculative and it is difficult to make further inferences. Findings of no daily occupation and lower education-levels predicting nonresponse, confirm earlier reports (Ramsawh et al., 2009; Roy-Byrne et al., 2003). This might bear on the broader concept of lower social economic status posing a risk factor (Roy-Byrne et al., 2003; Roy-Byrne et al., 2006), although both factors could also be a consequence of greater severity or chronicity of anxiety disorder and it should be noted that low education level did not reach significance in our model.

Figure 4.2 Prevalence of DSM-IV-TR anxiety disorders in the sample (n=917)



Numbers represent numbers of patients in each diagnostic category. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. AP denotes agoraphobia without panic; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; GAD, generalised anxiety disorder; PD/A, panic disorder with or without agoraphobia; SP, social phobia.

Table 4.1 Baseline characteristics in 917 outpatients diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder.

Categorical variables	**n**	**%**
Male gender	329	35.9%
Non-Dutch ethnicity	158	17.2%
Married or living together	484	52.8%
Living situation		
- living independently with partner and /or children	576	62.8%
- living independently and alone	195	21.3%
- residing with family	146	15.9%
Education-level		
- high	174	19.0%
- medium	377	41.1%
- low	366	39.9%
Daily occupation	553	60.3%
Comorbid DSM-IV-TR depressive or dysthymic disorder	475	51.8%
Comorbid DSM-IV-TR somatoform disorder	124	13.5%
Comorbid alcohol abuse or dependence	42	4.6%
Comorbid drug abuse or dependence	34	3.7%
Pre-adult onset of anxiety disorder	345	37.6%
DSM-IV-TR panic disorder with or without agoraphobia	393	42.9%
DSM-IV-TR agoraphobia	202	22.0%
DSM-IV-TR social phobia	266	29.0%
DSM-IV-TR generalised anxiety disorder	206	22.5%
single anxiety disorder	626	68.3%
Continuous variables	**Mean (±SD)**	**IQR**
Age	36.9 (11.8)	27.0 - 46.0
BSI-12 score	19.9 (9.0)	13.0 -26.0
BAS score	19.0 (5.6)	15.0 - 22.0
MADRS score	20.0 (8.5)	14.0 - 26.0
Inh score	3.6 (3.0)	2.0 - 5.0
SF-36		
- physical functioning	75.4 (22.7)	60.0 - 95.0
- social functioning	40.3 (25.2)	25.0 - 62.5
- physical problems	35.3 (39.1)	0 - 75.0
- emotional problems	23.6 (32.9)	0 - 33.3
- mental health	37.8 (15.7)	28.0 - 48.0
- vitality	33.4 (16.1)	20.0 - 45.0
- bodily pain	65.1 (26.9)	44.9 - 89.8
- general health	50.6 (19.9)	35.0 - 65.0

Categorical variables are presented as n (percentage), continuous variables are presented as mean (± standard deviation [SD]), interquartile range (IQR). The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. BAS denotes Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; Inh, Inhibition scale derived from the Comprehensive Psychopathological Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; SF-36,Short Form-36.

Table 4.2 Univariable Hazard Ratios of response for baseline categorical variables in 917 patients diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder.

