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Evidence That Environmental and Familial Risks for Psychosis Additively Impact a Multidimensional Subthreshold Psychosis Syndrome

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Background: **The observed link between positive psychotic experiences (PE) and psychosis spectrum disorder (PSD) may be stronger depending on concomitant presence of PE with other dimensions of psychopathology. We examined whether the effect of common risk factors for PSD on PE is additive and whether the impact of risk factors on the occurrence of PE depends on the co-occurrence of other symptom dimensions (affective dysregulation, negative symptoms, and cognitive alteration).** ***Method:*** **Data from the Netherlands Mental Health Survey and Incidence Study 2 were used. Risk factors included childhood adversity, cannabis use, urbanicity, foreign born, hearing impairment, and family history of affective disorders. Logistic regression models were applied to test (1) the additive effect of risk factors (4 levels) on PE and (2) the moderating effects of symptom dimensions on the association between risk factors (present/absent) and PE, using additive interaction, expressed as the interaction contrast ratio.** ***Results:*** **Risk factors were additive: the greater the number of risk factors, the greater the odds of PE. Furthermore, concomitant presence of the other symptom dimensions all increased the impact of risk factors on PE. After controlling for age, sex, and education, only affective dysregulation and negative symptoms remained significant moderators; only affective dysregulation remained a significant moderator if all dimensions were adjusted for each other.** ***Conclusions:*** **Risk factors may not be directly associated with PE but additively give rise to a multidimensional subthreshold state anticipating the multidimensional clinical syndrome. Early motivational and cognitive impairments in the context of PE may be reducible to affective dysregulation.**

Key words: risk factors/symptom dimensions/psychotic experiences

Introduction

The attenuated form of positive psychosis expression, commonly referred to as psychotic experiences (PE), is prevalent in the general population, with rates between 5% and 8%.[1,2] It frequently co-occurs with affective dysregulation,[3,4] and predicts both PSD[5–7] and mental disorders at large, including mood and anxiety disorders.[4,8] The WHO World Mental Health Surveys demonstrated a bidirectional temporal relation between PE and most mental disorders—the preceding condition increasing the risk of the other over time.[9] Similarly, increased levels of psychosis admixture in nonpsychotic disorders have been observed to impact illness severity,[10] comorbidity,[3] poor outcome,[11] functional impairment,[12,13] and suicidality.[14,15] Furthermore, in a recent study on the distribution of ultra-high risk criteria in the general population, however without applying the help-seeking criterion, the presence of nonpsychotic mental disorders and functional deficits was more likely when attenuated psychotic symptoms co-occurred with cognitive deficits (ie, cognitive–perceptive basic symptoms and cognitive disturbances).[16]

The initial manifestation of a mental condition typically represents a mixture of signs and symptoms accompanied by impairment in various emotional and neurocognitive processes that may include aberrant salience, motivational alterations, affective dysregulation, and anxiety states.[17] The degree of impairment in these dynamically interacting processes, mediated by underlying biological vulnerabilities, predict the degree of progression from a subtle mental state (subthreshold PE) toward clinical disorder (schizophrenia).[17] Taken together, these findings suggest that various symptom dimensions and underlying neurocognitive processes co-occur in both clinical and general populations, and interact with each other between traditional diagnostic categories (eg, depressed mood interact with delusions of reference)[11,18] and within traditional diagnostic categories (eg, auditory hallucinations interact with paranoid ideation).[19,20]

There is evidence that affective dysregulation and psychosis expression co-occur and share a considerable amount of pathoetiological background.[21] The Bipolar-Schizophrenia Network on Intermediate Phenotypes study yielded neurobiological commonalities cutting across the classical Kraepelinian dichotomy,[22,23] while genome-wide association studies consistently showed significant overlap between affective disorders and PSD.[24] In agreement with molecular genetic data, we demonstrated that polygenic risk score (PRS) for schizophrenia in healthy participants and nonill relatives of patients with PSD was expressed not only as positive schizotypy but also in the domains of affective regulation, neurocognition, and attribution of salience.[25] Furthermore, PRS for schizophrenia was associated with lifetime mood episodes (both depressive and manic) in relatives and healthy controls.[25] Confirming the shared vulnerability theory, environmental exposure (like cannabis use, childhood adversity, urbanicity, and hearing impairment) likewise is associated with psychosis and with affective and stress-related phenotypes.[26–29]

