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Predicting the course of anxiety disorders: The role of biological parameters

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ABSTRACT

Objective: Clinical characteristics appear limited in their ability to predict course of anxiety disorders, therefore we explored the predictive value of biological parameters on course of anxiety disorders.**Methods:** 907 persons with an anxiety (panic, social phobia, generalised anxiety) disorder with a baseline and two-year follow-up measure were selected from the Netherlands Study of Depression and Anxiety (NESDA). Previously, three course trajectories were distinguished which vary in terms of symptom severity and chronicity. Baseline clinical parameters like anxiety severity, anxiety duration, and disability were limited in their ability to predict the two-year course. This study explored whether metabolic syndrome, hypothalamic-pituitary-adrenal-axis functioning, inflammation markers, and neuroplasticity were indicators of two-year course and whether these parameters improved the model containing the most predictive clinical parameters only.**Results:** Baseline diastolic blood pressure of persons with chronic moderate symptoms was significantly higher than of persons with non-chronic mild symptoms (odds ratio [OR] = 1.18, 95% confidence interval [CI95%] 1.01 to 1.38). Baseline high-density lipid cholesterol of persons with severe chronic symptoms was significantly lower than of persons with non-chronic mild symptoms (OR = 0.77, CI95% 0.62 to 0.96). The predictive ability of both parameters was however low with concordance statistics of 0.55 and 0.57 respectively. Addition of biological parameters did not improve the predictive ability of the model containing the clinical parameters.**Conclusions:** In addition to clinical characteristics, biological parameters did not improve the predictive ability of the model for course trajectory of anxiety disorders. Prediction of course trajectory in anxiety disorders remains difficult and warrants further research.

1. Introduction

Anxiety disorders often have a chronic course and relapse or recurrence is common (e.g. (Bruce et al., 2005; Colman et al., 2007; Hendriks et al., 2013; Yonkers et al., 2003)), resulting in long-term disability of patients. Various studies investigated the long-term course of anxiety disorders and showed that over half of patients experience chronic symptoms with varying severity (Batelaan et al., 2014; Colman et al., 2007; Spinhoven et al., 2016). Clinical parameters and to a lesser extent diagnostic classification were indicators of course (Batelaan et al., 2014; Spinhoven et al., 2016). Unfortunately, the predictive ability of these parameters is limited (Batelaan et al., 2014; Spinhoven et al., 2016), while such information could be crucial for tailoring treatment towards the long-term needs of patients.

Investigation of factors that may be related to the pathogenesis of anxiety disorders is a next step. Previous research in cross-sectional studies provided mixed evidence for the association of biological parameters with presence of anxiety disorders compared to controls. Some studies found for example that metabolic syndrome was associated with anxiety (Carroll et al., 2009; Kahl et al., 2015), but other did not (Butnoriente et al., 2014; Skilton et al., 2007). Results were also mixed for studies regarding hypothalamic-pituitary-adrenal (HPA)-axis functioning (e.g. O'Donovan et al., 2010; Vreeburg et al., 2010), inflammation markers (e.g. O'Donovan et al., 2010; Vogelzangs et al., 2013), and brain derived neurotrophic factor (BDNF) (e.g. Molendijk et al., 2012; Moreira et al., 2015; Suliman et al., 2013). In longitudinal studies it was found that a higher cortisol awakening response predicted the first onset of anxiety disorders within six-years follow-up

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(Adam et al., 2014). It was also found that in patients with agoraphobia inflammation markers tumour-necrosis-factor- α (TNF- α) and c-reactive protein (CRP) were increased compared to controls at 5.5 years follow-up (Wagner et al., 2015). The presence of an anxiety disorder was however not predicted by baseline levels of inflammation (Glaus et al., 2018). Longitudinal studies investigating biological parameters in adult anxiety patients are however scarce and did not investigate whether these parameters were indicators of course trajectory.

A previous study from our group identified three two-year course trajectories of anxiety disorders (Batelaan et al., 2014). These trajectories included having minimal symptoms over time (41.7%), having a moderate severe chronic course (43.0%), and having a severe chronic course (15.3%). Significant indicators of course were baseline anxiety severity and duration, and disability. Compared to the course with minimal symptoms over time, the predictive ability of these parameters was low for a chronic course with moderate symptoms (concordance statistic [c-statistic] = 0.64) and reasonable for a chronic course with severe symptoms (c-statistic = 0.80). In this study we will explore whether baseline metabolic functioning, HPA-axis functioning, inflammation markers, and levels of BDNF are indicators for two-year course trajectory in adult anxiety patients and what their additive effect is on top of the previously identified clinical parameters. As little is known about the ability of biological parameters to differentiate between different course trajectories, we choose these parameters based on what is known from cross-sectional studies. In line with the clinical parameters (Batelaan et al., 2014), patients with minimal symptoms over time were expected to score relatively low on the included parameters (i.e. relatively unaffected metabolic functioning, relatively unaffected HPA functioning, low on inflammation markers and high on BDNF), whilst patients with a chronic severe course were expected to be relatively the worst off. Patients with a moderate chronic course were expected to be in between the other two groups.

2. Method

2.1. Participants

Baseline and two-year follow-up data were derived from the Netherlands Study of Depression and Anxiety (NESDA), a longitudinal cohort study including $n = 2981$ adults aged 18–65 years (Penninx et al., 2008). The research protocol was approved by the Ethics Committee of the participating universities and written informed consent was obtained from all participants. At baseline persons ($n = 1102$) had a six-month diagnosis of panic disorder with or without agoraphobia, agoraphobia, social phobia or generalised anxiety disorder and symptoms were confirmed in the month prior to baseline with the Composite International Diagnostic Interview (CIDI, version 2.1). At two years follow-up $n = 907$ participants were reassessed. In line with the entire baseline sample (Lamers et al., 2012), non-respondents ($n = 195$) at two years follow-up compared to respondents tended to have followed fewer years of education, were more frequently smokers, had more frequently a comorbid depressive disorder, and their anxiety symptoms were more severe on the Becks Anxiety Inventory (BAI). There were no indications for differences in any of the baseline biological variables between respondents and non-respondents at two years follow-up (see Appendix 1 for further details).

The two-year course of the respondents was determined based on anxiety and avoidance symptoms as assessed with the Life Chart Interview using Latent Class Growth Analyses (LCGA) (for detailed description, see Batelaan et al., 2014). These included 1) a group characterised by minimal symptoms over time ($n = 378$, 41.7%) (class 1); 2) persons characterised by a moderately severe chronic course ($n = 390$, 43%) (class 2); and 3) persons with a severe chronic course ($n = 139$, 15.3%) (class 3).

2.2. Measures

2.2.1. Metabolic syndrome

Presence of metabolic syndrome ($n = 891$) was based on 2005 adjusted criteria of the US National Cholesterol Education Program – Adult Treatment Panel III (Grundy et al., 2005) and assessed at baseline. Metabolic syndrome was considered present when three or more of the following criteria were met: 1) waist circumference > 102 cm in men, > 88 cm in women ($n = 906$); 2) triglycerides ≥ 1.7 mmol/l (150 mg/dl) or use of medication for hypertriglyceridemia ($n = 890$); 3) high-density lipoprotein (HDL) cholesterol < 1.03 mmol/l (40 mg/dl) in men; < 1.30 mmol/l (50 mg/dl) in women or use of medication to reduce HDL cholesterol ($n = 891$); 4) blood pressure $\geq 130/85$ mmHg or antihypertensive medication ($n = 903$); 5) fasting plasma glucose ≥ 5.6 mmol/l (100 mg/dl) or use of anti-diabetic medication ($n = 891$).

Waist circumference was measured with a tape, measured midway between the lowest rib and highest frontal part of the pelvis upon light clothing. Standard laboratory measures were used to determine levels of triglycerides, HDL-cholesterol and glucose on fasting blood samples. Blood pressure was measured twice on the right arm when the participant was in supine position. The mean of both measures was used in analysis. The use of medication was determined by copying the names from the containers brought by the participants.

2.2.2. Hypothalamic-pituitary-adrenal axis

Saliva cortisol was used to determine the functioning of the hypothalamic-pituitary-adrenal (HPA)-axis. Participants collected saliva samples at home on a regular (working) day shortly after the baseline measures. Salivettes (Sarstedt, Nümbrecht, Germany) were used to collect saliva samples at awakening (T1), and 30 (T2), 45 (T3), and 60 min (T4) after awakening. Evening samples were collected at 22.00 h (T5) and 23.00 h (T6). Following the sampling at 23.00 h participants took 0.5 mg dexamethasone and dexamethasone suppression was measured the following morning at awakening (T7). The dexamethasone suppression test provides information about the negative feedback loop of the HPA axis, as dexamethasone acts on the pituitary and thereby reduces the cortisol levels (Carroll et al., 1981). Fifteen minutes prior sampling participants were prohibited from smoking, eating, drinking coffee or tea, or brushing teeth and no dental work was allowed 24 h prior sampling. Participants were instructed to record the exact sampling times and stored the Salivettes in the refrigerator before returning them by mail. When received, Salivettes were centrifuged at $2000 \times g$ for 10 min, aliquoted and stored at -85°C . Cortisol analysis was performed using competitive electrochemiluminescence immunoassay (Roche, Basel, Switzerland). The functional detection limit was 2.0 nmol/l and the intra- and inter-assay variability coefficients were $< 10\%$.

The functioning of the HPA-axis was characterised by several measures (Vreeburg et al., 2009). For the cortisol awakening response (CAR), the area under the curve with respect to the increase (auci, $n = 573$) indicated the dynamics of CAR, while the area under the curve with respect to the ground (aucg, $n = 573$) indicated the total cortisol secretion over the first hour of awakening and is an estimate of the total cortisol secretion throughout the day (Vreeburg et al., 2009). Evening cortisol levels ($n = 619$) were based on the mean of T5 and T6 and dexamethasone suppression ($n = 589$) was based on the ratio between T1 and T7. More details about the saliva collection and cortisol measures are described elsewhere (Vreeburg et al., 2009).

