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RESEARCH

Risk factors of chronic course of anxiety and depressive disorders: a 3-year longitudinal study in the general population

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Abstract

Background Risk factors of a chronic course of anxiety and depressive disorders were previously studied using a limited definition of recovery, i.e. remission of the index disorder. However, frequently, other mental disorders are present at follow-up. Thus, the course of anxiety and depressive disorders was represented too rosy and the identified determinants may not apply when using a broader, more realistic definition. Additionally, physical health risk factors have often been ignored.

Methods Data were used from two waves of the Netherlands Mental Health Survey and Incidence Study-2 including 509 respondents with 12-month anxiety disorder (panic disorder, social phobia, agoraphobia or generalized anxiety disorder) or/and major depressive disorder at baseline. Chronic course was defined as (1) presence of index disorder; and (2) presence of any anxiety, mood or substance use disorder (overall course) during the subsequent three years. Regression models were built with sociodemographic, clinical, and lifestyle/physical health indicators. Predictive accuracy was evaluated with area under the curve (AUC).

Results Chronic course of the index disorder was present among 24.8% of cases, whereas 38.7% had a chronic overall course. The accuracy of prediction of chronic course of the index disorder was suboptimal (AUC = 0.68) compared to prediction of overall course (AUC = 0.75). The main risk factors were baseline number of mental disorders, neuroticism, childhood abuse, parental psychopathology and alcohol use. Lifestyle and physical health indicators were marginally relevant.

Conclusion Transdiagnostic risk factors are important in predicting overall course of anxiety and depressive disorders but cannot accurately predict chronic course of the index disorder.

Keywords Anxiety disorder · Depressive disorder · Depression · Chronic course · Chronicity · Risk factor

Introduction

About one of five people suffer from an anxiety or depressive disorder at some point in their life [1, 2]. These disorders substantially impact individuals and society through a reduced quality of life, absence from work, and costs of sick leave and treatment [3, 4]. Anxiety and depressive disorders have a chronic course with recurring or persistent episodes in 22–37% of the cases [5, 6]. To improve public health, it is important to identify those at risk of a chronic course.

Risk factors of a chronic course of anxiety and depressive disorders in the general population have been identified in previous research. It appeared that a younger age, characteristics of the primary disorder, comorbid mental disorders, neuroticism, and vulnerability characteristics such as childhood abuse, negative life events, and psychopathology in parents significantly predicted a chronic course of anxiety and/or depressive disorders [5, 7–10].

Chronic course is often defined as presence of the primary mental disorder during follow-up or as presence of a mental disorder from the same diagnostic category as the primary disorder. However, regularly, other mental disorders are present during follow-up consisting of either newly

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developed mental disorders or persistent or recurrent pre-existing comorbid disorders. In a community sample, about 20% of the individuals with a remitted anxiety disorder suffered from a new disorder from another diagnostic category at 6-year or 7-year follow-up [5, 6]. In addition, about 7% of those with a remitted depressive disorder had a new anxiety disorder within 7 years [6]. From a recent study in the general population, it appeared that the rates of a chronic course of major depressive disorder increased with 11% and of anxiety disorders with 18% when chronic course was defined as presence of any common mental disorder during follow-up (hereafter called overall course) rather than presence of the index disorder only [11]. So, although these subjects were labelled as 'recovered' in previous studies, they still had a mental disorder and thus should not be considered as such. Defining chronic course broader reflects the nature of mental illness better.

Risk factors of chronic overall course may differ from those of the index disorder. It can be hypothesized that transdiagnostic characteristics (present across disorders) drive overall course while disorder specific features determine course of the index disorder. The little that is known about risk factors of overall course is congruent with this hypothesis. From a recent study using machine learning to predict recovery from anxiety disorders in a mixed general and clinical population it appeared that recovery with a small definition was mainly predicted by anxiety features whereas recovery with a broad definition was predicted by depression features [12]. Previous cohort studies have shown that a chronic course of anxiety and depressive disorders with a broad definition was predicted by comorbidity, neuroticism, childhood adversity, and low functioning [6, 28]. It is important to identify predictors of a chronic overall course of mental disorders because it may reveal new risk factors and with that, change policy to enhance mental health.