It is therefore reasonable to hypothesize that environmental exposure, along with genetic vulnerability, may synergistically alter the degree of blending of affective dysregulation and psychosis expression, thus triggering progression toward a more serious clinical condition. Converging evidence indicates that the degree of psychotic admixture in affective disorders is contingent on the level of environmental exposure that is linked to PSD, such as cannabis use[30] and childhood trauma.[31,32] Previously, our group demonstrated that both childhood adversity and cannabis exposure additively increased the likelihood of admixture of psychosis expression in affective disorders in a dose–response fashion,[33] and that the level of connectivity between different psychopathological dimensions increased as a function of the environmental risk load.[34]

In line with our multidimensional approach to explore the impact of various risk factors on psychopathology in the general population, this study aimed to investigate to what degree the association between common risk factors for PSD (childhood adversity, cannabis use, urbanicity, foreign born, hearing impairment, and family history of affective disorders) and PE is contingent on other components of the multidimensional psychosis spectrum (affective dysregulation, negative symptoms, and cognitive alteration) in the general population. The study also aimed to clarify to what degree risk factors are additive (linearly increasing) or redundant (not adding to each other).

Method

Study Population

Data were obtained from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) designed to investigate the prevalence, incidence, course, and consequences of mental disorders in the Dutch general population. The baseline data of NEMESIS-2 were collected from 2007 to 2009. The study was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care and written informed consent was collected from participants. To ensure representativeness of the sample in terms of age (between the ages of 18 and 65 at baseline), region, and population density, a multistage random sampling procedure was applied.[35] Dutch literacy was an inclusion criterion. Nonclinician, trained interviewers applied the Composite International Diagnostic Interview (CIDI) version 3.0 and additional questionnaires during home visits. Details of NEMESIS-2 were provided elsewhere.[35,36] The first wave (T0) enrolled 6646 participants (response rate 65.1%; average duration: 95 minutes), who were followed up in 2 visits within 6 years: successive response rates at year 3 (T1) and year 6 (T2) were 80.4% (n = 5303; excluding those who deceased; duration: 84 minutes) and 87.8% (n = 4618; duration: 83 minutes), respectively. Data from all waves were utilized. Rates at baseline reflect lifetime occurrence; rates at T1 and T2 reflect interval (baseline T1 and T1–T2) occurrence. Attrition between T0 and T1[37] and between T1 and T2[38] was not significantly associated with any of the 12-month mental disorders at T0 controlled for sociodemographics, except for alcohol and drug dependence at T1 which were significantly related with attrition at T2.[38]

Dimensions of Psychopathology

Psychotic Experiences. To assess PE, a questionnaire constructed based on CIDI 1.1 was used. Participants were asked at baseline (T0; life time symptoms) and at follow-ups (T1 and T2; 3-year symptoms) whether they had experienced any of a list of 20 positive psychotic symptoms (with a binary response: 0 = "no" and 1 = "yes"; items are listed in supplementary table S1).[32,39] For the purpose of this analysis, a dichotomous PE variable was defined as positive if any of the positive symptom items were rated positively.

Affective Dysregulation. The CIDI 3.0 was used to assess depressive, manic, and anxiety symptoms. Affective dysregulation was considered present when participants endorsed at least one of the CIDI 3.0 core symptoms of Depressive Episode, Panic Disorder, Social Phobia, Generalized Anxiety Disorder, and Manic Episode. Affective dysregulation was assessed at each time-point (T0, T1, and T2).

Negative Symptoms. The negative symptom dimension was constructed using 4 items based on interviewer observation: poor personal hygiene and inadequate independent living skills (ie, neatness and cleanness of the participant's residence; were assessed at T1 and T2); lack of emotional expression and poverty of speech (were assessed at T2). Presence of negative symptoms was defined as a rating of "present" on any of these items, which were dichotomized as present = "0" and absent = "1." Presence of negative symptoms at T1 and/or T2 was used as a person-level indicator of "trait" negative symptom at T0.

Cognitive Alteration. The forward and backward digit span tasks from the Wechsler Adult Intelligence Scale—III[40] was used to assess short-term attention and working memory performance, respectively, at T1. A binary cognitive alteration variable was constructed using a cut-off point to define the group of participants with the lowest 20% raw scores of combined forward and backward tasks of digit span. Presence of cognitive alteration at T1 was used as a person-level trait indicator of cognitive alteration at T0 and T2.