2.2.3. Inflammation markers

Fasting blood samples were collected between 08.00 and 09.00 h in the morning of the baseline measures and kept frozen at -85°C . c-reactive protein (CRP) ($n = 894$) and interleukin (IL)-6 ($n = 893$) were assayed at the Clinical Chemistry department of the VU University Medical Center (Amsterdam, the Netherlands) and tumour-necrosis-

factor- α (TNF- α) ($n = 888$) was assayed in duplicate at Good Biomarker Science (Leiden, the Netherlands). High-sensitivity plasma levels of CRP were measured in duplicate by an in-house ELISA based on purified protein and polyclonal anti-CRP antibodies (Dako, Glostrup, Denmark); the mean value of both measures is reported. Intra- and inter-assay coefficients of variation were 5% and 10% respectively. IL-6 plasma levels were measured in duplicate by a high sensitivity ELISA (PeliKine Compact™ ELISA, Sanquin, Amsterdam, The Netherlands) and intra and inter-assay coefficient variations were 8% and 12% respectively. The mean value of both measures is reported. TNF- α plasma levels were assayed using high-sensitivity solid phase ELISA (Quantikine® HS Human TNF- α Immunoassay, R&D systems Inc., Minneapolis, MN, United States) and intra and inter-assay coefficients of variation were 10% and 15% respectively.

2.2.4. Brain derived neurotrophic factor

Fasting blood samples, collected between 08.00 and 09.00 h in the morning of the baseline interview, were transferred to the laboratory to start processing within 1 h and were stored at -85°C . Serum brain derived neurotrophic factor (BDNF) protein levels ($n = 880$) were assessed using the Emax Immuno Assay system from Promega according to the manufacturer's protocol (Madison, WI, USA). To increase the detectable BDNF in a dilution-dependent way the undiluted serum was acid treated. Serum samples were diluted 100 times and absorbency was read in duplicate using a Biorad Benchmark microplate reader at 450 nm. Serum BDNF protein levels were expressed in ng/ml. The intra- and inter-assay coefficients of variance were 3% and 9% respectively. More details are described elsewhere (Bus et al., 2011).

2.3. Statistical analysis

Descriptive statistics were used to assess differences in the biological parameters between the LCGA-derived course trajectories. Multinomial logistic regression analysis was used to explore which biological parameters predicted class membership. Analyses were adjusted for sex and age. The additive value of each biological parameter was assessed by adding it to a model containing the previously identified clinical parameters related to the anxiety severity and duration, and disability (Batelaan et al., 2014). The c-statistic (Hosmer and Lemeshow, 2000) was calculated per biological parameter to assess its predictive ability between the chronic courses (class 2 and 3) and the more favourable course (class 1). Given that effects could be missed due to the heterogeneity of the sample, analyses were repeated post-hoc for the different anxiety disorders separately. Moreover, major depressive disorder (MDD) has previously associated with biological dysregulation (Penninx et al., 2013), therefore analyses were repeated in the subsample of patients with also a six-month comorbid MDD. All analysis were conducted using SPSS version 24.

3. Results

A more extensive description of the three anxiety course trajectories can be found elsewhere (Batelaan et al., 2014). Briefly, with a more unfavourable course trajectory, participants had significantly higher anxiety severity, more avoidance symptoms, more functional limitations, more six-month CIDI anxiety diagnoses, an increased duration of pre-baseline illness, and more often a major depressive disorder or dysthymia (Table 1). There were no indications for significant differences in age, gender, years of education, and number of chronic somatic diseases (e.g. cardiovascular disease, diabetes) across the course trajectories.

3.1. Univariate analyses

Table 1 presents the characteristics of the biological parameters across the course trajectories. Univariate analyses showed that levels of

HDL cholesterol were significantly lower in the severe chronic class (class 3) compared to the mild severity (class 1) and moderate severity chronic class (class 2). This difference did not remain statistically significant when results were corrected for multiple testing. There were no indications for differences in distributions for any of the other biological variables.

Analyses were repeated for the different anxiety disorders separately, this provided no indications for altered conclusions (Appendix 2). For the subsample of patients with a comorbid 6-months diagnosis of MDD there were also no indications for altered conclusions (Appendix 3).

3.2. Multinomial logistic regression analyses

Persons with chronic moderate symptoms had a significantly higher diastolic blood pressure than persons with minimal symptoms over time (Table 2, Model 1), but the predictive ability was low with a c-statistic of 0.55. Moreover, persons with chronic severe symptoms had significantly lower HDL cholesterol compared to persons with minimal symptoms over time, but again the predictive ability was low with a c-statistic of 0.57. When corrected for multiple testing, differences were no longer statistically significant. Moreover, when anxiety severity and duration, and disability were included, none of the biological parameters added significantly to the predictive ability of the model (Table 2, Model 2). Analysis were repeated for the different anxiety disorders separately. For neither model there were indications that the outcomes were different for different anxiety disorders (Appendix 2). There were also no indications for altered conclusions for the subsample which also had a six-months MDD diagnosis (Appendix 3).

4. Discussion

This study found that increased diastolic blood pressure at baseline was an indicator for a chronic moderate course and that decreased baseline HDL cholesterol was associated with a chronic severe course. None of the other biological parameters were indicators for course trajectory nor did any of the biological parameters improve the model containing the clinical parameters.

This study shows that predicting the course of anxiety disorders based on clinical and biological variables is difficult. To what extent heterogeneity in anxiety disorders blurs an association between biological parameters and course remains to be settled. For example, in MDD different subtypes have been associated with different biological parameters (Penninx et al., 2013). Atypical depression has been characterised by metabolic disturbances and inflammation, whereas melancholic depression has been characterised by HPA-axis hyperactivity. Likewise, there are indications that the biological profile matters for treatment response (Eller et al., 2008; Kruse et al., 2018; Penninx et al., 2013). It remains to be investigated whether such profiles also exist for anxiety disorders and how these affect prediction of course trajectories and treatment response.

Another path to explore is the genetic underpinning of anxiety disorders. This could help to identify risk profiles for anxiety disorders (Otowa et al., 2016), which may provide indications for clinical representation of symptoms and their course. In MDD, genetic risk factors have been identified and associated with clinical characteristics of MDD (Wray et al., 2018). This type of research does however require large numbers of patients.

Strengths of this study are that it is the first to investigate the predictive potential of biological parameters for the two-year course of anxiety disorders and the use of a large, longitudinal, patient sample. A limitation of this study is that for the main analyses all anxiety disorders were analysed together. This could introduce heterogeneity and result into effects being missed for specific groups. It seems however likely that anxiety disorders share a common aetiology. For example the same circuits in the brain (e.g. HPA-axis and amygdala) and neurotransmitter

Table 1

Baseline psychosocial, clinical and biological characteristics across the three two-year anxiety course trajectories.

	Mild severity M (SD)	Moderate severity, chronic M (SD)	Severe, chronic M (SD)	Statistic df = 2	P
<i>Psychosocial and clinical characteristics</i>					
Age	42.59 (12.41)	41.5 (12.1)	42.5 (11.57)	F = 0.85	0.428
Gender, % female	65.1	69.7	61.9	X = 3.52	0.172
Years of education	11.84 (3.26)	11.69 (3.15)	11.21 (3.6)	F = 1.91	0.148
Number of chronic disease	0.98 (1.06)	1.05 (1.12)	1.13 (1.08)	F = 0.98	0.376
Anxiety severity					
BAI	16.78 (9.4)	19.02 (10.48)	25.13 (12.07)	F = 32.67	< 0.001
FQ	31.06 (19)	38.51 (18.41)	48.46 (21.8)	F = 43.28	< 0.001
Anxiety symptoms in months 5 years prior baseline	21.82 (19.27)	27.96 (19.89)	35.09 (19.94)	F = 25.11	< 0.001
Avoidance symptoms in months 5 years prior baseline	14.46 (21.4)	21.41 (23.28)	27.15 (24.24)	F = 18.64	< 0.001
Functioning (high score indicates low functioning)	34.68 (20.64)	40.31 (21.11)	54.22 (21.8)	F = 43.04	< 0.001
Number of 6 months anxiety disorders	1.43 (0.6)	1.63 (0.7)	1.79 (0.81)	F = 16.99	< 0.001
Depressive disorders 6 months diagnosis					
Major depressive disorder, % yes	50.3	52.8	69.1	X = 15.03	0.001
Dysthymia, % yes	14.6	17.4	36.7	X = 33.48	< 0.001
<i>Metabolic syndrome</i>					
Metabolic syndrome, % yes (n)	21.9% (n = 82)	23.8% (n = 91)	23.7% (n = 32)	X = 0.43	0.808
<i>Metabolic syndrome components</i>					
Triglycerides (mmol/l)	1.36 (1.03)	1.30 (0.79)	1.42 (0.86)	H = 1.96	0.375
HDL cholesterol (mmol/l)	1.63 (0.42)	1.64 (0.47)	1.52 (0.40)	F = 3.95	0.020
Fasting plasma glucose (mmol/l)	5.25 (0.98)	5.24 (1.13)	5.18 (0.87)	H = 0.66	0.721
Waist circumference (cm)	90.17 (13.94)	88.86 (14.93)	91.98 (15.43)	F = 2.44	0.088
Systolic blood pressure (mmHg)	136.55 (20.04)	136.53 (19.16)	136.71 (18.66)	F = 0.00	0.996
Diastolic blood pressure (mmHg)	80.86 (11.60)	82.88 (10.82)	82.94 (10.66)	F = 0.96	0.382
<i>Cortisol measures</i>					
Area Under the Curve with respect to Ground	19.66 (7.42)	19.69 (7.36)	18.12 (5.43)	F = 1.82	0.163
Area Under the Curve with respect to Increase	2.85 (6.58)	2.88 (6.57)	1.75 (6.41)	F = 1.09	0.337
Evening cortisol	5.48 (3.43)	5.47 (3.61)	5.20 (2.46)	H = 0.15	0.926
Dexamethasone suppression test	2.81 (1.68)	2.72 (1.82)	2.58 (1.62)	H = 3.58	0.166
<i>Inflammation markers</i>					
TNF- α (pg/ml)	1.03 (1.23)	0.99 (0.96)	1.15 (1.09)	H = 1.92	0.383
CRP (mg/l)	3.01 (5.39)	3.25 (6.24)	3.46 (5.85)	H = 1.24	0.537
IL-6 (pg/ml)	1.27 (2.93)	1.32 (2.22)	1.57 (4.14)	H = 5.92	0.052
<i>BDNF</i>					
BDNF (ng/ml)	9.13 (3.71)	9.38 (3.65)	9.66 (3.36)	F = 1.16	0.315

Abbreviations: HDL: high-density lipoprotein; TNF- α : tumour necrosis factor α ; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.