Lifestyle and physical health risk factors are often ignored in clinical research and practice. However, psychiatry and biology are linked. Patients with depression have a higher risk of somatic illness due to underlying mediating mechanisms such as an unhealthy lifestyle—for example smoking, excessive alcohol use, and physical inactivity—and stress-related biological dysregulations, such as autonomic, hypothalamic–pituitary–adrenal (HPA) axis, metabolic, and immune-inflammatory dysregulations [13, 14]. Biological factors may negatively impact the course of psychiatric disorders through these underlying mechanisms and also because physical symptoms may hinder seeking help or treatment. For instance, not being able to seek help or receive treatment by a lack of energy.

The purpose of the present study was to compare risk factors of a chronic overall course of anxiety and depressive disorders in the general population to those of the index disorder. We selected potential risk indicators based on previous studies, described above: demographic, clinical, vulnerability, social, lifestyle and physical health characteristics. A second purpose of this study was to explore whether the lifestyle and physical health indicators significantly contribute to predicting course. The results of this study may be used to improve clinical management.

Methods

Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) is a psychiatric epidemiological cohort study of the Dutch general population aged 18–64 at baseline. It is based on a multistage, stratified random sampling of households, with one respondent randomly selected from each household. The face-to-face interviews were laptop computer-assisted. In the first wave, performed from November 2007 to July 2009, 6646 individuals were interviewed (response rate 65.1%; average duration: 95 min). This sample was nationally representative, although younger subjects were somewhat underrepresented [15].

All respondents were approached for follow-up, three years after baseline ($n = 5303$; response rate 80.4%, with those deceased excluded; duration: 84 min). Attrition was not significantly associated with all in the study assessed 12-month common mental disorders at baseline after controlling for sociodemographic characteristics [15].

The study was approved by a medical ethics committee (the Medical Ethics Review Committee for Institutions on Mental Health Care, METIGG). After receiving information about the study aims, respondents provided written informed consent at each wave. A comprehensive description of the design can be found elsewhere [15].

This study is reported conform the STROBE statement [16].

Study groups

For this study respondents were selected with a 12-month anxiety disorder (panic disorder, social phobia, agoraphobia, generalized anxiety disorder; $n = 407$) or/and a 12-month major depressive disorder (MDD; $n = 361$) at baseline. Of these, 114 had comorbid anxiety disorder and MDD. Respondents who did not participate in the second wave (130 cases) and those with current schizophrenia (15 cases) were excluded, resulting in 509 respondents with 12-month anxiety disorder or/and MDD at baseline.

Course outcome definition

The Composite International Diagnostic Interview (CIDI) version 3.0 was used at both waves to assess DSM-IV mood, anxiety and substance use disorders. The CIDI 3.0 is a fully

structured lay-administered interview developed by the World Health Organization, which is used worldwide [17]. Clinical reappraisal interviews showed that it has generally good validity for assessing common mental disorders [18].

Chronic course of the index disorder was defined as presence of panic disorder, social phobia, agoraphobia or generalized anxiety disorder during 3-year follow-up for respondents with an anxiety disorder at baseline and presence of MDD during 3-year follow-up for respondents with MDD at baseline. Chronic overall course was defined as presence of any mood (MDD, dysthymic disorder, bipolar disorder), anxiety (panic disorder, social phobia, agoraphobia, generalized anxiety disorder) or substance use disorder (alcohol abuse, alcohol dependence, drug abuse, drug dependence) including the index disorder during the 3-year follow-up.

Risk indicators of disease course

Sociodemographic, clinical, vulnerability, and lifestyle/physical health characteristics were assessed at baseline, except for parental psychopathology which was assessed at 3-year follow-up. Most of these risk indicators were previously related to course of anxiety disorders or MDD in the general population [1, 5, 7–10, 19, 20].

Sociodemographic characteristics included: sex, age, education, living situation (with or without partner) and job status.