Risk Factors

Family History of Affective Disorders. Family history includes depressive, manic, and anxiety items (panic disorder, specific phobia, social phobia, agoraphobia, generalized anxiety disorder) as well as items on drugs and alcohol use. Assessment of family history was limited to the participants who screened positive for affective disorders: depression, mania, and anxiety disorders (panic disorder, specific phobia, and generalized anxiety disorder).

Childhood Adversity. Childhood adversity (CA) was assessed at baseline (T0) across 5 domains (emotional neglect, peer victimization, physical abuse, psychological abuse, and sexual abuse; before age 16) using a questionnaire based on the NEMESIS-1 trauma questionnaire.[35] Subjects were asked whether they experienced emotional neglect, psychological abuse, peer victimization or physical abuse on ≥2 occasions, or sexual abuse on ≥1 occasion. A person-level continuous CA variable was constructed using the sum score of the 5 domains. In accordance with previous research,[41] CA was dichotomized at the 80th percentile.

Cannabis Exposure. Cannabis use was assessed with the section Illegal Substance Use of the CIDI 3.0 at baseline (T0; lifetime) and at follow-ups (T1 and T2; 3-year). If subjects reported cannabis use, they were rated on frequency of use in the period of most frequent use on a scale of 1 (never) to 7 (every day). Consistent with previous work,[42] a binary variable was constructed by using the cut-off value of once per week or more in the period most frequent use.

Urban Environment. Exposure to an urban environment until age 16 years was assessed at baseline (T0) and analyzed as a person-level variable across the 3 waves at 5 levels: (1) countryside (distances to amenities is bigger), (2) village (<25 000 inhabitants), (3) small city (25 000–50 000 inhabitants), (4) medium city (50 000–100 000 inhabitants), 5) large city (>100 000 inhabitants). Conforming to previous work using the NEMESIS-I dataset,[34] the cut-off of more than 50 000 inhabitants was used to define the binary variable of urban area.

Foreign Born. Country of birth was assessed at baseline (T0) and analyzed as a person-level variable across the 3 waves. It was used as a proxy for minority status (born in the Netherlands = "0" and born in other countries = "1").

Hearing Impairment. Hearing impairment was assessed at each time-point (T0, T1, and T3), based on self-reported hearing impairment in the last 12 months (absent = "0" and present = "1").

Statistical Analysis

Analyses were performed using Stata 14.2.[43] Consistent with previous work,[33] data from all waves were analyzed cross-sectionally in the "long format" (each participant contributing 3 observations: T0, T1, and T2). This analytical strategy serves the purposes of increasing overall reliability and achieving consistency across a limited number of variables of interest that in some cases were assessed differently at different time points. Using the CLUSTER option, all analyses were corrected for clustering of multiple observations within subjects, and cluster-robust standard errors were computed. To evaluate the effect of the risk-loading on PE, logistic regression analysis, using the LOGISTIC command, was modeled with PE as dependent variable and the 4-level risk score (no = 0, low = 1, medium = 2, and high > 2 risk factors) as independent variable. The model was adjusted for sex, age, and education (1 = primary school, 2 = lower secondary education, 3 = higher secondary education, 4 = higher professional education). The LINCOM command was applied to test OR differences between groups with low and medium, medium and high, and low and high risk.

Logistic regression models were used to analyze whether the association between the presence of any risk factors (absent = 0; presence of one or more risk factors = 1) and PE was dependent on symptom dimensions (affective dysregulation, negative symptoms, and cognitive

alteration). The interaction contrast ratio (ICR) method was applied to explore the interaction between risk factors and symptom dimensions in the model of PE. To test additive interaction, 4 exposure states were produced by the combination of each dimension and risk. In logistic models, the combinations served as the independent variables (3 dummy variables with nonexposed state as the reference category) and PE served as dependent variable. Using the ORs from these models, ICRs for each model were calculated using the NLCOM command in Stata: eg, ICR = OR (risk) + OR (affective dysregulation) − OR (risk) − OR (affective dysregulation) + 1. These models were further adjusted for age (continuous), sex, and education level (4 levels). In the final adjusted models, psychopathology dimensions were additionally controlled for each other.

Results

The total sample for the analyses included 16 567 observations from subjects who participated at the 3 time-points (T0, n = 6646; T1, n = 5303; T2, n = 4618). The baseline demographics of the NEMESIS-2 sample have been described previously[32] and an overview of the 3 time-points is presented in table 1. Supplementary table S1 reports the frequencies of individual PE items at each time-point.

