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Research paper

Sociodemographic and clinical predictors of depression in children and adolescents at clinical high-risk for psychosis: Results of a two-year follow-up study

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ABSTRACT

Depressive disorders are a main cause of disability already in children and adolescents, in whom the clinical picture somewhat differs from adult-onset depression. Depression is also a frequent comorbidity in somatic and mental disorders and has been considered an actionable outcome for, for example, patients at clinical high-risk for psychoses (CHR—P). Thus, we studied sociodemographic and clinical predictors of depression/dysthymia in an underage sample with focus on those considered at CHR—P. Our baseline sample ($N = 676$) included CHR-P patients ($n = 183$), inpatients admitted for non-psychotic, non-affective disorders ($n = 277$), and community participants ($n = 216$) of age 8.0–17.9 years (43.8 % male). They were interviewed for mental disorders and symptoms with various instruments, including the Mini International Neuropsychiatric Interview for Children and Adolescents, which was also used to assess depression/dysthymia in the CHR-P group at one- and two-year-follow up ($n = 117/73$). Stepwise logistic regression analyses were used to first identify a cross-sectional baseline model in the complete sample that was then tested prospectively in CHR-P patients. The baseline model included nationality and 13 clinical variables, particularly mild depressive symptoms. Variables contributing significantly to the prediction of persistence or new occurrence of depression/dysthymia varied over time, indicating that depression/dysthymia in CHR-P minors may require different predictors depending on the follow-up time. Furthermore, the prospective accuracy of ruling out depression/dysthymia was superior to the accuracy of ruling it in. This lower positive likelihood ratio might be overcome in future by stepwise approaches that further stratify risk in those CHR-P minors identified as at increased risk of depression/dysthymia.

1. Introduction

Major depression (MD) is one of the most common diseases with a lifetime risk of 15–18 % and considered by WHO to be the third largest cause of global disease burden with a steadily increasing trend that will likely make MD the disease of most global economic and health importance by 2030 (Allgaier et al., 2014; GBD 2019 Mental Disorders Collaborators, 2022). Prevalence rates of MD vary by age, sex, and

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countries, with higher rates in females and lifetime rates in Europe between 9.9 % in Germany and 21.0 % in France (Allgaier et al., 2014; Baez and Heller, 2020). Peak of onset is between adolescence and age of 40 years, with a median age-of-onset in the early and middle 20s (Allgaier et al., 2014; Baez and Heller, 2020). Earlier age-of-onset and/or longer duration of untreated MD has been related to greater severity and poorer outcome (Maughan et al., 2013; Rice et al., 2019). Already in children and adolescents (CAD) of age 10 and older, unipolar MD was reported as the main cause of disability-adjusted life years (Roberts, 2013), and MD in childhood and adolescence (henceforth: pediatric MD) was associated with a multitude of poor psychosocial and mental health outcomes in adulthood (Kieling et al., 2019, 2021), indicating an urgent need for timely early detection and intervention in CAD (Rice et al., 2019; Kieling et al., 2019, 2021; Noyes et al., 2022; Cuijpers et al., 2021; Fusar-Poli et al., 2013; Schultze-Lutter et al., 2022). Yet, already the diagnosis of manifest MD is more difficult and, therefore, more delayed in CAD compared to adults, because the clinical picture of CAD differs in part from that of adults, and differentiating MD from puberty crises or other primary mental disorders is frequently problematic (Allgaier et al., 2014; Maughan et al., 2013). For example, compared to adult cases, CAD with MD more often show moodiness, irritability, disruptive behaviours, school refusal, vegetative symptoms (such as headaches), insomnia, and self-harm but less frequently anhedonia or loss of interest and concentration problems (Rice et al., 2019; Roberts, 2013; Kieling et al., 2019).

Regarding primary and secondary preventive approaches of MD in CAD, universal approaches addressing entire groups of CAD (e.g., in school-based interventions (Noyes et al., 2022)), have been less successful than targeted approaches. Targeted approaches involve selective and indicated interventions focusing on CAD who are at high-risk due to the presence of either proximal risk factors (frequently parental MD as one of the main risk factors for pediatric MD (Cornblatt et al., 2007)) or subclinical symptoms, such as subthreshold depression (Cuijpers et al., 2021; Fusar-Poli et al., 2013; Kessler and Bromet, 2013; Malhi and Mann, 2018). In addition to genetic and biological risk factors (e.g., dysfunctional neuro-regulatory factors), psychosocial risk factors of MD that are frequently rather unspecific but might be addressed with selective approaches include: low parental education, occupational group, or social status; negative school and family experiences; poor school involvement; lifestyle-related risk factors such as substance (mis)use and lower levels of physical activity; low sense of coherence and self-esteem; and maladaptive emotion regulation strategies and various cognitive styles (Noyes et al., 2022; Cornblatt et al., 2007; Kessler and Bromet, 2013; Malhi and Mann, 2018; Labaka et al., 2018; Piechaczek et al., 2020). However, given the multitude and interaction of risk factors of MD, selective approaches that address the complexity of risk factors and allow a risk stratification are needed (Kieling et al., 2019, 2021). Indicated prevention mainly focuses on CAD exhibiting a persistent low mood or subthreshold depression (Roberts, 2013; Noyes et al., 2022; Cuijpers et al., 2021). Yet, although subthreshold depression was reported as being clinically relevant in itself, with affected individuals sharing many features with MD patients (Noyes et al., 2022), there is currently only insufficient evidence that the treatment of subthreshold depression in CAD prevents the onset of MD (Cuijpers et al., 2021; Fusar-Poli et al., 2013). Thus, just as a single risk factor is insufficient to appropriately capture a high-risk of MD, subthreshold depression as commonly established with standardized diagnostic interviews (Cuijpers et al., 2021; Fusar-Poli et al., 2013) likely only insufficiently describes clinical high-risk for MD (Kieling et al., 2021).