Categorical variables	**HR (95% CI)**	**p-value**
Female gender	*1 (ref.)*	
Male gender	0.95 (0.77-1.17)	0.62
Dutch ethnicity	*1 (ref.)*	
Non-Dutch ethnicity	0.70 (0.52-0.95)	0.02
Married or living together	*1 (ref.)*	
Not married or cohabiting	1.01 (0.82-1.24)	0.91
Living situation independently with partner and /or children	*1 (ref.)*	
Living situation independently and alone	0.94 (0.72-1.23)	0.65
Living situation with family	1.39 (1.06-1.83)	0.02
Education level high	*1 (ref.)*	
Education level medium	1.03 (0.79-1.36)	0.82
Education level low	0.74 (0.56-0.98)	0.04
Daily occupation	*1 (ref.)*	
No daily occupation	0.74 (0.59-0.91)	0.005
Single anxiety disorder	*1 (ref.)*	
Multiple anxiety disorders	0.79 (0.63-1.00)	0.05
No comorbid depressive or dysthymic disorder	*1 (ref.)*	
Comorbid depressive or dysthymic disorder	0.84 (0.69-1.04)	0.10
No comorbid somatoform disorder	*1 (ref.)*	
Comorbid somatoform disorder	0.99(0.72-1.34)	0.92
No alcohol abuse or dependence	*1 (ref.)*	
Alcohol abuse or dependence	0.46 (0.24-0.89)	0.02
No drug abuse or dependence	*1 (ref.)*	
Drug abuse or dependence	1.00 (0.60- 1.68)	0.99
Adult onset	*1 (ref.)*	
Pre-adult onset	1.02 (0.82-1.26)	0.88
No DSM-IV-TR panic disorder with or without agoraphobia	*1 (ref.)*	
DSM-IV-TR panic disorder with or without agoraphobia	1.26 (1.03-1.55)	0.03
no DSM-IV-TR agoraphobia	*1 (ref.)*	
DSM-IV-TR agoraphobia	0.64 (0.48-0.85)	0.002
no DSM-IV-TR social phobia	*1 (ref.)*	
DSM-IV-TR social phobia	0.91 (0.73-1.15)	0.43
no DSM-IV-TR generalised anxiety disorder	*1 (ref.)*	
DSM-IV-TR generalised anxiety disorder	1.03 (0.81-1.32)	0.80

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value; ref. signifies the reference category. Response was defined as ≥50% reduction on the BSI-12 and the BAS. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition-text revision.

Table 4.3 Univariable Hazard Ratios of response for baseline continuous variables in 917 patients diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder.

Continuous variables	**HR (95% CI)**	**p-value**
Age	0.90 (0.81-1.00)	0.05
MADRS score	0.97 (0.87-1.09)	0.66
Inh score	1.05 (0.95-1.18)	0.33
DAPP-SF		
- submissiveness	0.90 (0.81-1.00)	0.04
- cognitive distortion	0.83 (0.75-0.92)	0.001
- identity problems	0.86 (0.77-0.95)	0.005
- affective lability	0.78 (0.70-0.87)	<0.001
- stimulus seeking	0.92 (0.82-1.03)	0.14
- compulsivity	0.92 (0.83-1.02)	0.12
- restricted expression	0.94 (0.85-1.04)	0.35
- callousness	0.93 (0.83-1.04)	0.19
- oppositionality	0.83 (0.75-0.92)	<0.001
- intimacy problems	0.91 (0.82-1.01)	0.07
- rejection	1.04 (0.94-1.15)	0.41
- anxiousness	0.84 (0.76-0.94)	0.002
- conduct problems	0.81 (0.71-0.92)	0.001
- suspiciousness	0.83 (0.74-0.93)	0.001
- social avoidance	0.87 (0.79-0.97)	0.01
- narcissism	0.96 (0.86-1.07)	0.46
- insecure attachment	0.89 (0.81-0.99)	0.04
- self-harm	0.84 (0.75-0.95)	0.004
SF-36		
- physical functioning	0.93 (0.84-1.04)	0.22
- social functioning	0.95 (0.85-1.06)	0.37
- physical problems	0.95 (0.86-1.06)	0.38
- emotional problems	0.95 (0.85-1.07)	0.40
- mental health	0.98 (0.87-1.10)	0.68
- vitality	0.97 (0.86-1.09)	0.58
- bodily pain	0.89 (0.80-0.99)	0.04
- general health	0.80 (0.71-0.89)	<0.001

Hazard Ratios (HR) are presented with 95% confidence interval (CI)l and p-value, ref. signifies the reference category. Response was defined as ≥50% reduction on the BSI-12 and the BAS; BAS denotes Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DAPP-SF, Dimensional Assessment of Personality Pathology-Short Form; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; Inh, Inhibition scale derived from the Comprehensive Psychopathological Rating Scale; MADRS, Montgomery Åsberg Depression Rating Scale; SF-36, Short Form-36. To facilitate comparability of hazard ratios, z-values were used and SF-36 scores were inverted.