Dose–Response Relationship Between the Risk-Loading and PE

Analyzing environmental and familial risk load at 4 levels (no = 0, low = 1, medium = 2, and high > 2 risk factors), irrespective of PSD dimensions, revealed a dose–response relationship between risk and PE: With "no exposure" as the reference group, risk categories displayed progressively higher odds ratios: OR = 1.84, 95% CI = 1.58–2.13, P < .001 for the low risk group; OR = 3.11, 95% CI = 2.64–3.66, P < .001 for the medium risk group; OR = 5.78, 95% CI = 4.77–7, P < .001 for the high risk group. Furthermore, comparison with the LINCOM command indicated significant differences between the groups with low and medium risk (OR = 1.7, 95% CI = 1.47–1.94, P < .001), medium and high risk (OR = 1.86, 95% CI = 1.56–2.22, P < .001), and low and high risk (OR = 3.15 95% CI = 2.64–3.74, P < .001). Figure 1 shows the frequencies of individual risk factors within risk strata (no = 0, low = 1, medium = 2, and high > 2 risk factors) at baseline level. Figure 2 shows the prevalence of PE across the risk strata, including data from participants with information from all time-points.

Testing the Moderating Effects of Affective Dysregulation

The association between risk and PE was greater if there was also evidence for affective dysregulation (table 2). Figure 3A shows that the adjusted OR for those with affective dysregulation and risk factors was 6.29, in comparison with ORs of 1.27 for those with risk factors only, and 3.04 for those with affective dysregulation only, yielding an ICR of 2.98 (P < .001). The additive effect of affective dysregulation remained significant after the other dimensions of psychopathology (negative symptoms, cognitive alteration) were controlled for, with an ICR of 2.74 (95% CI = 1.92–3.55, P < .001).

Testing the Moderating Effects of Negative Symptoms

The association between risk and PE was greater if there was also evidence for negative symptoms (table 2). Figure 3B shows that the adjusted OR for those with negative symptoms and risk factors was 5.35, in comparison with ORs of 2.45 for those with risk factors only, and 1.69 for those with negative symptoms only, yielding an ICR of 2.20 (P = .004). After controlling for the other

Table 1. Summary of Descriptive Data

	Baseline, n = 6646	3-Year Follow-Up, n = 5303	6-Year Follow-Up, n = 4618
Sex, female	3672 (55.3)	2922 (55.1)	2558 (55.4)
Mean age, years (SD)	44.3 (12.5)	47.6 (12.4)	50.9 (12.3)
Education			
Primary education	332 (5)	226 (4.3)	186 (4)
Lower secondary education	1826 (27.5)	1388 (26.2)	1193 (25.8)
Higher secondary education	2145 (32.3)	1728 (32.6)	1479 (32)
Higher professional education, university degree	2343 (35.3)	1961 (37)	1760 (38.1)
Foreign born	920 (13.8)	650 (12.3)	529 (11.5)

Note: Data are given as number (percentage) unless otherwise indicated.

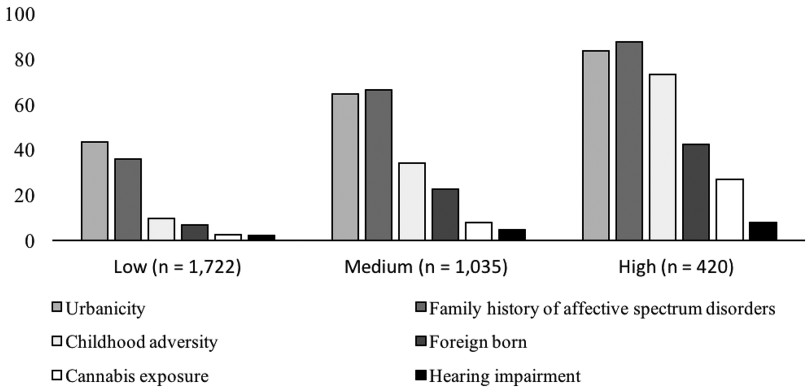

Fig. 1. The frequencies of risk factors within risk factor strata at baseline assessment. This figure shows the frequencies of individual risk factors in each risk stratum at baseline: No risk factor = 0, low risk = 1 risk factor, medium risk = 2 risk factors, and high risk > 2 risk factors. Data were given in percentages based on the individual sample sizes of the low, medium, and high risk groups, respectively.