Another characteristic of MD is its high rate of co-occurrence with other somatic and mental conditions that includes the clinical high-risk of psychosis (CHR—P) condition (Melartin et al., 2002; Penninx and van Dyck, 2010; Addington et al., 2021; Solmi et al., 2023). The CHR-P condition includes three ultra-high risk (UHR) criteria and two basic symptom (BS) criteria (Schultze-Lutter et al., 2015). Accounting for at least 80 % of UHR cases, the UHR criterion based on attenuated positive symptoms, i.e., hallucinatory and delusional phenomena with insight into their abnormal nature as well as odd thinking and speech, is the most common UHR criterion. The other two, less frequent UHR criteria include transient psychotic symptoms that spontaneously remit within a short period of time and a combination of genetic risk, the presence of a first-degree psychotic disorder in a relative, and significant functional impairment. The two BS criteria encompass subtle, subclinical self-experienced disturbances in cognitive and perceptual processes that are regarded by the patients as deviations from their 'normal' mental processes (Penninx and van Dyck, 2010). Standard instruments for the assessment of these CHR-P criteria include the "Structured Interview for Psychosis-Risk Syndromes" (SIPS (McGlashan et al., 2010)) and the "Schizophrenia Proneness Instrument, Child & Youth version" (SPI-CY (Schultze-Lutter and Koch, 2010)).

Because depression was identified as a domain of substantial unmet clinical need in CHR-P patients (Addington et al., 2021), the aim of the current study was to identify psychosocial risk factors and early signs of depression and/or dysthymia that promote the occurrence/persistence of pediatric MD, particularly in CHR-P patients. In analogy to the indicated prediction of psychoses by early signs (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2022), the focus was on the consideration of the suitability of subthreshold or subtle subjective symptoms as assessed with the SPI-CY and the SIPS. Because of the phenomenological proximity to depressive symptoms, subtle subjective disturbances in energy level and stress tolerance as well as in affect processing – as captured by the SPI-CY dimensions Adynamia and Neuroticism, and the SIPS Negative and General Symptoms subscales – were expected to be predictive for pediatric MD.

2. Methods

2.1. Sample

The sample (N = 676; 43.7 % male) was recruited as part of the Binational Evaluation of At-Risk Symptoms in Children and Adolescents (BEARS-Kid) study (Schultze-Lutter et al., 2022) between 09-2013 and 12-2017, and followed up annually until March 2018, for a maximum of two years (see sText1 for more information on recruitment and follow-up). General inclusion criteria were age between 8.0 and 17.9 years, and sufficient language skills in German or English. Two patient groups were included at three sites (child and adolescent psychiatric units of the Universities of Bern, Zurich and Cologne): (1) inpatients not clinically suspected to develop psychosis with a principal diagnosis of attention deficit hyperactivity disorder, anxiety disorder, obsessive-compulsive disorder, Asperger's syndrome, or eating disorder (n = 277), and (2) predominantly outpatients who met CHR-P criteria according to the UHR and BS criteria (n = 183). A third community sample (n = 216) was recruited by the Bern site only and randomly drawn from the population register of the greater Bern area (Switzerland). General exclusion criteria were lifetime diagnosis of psychosis, IQ < 70 and symptoms being due to the direct physiological effects of a general medical condition or of substance use. Additional exclusion criteria for inpatients and community participants were current antipsychotic medication and clinical suspicion of an emerging psychosis and, consequently, consultation of the local early detection service. Community and clinical controls who met any CHR-P criteria at T0 were included into the CHR-P sample (Fig. 1). Except for sex, the three samples differed significantly, in particular the community sample from the two clinical samples (Table 1).

Since follow-up examinations in BEARS-Kid focused on CHR-P and a possible transition to psychosis, all mental disorders including depressive disorders were assessed at follow-ups only in the CHR-P sample (n = 117) at one-year follow-up (T1) and n = 73 at two-year follow-up (T2; Fig. 1).

At each stage, the BEARS-Kid study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the ethics committee of the Universities of Bern (No.174/10), Zurich

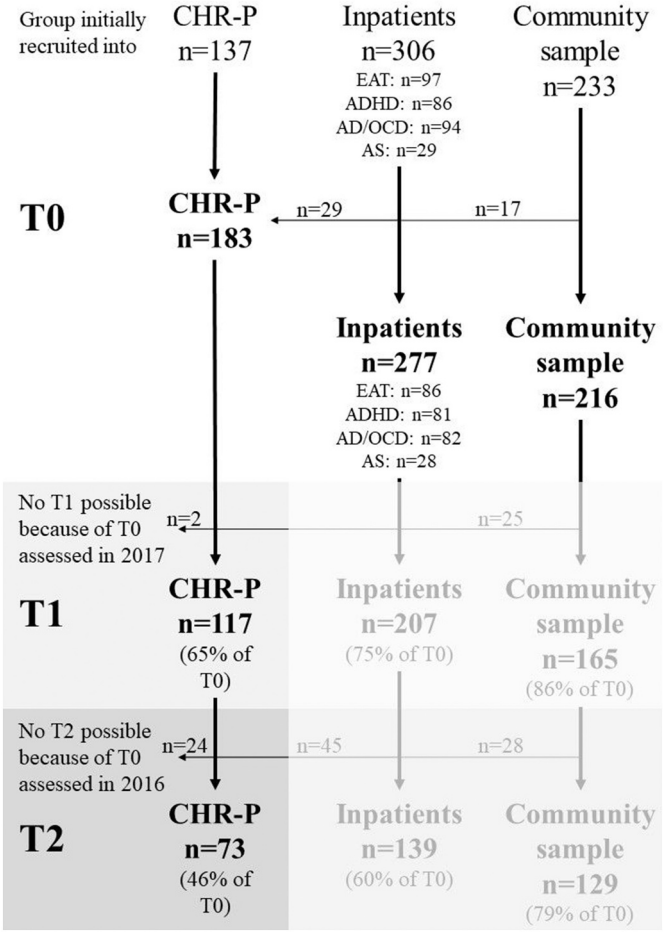

Fig. 1. CONSORT chart of the BEARS-Kid study. T0: baseline assessment; T1: one-year follow-up; T2: two-year follow-up CHR—P: clinical high-risk for psychosis; EAT: eating disorders; ADHD: attention deficit, hyperactivity disorder; AD/OCD: anxiety disorders incl. obsessive-compulsive disorders; AS: Asperger's syndrome.