Table 4.4 Multivariable Hazard Ratios of response in 917 patients diagnosed with panic disorder, agoraphobia, social phobia or generalised anxiety disorder.

		HR (95% CI)	p value
Block 1	Age	1.00 (0.88- 1.13)	0.95
	Gender		
	- Female	1 (ref.)	
	- Male	1.12 (0.88-1.43)	0.36
	DSM-IV-TR panic disorder with or without agoraphobia		
	- no PD	1 (ref.)	
	- PD	1.11 (0.79-1.55)	0.56
	DSM-IV-TR agoraphobia		
	- no AP	1 (ref.)	
	- AP	0.67 (0.45-0.99)	0.04
	DSM-IV-TR social phobia		
	- no SP	1 (ref.)	
	- SP	0.92 (0.67-1.26)	0.59
	DSM-IV-TR generalised anxiety disorder		
	- no GAD	1 (ref.)	
	- GAD	1.07 (0.77-1.48)	0.71
Block 2	Ethnicity		
	- Dutch	1 (ref.)	
	- Non-Dutch	0.71 (0.52-0.96)	0.02
	Occupation		
	- daily occupation	1 (ref.)	
	- no daily occupation	0.76 (0.61-0.95)	0.02
	Education-level		
	- High	1 (ref.)	
	- Medium	1.00 (0.75-1.34)	0.98
	- Low	0.76 (0.56-1.02)	0.07
	Living situation		
	- Independently with partner and/or children	1 (ref.)	
	- Independently alone	0.95 (0.72-1.24)	0.69
	- With family	1.41 (1.01-1.97)	0.045
	Alcohol abuse or dependence		
	- No alcohol abuse or dependence	1 (ref.)	
	- Alcohol abuse or dependence	0.54 (0.27-1.06)	0.07
	DAPP-SF affective lability	0.80 (0.71-0.89)	<0.001
	DAPP-SF conduct problems	0.84 (0.73-0.98)	0.02

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value, ref. signifies the reference category. Response was defined as ≥50% reduction on the BSI-12 and the BAS. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. AP denotes agoraphobia without panic; BAS, Brief Anxiety Scale; BSI-12, Brief Symptom Inventory twelve item version; DAPPS-SF, Dimensional Assessment of Personality Pathology-Short Form; DSM-IV-TR, Diagnostic and Statistical Manual of mental disorders fourth edition- text revision; GAD, generalised anxiety disorder; PD/A, panic disorder with or without agoraphobia; SP, social phobia. To facilitate comparability of hazard ratios among continuous variables, z-values were used. The variables in block 1 (Age, gender, panic disorder with or without agoraphobia, agoraphobia, social phobia and generalised anxiety disorder) were forced in the model, the variables in Block 2 were selected through a backward stepwise procedure described in the methods section.

The finding that living with family was a protective factor was counter-intuitive as in the Netherlands it is abnormal for adults to live with family and this could be perceived as a sign of poor functioning. In addition, family members often accommodate anxiety, which is known to contribute to maintaining anxiety (Chambless, 2012). However, as the group of patients living with family in our study largely consisted of younger patients (e.g. under 26), a group in which living with family might be considered a more 'normal' and therefore possibly healthy attribute, it could be hypothesized that this association is typical for younger patients. Finally the present findings concur with studies reporting no predictive value of age (Chavira et al., 2009; Van Ameringen et al., 2004; Beutel et al., 2011; Beard et al., 2010; Serretti et al., 2009).