Numbers presented in bold are significant at $p=0.05$.

systems (e.g. serotonin system) seem involved (Elnazer and Baldwin, 2014; Paul and Lowry, 2013; Ressler and Nemeroff, 2000). Moreover, the long-term prognoses, including the relapse rates of individual anxiety disorders, are similar for all anxiety disorders and the clinical representation is more informative for the prognosis than the diagnostic classification (Batelaan et al., 2014; Scholten et al., 2013; Spinhoven et al., 2016). Analyses were repeated for the separate anxiety disorders, but there were no indications for altered conclusions (Appendix 2) although these analyses may have been underpowered. There was probably still substantial heterogeneity in the different subgroups as anxiety disorders are often comorbid, not only with other anxiety disorders but also with depressive disorders (Kessler et al., 2005; The ESEMeD/MHEDEA 2000 investigators et al., 2004) and anxiety disorders are often diagnostically unstable (Hovenkamp-Hermelink et al., 2016; Scholten et al., 2013). Analysis of the subgroup of patients with a comorbid MDD did also not alter the conclusions (Appendix 3), though the heterogeneity of this subsample may have blurred associations for specific subtypes of MDD (e.g. atypical or melancholic depression) (Penninx et al., 2013). Focussing on specific symptom dimensions, e.g. avoidance symptoms, may therefore result in more homogeneous groups and possibly more insight into the course and predictors of anxiety disorders. Another limitation is that saliva cortisol samples were collected on only one day. The reliability of this measure could have been increased by measuring over multiple consecutive days (Hellhammer et al., 2007). The large sample size of this study may

however at least partly account for this.

5. Conclusion

Overall this study provides no indications that biological parameters improve the predictive ability in addition to clinical parameters. This shows that it remains difficult to predict the course of anxiety disorders. As insight into the likely course would help tailoring treatment towards the individual patient needs, further research is warranted.

Author statement

RCB contributed to the design of this study, conducted the statistical analysis and interpretation of the data, as well as the writing of the manuscript. AJLMvB and NMB contributed to the design of this study, interpretation of the data, and reviewed and edited the manuscript. DR was involved in the design of this study, provided support with the statistical analysis, and reviewed and edited the manuscript. AMvH, RAS, and BWJHP reviewed and edited the manuscript. All authors contributed to and approved of the manuscript.

Ethical statement

The research protocol was approved by the Ethics Committee of the participating universities and written informed consent was obtained

Table 2
Results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

Model 1: corrected for sex and age				Model 2: corrected for anxiety severity and duration, and disability				
Class 1 (reference): Mild severity, non-chronic n = 378 (41.7%)	Class 2: Moderate severity, chronic n = 390 (43.0%) OR (95%CI)	C-statistic	P	Class 3: Severe, chronic n = 139 (15.3) OR (95%CI)	C-statistic	P	C-statistic	P
Without biological parameters								
Model 1								
Age	0.99 (0.98–1.01)	0.54	0.282	1 (0.98–1.02)	0.52	0.874		
Gender	1.21 (0.89–1.64)		0.216	0.87 (0.58–1.3)	0.491			
Model 2								
Total score BAI							0.64	0.80
Total score FQ					1.04 (0.86–1.26)	0.681	1.32 (1.03–1.70)	0.031
Anxiety symptoms in months 5 years prior baseline					1.33 (1.10–1.61)	0.003	1.49 (1.15–1.94)	0.003
Avoidance symptoms in months 5 years prior baseline					1.24 (1.06–1.45)	0.008	1.59 (1.26–2.00)	< 0.001
Functioning					1.17 (0.99–1.38)	0.060	1.24 (0.98–1.56)	0.073
					1.10 (0.90–1.34)	0.368	1.64 (1.25–2.17)	< 0.001
Metabolic syndrome								
Metabolic syndrome % yes	0.82 (0.58–1.17)	0.54	0.278	0.91 (0.56–1.47)	0.52	0.695	0.88 (0.62–1.26)	0.64
Metabolic syndrome components								
Triglycerides (mmol/l) ^a	0.97 (0.83–1.14)	0.54	0.738	1.05 (0.87–1.26)	0.52	0.613	0.94 (0.80–1.12)	0.64
HDL cholesterol (mmol/l) ^a	1.00 (0.86–1.16)	0.54	0.984	0.77 (0.62–0.96)	0.57	0.021	1.03 (0.89–1.19)	0.64
Fasting plasma glucose (mmol/l) ^a	1.03 (0.89–1.20)	0.54	0.657	0.92 (0.73–1.16)	0.54	0.483	1.00 (0.86–1.15)	0.64
Waist circumference (cm) ^a	0.96 (0.82–1.13)	0.54	0.604	1.13 (0.92–1.40)	0.53	0.258	0.90 (0.77–1.05)	0.64
Systolic blood pressure (mmHg) ^a	1.08 (0.92–1.28)	0.54	0.343	0.99 (0.78–1.24)	0.51	0.912	1.00 (0.86–1.16)	0.64
Diastolic blood pressure (mmHg) ^a	1.18 (1.01–1.38)	0.55	0.037	1.11 (0.90–1.38)	0.54	0.331	1.08 (0.93–1.25)	0.64
Cortisol measures								
Area Under the Curve with respect to Ground ^a	1.02 (0.85–1.22)	0.54	0.859	0.79 (0.61–1.03)	0.57	0.079	1.03 (0.85–1.24)	0.65
Area Under the Curve with respect to Increase ^a	1.00 (0.84–1.20)	0.54	0.989	0.85 (0.66–1.09)	0.56	0.192	0.98 (0.81–1.18)	0.65
Evening cortisol ^a	1.02 (0.85–1.19)	0.54	0.950	0.92 (0.72–1.18)	0.52	0.499	0.98 (0.82–1.16)	0.65
Dexamethasone suppression test ^a	0.95 (0.80–0.13)	0.55	0.548	0.87 (0.66–1.14)	0.55	0.301	0.97 (0.80–1.16)	0.65
Inflammation markers								
TNF-α (pg/ml) ^a	0.96 (0.83–1.12)	0.54	0.623	1.09 (0.92–1.29)	0.55	0.306	0.92 (0.78–1.07)	0.64
CRP (mg/l) ^a	1.04 (0.90–1.21)	0.54	0.615	1.08 (0.90–1.31)	0.53	0.398	1.04 (0.90–1.21)	0.64
IL-6 (pg/ml) ^a	1.03 (0.88–1.21)	0.54	0.741	1.10 (0.92–1.30)	0.53	0.310	1.03 (0.88–1.20)	0.64
BDNF								
BDNF (ng/ml) ^a	1.09 (0.94–1.27)	0.55	0.234	1.16 (0.95–1.41)	0.56	0.140	1.04 (0.89–1.21)	0.64
								0.80
								0.563

Abbreviations: BAI: Beck's Anxiety Inventory; FQ: Fear Questionnaire; HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor. Numbers presented in bold are significant at p = 0.05.

^a Reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for IL-6 = 2.88; SD for BDNF = 3.63.

from all participants.

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Declaration of Competing Interest

Declarations of interest: BP has received (non-related) research funding from Jansen Research and Boehringer Ingelheim. The other authors have nothing to declare.

Appendix 1. Respondents versus non-respondents at two years follow-up

Baseline characteristics of respondents versus non-respondents at two years follow-up.

	Respondents (n = 907)	Non-respondents (n = 195)	N _{total}	Statistic df = 1	P
<i>Sociodemographic variables</i>					
Gender % female	66.6	70.3	1102	X = 0.98	0.355
Age in years	42.11	40.51	1102	F = 2.70	0.099
North European descent (% yes)	93.7	90.8	1102	X = 2.20	0.157
Education in years	11.68	11.01	1102	F = 6.96	0.008
Smoking % yes	42.9	61.5	1102	X = 22.46	< 0.001
Alcohol use	4.95	4.64	1085	F = 0.52	0.472
Number of chronic disease	1.04	1.02	1102	F = 0.05	0.82
<i>Psychopathology</i>					
Depressive disorder % yes					
MDD	54.2	68.7	1102	X = 13.70	< 0.001
Dysthymia	19.2	27.2	1102	X = 6.27	0.015
Anxiety severity					
BAI mean (SD)	19.01 (10.67)	21.76 (11.92)	1087	F = 9.91	0.002
FQ mean (SD)	36.91 (20.09)	39.90 (23.46)	1087	F = 3.21	0.072
<i>Metabolic syndrome</i>					
Metabolic syndrome, % yes	23.0	21.7	1080	X = 0.15	0.775
<i>Metabolic syndrome components</i>					
Triglycerides (mmol/l)	1.34 (0.91)	1.28 (0.74)	1078	H = 0.27	0.601
HDL cholesterol (mmol/l)	1.62 (0.44)	1.56 (0.41)	1080	F = 2.92	0.088
Fasting plasma glucose (mmol/l)	5.23 (1.03)	5.21 (0.81)	1082	H = 0.24	0.623
Waist circumference (cm)	89.78 (14.93)	88.83 (15.21)	1102	F = 0.65	0.419
Systolic blood pressure (mmHg)	136.57 (19.44)	136.00 (19.95)	1098	F = 0.13	0.714
Diastolic blood pressure (mmHg)	82.46 (11.13)	82.10 (12.08)	1098	F = 0.17	0.684
<i>Cortisol measures</i>					
Area Under the Curve with respect to Ground	19.43 (7.13)	19.84 (8.84)	641	F = 0.19	0.663
Area Under the Curve with respect to Increase	2.69 (6.55)	1.16 (6.11)	641	F = 3.35	0.068
Evening cortisol	5.43 (3.37)	5.74 (3.61)	690	H = 1.27	0.259
Dexamethasone suppression test	2.73 (1.73)	3.14 (2.50)	659	H = 3.29	0.070
<i>Inflammation markers</i>					
TNF-α (pg/ml)	1.03 (1.10)	1.34 (2.26)	1080	H = 0.01	0.933
CRP (mg/l)	3.18 (5.83)	3.17 (5.16)	1086	H = 0.33	0.566
IL-6 (pg/ml)	1.34 (2.88)	4.90 (50.45)	1085	H = 0.24	0.624
<i>BDNF</i>					
BDNF (ng/ml)	9.32 (3.63)	8.80 (3.33)	1071	F = 3.34	0.068

Abbreviations: F = one way ANOVA; X = chi square; MDD = Major Depressive Disorder; BAI = Beck's Anxiety Inventory; FQ = Fear Questionnaire; HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor.