(No. 2010-0415/3) and Cologne (No.11-071).

2.2. Assessments

CHR-P criteria were assessed with the SPI-CY and SIPS. The SPI-CY assesses the BS criteria Cognitive Disturbances and Cognitive-Perceptive Basic Symptoms, along with other BS in four main domains: Adynamia (A), Perception Disturbances (B), Neuroticism (C), and Thought And Motor Disturbances (D) (Schultze-Lutter and Koch, 2010). BS are subtle, subclinical self-experienced disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action that are rated for severity according to their frequency, with scores ranging from 0 (absent) to 6 (daily). Additionally, scores of 7 (always been present in the same severity), 8 (present but frequency unknown) and 9 (questionably present) are available; these were recoded for the present analyses as follows: 7 = 0, 8 = 1, and 9 = 0. The SIPS assesses the UHR criteria, including the Attenuated Positive Symptom Syndrome, the Brief Intermittent Psychosis Syndrome and the Genetic Risk and Functional Decline Syndrome. It comprises four subscales, i.e., Positive (P), Negative (N), Disorganized (Dis) and General Symptoms (G) (McGlashan et al., 2010). The main items are rated syndromally for their severity, with scores ranging from 0 (absent) to 6 ('severe and psychotic' in case of positive symptoms and 'extreme' in case of other symptoms); the symptoms constituting the main items are rated for their presence and absence.

Table 1
Group comparisons of sociodemographic variables in the total baseline sample ($N = 676$).

	CHR-P patients ($n = 183$)	Inpatients (clinical controls; $n = 277$)	General population (healthy controls; $n = 216$)	Statistics
Age (yrs.); mean ± SD, median	15.3 ± 2.1, 15.7	14.3 ± 2.5, 14.9	13.0 ± 2.8, 12.8	$H_{(2)} = 71.2$, $p < 0.001$
Sex, male; n (%)	69 (37.7 %)	126 (45.5 %)	101 (47.0 %)	$\chi^2_{(2)} = 4.2$, $p = 0.124$; Cramer's V = 0.079
Nationality; n (%)				
Swiss	102 (56.0 %)	153 (55.2 %)	181 (83.8 %)	$\chi^2_{(4)} = 85.9$, p < 0.001; Cramer's V = 0.252
German	57 (31.0 %)	108 (39.0 %)	9 (4.2 %)	
Other	24 (13.0 %)	16 (5.8 %)	26 (12.0 %)	
Religion; n (%)				
None	50 (27.7 %)	65 (23.5 %)	34 (15.7 %)	$\chi^2_{(6)} = 22.1$, $p = 0.001$; Cramer's V = 0.129
Protestant	63 (34.2 %)	104 (37.6 %)	111 (51.4 %)	
Catholic	50 (27.2 %)	87 (31.4 %)	45 (20.8 %)	
Other	20 (10.9 %)	21 (7.6 %)	26 (12.0 %)	
Education, ISCED level; n (%)				
1	21 (11.4 %)	68 (24.6 %)	107 (49.5 %)	$\chi^2_{(4)} = 74.2$, p < 0.001; Cramer's V = 0.235
2	91 (50.0 %)	118 (42.6 %)	66 (30.6 %)	
3	71 (38.6 %)	91 (32.9 %)	43 (19.9 %)	
Current psychosocial functioning; mean ± SD, median				
SOFAS score	59.6 ± 12.1, 60.0	60.3 ± 11.1, 60.0	84.6 ± 8.0, 88.0	$H_{(2)} = 361.1$, p < 0.001
GF:Social score	6.5 ± 1.3, 6.0	6.6 ± 1.1, 7.0	8.6 ± 0.9, 9.0	$H_{(2)} = 299.9$, p < 0.001
GAF score	50.3 ± 12.4, 50.0	52.9 ± 8.7, 53.0	82.2 ± 9.5, 85.5	$H_{(2)} = 398.3$, p < 0.001
Current mental disorders at T0, present; n (%)				
Depression/ dysthymia	70 (61.9 %)	43 (38.1 %)	0 (0.0 %)	$\chi^2_{(2)} = 104.6$, p < 0.001; Cramer's V = 0.393
Bipolar disorder	1 (0.5 %)	0 (0.0 %)	1 (0.5 %)	$\chi^2_{(2)} = 1.4$, $p = 0.346$; Cramer's V = 0.046
Anxiety disorder without special phobia	62 (33.7 %)	56 (20.2 %)	4 (1.9 %)	$\chi^2_{(2)} = 69.7$, p < 0.001; Cramer's V = 0.321
Obsessive-compulsive disorder	15 (8.2 %)	31 (11.2 %)	1 (0.5 %)	$\chi^2(2) = 22.2$, p < 0.001; Cramer's V = 0.181
Eating disorder	16 (8.7 %)	86 (31.0 %)	0 (0.0 %)	$\chi^2_{(2)} = 99.4$, p < 0.001; Cramer's V = 0.383

(continued on next page)

Table 1 (*continued*)