Clinical features included: age of onset of the index disorder or the youngest age of onset in respondents with comorbid anxiety disorder and MDD, and number of 12-month common mental disorders, based on CIDI information. Mental functioning was measured with the mental subscale of the Short-Form Health Survey (SF-36; [21]). Service use for mental health problems refers to at least one contact with a psychiatrist, psychologist or psychotherapist in specialized mental health care services in the past 12 months or use of psychotropic medication mainly antidepressants and/or benzodiazepines in the past 12 months, prescribed by a mental health professional.

Vulnerability characteristics included: neuroticism and extroversion measured using 12 items (0 = low neuroticism/extroversion; 12 = high neuroticism/extroversion) from the Eysenck Personality Questionnaire–Revised Short Scale [22, 23], childhood abuse (whether before age 16 one had experienced emotional neglect, psychological abuse or physical abuse on ≥ 2 occasions, or sexual abuse on ≥ 1 occasion), negative life events [any of 10 negative life events in the past 12 months, such as death of a relative or friend, divorce and financial difficulties, based on Brugha et al. [24] and parental psychopathology (≥ 1 biological parent ever having been treated by a psychiatrist, or hospitalized in a mental health institution, or ever having exhibited severe depression, delusions or hallucinations, severe anxiety or phobias, alcohol abuse, drug abuse, regular problems with the police and/or suicidal behaviour).

Lifestyle and physical health characteristics included: chronic physical disorder (any of 17 chronic physical disorders treated or monitored by a medical doctor in the past 12 months, assessed with a standard checklist; these conditions were: respiratory disorders (asthma, chronic obstructive pulmonary disease, chronic bronchitis, emphysema), cardiovascular disorders (severe heart disease, heart attack, hypertension, stroke), digestive disorders (stomach or intestinal ulcers, severe intestinal disorders like irritable bowel syndrome), diabetes, thyroid disorder, chronic back pain, arthritis, migraine, impaired vision or hearing, and other chronic physical disorder), body mass index (BMI; kg/m^2), smoking (in the past month), alcohol use (number of drinks per week), cannabis use (in the past 12 months), physical activity (number of days per week at least 30 min of moderate physical activity) and physical functioning as measured with the physical subscale of the SF-36.

Statistical analysis

Characteristics of the sample were presented using descriptive statistics (percentages and means; Table 1). Also, percentages of participants with a chronic course were described (Table 2). Furthermore, two prediction models were built with logistic regression analyses to examine risk indicators of chronic course of the index disorder and chronic overall course. Analyses were performed on the total sample ($n = 509$). First, univariable regression analyses were conducted (Table 3). Second, risk indicators were selected with an automatic backward selection method. Initially, all 21 variables were included in the model. Next, one by one, variables with the smallest contribution were removed from the model. The significance level for removal was set at ≥ 0.10. Next, the selected risk indicators that were significant at $p < 0.05$ were entered together to calculate the final multivariable model. These results are shown in Table 3. Missing values were few (between 0 and 13 cases) and were deleted listwise. To assess the predictive accuracy of both multivariable models, the area under the curve (AUC) was determined (Fig. 1). To examine whether lifestyle and physical health characteristics improved the predictive accuracy of the models, the AUC of the models with and without these risk factors were calculated. The predictive accuracy was interpreted as small (AUC values between 0.5 and 0.7), medium (0.7–0.8) or large (0.8–1.0) [25]. Analyses were performed using STATA 16.1.

Results

Sample characteristics

Table 1 presents the characteristics of the sample ($n = 509$). The mean age was 43.2 years ($SD = 12.0$) and 66.6% was female. 61.1% of the sample had an anxiety disorder, 56.0% MDD, and 17.1% had comorbid anxiety disorder and MDD. Two-thirds had experienced a negative life event in the past 12 months and more than half had experienced childhood abuse.

Table 2 shows the percentages of people with a chronic 3-year course of anxiety and depressive disorders. A total of 24.8% of the respondents had a chronic course of the index disorder during 3-year follow-up. This proportion increased to 38.7% when outcome was broadened to presence of any mental disorder. This illustrates that quite a large group (13.9%) developed a mental disorder other than the index disorder during follow-up.