Appendix 2. Baseline characteristics and multinomial logistic regression analysis per disorder

Panic disorders with agoraphobia (6 months diagnosis) baseline characteristics and results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

	Baseline characteristics				Model 1: corrected for sex and age				Model 2: corrected for anxiety severity and duration, and disability			
	Mild se- verity M (SD) N = 94	Moderate se- verity, chronic M (SD) N = 151	Severe, chronic M (SD) N = 30	Statistics df = 2	P	Class 2: Moderate severity, chronic OR (95%CI)	C-sta- tistic	P	Class 2: Moderate severity, chronic OR (95%CI)	C-sta- tistic	P	Class 3: Severe, chronic OR (95%CI)
<i>Without biological parameters</i>												
<i>Metabolic syndrome</i>												
Metabolic syndrome, % yes (n)	22.0 (20)	25.7 (38)	30.5 (18)	X = 1.38	0.503	0.79 (0.41–1.50)	0.58	0.466	0.72 (0.34–1.56)	0.60	0.408	0.84 (0.44–1.59)
<i>Metabolic syndrome components</i>												
Triglycerides (mmol/l) ^a	1.22 (0.69)	1.41 (0.88)	1.54 (1.00)	H = 4.50	0.106	1.45 (1.02–2.06)	0.59	0.039	1.52 (1.02–2.26)	0.63	0.038	1.27 (0.91–1.77)
HDL cholesterol (mmol/l) ^a	1.61 (0.42)	1.59 (0.44)	1.43 (0.40)	F = 3.77	0.024	0.89 (0.67–1.17)	0.56	0.400	0.59 (0.40–0.87)	0.65	0.007	0.97 (0.73–1.29)
Fasting plasma glucose (mmol/l) ^a	5.19 (0.87)	5.22 (0.86)	5.21 (0.81)	H = 0.09	0.957	1.06 (0.74–1.50)	0.58	0.760	0.92 (0.59–1.43)	0.58	0.710	1.08 (0.76–1.53)
Waist circumference (cm) ^a	89.18 (13.83)	89.72 (14.58)	94.00 (14.77)	F = 2.36	0.097	1.13 (0.83–1.53)	0.56	0.431	1.40 (0.97–2.02)	0.61	0.076	1.02 (0.76–1.35)
Systolic blood pressure (mmHg) ^a	139.84 (19.76)	135.56 (15.56)	135.84 (17.1)	F = 1.92	0.148	0.72 (0.51–1.01)	0.57	0.056	0.62 (0.40–0.95)	0.61	0.030	0.75 (0.55–1.01)
Diastolic blood pressure (mmHg) ^a	83.84 (12.19)	82.97 (8.85)	82.9 (9.95)	F = 0.25	0.780	0.92 (0.68–1.25)	0.55	0.591	0.81 (0.55–1.20)	0.60	0.300	0.91 (0.68–1.21)
<i>Cortisol measures</i>												
Area Under the Curve with respect to Gro- und ^a	19.92 (7.52)	20.15 (7.09)	18.59 (6.38)	F = 0.69	0.503	0.99 (0.71–1.39)	0.58	0.965	0.80 (0.51–1.23)	0.55	0.307	1.13 (0.79–1.62)
Area Under the Curve with respect to Incr- ease ^a	3.67 (7.41)	3.57 (6.55)	2.86 (6.87)	F = 0.19	0.830	0.96 (0.70–1.31)	0.58	0.779	0.89 (0.61–1.31)	0.54	0.562	1.03 (0.73–1.45)
Evening cortisol ^a	5.38 (2.61)	5.93 (4.01)	5.72 (2.64)	H = 0.57	0.754	1.16 (0.83–1.63)	0.61	0.377	1.12 (0.75–1.69)	0.55	0.584	1.21 (0.86–1.72)
Dexamethasone suppres- sion test ^a	2.70 (1.05)	2.72 (2.33)	2.34 (0.98)	H = 3.50	0.174	1.07 (0.79–1.45)	0.60	0.645	0.71 (0.40–1.28)	0.62	0.258	0.94 (0.69–1.29)
<i>Inflammation markers</i>												
TNF-α (pg/ml) ^a	1.04 (1.47)	1.00 (1.13)	1.26 (1.35)	1.58	0.454	0.94 (0.73–1.22)	0.56	0.651	1.1 (0.86–1.41)	0.58	0.439	0.91 (0.71–1.18)
CRP (mg/l) ^a	3.07 (6.21)	3.77 (7.62)	3.24 (4.15)	H = 1.72	0.423	1.09 (0.84–1.4)	0.57	0.533	1.03 (0.74–1.45)	0.56	0.849	1.10 (0.87–1.39)
IL-6 (pg/ml) ^a	1.04 (1.12)	1.36 (2.21)	2.15 (6.17)	H = 10.64	0.005	1.44 (0.78–2.66)	0.58	0.244	1.65 (0.88–3.09)	0.61	0.116	1.47 (0.79–2.72)

BDNF
BDNF (ng/ml)^a 9.28 (3.88) 9.25 (3.57) 9.55 (3.47) F = 0.15 0.861 0.99 (0.76–1.29) 0.55 0.940 1.06 (0.77–1.47) 0.56 0.729 0.97 (0.74–1.27) 0.61 0.823 1.06 (0.74–1.53) 0.82 0.750

Abbreviations: HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.
^a For Model 1 and Model 2 reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for Waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for CRP = 5.83; SD for IL-6 = 2.88; SD for BDNF = 3.63.

Panic disorders without agoraphobia (6 months diagnosis) baseline characteristics and results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

	Baseline characteristics			Model 1: corrected for sex and age				Model 2: corrected for anxiety severity and duration, and disability			
	Mild severity M (SD) N = 72	Moderate severity, chronic M (SD) N = 63	Severe, chronic M (SD) N = 18	Statistics df = 2	P	Class 2: Moderate severity, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic	P
Without biological variables											
Metabolic syndrome											
Metabolic syndrome, % yes (n)	21.1 (15)	27.4 (17)	33.3 (6)	X = 1.42	0.492	0.57 (0.24–1.34)	0.57	0.196	0.39 (0.11–1.31)	0.62	0.127
Metabolic syndrome components											
Triglycerides (mmol/l) ^a	1.51 (1.66)	1.19 (0.52)	1.35 (0.72)	H = 0.78	0.676	0.74 (0.46–1.19)	0.54	0.214	0.97 (0.65–1.44)	0.60	0.884
HDL cholesterol (mmol/l) ^a	1.58 (0.44)	1.59 (0.43)	1.45 (0.36)	F = 0.77	0.466	0.97 (0.67–1.4)	0.56	0.858	0.67 (0.36–1.24)	0.65	0.200
Fasting plasma glucose (mmol/l) ^a	5.01 (0.68)	5.13 (0.81)	5.04 (0.8)	H = 0.18	0.914	1.57 (0.91–2.72)	0.60	0.105	1.4 (0.61–3.22)	0.61	0.430
Waist circumference (cm) ^a	90.07 (14.37)	89 (15.62)	96.06 (22.53)	F = 1.38	0.255	1.03 (0.72–1.48)	0.56	0.871	1.6 (1–2.57)	0.65	0.051
Systolic blood pressure (mmHg) ^a	135.19 (18.16)	136.32 (22.75)	130.97 (14.01)	F = 0.49	0.616	1.24 (0.84–1.83)	0.57	0.268	0.88 (0.43–1.78)	0.62	0.717
Diastolic blood pressure (mmHg) ^a	81.07 (11.69)	82.38 (13.12)	80.32 (9.74)	F = 0.29	0.478	1.25 (0.88–1.77)	0.58	0.222	1.12 (0.63–1.97)	0.61	0.701
Cortisol measures											
Area Under the Curve with respect to Ground ^a	19.68 (7.94)	20.45 (8.24)	17.38 (5.08)	F = 0.51	0.602	1.13 (0.75–1.7)	0.59	0.599	0.74 (0.33–1.65)	0.62	0.464
Area Under the Curve with respect to Increase ^a	1.63 (6.00)	2.41 (5.78)	2.16 (5.00)	F = 0.19	0.832	1.19 (0.72–1.98)	0.57	0.505	1.14 (0.48–2.68)	0.60	0.768
Evening cortisol ^a	6.25 (4.93)	5.25 (2.24)	6.37 (2.80)	H = 1.39	0.499	0.78 (0.51–1.21)	0.55	0.271	1.07 (0.61–1.85)	0.59	0.824
Dexamethasone suppression test ^a	3.05 (2.01)	2.67 (1.13)	2.03 (1.03)	H = 3.36	0.186	0.77 (0.47–1.26)	0.58	0.293	0.32 (0.08–1.23)	0.70	0.096
Inflammation markers											
TNF-α (pg/ml) ^a	1.22 (1.61)	0.95 (0.69)	1.22 (0.84)	H = 1.78	0.411	0.76 (0.49–1.17)	0.57	0.214	0.99 (0.67–1.45)	0.62	0.956
CRP (mg/l) ^a	3.21 (5.51)	3.18 (7.40)	4.09 (7.07)	H = 0.20	0.905	1.02 (0.73–1.41)	0.57	0.925	1.14 (0.76–1.71)	0.59	0.514

IL-6 (pg/ml) ^a	1.98 (6.23)	1.13 (1.14)	1.10 (0.93)	H = 0.08	0.957	0.79 (0.43–1.44)	0.57	0.433	0.76 (0.25–2.31)	0.62	0.624	0.82 (0.54–1.24)	0.69	0.356	0.81 (0.18–3.68)	0.91	0.805
BDNF																	
BDNF (ng/ml) ^a	8.32 (2.87)	9.84 (3.66)	9.32 (2.93)	F = 3.59	0.030	1.76 (1.16–2.68)	0.63	0.008	1.48 (0.81–2.7)	0.66	0.204	1.94 (1.20–3.14)	0.74	0.007	1.18 (0.54–2.61)	0.91	0.678

Abbreviations: HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.