	CHR-P patients ($n = 183$)	Inpatients (clinical controls; $n = 277$)	General population (healthy controls; $n = 216$)	Statistics
Somatoform disorder	3 (1.6 %)	3 (1.1 %)	0 (0.0 %)	$\chi^2_{(2)} = 3.2$, $p = 0.201$; Cramer's V = 0.069
Stress-related disorder/PTSD	15 (8.2 %)	2 (0.7 %)	0 (0.0 %)	$\chi^2_{(2)} = 33.1$, $p < 0.001$; Cramer's V = 0.221
Developmental disorder incl. ADHD	20 (10.9 %)	101 (36.5 %)	7 (3.2 %)	$\chi^2_{(2)} = 98.0$, $p < 0.001$; Cramer's V = 0.380
Tic/Tourette disorder	2 (1.1 %)	8 (2.9 %)	0 (0.0 %)	$\chi^2_{(2)} = 7.2$, $p = 0.027$; Cramer's V = 0.103
Substance misuse	15 (8.2 %)	4 (1.4 %)	2 (0.9 %)	$\chi^2_{(2)} = 21.6$, $p < 0.001$; Cramer's V = 0.178
Current suicidality	74 (40.2 %)	50 (18.1 %)	0 (0.0 %)	$\chi^2_{(2)} = 107.4$, $p < 0.001$; Cramer's V = 0.398

ADHD = Attention-deficit Hyperactivity disorder; GAF = Global Assessment of Functioning; GF = Global Functioning; ISCED=International Standard Classification of Education; PTSD = Post-traumatic stress disorder; SOFAS=Social and Occupational Functioning Assessment Scale.

Mental disorders according to the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994) were assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Högberg et al., 2019; Sheehan et al., 2010), a short standardized diagnostic interview for mental disorders in CAD. Level of psychosocial functioning was assessed by the Global Assessment of Functioning (GAF) that is part of the SIPS, the Global Functioning: Social Scale (GF:Social (Cornblatt et al., 2007)) and the Social and Occupational Functioning Assessment Scale (SOFAS) of the DSM-IV with ratings ranging from 0 (poor) to 100 or 10 (superior).

Assessments were carried out by well-trained clinical psychologists who were supervised monthly by two expert raters, C.M. and F.S.L.

2.3. Data analyses

For the multitude of variables, we followed a stepwise protocol to detect potential predictors, in doing so, targeting a sufficient event: variable ratio of at least 1:5 for regression analyses (Vittinghoff and McCulloch, 2007) at each step. First, we conducted group comparisons using Chi^2-tests for categorical data and Mann-Whitney-*U* Tests for continuous data with depression/dysthymia at baseline (T0) as outcome. Since this and the following step only served the detection of possibly relevant variables, we did not correct for multiple testing. Second, all variables with a significant group difference ($p < 0.050$) were analyzed group-wise (sociodemographic variables, psychosocial functioning, mental disorders, CHR-P criteria, SIPS main items and symptoms, domain-wise, and SPI-CY variables) in forward and backward stepwise logistic regression analyses with depression/dysthymia at T0 as outcome. Variables that were identified as significant predictors in both forward and backward selection were used for further analyses. Third, using these extracted variables, we performed a cross-sectional blockwise regression analysis with depression/dysthymia at T0 as outcome. Finally, significant and trend-significant variables ($p < 0.100$) from this analysis were used for the restricted final cross-sectional blockwise regression analysis with depression/dysthymia at T0 as outcome and for longitudinal blockwise regression analyses with depression/dysthymia at T1 and T2 as outcome, respectively. Internal validation of the regression models was done by the bootstrap method. Statistical analyses were conducted using SPSS version 27.

3. Results

3.1. Prevalence and course of depression/dysthymia

At baseline (T0), a significantly higher rate of current depression/dysthymia was found in CHR-P (61.9 %) compared to inpatients (38.1 %) and community participants (0 %) (Table 1), although 1.9 % of the community sample met MINI-KID criteria for major depression in the past. In 96.0 % of followed-up CHR-P cases with depression/dysthymia at T0, depression/dysthymia persisted until T1 or T2. In addition, in 54.3 % of CHR-P cases without depression/dysthymia at T0, it had newly developed by T1 or T2.

3.2. Selected variables by group comparisons

Compared to non-depressed participants, depressed participants were older, more likely female, German, or inpatients, higher educated, more likely to suffer from anxiety, substance use disorders, suicidality or CHR—P, showed lower functioning, and more often had divorced parents (sTable 1). Baseline group comparisons led to significant or trend-significant results in ten sociodemographic variables (sTable 1), all functioning variables (sTable 2), eight mental disorders incl. suicidality (sTable 3), twelve CHR-P criteria related variables (sTable 4), 98 SIPS variables (17 main items, 81 symptoms) (sTable 5), and 67 SPI-CY variables (sTable 6), which entered subsequent domain-specific stepwise regression analyses.

3.3. Selected variables by domain-specific stepwise logistic regression

From the domain-specific stepwise regression analyses, four sociodemographic variables, one psychosocial functioning variable, four mental disorders, one CHR-P criteria related variable, 22 SIPS variables (three main items, 19 symptoms), and six SPI-CY variables (sTable 7) were selected. These were used for further cross-sectional blockwise logistic regression analysis on depression/dysthymia at T0.

3.4. Final cross-sectional model

Nine variables contributed significantly to the prediction of depression/dysthymia at T0 (sTable 8): nationality other than Swiss or German, past anxiety disorder (without specific phobia), current suicidality, avolition (SIPS-N2), dysphoric mood (SIPS-G2), increased stress from daily work (SIPS-N6.1), feeling worthless and/or guilty (SIPS-G2.10), increased emotional reactivity in response to everyday events (SPI-CY-A9), and increased excitability and irritability (SPI-CY-C3). Additional five variables contributed at trend-level significance ($p < 0.10$) and were also considered as predictors (sTable 8): current GAF, strange, fantastic or bizarre thoughts (SIPS-D2.1), early waking (SIPS-G1.3), motor blockages (SIPS-G3.6), and decreased ability to discriminate between ideas and perception, fantasy and true memories (SPI-CY-B1).