Risk factors of chronic course and prediction models

Table 3 shows the results of the logistic regression analyses of risk factors of (1) a chronic course of the index disorder and (2) a chronic overall course during the 3-year follow-up.

From the univariate analyses it appeared that living without a partner, a younger age at onset of the index disorder, higher number of mental disorders, poorer mental functioning, service use, higher neuroticism, childhood abuse, negative life events, parental psychopathology, and poorer physical functioning predicted a chronic course of the index disorder. In the multivariate analyses, higher number of mental disorders and higher neuroticism continued to predict a chronic course of the index disorder.

Furthermore, a younger age, living without a partner, a younger age at onset of the index disorder, higher number of mental disorders, poorer mental functioning, service use, higher neuroticism, childhood abuse, negative life events, parental psychopathology, smoking, higher alcohol and cannabis use, and poorer physical functioning predicted a chronic overall course. In addition, higher number of mental disorders, higher neuroticism, childhood abuse, parental psychopathology and higher alcohol use independently predicted a chronic overall course.

Predictive accuracy

The AUC of the prediction model of chronic course of the index disorder was 0.68 (95% CI 0.62, 0.73), which is a small predictive accuracy. None of the lifestyle and physical health characteristics were part of this model.

The AUC of the prediction model of chronic overall course was 0.75 (95% CI 0.70, 0.79; Fig. 1), which is an acceptable predictive accuracy. The AUC of this model without the lifestyle and physical health characteristics (alcohol use) was 0.73 (95% CI 0.68, 0.78), which is a medium size predictive accuracy.

Hence, adding lifestyle and physical health risk factors did not improve the predictive accuracy of the model of chronic course of the index disorder, while it did improve the predictive accuracy of chronic overall course, but only modestly.

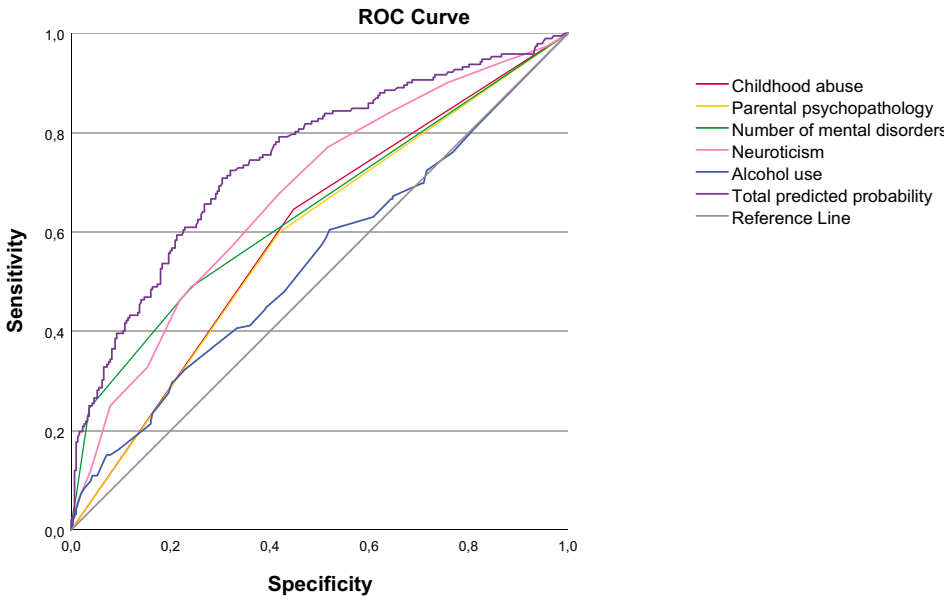

Fig. 1 Receiver operating characteristic curve (ROC) for prediction of chronic overall course of anxiety and depressive disorders. AUC = 0.75

Table 1 Baseline characteristics of people with anxiety disorders or/and major depressive disorder in the general population ($n = 509$)