^a For Model 1 and Model 2 reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for Waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for CRP = 5.83; SD for IL-6 = 2.88; SD for BDNF = 3.63.

Agoraphobia (6 months diagnosis) baseline characteristics and results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

Baseline characteristics				Model 1: corrected for sex and age				Model 2: corrected for anxiety severity and duration, and disability									
Mild severity M (SD) N = 71	Moderate severity, chronic M (SD) N = 52	Severe, chronic M (SD) N = 19	Statistics df = 2	P	Class 2: Moderate severity, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic	P				
Without biological variables														0.60	0.79		
Metabolic syndrome																	
Metabolic syndrome, % yes (n)	29.6 (21)	20.0 (10)	X = 1.96	0.375	1.7 (0.69–4.18)	0.56	0.245	2.25 (0.54–9.27)	0.72	0.263	1.78 (0.74–4.31)	0.62	0.200	2.03 (0.45–9.03)	0.82	0.355	
Metabolic syndrome components																	
Triglycerides (mmol/l) ^a	1.51 (0.89)	1.35 (0.95)	1.58 (0.89)	H = 3.32	0.190	0.83 (0.55–1.24)	0.59	0.355	0.93 (0.54–1.6)	0.72	0.782	0.79 (0.53–1.18)	0.62	0.253	0.99 (0.57–1.73)	0.81	0.984
HDL cholesterol (mmol/l) ^a	1.61 (0.44)	1.76 (0.53)	1.49 (0.31)	F = 2.82	0.063	1.38 (0.95–2.01)	0.60	0.090	0.99 (0.52–1.86)	0.72	0.968	1.42 (0.98–2.06)	0.63	0.061	0.8 (0.43–1.52)	0.82	0.500
Fasting plasma glucose (mmol/l) ^a	5.55 (1.34)	5.51 (1.65)	5.15 (0.89)	H = 1.40	0.497	0.99 (0.75–1.31)	0.52	0.962	0.6 (0.28–1.28)	0.75	0.190	0.95 (0.73–1.25)	0.61	0.712	0.68 (0.36–1.27)	0.81	0.228
Waist circumference (cm) ^a	92.65 (14.48)	90.00 (17.00)	92.84 (12.13)	F = 0.52	0.597	0.85 (0.57–1.26)	0.56	0.426	0.85 (0.45–1.6)	0.65	0.622	0.79 (0.55–1.15)	0.62	0.226	1.01 (0.58–1.76)	0.79	0.967
Systolic blood pressure (mmHg) ^a	137.57 (21.42)	140.59 (18.39)	140.24 (19.03)	F = 0.38	0.685	1.31 (0.87–1.99)	0.56	0.197	0.95 (0.52–1.74)	0.65	0.872	1.16 (0.81–1.66)	0.62	0.431	1.24 (0.71–2.16)	0.79	0.442
Diastolic blood pressure (mmHg) ^a	82.13 (11.72)	84.76 (11.27)	84.50 (13.83)	F = 0.83	0.439	1.35 (0.93–1.97)	0.58	0.119	1.12 (0.66–1.92)	0.66	0.670	1.23 (0.86–1.75)	0.63	0.253	1.36 (0.8–2.3)	0.80	0.256
Cortisol measures																	
Area Under the Curve with respect to Ground ^a	20.18 (8.24)	18.73 (7.64)	15.63 (3.64)	F = 2.05	0.135	0.84 (0.55–1.3)	0.56	0.440	0.48 (0.23–1)	0.75	0.051	0.76 (0.48–1.2)	0.68	0.235	0.41 (0.18–0.93)	0.80	0.034
Area Under the Curve with respect to Increase ^a	2.72 (6.77)	1.97 (5.84)	−1.88 (6.43)	F = 2.94	0.058	0.87 (0.55–1.38)	0.57	0.548	0.39 (0.18–0.86)	0.74	0.020	0.78 (0.47–1.29)	0.66	0.338	0.27 (0.11–0.7)	0.85	0.007
Evening cortisol ^a	5.02 (2.28)	5.59 (4.16)	3.93 (1.31)	H = 3.16	0.207	1.25 (0.75–2.07)	0.58	0.399	0.38 (0.12–1.2)	0.72	0.099	1.21 (0.73–1.98)	0.66	0.458	0.41 (0.12–1.42)	0.80	0.160
Dexamethasone suppression test ^a	3.06 (2.24)	2.91 (1.86)	2.81 (1.61)	H = 0.33	0.849	0.93 (0.63–1.37)	0.57	0.702	0.93 (0.52–1.65)	0.61	0.799	0.95 (0.64–1.43)	0.65	0.814	0.95 (0.49–1.86)	0.77	0.892

<i>Inflammation markers</i>	TNF-α (pg/ml) ^a	1.06 (1.23)	0.92 (0.51)	0.73 (0.20)	H = 1.18	0.554	0.82 (0.5–1.34)	0.50	0.431	0.23 (0.03–1.6)	0.72	0.138	0.84 (0.5–1.42)	0.61	0.506	0.16 (0.02–1.25)	0.82	0.081
	CRP (mg/l) ^a	3.80 (7.12)	3.31 (4.54)	3.15 (4.28)	H = 0.18	0.914	0.92 (0.64–1.33)	0.51	0.669	0.9 (0.51–1.59)	0.67	0.713	0.88 (0.61–1.27)	0.63	0.503	0.82 (0.43–1.57)	0.78	0.549
	IL-6 (pg/ml) ^a	1.14 (1.12)	1.11 (0.99)	1.30 (0.89)	H = 1.13	0.569	0.92 (0.33–2.58)	0.54	0.869	1.54 (0.42–5.64)	0.69	0.516	0.89 (0.3–2.64)	0.61	0.837	1.62 (0.41–6.39)	0.78	0.490
	BDNF																	
BDNF (ng/ml) ^a		9.52 (4.74)	9.84 (3.95)	10.00 (2.94)	F = 0.13	0.880	1.07 (0.79–1.46)	0.57	0.656	1.13 (0.69–1.83)	0.69	0.633	1.08 (0.78–1.49)	0.62	0.632	1.04 (0.65–1.67)	0.77	0.868

Abbreviations: HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.

^a For Model 1 and Model 2 reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for Waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for CRP = 5.83; SD for IL-6 = 2.88; SD for BDNF = 3.63.

Social phobia (6 months diagnosis) baseline characteristics and results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

Baseline characteristics				Model 1: corrected for sex and age				Model 2: corrected for anxiety severity and duration, and disability									
	Mild severity M (SD) N = 170	Moderate severity, chronic M (SD) N = 234	Severe, chronic M (SD) N = 89	Statistics df = 2	P	Class 2: Moderate severity, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic	P			
Without biological variables																	
Metabolic syndrome																	
Metabolic syndrome, % yes (n)	18.5 (31)	24.1 (55)	23.0 (20)	X = 1.88	0.390	0.70 (0.42–1.16)	0.53	0.161	0.82 (0.43–1.57)	0.56	0.548	0.68 (0.41–1.12)	0.62	0.132	0.881 (0.436–1.778)	0.78	0.723
Metabolic syndrome components																	
Triglycerides (mmol/l) ^a	1.21 (0.77)	1.30 (0.81)	1.41 (0.88)	H = 2.94	0.230	1.17 (0.91–1.52)	0.54	0.220	1.26 (0.94–1.71)	0.58	0.126	1.10 (0.86–1.41)	0.61	0.439	1.12 (0.82–1.53)	0.78	0.474
HDL cholesterol (mmol/l) ^a	1.67 (0.38)	1.66 (0.51)	1.53 (0.40)	F = 3.13	0.045	0.95 (0.78–1.16)	0.52	0.608	0.72 (0.54–0.95)	0.61	0.021	0.95 (0.78–1.17)	0.61	0.641	0.82 (0.62–1.09)	0.79	0.173
Fasting plasma glucose (mmol/l) ^a	5.09 (0.77)	5.21 (1.07)	5.18 (0.89)	H = 0.53	0.768	1.18 (0.92–1.51)	0.53	0.183	1.07 (0.78–1.47)	0.56	0.680	1.16 (0.92–1.47)	0.62	0.208	1.12 (0.81–1.56)	0.79	0.494
Waist circumference (cm) ^a	88.43 (14.06)	88.46 (15.34)	91.33 (15.18)	F = 1.36	0.258	1.02 (0.82–1.27)	0.51	0.863	1.15 (0.87–1.52)	0.56	0.315	0.98 (0.80–1.21)	0.61	0.876	1.04 (0.79–1.37)	0.78	0.792
Systolic blood pressure (mmHg) ^a	134.45 (18.75)	136.86 (19.3)	136.28 (20.16)	F = 0.78	0.457	1.20 (0.95–1.52)	0.54	0.126	1.03 (0.75–1.40)	0.54	0.871	1.11 (0.9–1.36)	0.61	0.324	1.06 (0.79–1.43)	0.78	0.678
Diastolic blood pressure (mmHg) ^a	80.86 (10.47)	83.11 (11.1)	82.36 (11.03)	F = 2.12	0.121	1.31 (1.04–1.65)	0.57	0.021	1.10 (0.82–1.48)	0.54	0.520	1.20 (0.97–1.48)	0.62	0.089	1.08 (0.80–1.45)	0.78	0.613
Cortisol measures																	
Area Under the Curve with respect to Ground ^d	19.79 (7.16)	19.81 (7.13)	18.40 (5.80)	F = 0.98	0.377	1.00 (0.78–1.28)	0.53	0.993	0.80 (0.56–1.13)	0.56	0.197	1.06 (0.81–1.37)	0.63	0.688	0.87 (0.59–1.28)	0.81	0.475
Area Under the Curve with respect to Increase ^e	3.23 (7.04)	2.69 (6.46)	2.05 (6.60)	F = 0.62	0.541	0.92 (0.72–1.17)	0.53	0.489	0.84 (0.61–1.16)	0.55	0.289	0.91 (0.71–1.17)	0.63	0.446	0.80 (0.56–1.14)	0.81	0.210