In the restricted final cross-sectional model (Table 2), these 14 variables explained 73.3 % of the variance between CAD with and without depression/dysthymia. All variables but decreased ability to discriminate between ideas and perception, fantasy and true memories (SPI-CY-B1) contributed significantly to the classification with Odds Ratios between 0.229 and 14.152 (Table 2). The cross-sectional model classified 92.3 % of cases correctly, and had a sensitivity of 71.6 %, a specificity of 96.5 %, and a positive and negative likelihood ratio (LR) of 20.34 and 0.29, respectively.

Table 2
Final model of depression/dysthymia at T0 in the whole sample (N = 676), blockwise logistic regression analysis.

	Beta	SE	Wald	df	P[a]	Exp (Beta)	95 % CI; lower	95 % CI; upper
Nationality (reference: Swiss)			15.190	2	<0.001			
German	1.022	0.406	6.343	1	0.023	2.778	1.254	6.152
Other	−1.474	0.698	4.456	1	0.008	0.229	0.058	0.900
Current GAF	−0.047	0.021	4.787	1	0.029	0.954	0.915	0.995
Past anxiety disorder without specific phobia	1.573	0.815	3.722	1	0.043[b]	4.819	0.975	23.814
Current suicidality	1.269	0.399	10.116	1	0.005	3.557	1.627	7.773
SIPS-N2 Avolition	0.579	0.152	14.594	1	<0.001	1.784	1.326	2.401
SIPS-G2 Dysphoric mood	0.790	0.199	15.811	1	<0.001	2.204	1.493	3.254
SIPS-N6.1 Increased stress from daily work	0.957	0.402	5.665	1	0.024	2.605	1.184	5.731
SIPS-D2.1 Strange, fantastic or bizarre thoughts	−1.344	0.548	6.010	1	0.006	0.261	0.089	0.764
SIPS-G1.3 Early waking	1.028	0.428	5.766	1	0.020	2.796	1.208	6.472
SIPS-G2.10 Feeling worthless and/or guilty	0.946	0.399	5.625	1	0.028	2.574	1.178	5.623
SIPS-G3.6 Motor blockages	2.650	1.192	4.938	1	0.002	14.152	1.367	146.511
SPI-CY-A9 Increased emotional reactivity in response to everyday events	0.376	0.110	11.664	1	<0.001	1.456	1.174	1.807
SPI-CY-B1 Decreased ability to discriminate between ideas and perception, fantasy and true memories	−0.269	0.170	2.518	1	0.138	0.764	0.548	1.065
SPI-CY-C3 Increased excitability and irritability	−0.207	0.089	5.424	1	0.022	0.813	0.682	0.968

Reference group: children and adolescents without depression or dysthymia at T0.
GoF: $\chi^2(15) = 372.290$; $p < 0.001$; Nagelkerke's $R^2 = 0.733$.
SIPS = Structured Interview for Psychosis-Risk Syndromes; SPI-CY = Schizophrenia Proneness Instrument, Child & Youth version.
[a] Values from Bootstrapping ($N = 1000$).
[b] Because bootstrapping does not require distributional assumptions, the bootstrap provides more accurate inferences when the data are not well behaved, e.g., including little events, or when the sample size is small (Fox, 2008). Thus, we followed the bootstrapping results, and considered variables significant predictors if the bootstrapping became significant, even if these were non-significant in the initial regression analysis and, therefore, included the 1 within the 95 %-CI.

3.5. One-year prospective model

In the one-year prospective model (Table 3), the pre-selected 14 variables explained 56.5 % of the variance between patients with and without depression/dysthymia at T1. Dysphoric mood (SIPS-G2) and motor blockages (SIPS-G3.6) contributed significantly to the classification with Odds Ratios between 2.201 and 8.993 (Table 3). The prospective model classified 83.2 % of cases correctly, and had a sensitivity of 90.9 %, a specificity of 72.3 %, and a positive and negative LR of 3.29 and 0.13, respectively.

3.6. Two-year prospective model

In the two-year prospective model (Table 4), the 14 variables explained 61.6 % of the variance between patients with and without depression/dysthymia at T2. Early waking (SIPS-G1.3) and increased excitability and irritability (SPI-CY-C3) at T0 contributed significantly to the classification with Odds Ratios between 1.605 and 20.437 (Table 4). This prospective model classified 85.9 % of cases correctly, and had a sensitivity of 90.2 %, a specificity of 80.0 %, and a positive and negative LR of 4.51 and 0.12, respectively.

4. Discussion

The aim of this study was to identify psychosocial risk factors and early signs of depression/dysthymia that can predict the occurrence or persistence of depression/dysthymia, a domain of substantial unmet clinical need in CHR-P (Addington et al., 2021), in CAD with CHR-P within two years. In a stepwise analytical procedure, 14 variables were selected into the baseline model, one sociodemographic and 13

Table 3
Prediction of depression/dysthymia at T1 by the final model in the CHR-P subsample ($N = 117$), blockwise logistic regression analysis.

	Beta	SE	Wald	df	P[a]	Exp (Beta)	95 % CI; lower	95 % CI; upper
Nationality (reference: Swiss)			1.118	2	0.572			
German	−0.356	0.649	0.301	1	0.619	0.700	0.196	2.498
Other	−0.917	0.869	1.113	1	0.406	0.400	0.073	2.195
Current GAF	0.033	0.033	1.031	1	0.350	1.034	0.970	1.103
Past anxiety disorder without specific phobia	−0.047	1.028	0.002	1	0.818	0.954	0.127	7.148
Current suicidality	−0.410	0.700	0.343	1	0.592	0.664	0.169	2.616
SIPS-N2 Avolition	0.127	0.246	0.265	1	0.569	1.135	0.701	1.839
SIPS-G2 Dysphoric mood	0.789	0.286	7.591	1	0.006	2.201	1.256	3.857
SIPS-N6.1 Increased stress from daily work	1.384	0.742	3.477	1	0.069	3.990	0.932	17.082
SIPS-D2.1 Strange, fantastic or bizarre thoughts	0.383	0.656	0.341	1	0.595	1.467	0.405	5.307
SIPS-G1.3 Early waking	−0.093	0.634	0.021	1	0.900	0.912	0.263	3.157
SIPS-G2.10 Feeling worthless and/or guilty	0.790	0.626	1.591	1	0.256	2.204	0.646	7.524
SIPS-G3.6 Motor blockages	2.196	1.465	2.249	1	0.021[b]	8.993	0.509	158.727
SPI-CY-A9 Increased emotional reactivity in response to everyday events	0.167	0.158	1.114	1	0.367	1.182	0.867	1.611
SPI-CY-B1 Decreased ability to discriminate between ideas and perception, fantasy and true memories	0.297	0.214	1.927	1	0.169	1.345	0.885	2.045
SPI-CY-C3 Increased excitability and irritability	0.207	0.130	2.541	1	0.191	1.230	0.954	1.585