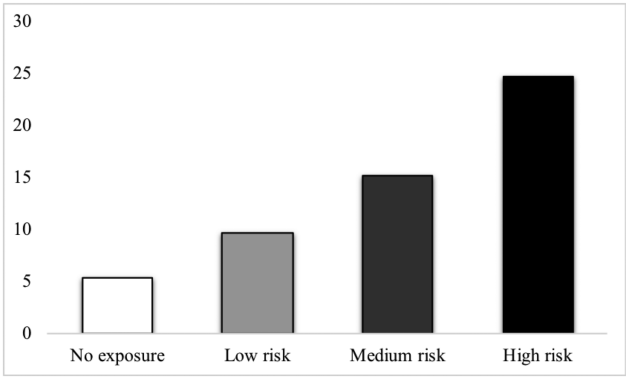

Fig. 2. The prevalence of psychotic experience across risk strata. This figure reports the percentage of people with at least one PE within each risk stratum: No risk factors = 0, low risk = 1 risk factor, medium risk = 2 risk factors, and high risk > 2 risk factors.

dimensions of psychopathology (affective dysregulation, cognitive alteration), there was no significant additive effect (ICR = −0.35, 95% CI = −1.09 to 0.39, P = .36).

Testing the Moderating Effects of Cognitive Alteration

The association between risk factors and PE was greater if there was also evidence for cognitive alteration (table 2). However, the additive effect was no longer significant in either the adjusted model (Figure 3C) nor in the model controlled for the other symptom dimensions (negative symptoms, affective dysregulation; ICR = −0.28, 95% CI = −0.71 to 0.15, P = .20).

Discussion

We explored the possible existence of a risk-loading effect on PE and investigated whether the association between the risk for PSD and PE was contingent on multidimensional psychopathology (affective dysregulation, negative symptoms, and cognitive alteration). The findings were that: (1) risk factors additively increased the likelihood of PE in a dose–response fashion; (2) affective dysregulation, negative symptoms, and cognitive alteration additively increased the association between risk factors and PE; (3) the association of risk factors with affective dysregulation and negative symptoms remained significant in the model adjusted for age, sex, and education; (4) the association of risk factors with affective dysregulation remained significant in the final model, when all PSD dimensions were controlled for each other.

Multidimensional Psychopathology

There is growing evidence that psychosis expression represents a severity indicator for multidimensional psychopathology cutting across traditional diagnostic boundaries,[8,14,44] and that nonpsychotic symptoms, such as affective dysregulation,[12,45] negative symptoms,[13,46] and neurocognitive alteration[13,46,47] precede the early stages of PSD and predict progression to more severe states. The current population-based study provides additional support for this concept by showing that epidemiological risk factors for PSD are not exclusively associated with PE, but rather with the degree of amalgamated multidimensional psychopathology.[48–50]

Our findings are in agreement with the literature showing symptom dimensions interrelate within[19,20] and between[11,18] different diagnoses, and that the severity of clinical outcomes of diverse clinical representations may depend on the degree of interconnection between those dimensions.[7,13,20,51] For instance, the presence of PE in anxiety or depression disorders was shown to predict severity of clinical outcomes and treatment response[7,52,53]; and by investigating fluctuations of momentary mental states (eg, paranoia, positive, and negative affect) in daily life, studies using the experience sampling methodology found that an increased connectivity between momentary states was associated with symptom severity and need for care.[54–56]

Consistent with previous research, current findings suggest that risk factors operate by intensifying the multidimensional blending of affective and

Table 2. Additive Effect of Dimensional Components on the Association Between Risk Factors and Psychosis Expression

	Unadjusted Model			Adjusted Model[a]			Adjusted Model[a] (Corrected for the Other Dimensions)		
	ICR	95% CI	*P*	ICR	95% CI	*P*	ICR	95% CI	*P*
Affective dysregulation	3.18	2.37; 3.98	<.001	2.98	2.21; 3.75	<.001	2.74	1.92; 3.55	<.001
Negative symptoms	2.68	1.13; 4.23	.001	2.20	0.71; 3.69	.004	−0.35	−1.09; 0.39	.355
Cognitive alteration	0.74	0.025; 1.45	.042	0.55	−0.16; 1.26	.128	−0.28	−0.71; 0.15	.199

Note: ICR, interaction contrast ratio; CI, confidence interval.
[a]Adjusted for age, sex, and education; controlled.