	Mean (SD) or *n* (%)
Sociodemographics	
Gender, female	339 (66.6%)
Age, years	43.2 (12.0)
Education	172 (33.8%)
Primary education, lower secondary education	182 (35.8%)
Higher secondary education	155 (30.5%)
Higher professional education, university	
Living without partner	235 (46.2%)
No paid job	156 (30.7%)
Clinical characteristics	
Age of onset of the index disorder	22.8 (15.1)
Major depressive disorder	285 (56.0%)
Anxiety disorder	311 (61.1%)
Substance use disorder	53 (10.4%)
Number of mental disorders	1.5 (0.8)
Mental functioning[1]	69.0 (21.2)
Service or medication use for mental health problems[2], yes	205 (40.9%)
Vulnerability	
Neuroticism[3]	5.7 (3.2)
Extroversion[3]	7.3 (3.4)
Childhood abuse, yes	262 (52.3%)
Negative life events in past 12 months[4], yes	351 (69.0%)
Parental psychopathology[5], yes	248 (48.7%)
Physical health indicators	
Chronic physical disorder, yes	232 (45.6%)
Body Mass Index (BMI)	25.0 (4.6)
Current smoker, yes	207 (41.3%)
Alcohol use, number of drinks per week in past 12 months	7.2 (13.0)
Cannabis use in past 12 month, yes	54 (10.6%)
Physical active, number of days a week	3.5 (2.6)
Physical functioning[1]	74.3 (21.5)

[1]Subscale of 36-Item Short Form Health Survey (SF-36)

[2]Use of psychotropic medication or mental health care

[3]Subscale of Eysenck Personality Questionnaire (EPQ)

[4]Negative life-events in the past 12 months

[5] Measured at 3-year follow-up

Table 2 Number of people with a chronic course of anxiety disorders or/and major depressive disorder during 3-year follow-up

	Baseline *n*	Chronic course of index disorder[1] *n* (%)	Chronic overall course[2] *n* (%)
Major depressive disorder—pure	198	42 (21.2%)	68 (34.3%)
Anxiety disorder—pure	224	41 (18.3%)	82 (36.6%)
Comorbid MDD and anxiety disorder	87	43 (49.4%)	47 (54.0%)
Total sample	509	126 (24.8%)	197 (38.7%)

[1]Presence of a mental disorder from the same diagnostic category as the index mental disorder during follow-up

[2]Presence of any anxiety, mood or substance use disorder during follow-up

Table 3 Risk-indicators of a 3-year chronic course of anxiety disorders or/and major depressive disorder in the general population

	Course of index disorder[1] OR [95% CI]		Chronic overall course[2] OR [95% CI]	
	Univariate analyses	Multivariate analysis	Univariate analyses	Multivariate analysis
Sociodemographics				
Gender, female	1.10 [0.72, 1.70]		1.07 [0.73, 1.56]	
Age, years	0.99 [0.97, 1.01]		0.98* [0.96, 0.99]	0.98 [0.97, 1.00]
Education	0.99 [0.60, 1.62]		1.03 [0.66, 1.60]	
Primary education, lower secondary education	0.86 [0.52, 1.42]		0.83 [0.54, 1.30]	
Higher secondary education	Reference		Reference	
Higher professional education, university				
Living without partner	1.72* [1.15, 2.59]		2.10* [1.46, 3.01]	
No paid job	1.43 [0.93, 2.18]		1.39 [0.95, 2.05]	
Clinical characteristics				
Age of onset of the index disorder	0.98* [0.97, 1.00]		0.98* [0.97, 0.99]	
Number of mental disorders	1.99* [1.56, 2.53]	1.68* [1.30, 2.18]	2.35* [1.82, 3.04]	1.80* [1.36, 2.39]
Mental functioning[4]	0.98* [0.97, 0.99]		0.98* [0.97, 0.98]	
Service use for mental health problems[5], yes	2.13* [1.41, 3.21]		2.48* [1.71, 3.59]	
Vulnerability				
Neuroticism	1.18* [1.10, 1.26]	1.12* [1.04, 1.20]	1.22* [1.14, 1.29]	1.15* [1.07, 1.23]
Extroversion	0.95 [0.90, 1.01]		0.98 [0.93, 1.03]	
Childhood abuse, yes	1.86* [1.23, 2.83]		2.21* [1.53, 3.21]	1.62* [1.07, 2.44]
Negative life events[3], yes	1.74* [1.08, 2.81]		1.78* [1.18, 2.68]	
Parental psychopathology, yes	1.64* [1.09, 2.46]	1.52 [0.99, 2.34]	2.02* [1.41, 2.90]	1.69* [1.12, 2.54]
Area under curve		0.68 [0.62, 0.73]		0.73 [0.68, 0.78]
Physical health indicators				
Chronic physical disorder, yes	1.03 [0.68, 1.54]		0.86 [0.60, 1.24]	
Body Mass Index (BMI)	1.01 [0.96, 1.05]		1.00 [0.96, 1.04]	
Current smoker, yes	0.99 [0.66, 1.49]		1.48* [1.03, 2.13]	
Alcohol use, number of drinks per week	1.00 [0.99, 1.02]		1.02* [1.00, 1.04]	1.02* [1.01, 1.04]
Cannabis use, yes	1.32 [0.71, 2.46]		2.16* [1.22, 3.81]	
Physical active, number of days a week	0.98 [0.91, 1.07]		0.94 [0.88, 1.01]	
Physical functioning[4]	0.99* [0.98, 1.00]		0.99* [0.98, 1.00]	
Area under the curve of model with physical health indicators		0.68 [0.62, 0.73]		0.75 [0.70, 0.79]