Reference group: children and adolescents without depression or dysthymia at T1.
GoF: $\chi^2(15) = 61.437$; $p < 0.001$; Nagelkerke's $R^2 = 0.565$.
SIPS = Structured Interview for Psychosis-Risk Syndromes; SPI-CY = Schizophrenia Proneness Instrument, Child & Youth version.
[a] Values from Bootstrapping ($N = 999$).
[b] See footnote Table 2.

Table 4
Prediction of depression/dysthymia at T2 by the final model in the CHR-P subsample (N = 73), blockwise logistic regression analysis.

	Beta	SE	Wald	df	P[a]	Exp (Beta)	95 % CI; lower	95 % CI; upper
Nationality (reference: Swiss)			1.475	2	0.478			
German	−1.161	0.958	1.468	1	0.284	0.313	0.048	2.048
Other	−0.777	1.231	0.399	1	0.405	0.460	0.041	5.129
Current GAF	−0.039	0.054	0.525	1	0.477	0.962	0.866	1.068
Past anxiety disorder without specific phobia	−0.873	1.834	0.226	1	0.265	0.418	0.011	15.223
Current suicidality	−0.761	1.278	0.354	1	0.457	0.467	0.038	5.723
SIPS-N2 Avolition	0.182	0.373	0.237	1	0.565	1.199	0.577	2.493
SIPS-G2 Dysphoric mood	0.066	0.332	0.039	1	0.714	1.068	0.557	2.048
SIPS-N6.1 Increased stress from daily work	1.627	0.994	2.678	1	0.124	5.088	0.725	35.709
SIPS-D2.1 Strange, fantastic or bizarre thoughts	−0.309	0.963	0.103	1	0.623	0.734	0.111	4.841
SIPS-G1.3 Early waking	3.017	1.170	6.648	1	0.006	20.437	2.062	202.563
SIPS-G2.10 Feeling worthless and/or guilty	1.812	1.127	2.587	1	0.059	6.122	0.673	55.691
SIPS-G3.6 Motor blockages	2.259	1.780	1.610	1	0.088	9.571	0.292	313.588
SPI-CY-A9 Increased emotional reactivity in response to everyday events	−0.007	0.224	0.001	1	0.812	0.993	0.640	1.542
SPI-CY-B1 Decreased ability to discriminate between ideas and perception, fantasy and true memories	−0.270	0.273	0.977	1	0.298	0.763	0.447	1.304
SPI-CY-C3 Increased excitability and irritability	0.473	0.211	5.007	1	0.004	1.605	1.060	2.429

Reference group: children and adolescents without depression or dysthymia at T2.
GoF: $\chi^2(15) = 43.558$; $p < 0.001$; Nagelkerke's $R^2 = 0.616$.
SIPS = Structured Interview for Psychosis-Risk Syndromes; SPI-CY = Schizophrenia Proneness Instrument, Child & Youth version.
[a] Values from Bootstrapping ($N = 984$).

clinical variables that varied with respect to their significance over time. While these predicted depression/dysthymia to a large and often conclusive degree at T0 in all three examined groups (positive LR = 20.34), at follow-ups, the model generated only small but sometimes important changes in pre-test-probability in the CHR-P group (positive LR < 5.0). Yet, the prediction of 'no depression/dysthymia' increased from a small but sometimes important change at T0 to a moderate change in pretest-probability at follow-ups (negative LR < 0.20).

4.1. Prevalence of current depression/dysthymia at baseline

While the 62 % prevalence rate of current depression/dysthymia in the CHR-P sample is well in line with reports of mood disorder rates between 43 % and 69 % in other CAD CHR-P samples (Tor et al., 2018) and the comorbidity rate of depression/dysthymia of 31 % in the inpatient sample is higher than the 2–6 % comorbidity rate of clinically diagnosed mood disorders reported from German CAD inpatient samples (Noterdaeme et al., 2004), the absence of current depression/dysthymia in the community sample is surprising. However, epidemiological studies including not only adolescents but also children commonly reported low one-year prevalence rates of strictly defined depressive disorders of only 1–3 % (Thapar et al., 2022), which corresponds with the 2 % lifetime report of strictly defined depressive disorders in our community sample.

4.2. The role of sociodemographic variables

Nationality was the only sociodemographic variable selected into the model. Compared to Swiss nationality, German nationality increased and other nationality decreased the likelihood of baseline depression/dysthymia in the whole sample, although similar prevalence rates for depression/dysthymia of about 7–10 % were reported for Switzerland and Germany (Sjöberg et al., 2017; Wirz-Justice et al., 2019). This effect was likely due to a sampling bias in disfavour of baseline depression/dysthymia in the total Swiss baseline sample because the general population sample with no case of depression/dysthymia was exclusively recruited in Switzerland. Thus, nationality was no significant predictor for depression/dysthymia in CHR-P patients recruited in both countries at follow-ups. This sampling bias had possibly mediated also the significant negative role of other nationalities at T0, which was also not reproduced in follow-up models.

Interestingly, although depressed participants were significantly older than non-depressed ones at T0, age was not selected into the final model. This may be due to our focus on the vulnerable group of CAD who are regarded a particular important target for preventive efforts (Elovainio et al., 2012; Ghio et al., 2015; Mendelson and Tandon, 2016; Herzog et al., 2021).