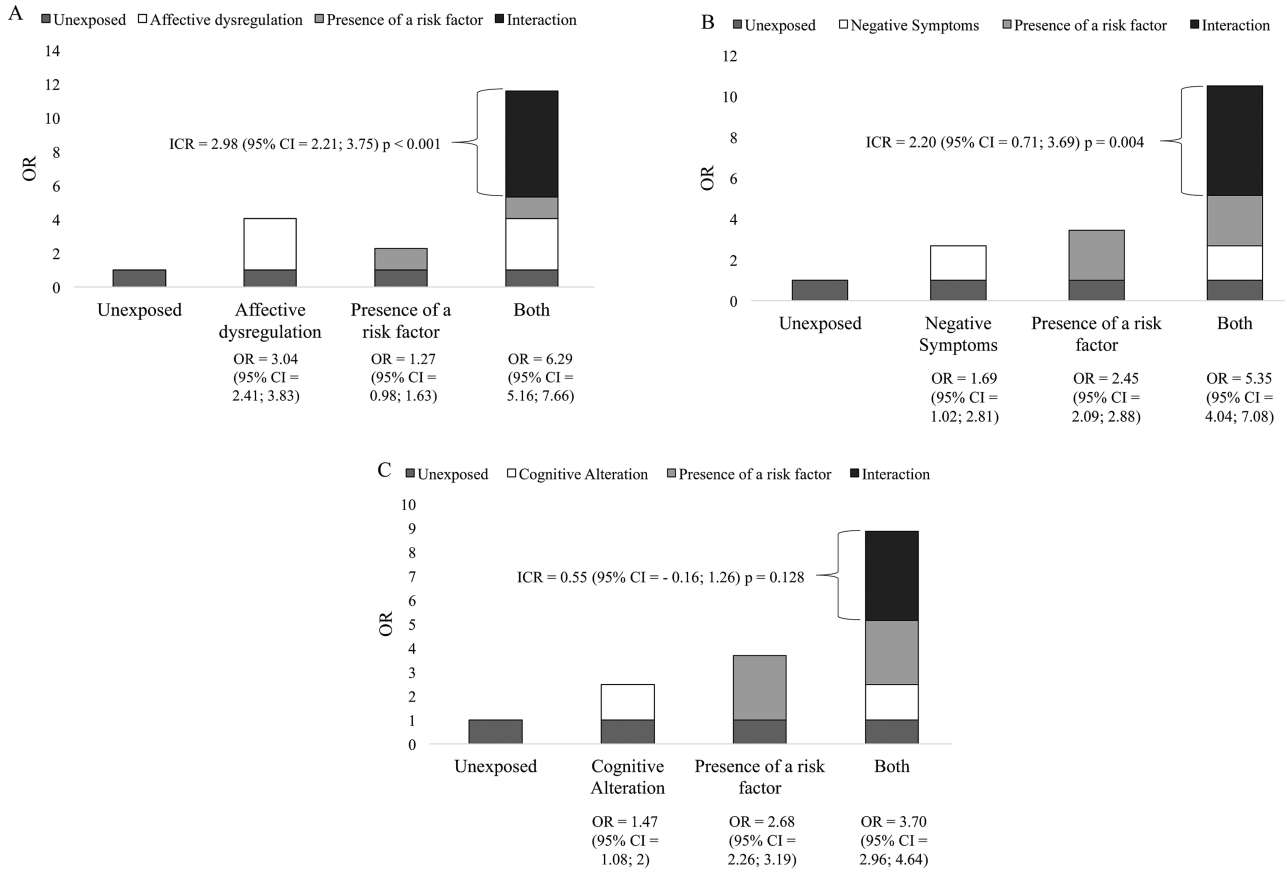

Fig. 3. Figure shows the additive effects of symptom dimensions (A: affective dysregulation, B: negative symptoms, C: cognitive alteration) on the association between risk factors and PE adjusted for sex, age, and education.

cognitive processes,[51,57–60] as well as the negative symptom domain[13,61] in the development of PSD. This finding fits well with our previous findings showing that the risk-loading (childhood trauma, urbanicity, cannabis use, and discrimination) amplifies connectivity between different symptom dimensions.[34] Similarly, exposure to cannabis use and childhood trauma was found to increase associations between hallucination and delusion in healthy and in genetically at risk populations[18,19]; while another study reported that exposure to childhood trauma had a stronger correlation with a combined symptom network rather than the individual symptoms.[32] Our finding that only the effect of affective dysregulation remained significant after the adjustment for the other dimensions is furthermore compatible with the theory of an "affective path to psychosis."[57,62]