Evening cortisol ^a	5.24 (3.11)	5.55 (4.16)	5.18 (2.33)	H = 0.47	0.793	1.08 (0.86–1.36)	0.55	0.485	0.97 (0.71–1.33)	0.52	0.862	1.08 (0.86–1.37)	0.62	0.492	0.93 (0.65–1.32)	0.80	0.670
Dexamethasone suppression test ^a	2.82 (1.55)	2.87 (2.01)	2.41 (1.62)	H = 6.72	0.035	1.03 (0.82–1.29)	0.54	0.795	0.71 (0.46–1.09)	0.61	0.120	1.04 (0.81–1.33)	0.62	0.761	0.72 (0.45–1.15)	0.80	0.172
<i>Inflammation markers</i>																	
TNF-α (pg/ml) ^a	1.03 (1.35)	1.03 (1.14)	1.28 (1.26)	H = 5.54	0.063	1.11 (0.82–1.22)	0.51	0.998	1.16 (0.94–1.43)	0.59	0.155	0.99 (0.80–1.22)	0.61	0.900	1.05 (0.82–1.33)	0.78	0.710
CRP (mg/l) ^a	2.28 (3.90)	2.99 (4.38)	3.10 (5.76)	H = 3.83	0.148	1.28 (0.94–1.74)	0.55	0.118	1.34 (0.93–1.93)	0.57	0.111	1.26 (0.93–1.71)	0.62	0.141	1.25 (0.85–1.83)	0.78	0.255
IL-6 (pg/ml) ^a	0.98 (0.92)	1.33 (2.38)	1.21 (1.12)	H = 6.94	0.031	1.81 (1.00–3.25)	0.55	0.049	1.61 (0.83–3.1)	0.58	0.157	1.69 (0.92–3.12)	0.62	0.091	1.44 (0.70–2.96)	0.78	0.328
BDNF																	
BDNF (ng/ml) ^a	8.95 (3.64)	9.28 (3.66)	9.50 (3.37)	F = 0.77	0.464	1.11 (0.9–1.37)	0.54	0.315	1.15 (0.89–1.5)	0.56	0.285	1.06 (0.86–1.31)	0.62	0.598	1.05 (0.79–1.40)	0.78	0.711

Abbreviations: HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.

^a For Model 1 and Model 2 reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for Waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for CRP = 5.83; SD for IL-6 = 2.88; SD for BDNF = 3.63.

Generalised Anxiety Disorder (6 months diagnosis) baseline characteristics and results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

	Baseline characteristics			Model 1: corrected for sex and age					Model 2: corrected for anxiety severity and duration, and disability				
	Mild severity M (SD) N = 134	Moderate severity, chronic M (SD) N = 137	Severe, chronic M (SD) N = 63	Statistics df = 2	P	Class 2: Moderate severity, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic	P	Class 3: Severe, chronic OR (95%CI)	C-statistic
<i>Without biological variables</i>													
<i>Metabolic syndrome</i>													
Metabolic syndrome. % yes (n)	20.1 (27)	28.9 (39)	25.8 (16)	X = 2.80	0.247	0.63 (0.35–1.13)	0.57	0.123	0.73 (0.35–1.51)	0.55	0.397	0.58 (0.32–1.06)	0.68
<i>Metabolic syndrome components</i>													
Triglycerides (mmol/l) ^a	1.44 (1.32)	1.41 (0.88)	1.44 (0.81)	H = 0.21	0.901	0.97 (0.78–1.20)	0.54	0.758	0.99 (0.77–1.29)	0.51	0.958	1.09 (0.82–1.45)	0.68
HDL cholesterol (mmol/l) ^a	1.61 (0.44)	1.61 (0.53)	1.53 (0.44)	F = 0.67	0.514	0.98 (0.77–1.24)	0.54	0.859	0.84 (0.61–1.14)	0.56	0.261	0.99 (0.78–1.26)	0.68
Fasting plasma glucose (mmol/l) ^a	5.33 (1.27)	5.35 (1.32)	5.20 (0.94)	H = 0.25	0.884	1.00 (0.82–1.22)	0.54	0.995	0.89 (0.65–1.21)	0.53	0.455	1.02 (0.83–1.25)	0.68
Waist circumference (cm) ^a	89.84 (14.00)	92.15 (16.56)	91.65 (15.67)	F = 0.80	0.450	1.17 (0.91–1.51)	0.56	0.216	1.13 (0.82–1.55)	0.53	0.460	1.19 (0.93–1.53)	0.68
Systolic blood pressure (mmHg) ^a	134.17 (18.36)	137.62 (18.63)	136.52 (18.11)	F = 1.22	0.298	1.25 (0.93–1.69)	0.57	0.139	1.20 (0.82–1.74)	0.53	0.347	1.20 (0.92–1.56)	0.68
Diastolic blood pressure (mmHg) ^a	80.78 (11.03)	82.75 (10.52)	83.63 (10.64)	F = 1.90	0.151	1.21 (0.92–1.60)	0.56	0.167	1.38 (0.98–1.94)	0.59	0.063	1.17 (0.90–1.52)	0.68

<i>Cortisol measures</i>	Area Under the Curve with respect to Gro-und ^a	19.68 (7.69)	20.9 (8.25)	17.94 (6.12)	F = 1.97	0.143	1.13 (0.85–1.52)	0.56	0.400 (0.52–1.17)	0.78	0.59	0.228	1.18 (0.87–1.59)	0.69	0.281 (0.52–1.28)	0.82	0.84	0.378
	Area Under the Curve with respect to Incr-ease ^a	2.64 (6.89)	2.54 (7.54)	1.67 (6.81)	F = 0.26	0.776	0.99 (0.74–1.31)	0.56	0.926 (0.61–1.3)	0.89	0.58	0.547	0.99 (0.74–1.34)	0.68	0.993 (0.56–1.32)	0.86	0.84	0.862
<i>Evening cortisol^a</i>		5.39 (3.60)	5.01 (2.53)	5.31 (2.30)	H = 1.16	0.561	0.83 (0.57–1.21)	0.57	0.331 (0.65–1.46)	0.97	0.52	0.890	0.82 (0.56–1.20)	0.68	0.821 (0.49–1.34)	0.81	0.83	0.812
	Dexamethasone suppres-sion test ^a	3.00 (1.77)	2.87 (1.62)	2.75 (2.01)	H = 3.05	0.218	0.93 (0.68–1.26)	0.57	0.644 (0.58–1.29)	0.87	0.57	0.490	0.96 (0.69–1.33)	0.67	0.813 (0.60–1.46)	0.94	0.82	0.778
<i>Inflammation markers</i>		1.10 (1.47)	1.11 (0.72)	1.09 (1.12)	H = 8.22	0.016	1.01 (0.80–1.27)	0.54	0.963 (0.73–1.32)	0.99	0.50	0.922	0.95 (0.75–1.21)	0.68	0.672 (0.58–1.21)	0.84	0.82	0.348
	CRP (mg/l) ^a	2.82 (4.32)	3.65 (6.64)	3.44 (5.06)	H = 2.54	0.280	1.20 (0.9–1.59)	0.56	0.222 (0.82–1.64)	1.16	0.55	0.392	1.22 (0.89–1.68)	0.68	0.211 (0.77–1.65)	1.13	0.82	0.539
<i>IL-6 (pg/ml)^a</i>		1.31 (1.77)	1.40 (1.89)	1.34 (1.34)	H = 2.43	0.297	1.09 (0.73–1.63)	0.55	0.678 (0.62–1.73)	1.04	0.52	0.894	1.09 (0.72–1.66)	0.68	0.674 (0.51–1.71)	0.93	0.82	0.820
	BDNF																	
<i>BDNF (ng/ml)^a</i>		9.09 (3.56)	9.05 (3.54)	9.60 (2.97)	F = 0.60	0.552	0.98 (0.75–1.27)	0.53	0.865 (0.85–1.59)	1.16	0.57	0.352	0.91 (0.69–1.19)	0.68	0.499 (0.74–1.49)	1.05	0.82	0.798

Abbreviations: HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.

^a For Model 1 and Model 2 reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for Waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for CRP = 5.83; SD for IL-6 = 2.88; SD for BDNF = 3.63.

Appendix 3. Baseline characteristics and multinomial logistic regression analysis for the subgroup with comorbid major depressive disorder

Subgroup with comorbid 6-months diagnosis of major depressive disorder baseline characteristics and results of multinomial logistic regression analysis associating baseline biological parameters with LCGA derived two-year anxiety course trajectories with metabolic syndrome and its components, cortisol measures, inflammation markers, and brain derived neurotrophic factor. Reference group: mild severity class 1.

	Baseline characteristics			Model 1: corrected for sex and age				Model 2: corrected for anxiety severity and duration, and disability			
	Mild se-verity M (SD) N = 190	Moderate se-verity, chronic M (SD) N = 206	Severe, chronic M (SD) N = 96	Statistics df = 2	P	Class 2: Moderate severity, chronic OR (95%CI)	C-sta-tistic	P	Class 3: Severe, chronic OR (95%CI)	C-sta-tistic	P
<i>Without biological para-meters</i>											
							0.52			0.72	0.85
<i>Metabolic syndrome</i>											
Metabolic syndrome, % yes (n)	21.4 (n = 40)	25.5 (n = 51)	24.5 (n = 23)	X = 0.941	0.625	0.84 (0.52–1.37)	0.55	0.492 (0.51–1.73)	0.854 (0.52–1.93)	0.417	0.999
<i>Metabolic syndrome components</i>											
Triglycerides (mmol/l) ^a	1.42 (1.26)	1.30 (0.76)	1.38 (0.76)	H = 0.401	0.818	0.87 (0.71–1.07)	0.53	0.191 (0.72–1.15)	0.428 (0.61–1.14)	0.260	0.259
HDL cholesterol (mmol/l) ^a	1.62 (0.41)	1.66 (0.50)	1.49 (0.40)	F = 4.40	0.013	1.07 (0.88–1.31)	0.53	0.511 (0.58–1)	0.054 (0.69–1.24)	0.220	0.603
Fasting plasma glucose (mmol/l) ^a	5.19 (1.09)	5.29 (1.22)	5.25 (0.92)	H = 1.57	0.456	1.07 (0.88–1.30)	0.54	0.506 (0.79–1.30)	0.936 (0.80–1.34)	0.445	0.778