4.3. The role of clinical predictors

Of the 13 clinical variables, three were part of the SPI-CY, expectantly, mostly of Adynamia and Neuroticism, and seven were part of the SIPS, expectantly, all but one of them of the Negative and General Symptoms subscale. Additionally, lower current global functioning, current suicidality and any past anxiety disorder (without specific phobia) at T0 were selected into the model.

As with nationality, the significant negative association of current GAF with baseline depression/dysthymia was likely a reflection of sampling bias and due to the inclusion of community participants with predominately good functioning and without depression/dysthymia, and consequently reflected a general association of low global functioning with mental health problems and disorders.

Suicidality is part of the diagnostic criteria of MD, and current suicidality was predictive of concurrent depression/dysthymia at T0 but not at follow-ups. In the CHR-P sample, suicidality decreased over time in both frequency (T0: 42.5 %; T1: 35.9 %; T2: 33.8 %) and severity (T0: 1/3 low and 1/3 high suicidality; T1: 2/3 low and 2 % high suicidality; T2: 3/4 low and no high suicidality), whereas depression/dysthymia increased in frequency. Thus, contrary to meta-analytical reports of significantly higher prevalence rates of past but not of recent suicidality in MD compared to non-MD adult patients (Cai et al., 2021), the association between baseline suicidality and depression/dysthymia weakened over time, i.e., baseline suicidality was not a significant predictor of depression/dysthymia at T1 or T2 in our study. This decreasing association might be linked to development, i.e., increasing age, as CAD MD has consistently been linked to increased risk of suicidality compared to adult-onset MD (Williams et al., 2012). Another explanation might be a possibly conversed role of depression/dysthymia and suicidality, i.e., that MD might actually be a predictor of suicidality (Wiebenga et al., 2021). Thus, newly developed depression/dysthymia at T1 or T2 might not (yet) have resulted in suicidality. This latter interpretation would clearly reinforce calls for an earlier detection and prevention of depressive disorders in order to reduce suicidality.

Despite anxiety and depressive disorders being highly comorbid with

each other and, together, being considered to belong to the broader category of internalizing disorders (Kalin, 2020), past and not current anxiety disorder (without specific phobia) was a significant predictor of depression/dysthymia at T0 but not T1 and T2. This temporal relationship between anxiety and depressive disorders likely reflects differences in age-of-onset. Studies reported that anxiety disorders mostly precede MD, with anxiety disorders usually beginning in preadolescence and early adolescence, whereas MD typically occurs in adolescence and early to middle adulthood (Kalin, 2020). Therefore, early treatment of anxiety disorders might help to prevent developing depression in the following years (Tiller, 2013).

Single symptoms of SPI-CY and SIPS were mostly associated with depression/dysthymia at T0. Only dysphoric mood (SIPS-G2) and motor blockages (SIPS-G3.6) were significant predictors of depression/dysthymia at T1, and early wakening (SIPS-G1.3) and increased excitability and irritability (SPI-CY-C3) were significant predictors of depression/dysthymia at T2. Dysphoric mood (SIPS-G2) can include subthreshold as well as manifest affective disorders by rating phenomena for severity on an assumed continuum from "absent" (0) and "Feeling 'down' or edgy often" (1) to "Painfully unpleasant mixtures of depression, irritability, or anxiety that may trigger highly destructive behaviours like suicide attempts or self-mutilation" (6). Thus, higher severity of mood disturbances was predictive of persistence or new occurrence of depression/dysthymia over one year. Additionally, motor blockages (SIPS-G3.6) predicted depression/dysthymia at T0 and T1. These motor blockages were mostly self-reported by CAD as mainly fleeting moments in that an intended movement could not be performed immediately. Studies showed that especially motor retardation or slowing, of that such temporary blockages may represent a severe form, is a core feature of MD (Caligiuri and Ellwanger, 2000) and was reported to reflect depression risk in CAD (Damme et al., 2022), though it did not predict relapse to MD in adults (Taylor et al., 2010).

Insomnia is part of the diagnostic criteria of MD, and insomnia, in particular problems falling and staying asleep and early wakening, was a significant short- and long-term predictor of MD in a recent meta-analysis across the lifespan (Zhang et al., 2022). Thus, our finding of early wakening being significantly associated with depression/dysthymia at T0 and T2 is well in line with previous studies.

Interestingly, although irritability is considered both an antecedent and a prominent feature of MD in CAD and allowed as a cardinal mood symptom in DSM for CAD only (Copeland et al., 2015; American Psychiatric Association, 1994), increased excitability and irritability (SPI-CY-C3) was positively associated with depression/dysthymia significantly only at T2 and insignificantly at T1 but negatively associated with depression/dysthymia at T0. This may be due to the particular definition of this BS as an irritability that is immediately self-perceived as a deviation of the person's 'normal' emotional reaction and, thus, often reined in. Thus, the behavioural correlates of irritability (e.g., temper tantrums/outbursts, short temper, sulking, snappiness, or shouting) that are usually assessed (Copeland et al., 2015) may not manifest; and the ability to control acting on excessive emotions because of their immediate recognition may also protect against the development of affective disorders in the short- but not the longer-term, when it may get increasingly lost with growing intensity.

Furthermore, an immediately self-experienced increased emotional reactivity in response to everyday events leading to depressive rumination about the event (SPI-CY-A9), feeling worthless and guilty (SIPS-G2.10), increased stress from daily work (SIPS-N6.1) and avolition manifesting in functional impairments (SIPS-N2) were related to depression/dysthymia at T0 but not predictive of depression/dysthymia at follow-up. These symptoms overlap phenomenologically with diagnostic criteria of MD, i.e., with feeling worthless or excessive/inappropriate guilt and fatigue, respectively, Their lack of a predictive power over time is in line with findings of a treatment study (Taylor et al., 2010) in that anergia and feelings of guilt were no predictors of relapse of MD.