The Risk-Loading in the Context of Liability Threshold Model

The results echo findings from previous research showing a dose–response relationship between risk factors and PE,[33,63] emphasizing the effects of risk-loading for PSD. Recently, researchers attempted to construct a "polyenviromic risk score" (PERS) for psychosis (the sum of weighted scores of known environmental risk factors based on their association with psychosis reported in meta-analyses). Despite several methodological issues, this proof-of-concept study showed that higher PERS predicted greater risk of developing psychosis in genetically at-risk individuals.[64] Additionally, recent studies of individualized risk calculators for psychosis focusing on demographic, clinical, and some environmental predictors may provide insight into estimating psychosis risk in clinical settings.[65,66]

It is plausible to argue that the mechanisms underlying the development of PSD may be best understood in the context of the liability-threshold model[67] that posits the combination of various genetic and environmental factors—with each factor adding to the risk load—adding to the manifestation of a phenotypic outcome. The distribution of liability may not be continuous, as the apparent phenomenological and temporal continuity of psychotic experiences with PSD may in fact reflect an underlying discontinuous population distribution consisting of vulnerable and nonvulnerable individuals.[68,69]

To further investigate environmental and genetic risk loading, future studies should focus on constructing reproducible total scores of environmental exposures, along with a single metric of aggregated molecular genetic variation (PRS), to disentangle the additive effects of gene–environment interplay on the development and course of PSD.

Given the complexity of multi-dimensional psychopathology, the network approach to symptoms ("symptomics"), a rapidly evolving analytical strategy, may also provide an alternative platform to gain insight into the role of gene–environment interplay in the development and progression of PSD, with initial findings showing (at least) some promise but requiring replication.[70,71]

Limitations

The primary strength of this study was the multi-domain clinical phenotyping and the use of a large and representative population cohort collected at 3 time-points over 6 years. However, various methodological limitations should be considered when interpreting the findings.

First, the cross-sectional analysis of the dataset merging data from each time-point in the "long-format," while decreasing threats to external validity, cannot be taken as absolutely confirmatory of causality.[72] Ideally, a time series analysis of a birth cohort—followed up with regular in-depth assessments at short-enough intervals to capture emerging psychopathology stretching over the period at risk for emerging mental disorders—is required to yield essential information to understand the impact of psychosis liability on the emotional, behavioral, and cognitive components of PSD. With no such data available now or in the near future, our practical strategy, despite its shortcomings, expands our knowledge-base, implying that the association between psychosis risk and psychosis expression is moderated by existing multidimensional psychopathology.

Second, although the dataset includes a fine-grained assessment of positive PE and affective symptomatology, there were only 4 proxy items appraising the negative symptom dimension. A more thorough assessment, using a validated rating scale with focus on measuring the negative symptom dimension as well as PE in the general population (such as the Structured Interview for Schizotypy—Revised (SIS-R) and the Community Assessment of Psychic Experiences (CAPE)) could have been beneficial in capturing the negative symptom dimension across the full range.

Third, our approach to risk stratification through aggregating vulnerability factors assumes a linear increase in the risk for psychosis as a function of the number of risk factors and weighs each risk factors equally by overlooking any specific feature pertaining to individual risk factors and their synergistic effects.

Although current findings are in line with those of previous studies in different population-based datasets, replications are necessary. We aim for reproducing the findings in the European network of national schizophrenia networks studying gene–environment interaction dataset, which includes heterogeneous, international, multi-ethnic samples of patients, relatives, and healthy controls.[73,74]

Conclusion

Consistent with previous findings, this study demonstrates that the association between psychosis expression and risk-loading (environmental and familial) is contingent on the dimensions of PSD, lending further support to the framework of an affective path to psychosis. Also, as predicted by the liability-threshold model, in which vulnerability for a phenotypic outcome can be modeled as a continuous metric of quantifiable risk, the aggregated risk-loading increased the odds of psychosis expression in a dose–response fashion.

Overall, our recent findings, combined with strong evidence from unbiased population-based cohorts, demonstrate the need for reconstructing the framework of psychosis by integrating multidimensional measurement of psychopathology to advance our understanding of the complex network of biopsychosocial mechanisms underlying the early progression of psychopathology and to dissect diverse developmental paths to psychosis.[75]

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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