Waist circumference (cm) ^a	90.22 (14.04)	89.95 (15.42)	93.21 (16.43)	F = 1.66	0.191	0.95 (0.77–1.17)	0.52	0.650	1.12 (0.87–1.44)	0.55	0.383	0.96 (0.78–1.18)	0.72	0.722	1.05 (0.80–1.37)	0.85	0.733
Systolic blood pressure (mmHg) ^a	135.65 (19.24)	136.93 (18.89)	137.62 (19.47)	F = 0.40	0.673	1.03 (0.82–1.30)	0.53	0.806	0.99 (0.74–1.33)	0.53	0.962	1.06 (0.86–1.31)	0.72	0.608	1.09 (0.83–1.44)	0.85	0.547
Diastolic blood pressure (mmHg) ^a	81.42 (10.98)	82.85 (10.72)	83.12 (10.61)	F = 1.16	0.314	1.12 (0.90–1.41)	0.54	0.311	1.11 (0.84–1.47)	0.56	0.475	1.14 (0.92–1.41)	0.72	0.233	1.18 (0.89–1.58)	0.85	0.250
<i>Cortisol measures</i>																	
Area Under the Curve with respect to Ground ^a	20.17 (8.26)	19.81 (7.21)	17.70 (5.18)	F = 2.30	0.102	0.94 (0.73–1.20)	0.54	0.609	0.67 (0.47–0.95)	0.61	0.025	1.04 (0.8–1.35)	0.72	0.771	0.83 (0.56–1.21)	0.87	0.330
Area Under the Curve with respect to Incr ^a	3.04 (7.05)	2.43 (6.22)	1.58 (6.38)	F = 0.935	0.394	0.91 (0.71–1.18)	0.53	0.482	0.82 (0.59–1.14)	0.60	0.227	0.94 (0.72–1.23)	0.72	0.651	0.82 (0.56–1.2)	0.87	0.309
Evening cortisol ^a	5.96 (3.61)	5.52 (3.43)	5.27 (2.44)	H = 1.48	0.477	0.85 (0.66–1.09)	0.55	0.201	0.79 (0.57–1.10)	0.55	0.167	0.88 (0.68–1.14)	0.72	0.338	0.83 (0.58–1.20)	0.86	0.324
Dexamethasone suppression test ^a	2.74 (1.73)	2.96 (2.23)	2.56 (1.46)	H = 2.09	0.351	1.11 (0.88–1.39)	0.53	0.373	0.89 (0.62–1.27)	0.59	0.510	1.12 (0.86–1.44)	0.71	0.401	0.87 (0.59–1.29)	0.86	0.490
<i>Inflammation markers</i>																	
TNF-α (pg/ml) ^a	1.15 (1.62)	1.08 (1.18)	1.19 (1.22)	H = 2.10	0.349	0.96 (0.81–1.13)	0.54	0.610	1.04 (0.86–1.25)	0.56	0.688	0.90 (0.76–1.08)	0.72	0.251	0.91 (0.74–1.13)	0.85	0.411
CRP (mg/l) ^a	3.41 (6.28)	3.31 (5.83)	3.37 (4.7)	H = 1.42	0.492	0.98 (0.80–1.20)	0.53	0.860	1.01 (0.79–1.29)	0.55	0.936	0.96 (0.78–1.19)	0.71	0.731	0.91 (0.69–1.21)	0.85	0.512
IL-6 (pg/ml) ^a	1.07 (1.11)	1.31 (1.68)	1.71 (4.9)	H = 4.92	0.086	1.37 (0.86–2.19)	0.54	0.190	1.53 (0.94–2.48)	0.56	0.085	1.44 (0.86–2.42)	0.71	0.170	1.58 (0.92–2.71)	0.85	0.099
<i>BDNF</i>																	
BDNF (ng/ml) ^a	8.98 (3.6)	9.42 (3.85)	9.89 (3.42)	F = 2.013	0.135	1.12 (0.92–1.38)	0.53	0.262	1.27 (0.99–1.62)	0.59	0.060	1.10 (0.89–1.36)	0.72	0.396	1.18 (0.90–1.54)	0.85	0.228

Abbreviations: HDL: high-density lipoprotein; TNF-α: tumour necrosis factor α; CRP: c-reactive protein; IL-6: interleukin-6; BDNF: brain derived neurotrophin factor; F = one way ANOVA; X = chi square; H = Kruskal-Wallis.

^a For Model 1 and Model 2 reported per standard deviation (SD) increase. SD for triglycerides = 0.91; SD for HDL cholesterol = 0.44; SD for fasting plasma glucose = 1.03; SD for Waist circumference = 14.63; SD for systolic blood pressure = 19.44; SD for diastolic blood pressure = 11.13; SD for area under the curve with respect to ground = 7.13; SD for area under the curve with respect to increase = 6.55; SD for evening cortisol = 3.37; SD for dexamethasone suppression test = 1.73; SD for TNF-α = 1.10; SD for CRP = 5.83; SD for IL-6 = 2.88; SD for BDNF = 3.63.