*$p < 0.05$

[1]Presence of a mental disorder from the diagnostic category of the index mental disorder during follow-up

[2]Presence of any anxiety, mood or substance use disorder during follow-up

[3]Negative life event in the 12 months before baseline

[4]Subscale of 36-Item Short Form Health Survey (SF-36)

[5]Use of psychotropic medication or mental health care

Discussion

The aim of this study was to compare risk factors of a chronic overall course of anxiety and depressive disorders in the general population to those of the index disorder. A second purpose was to explore whether lifestyle and physical health indicators significantly contribute to predicting course.

We may conclude that chronic course of the index disorder was predicted by higher number of mental disorders and higher neuroticism. Meta-analyses of studies in general and clinical populations identified these characteristics before as risk factors of a chronic course of depression while in anxiety disorders previous results were mixed [26, 27]. Chronic overall course was also predicted by higher number of mental disorders and higher neuroticism, in addition to childhood abuse, parental psychopathology and higher alcohol use. Most of these results corroborate previous preliminary findings of chronic overall course of anxiety and depressive disorders in general and mixed populations [6, 12, 28, 29].

Parental psychopathology was not studied before as predictor of overall course. This result may reflect the heritability of anxiety and depressive disorders, which is estimated at 30–50% [30, 31] and may also reflect impact of parenting [32]. Particularly cold and protective parenting styles cause a risk for a wide range of adult psychopathology, including MDD and anxiety disorders [33, 34]. More alcohol use was a small risk factor of a chronic overall course of anxiety and depressive disorders. At the same time, alcohol use contributed little to the prediction model, as the overlapping confidence intervals of the AUC for models with or without alcohol use did not support a significant improvement in predictive accuracy. Previously, alcohol use was not a predictor of overall course of depressive disorders in a mixed general and clinical sample [29]. More research is needed to determine the effect of alcohol consumption on overall course of anxiety and depressive disorders.

Our results support that transdiagnostic risk factors are important in predicting overall course of anxiety and depressive disorders. However, they cannot accurately predict chronic course of the index disorder. Apparently, vulnerability characteristics determine the risk of developing a broader spectrum of psychiatric symptoms but not of chronicity of the baseline disorder. Last, our results suggest that anxiety and depressive disorders have common transdiagnostic risk factors, such as personality traits, social development, and coping style. Lifestyle and physical health risk factors were not part of the prediction model of chronic course of the index disorder, while the model of overall course included alcohol use but it improved the predictive accuracy only modestly. Congruent with previous studies, our results may indicate that physical health indicators have modest value in predicting chronic course of anxiety and depressive disorders in the general population [29, 35].