It is also noteworthy that, contrary to assumptions that CHR-P symptoms and criteria were transdiagnostic risk factors (Schultze-Lutter et al., 2022), the only CHR-P symptom included in the final model, i.e., decreased ability to discriminate between ideas and perception, fantasy and true memories (SPI-CY-B1) involved in the Cognitive-Perceptive Basic Symptoms criterion, was not significantly and moreover negatively related to depression/dysthymia at T0. A negative association at T0 was also found for strange, fantastic or bizarre thoughts (SIPS-D2.1), a rating of bizarreness that is relevant only in case of potential attenuated psychotic symptoms, i.e., in case of unusual or delusion-like thought contents. This is in line with findings that attenuated psychotic symptoms are linked with the development of psychotic disorders but not of non-psychotic affective disorders (Schultze-Lutter et al., 2012).

4.4. Strengths and limitations

The strengths of our study include the prospective design, the focus on CAD, the large sample size and various groups at baseline, including community participants, the assessment of disorders and symptoms in clinical interviews by clinical psychologists, and the assessment of broad spectrum of symptoms, including subjective, subclinical disturbances. Furthermore, by using established CHR-P assessment tools, i.e. SIPS and SPI-CY, along with routine clinical information, such as suicidality, history of mental disorders and background, our prediction models for persistence/new occurrence of depressive disorders in underage CHR-P patients do not require additional assessments in this patient group in that depression was identified as a domain of substantial unmet clinical need (Addington et al., 2021).

Although the focus of our study was on CHR-P patients, a main limitation is the restriction of the prospective models to the CHR-P group that limits its generalisability to other CAD samples. Yet, this group had been mostly affected by depression/dysthymia already at T0 – confirming the notion of depressive disorders constituting a domain of substantial unmet clinical need in CHR-P patients (Addington et al., 2021). Additionally, half of the CHR-P patients without baseline depression/dysthymia had newly developed depression/dysthymia at any follow-up, this being in line with the significant new-occurrence rate of depression reported earlier (Addington et al., 2021). However, future studies should examine if the same predictors can also be used in other cohorts, such as inpatients without a primary diagnosis of depression/dysthymia or community subjects, as an urgent need for timely early detection and treatment of depressive disorders in CAD has generally been reported (Rice et al., 2019; Roberts, 2013; Kieling et al., 2019, 2021; Noyes et al., 2022; Cuijpers et al., 2021; Fusar-Poli et al., 2013; Schultze-Lutter et al., 2022).

Another main limitation that affects the generalisability of our findings to other CHR-P samples is the lack of an independent validation sample of CHR-P patients. Yet, to account for this lack, we had employed bootstrapping as a method of internal validation.

Furthermore, in case of some symptoms, the low numbers of affirmations, especially in the follow-up samples, had led to problems in the analyses and non-interpretable regression results for some symptoms, which is certainly another limitation. This is also the case for the fact that the relatively low number of CHR-P patients with depression/dysthymia, in particular at follow-ups, prevented the inclusion of possible interactions between the sociodemographic and clinical variables as additional predictors (Vittinghoff and McCulloch, 2007), such as the reported interaction between sex and the association of anxiety/depressive symptoms with self-rated psychotic-like experiences (Long et al., 2024).

Lastly, the study design and our focus on an indicated preventive approach, i.e., on early signs and symptoms, did not allow the consideration of general risk features, in particular quality of family relationships and conflicts in the family as well as school and peer factors (Thapar et al., 2022), relevant to identify risk groups of CAD in terms of

a selective prevention.

5. Conclusions and outlook

Our study indicated that CAD depression/dysthymia in young CHR-P patients may require different predictors depending on the follow-up time. In doing so, mild symptoms of the depressive spectrum played a major role and should be treated early on to address the current unmet clinical need that depressive disorders pose in CAD with CHR-P (Addington et al., 2021). Since the reported prescription of antidepressants was highest in the CHR-P group with persistent depression (Addington et al., 2021), indicating limited efficiency, in line with the intervention guidelines for CHR-P (Schultze-Lutter et al., 2015), psychotherapeutic interventions, in particular interpersonal therapy, cognitive-behavioural therapy or brief problem-solving intervention (Thapar et al., 2022), may be considered a first-line or obligate additional therapy to prevent new occurrence or persistence of depression/dysthymia in this population. Furthermore, in line with findings from other areas of research such as psychosis, the accuracy of ruling out depression/dysthymia seems superior to the accuracy of ruling it in. This might be overcome in future by stepwise approaches that include general risk features and that further stratify risk in those initially identified as at increased risk of depression/dysthymia (Schultze-Lutter and Meisenzahl, 2023).

CRediT authorship contribution statement

Nick Styss: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Chantal Michel:** Project administration, Data curation. **Naweed Osman:** Methodology, Data curation. **Petra Walger:** Conceptualization. **Mauricia Franscini:** Conceptualization. **Nina Traber-Walker:** Conceptualization. **Benno G. Schimmelmann:** Conceptualization. **Rahel Flückiger:** Conceptualization. **Marcel Romanos:** Conceptualization. **Georg Romer:** Conceptualization. **Gerd Schulte-Körne:** Conceptualization. **Ellen Greimel:** Conceptualization. **Eva Meisenzahl:** Project administration, Conceptualization. **Volker Reissner:** Project administration, Conceptualization. **Frauke Schultze-Lutter:** Writing – original draft.

Declaration of competing interest

Mr. Styss and Osman, and Drs. Michel, Walger, Franscini, Traber-Walker, Schimmelmann, Flückiger, Romanos, Romer, Schulte-Körne, Greimel, Meisenzahl, Reissner and Schultze-Lutter have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.04.002.

Data statement

Data is available upon reasonable request for clearly defined scientific purposes from the corresponding author at frauke.schultze-lutter@lvr.de. Participants of the BEARS-Kid study gave informed consent for sharing of anonymized data.

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