References

- Adam, E.K., Vrshek-Schallhorn, S., Kendall, A.D., Mineka, S., Zinbarg, R.E., Craske, M.G., 2014. Prospective associations between the cortisol awakening response and first onsets of anxiety disorders over a six-year follow-up. *Psychoneuroendocrinology* 44, 47–59. <https://doi.org/10.1016/j.psyneuen.2014.02.014>.
- Batelaan, N.M., Rhebergen, D., van Balkom, A.J.L.M., Penninx, B.W.J.H., 2014. Two-year course trajectories of anxiety disorders: do DSM classifications matter? *J. Clin. Psychiatry* 75, 985–993. <https://doi.org/10.4088/JCP.13m08837>.
- Bruce, S.E., Yonkers, K.A., Otto, M.W., Eisen, J.L., Weisberg, R.B., Pagano, M., Shea, M.T., Keller, M.B., 2005. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. *Am. J. Psychiatry* 162, 1179–1187. <https://doi.org/10.1176/appi.ajp.162.6.1179>.
- Bus, B.A.A., Molendijk, M.L., Penninx, B.W.J.H., Buitelaar, J.K., Kenis, G., Prickaerts, J., Elzinga, B.M., Voshhaar, R.C.O., 2011. Determinants of serum brain-derived neurotrophic factor. *Psychoneuroendocrinology* 36, 228–239. <https://doi.org/10.1016/j.psyneuen.2010.07.013>.
- Butnorione, J., Bunevicius, A., Norkus, A., Bunevicius, R., 2014. Depression but not anxiety is associated with metabolic syndrome in primary care based community sample. *Psychoneuroendocrinology* 40, 269–276. <https://doi.org/10.1016/j.psyneuen.2013.11.002>.
- Carroll, B.J., Feinberg, M., Greden, J.F., Tarika, J., Albala, A.A., Haskett, R.F., James, N.M., Kronfol, Z., Lohr, N., Steiner, M., de Vigne, J.P., Young, E., 1981. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. *Arch. Gen. Psychiatry* 38, 15–22. <https://doi.org/10.1001/archpsyc.1981.01780260017001>.
- Carroll, D., Phillips, A.C., Thomas, G.N., Gale, C.R., Deary, I., Batty, G.D., 2009. Generalized anxiety disorder is associated with metabolic syndrome in the Vietnam Experience Study. *Biol. Psychiatry* 66, 91–93. <https://doi.org/10.1016/j.biopsych.2009.02.020>.
- Colman, I., Ploubidis, G.B., Wadsworth, M.E.J., Jones, P.B., Croudace, T.J., 2007. A longitudinal typology of symptoms of depression and anxiety over the life course. *Biol. Psychiatry* 62, 1265–1271. <https://doi.org/10.1016/j.biopsych.2007.05.012>.
- Eller, T., Vasar, V., Shlik, J., Maron, E., 2008. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 32, 445–450. <https://doi.org/10.1016/j.pnpb.2007.09.015>.
- Elnazer, H.Y., Baldwin, D.S., 2014. Investigation of cortisol levels in patients with anxiety disorders: a structured review. In: Pariente, C.M., Lapiz-Blum, M.D. (Eds.), *Behavioral Neurobiology of Stress-Related Disorders*. Springer, Berlin Heidelberg, Berlin, Heidelberg, pp. 191–216. <https://doi.org/10.1007/97854.2014.299>.
- Glaus, J., von Känel, R., Lasserre, A.M., Strippoli, M.-P.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.-Y.N., Marques-Vidal, P., Waerber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018. The bidirectional relationship between anxiety disorders and circulating levels of inflammatory markers: results from a large longitudinal population-based study. *Depress. Anxiety* 35, 360–371. <https://doi.org/10.1002/da.22710>.
- Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., Gordon, D.J., Krauss, R.M., Savage, P.J., Smith, S.C., Spertus, J.A., Costa, F., 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Circulation* 112, 2735–2752. <https://doi.org/10.1161/CIRCULATIONAHA.105.169404>.
- Hellhammer, J., Fries, E., Schweithal, O.W., Schlotz, W., Stone, A.A., Hagemann, D., 2007. Several daily measurements are necessary to reliably assess the cortisol rise after awakening: state- and trait components. *Psychoneuroendocrinology* 32, 80–86. <https://doi.org/10.1016/j.psyneuen.2006.10.005>.
- Hendriks, S.M., Spijker, J., Licht, C.M.M., Beekman, A.T.F., Penninx, B.W.J.H., 2013. Two-year course of anxiety disorders: different across disorders or dimensions? *Acta Psychiatr. Scand.* 128, 212–221. <https://doi.org/10.1111/acps.12024>.
- Hosmer, D.W., Lemeshow, S., 2000. *Applied Logistic Regression*, 2 ed. Wiley, New York, NY Wiley Series in Probability and Statistics.
- Hovenkamp-Hermelink, J.H., Riese, H., van der Veen, D.C., Batelaan, N.M., Penninx, B.W.J.H., Schoevers, R.A., 2016. Low stability of diagnostic classifications of anxiety disorders over time: a six-year follow-up of the NESDA study. *J. Affect. Disord.* 190, 310–315. <https://doi.org/10.1016/j.jad.2015.10.035>.
- Kahl, K.G., Schweiger, U., Correll, C., Müller, C., Busch, M.-L., Bauer, M., Schwarz, P., 2015. Depression, anxiety disorders, and metabolic syndrome in a population at risk for type 2 diabetes mellitus. *Brain Behav.* 5. <https://doi.org/10.1002/brb3.306>. n/a–n/a.
- Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62, 12.
- Kruse, J.L., Congdon, E., Olmstead, R., Njau, S., Breen, E.C., Narr, K.L., Espinoza, R., Irwin, M.R., 2018. Inflammation and improvement of depression following electroconvulsive therapy in treatment-resistant depression. *J. Clin. Psychiatry* 79. <https://doi.org/10.4088/JCP.17m11597>.
- Lamers, F., Hoogendoorn, A.W., Smit, J.H., van Dyck, R., Zitman, F.G., Nolen, W.A., Penninx, B.W., 2012. Sociodemographic and psychiatric determinants of attrition in the Netherlands Study of Depression and Anxiety (NESDA). *Compr. Psychiatry* 53, 63–70. <https://doi.org/10.1016/j.comppsy.2011.01.011>.
- Molendijk, M.L., Bus, B.A.A., Spinhoven, P., Penninx, B.W.J.H., Prickaerts, J., Oude Voshhaar, R.C., Elzinga, B.M., 2012. Gender specific associations of serum levels of brain-derived neurotrophic factor in anxiety. *World J. Biol. Psychiatry* 13, 535–543. <https://doi.org/10.3109/15622975.2011.587892>.
- Moreira, F.P., Fabião, J.D., Bittencourt, G., Wiener, C.D., Jansen, K., Oses, J.P., Quevedo, L., de Souza, L.D.M., Crispim, D., Portela, L.V., Pinheiro, R.T., Lara, D.R., Kaster, M.P., da Silva, R.A., Ghisleni, G., 2015. The met allele of BDNF Val66Met polymorphism is associated with increased BDNF levels in generalized anxiety disorder. *Psychiatr. Genet.* 25, 201–207. <https://doi.org/10.1097/YPG.0000000000000097>.
- O'Donovan, A., Hughes, B.M., Slavich, G.M., Lynch, L., Cronin, M.-T., O'Farrelly, C., Malone, K.M., 2010. Clinical anxiety, cortisol and interleukin-6: evidence for specificity in emotion–biology relationships. *Brain Behav. Immun.* 24, 1074–1077. <https://doi.org/10.1016/j.bbi.2010.03.003>.
- Otowa, T., Hek, K., Lee, M., Byrne, E.M., Mirza, S.S., Nivard, M.G., Bigdeli, T., Aggen, S.H., Adkins, D., Wolen, A., Fanous, A., Keller, M.C., Castelao, E., Kutalik, Z., der Auwer, S.V., Homuth, G., Nauck, M., Teumer, A., Milanese, Y., Hottenga, J.-J., Direk, N., Hofman, A., Uitterlinden, A., Mulder, C.L., Henders, A.K., Medland, S.E., Gordon, S., Heath, A.C., Madden, P.A.F., Pergadia, M.L., van der Most, P.J., Nolte, I.M., van Oort, F.V.A., Hartman, C.A., Oldehinkel, A.J., Preisig, M., Grabe, H.-J., Middeldorp, C.M., Penninx, B.W.J.H., Boomsma, D., Martin, N.G., Montgomery, G., Maher, B.S., van den Oord, E.J., Wray, N.R., Tiemeier, H., Hettema, J.M., 2016. Meta-analysis of genome-wide association studies of anxiety disorders. *Mol. Psychiatry* 21, 1391–1399. <https://doi.org/10.1038/mp.2015.197>.
- Paul, E.D., Lowry, C.A., 2013. Functional topography of serotonergic systems supports the Deakin/Graeff hypothesis of anxiety and affective disorders. *J. Psychopharmacol. (Oxf.)* 27, 1090–1106. <https://doi.org/10.1177/0269881113490328>.
- Penninx, B.W.J.H., Beekman, A.T.F., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., de Jong, P.J., van Marwijk, H.W.J., Assendelft, W.J.J., van Der Meer, K., Verhaak, P., Wensing, M., de Graaf, R., Hoogendijk, W.J., Ormel, J., van Dyck, R., For the NESDA Research Consortium, 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *Int. J. Methods Psychiatr. Res.* 17, 121–140. <https://doi.org/10.1002/MP.256>.
- Penninx, B.W.J.H., Milanese, Y., Lamers, F., Vogelzangs, N., 2013. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med.* 11. <https://doi.org/10.1186/1741-7015-11-129>.
- Ressler, K.J., Nemeroff, C.B., 2000. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. *Depress. Anxiety* 12 (Suppl. 1), 2–19. [https://doi.org/10.1002/1520-6394\(2000\)12:1+<2:AID-DA2>3.0.CO;2-4](https://doi.org/10.1002/1520-6394(2000)12:1+<2:AID-DA2>3.0.CO;2-4).
- Scholten, W.D., Batelaan, N.M., van Balkom, A.J.L.M., Penninx, B.W.J.H., Smit, J.H., van Oppen, P., 2013. Recurrence of anxiety disorders and its predictors. *J. Affect. Disord.* 147, 180–185. <https://doi.org/10.1016/j.jad.2012.10.031>.
- Skilton, M.R., Moulin, P., Terra, J.-L., Bonnet, F., 2007. Associations between anxiety, depression, and the metabolic syndrome. *Biol. Psychiatry* 62, 1251–1257. <https://doi.org/10.1016/j.biopsych.2007.01.012>.
- Spinhoven, P., Batelaan, N.M., Rhebergen, D., van Balkom, A.J.L.M., Schoevers, R.A., Penninx, B.W.J.H., 2016. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. *J. Anxiety Disord.* 44, 92–101. <https://doi.org/10.1016/j.janxdis.2016.10.011>.
- Suliman, S., Hemmings, S.M.J., Seedat, S., 2013. Brain-Derived Neurotrophic Factor (BDNF) levels in anxiety disorders: systematic review and meta-regression analysis. *Front. Integr. Neurosci.* 7. <https://doi.org/10.3389/fnint.2013.00055>.
- The ESEMEd/MHEDEA 2000 investigators, Alonso, J., Angermeyer, M.C., Bernert, S., Bruffaerts, R., Brugha, T.S., Bryson, H., Girolamo, G., de Graaf, R., Demyttenaere, K., Gasquet, I., Haro, J.M., Katz, S.J., Kessler, R.C., Kovess, V., Lepine, J.P., Ormel, J., Polidori, G., Russo, L.J., Vilagut, G., Almansa, J., Arbabzadeh-Bouchez, S., Autonell, J., Bernal, M., Buist-Bouwman, M.A., Codony, M., Domingo-Salvany, A., Ferrer, M., Joo, S.S., Martinez-Alonso, M., Matschinger, H., Mazzi, F., Morgan, Z., Morosini, P., Palacin, C., Romera, B., Taub, N., Vollebergh, W.A.M., 2004. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMEd) project. *Acta Psychiatr. Scand.* 109, 28–37. <https://doi.org/10.1111/j.1600-0047.2004.00328.x>.
- Vogelzangs, N., Beekman, A.T.F., de Jonge, P., Penninx, B.W.J.H., 2013. Anxiety disorders and inflammation in a large adult cohort. *Transl. Psychiatry* 3, e249. <https://doi.org/10.1038/tp.2013.27>.
- Vreeburg, S.A., Kruijter, B.P., van Pelt, J., van Dyck, R., DeRijk, R.H., Hoogendijk, W.J.G., Smit, J.H., Zitman, F.G., Penninx, B.W.J.H., 2009. Associations between sociodemographic, sampling and health factors and various salivary cortisol indicators in a large sample without psychopathology. *Psychoneuroendocrinology* 34, 1109–1120. <https://doi.org/10.1016/j.psyneuen.2009.04.024>.
- Vreeburg, S.A., Zitman, F.G., van Pelt, J., DeRijk, R.H., Verhagen, J.C.M., van Dyck, R., Hoogendijk, W.J.G., Smit, J.H., Penninx, B.W.J.H., 2010. Salivary cortisol levels in persons with and without different anxiety disorders. *Psychosom. Med.* 72, 340–347. <https://doi.org/10.1097/PSY.0b013e3181d2f0c8>.
- Wagner, E.-Y.N., Wagner, J.T., Glaus, J., Vandeleur, C.L., Castelao, E., Strippoli, M.-P.F., Vollenweider, P., Preisig, M., von Känel, R., 2015. Evidence for chronic low-grade systemic inflammation in individuals with agoraphobia from a population-based prospective study. *PLoS One* 10, e0123757. <https://doi.org/10.1371/journal.pone.0123757>.
- Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A.T.F., Bigdeli, T.B., Binder, E.B., Blackwood, D.R.H., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.-K., Coleman, J.I.R., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Crowley, C.A., Dashti, H.S., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Eriksson, N., Escott-Price, V., Kiadeh, F.H.F., Finucane, H.K., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Giusti-Rodríguez, P., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hannon, E., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Hu, M., Hyde, C.L., Ising, M., Jansen, R., Jin, F.,

- Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretschmar, W.W., Krogh, J., Kutalik, Z., Lane, J.M., Li, Yihan, Li, Yun, Lind, P.A., Liu, X., Lu, L., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E., Milanese, Y., Milani, L., Mill, J., Mondimore, F.M., Montgomery, G.W., Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pistis, G., Posthuma, D., Purcell, S.M., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M., Saeed Mirza, S., Saxena, R., Schoevers, R.A., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamoni, G.B.C., Smit, J.H., Smith, D.J., Stefansson, H., Steinberg, S., Stockmeier, C.A., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgerisson, T.E., Tian, C., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., eQTLGen, 23andMe, Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.C.J., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Hinds, D.A., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.F.A., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow, A.R., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat. Genet.* 50, 668–681. <https://doi.org/10.1038/s41588-018-0090-3>.
- Yonkers, K.A., Bruce, S.E., Dyck, I.R., Keller, M.B., 2003. Chronicity, relapse, and illness? Course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depress. Anxiety* 17, 173–179. <https://doi.org/10.1002/da.10106>.