With regard to clinical factors, a diagnosis of AP was associated with poor response, partially corroborating previous findings (Beard et al., 2010). Agoraphobia was associated with a higher degree of morbidity and more treatment resistant symptoms of phobic avoidance in patients with PD/A (Keller et al., 1994), possibly, present findings reflect a broader refractoriness of agoraphobia. Comorbid alcohol abuse or dependence was associated with poor response. Although this finding was based on a relatively small group of patients and was not significant, it does support previous reports (Bruce et al., 2005). Alcohol abuse or dependence is frequently reported in anxiety disorders (Kushner et al., 2000), with suggestions of the two disorders feeding into each other, possibly through self-medication (Menary et al., 2011). Finally, affective lability, a factor found to be related to neuroticism and emotional dysregulation (Van Kampen et al., 2008), and behaviour problems posed risk factors, confirming earlier reports of personality disorders or maladaptive personality traits predicting poor outcome (Ansell et al., 2011; Telch et al., 2011; Beutel et al., 2011).

Other candidate clinical predictors like SP, comorbid MDD, somatoform disorder, the concurrence of multiple anxiety disorders, or drug abuse or dependence were not independently associated with response. These findings contradict earlier reports (Bruce et al., 2005; Beutel et al., 2011), although the absence of an association with MDD has been previously reported (Beutel et al., 2011; Roy-Byrne et al., 2003; Serretti et al., 2009). Part of the dissimilar findings may be due to methodological differences. Pre-adult onset did not predict response, substantiating previous findings (Ramsawh et al., 2011), but contradicting others (Penninx et al., 2011; Van Ameringen et al., 2004). Possibly this finding is specific to MDD and SP. Also, the retrospective method of determining age of onset might have resulted in a retrospective bias, although this is true for the majority of studies assessing age of onset (Simon & Vonkorff, 1995; Kessler et al., 2007). Another possible explanation might lie in the existence of different age of onset distributions for different anxiety disorders (Ramsawh et al., 2011).

The present study has high external validity due to the large sample size and the naturalistic approach, with limited use of in- and exclusion criteria. The use of a structured clinical diagnostic instrument, self-report measures as well as observer-rated measures, computerized data collection, and data collection by trained research nurses who were not involved in treatment, further strengthen our study. Nevertheless, results have to be interpreted in light of a number of limitations. First of all, the design may be subject to selection bias (Rothwell, 2005). We have no information on patients not included in ROM and they might differ from included patients. However, inclusion in ROM is high at about 80% and a previous study of our depressed sample demonstrated no differences in baseline characteristics between patients who were and were not included (van der Lem et al., 2011). Second, as in many observational studies, attrition is high and we do not know the reasons for loss to follow-up (van Noorden et al., 2012). Furthermore, treatment data were unavailable, therefore we could not incorporate this in analyses. Previous studies in our ROM cohort did demonstrate that treatment for anxiety disorders is generally delivered according to guidelines and exists of pharmacotherapy (23%), psychotherapy (59%) or combination therapy (16%) (van Fenema et al., 2012).

Additionally, no data on psychiatric history, somatic comorbidity, cultural background or family history were available. Also, prevalence of agoraphobia in our sample was high compared to reports based on the general population (Somers et al., 2006), although in a recent Dutch general population study, comparable prevalence has been reported (Penninx et al., 2011). The MINI lacks sensitivity and specificity with regard to AP in clinical samples (Lecrubier et al., 1997). Possibly the high prevalence of AP is a by-product of other diagnoses. Therefore, results with regard to AP may reflect a negative predictive value of agoraphobic symptoms occurring with other disorders, rather than of a diagnosis of AP per se. Furthermore, as age of onset was assessed retrospectively, measurement error is possible (Simon & Vonkorff, 1995; Knauper et al., 1999). Memory for psychiatric history has been demonstrated to be unreliable (Moffitt et al., 2010; Giuffra & Risch, 1994) and the possibility of underreporting of psychiatric history should be taken into account. Also, response was measured over a limited period of up to 2 years without taking possible relapse into account, subjects with less than 2-year follow-up who did not reach the response criterion were classified as non-responders. This classification is arbitrary and could have influenced results. Finally, due to the observational design, results reflect associations; therefore, causality cannot be inferred. However, our results provide a valuable addition to and validation of previous findings (Rothwell, 2005; van der Lem et al., 2011).