The identified risk factors of our study may be used to improve mental health. Mental health literacy interventions by the government, health professionals, and patient organisations should inform the concerned people about the high risk to relapse or to develop another mental disorder even after remission of the index disorder. In addition, people at high risk should be encouraged to seek help. This is important given that only a minority of our sample had sought specialized help at baseline. Furthermore, our results suggest that mental health may be enhanced by adopting a broader perspective on mental disorders, including focus on comorbid mental disorders and aetiological or vulnerability factors, such as childhood abuse, dysfunctional personality characteristics and dysfunctional coping. However, the worldwide used classification system for mental disorders—the Diagnostic and Statistical Manual of Mental Disorders (DSM)—ignores the frequent occurrence of comorbidity and the probable common aetiology with the index disorder. To overcome these shortcomings of the DSM, it has been proposed to develop new systems that classify symptoms according to their underlying aetiology. For example, the Research Domain Criteria (RdoC), a research framework aiming to develop a classification system based on neurobiological and behavioural risk factors [36, 37]. Another example is the Hierarchical Taxonomy of Psychopathology (HiTOP), in which symptoms and personality traits are grouped into a hierarchical model of psychopathology, based on observed covariation of symptoms [38]. Last, it has been proposed to capture the fluctuating course of anxiety and depressive symptoms associated with cluster C personality dysfunction and parental psychopathology in a classification named ‘general neurotic syndrome’ [39].

The findings of this study should be interpreted in the light of the following strengths and limitations. Strength was that we had a representative sample of the Dutch population. Furthermore, mental disorders were assessed with a valid, standardized instrument (CIDI 3.0). Last, a broad range of putative risk factors were measured. Limitation is an attrition of 20% in the second wave. However, since the attrition was not correlated to psychopathology at baseline it probably did not bias the results. A second limitation is that risk factors of chronic course might differ in anxiety and depressive disorders and therefore, remain concealed in our heterogeneous sample. However, it was not possible to analyse subsamples due to sample size. Next, many of the variables are based on retrospective self-report, carrying a risk of state-dependent bias or general recall bias. Furthermore, some people may have been incorrectly assigned to the good-course group as the possible presence of lifetime mental disorders was not taken into account. Additionally, results were obtained in a sample from the general community and cannot automatically be generalised to a clinical population. Also, it cannot be established whether the relation between the significant predictors and the outcome measure is causal or not. Last limitation is that relevant risk factors of chronic course (of the index disorder) might not be present in our study, for example disorder-specific risk factors.

In conclusion, this study identified risk factors of a chronic overall course of anxiety and depressive disorders in the general population: higher number of mental disorders, higher neuroticism, childhood abuse, parental psychopathology and higher alcohol use. In addition, it was explored whether lifestyle and physical health indicators are relevant predictors, which turned out not to be the case. Our results support that the nature of mental disorders may in the future be better understood with a broader perspective on mental disorders including comorbid mental disorders and underlying transdiagnostic risk factors, such as childhood abuse, dysfunctional personality characteristics and dysfunctional coping. The current study should be replicated in a clinical sample. Furthermore, future research should examine

whether intervening on the found risk factors indeed prevents chronicity in the broad sense.

Author contributions KR wrote manuscript, conducted literature searches MH conducted statistical analyses BP and NB designed and supervised the study All authors reviewed the manuscript

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Data availability The data on which this manuscript is based are not publicly available. However, data from NEMESIS-2 are available upon request. The Dutch ministry of health financed the data and the agreement is that these data can be used freely under certain restrictions and always under the supervision of the Principal Investigator (PI) of the study. Thus, some access restrictions do apply to the data. The PI of the study is second author of this paper and can at all times be contacted to request data. At any time, researchers can contact the PI of NEMESIS-2 and submit a research plan, describing its background, research questions, variables to be used in the analyses, and an outline of the analyses. If a request for data sharing is approved, a written agreement will be signed stating that the data will only be used for addressing the agreed research questions described and not for other purposes.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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