In conclusion, we have identified important predictors of outcome in anxiety disorders from a broad set of general social demographic as well as clinical patient characteristics. Our results show that patients who are non-Dutch, have no daily occupation,

have a low education-level, do not live with family, suffer from alcohol abuse or dependence, are diagnosed with AP and display high levels of affect lability and behaviour problems, are at elevated risk of poor response. Possibly these findings indicate that the same factors that may limit patients' participation in society, e.g. no occupation, low education, agoraphobia, or maladjusted personality characteristics, are associated with impaired response. As this study is explorative in nature, additional studies examining a broad spectrum of possible predictors are called for. Even so, valuable new insights have been added, advocating broad screening of patients at intake on various domains to help clinicians identify patients who are at risk of poor outcome as they deserve special attention in treatment.

Figure 4.3 Kaplan Meier curves for response in 917 patients with DSM-IV-TR anxiety disorders

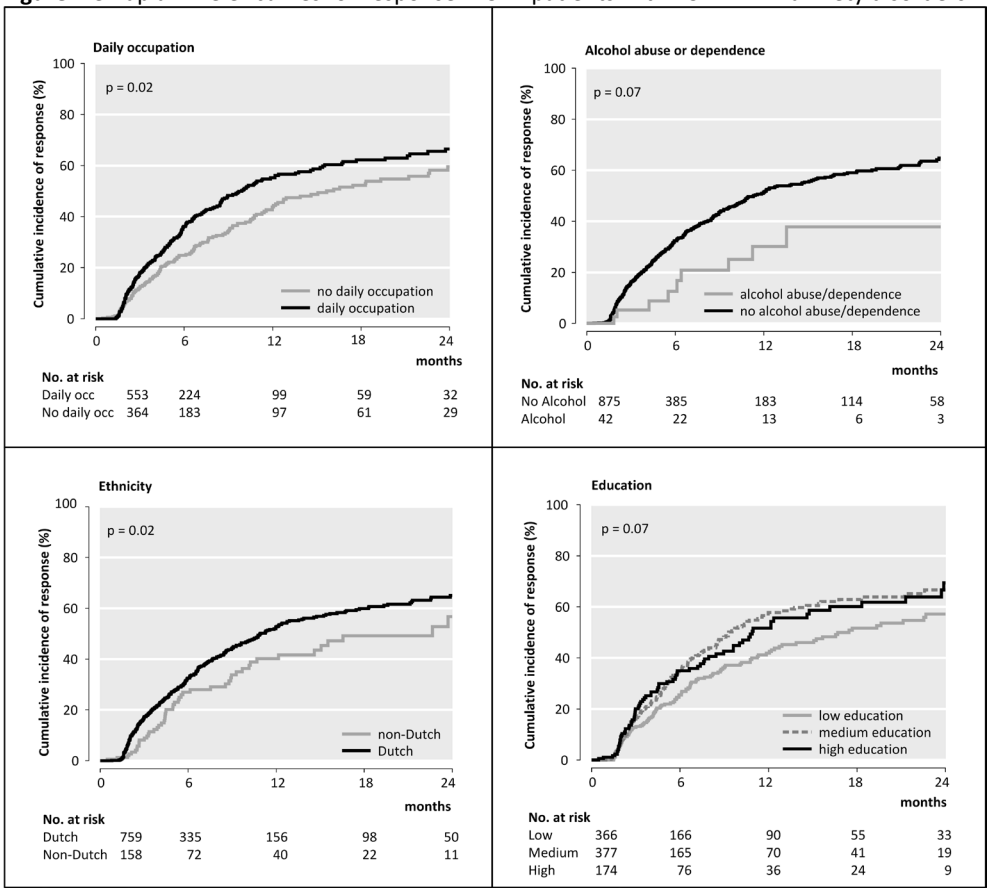
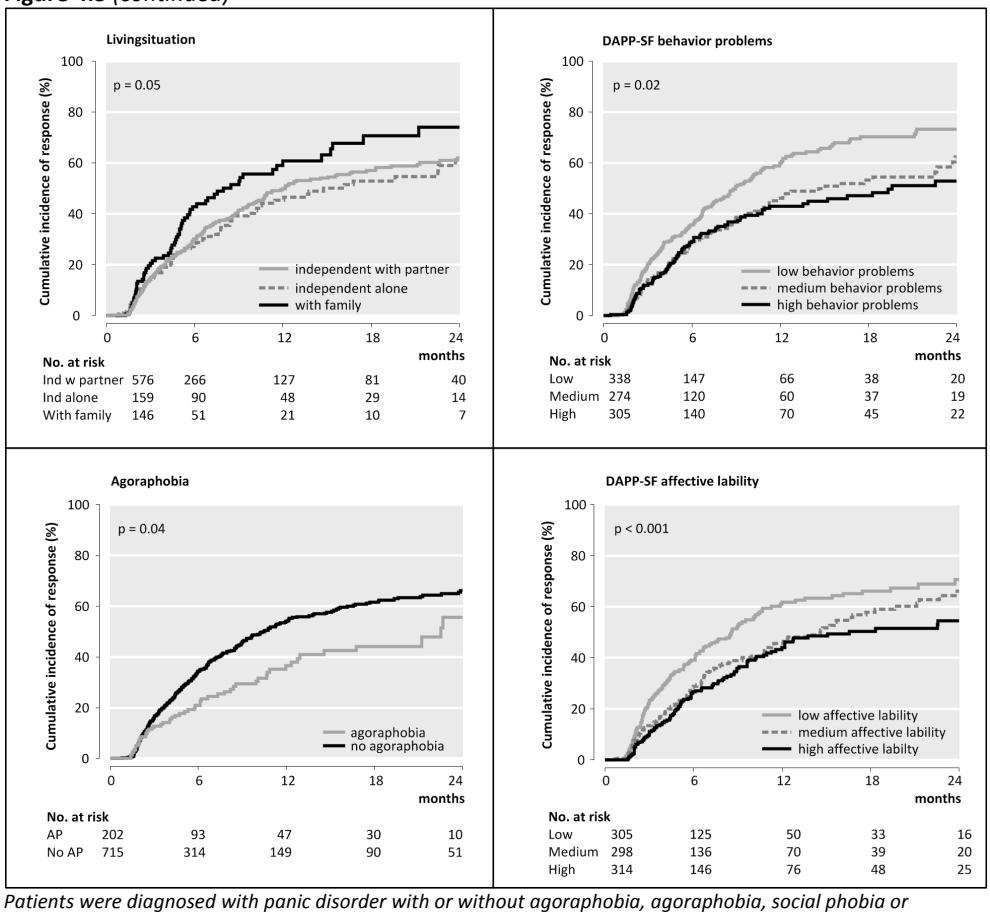


Figure 4.3 *(continued)*



Patients were diagnosed with panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety dis-order. Kaplan Meier curves are shown for the cumulative incidence of response, de-fined as ≥ 50% reduction on the BSI-12 and the BAS in a naturalistic sample. DAPP-SF denotes Dimensional Assessment of Personality Pathology Short Form. To faci-litate compa-rability, tertiles were construc-ted for DAPP-SF affective lability and DAPP-SF behaviour pro-blems. The MINI International Neuropsychiatric Interview- plus was used to collect diagnostic information.

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