Association of Attenuated Niacin Response With Inflammatory Imbalance and Prediction of Conversion to Psychosis From Clinical High-risk Stage

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ABSTRACT

Objective: Attenuated niacin responses and changes in cytokine levels have been reported in schizophrenia. However, prior studies have typically focused on schizophrenia, and little is known about the association between niacin response and inflammatory imbalance in clinically high-risk psychosis (CHR). This study aimed to assess the niacin response to inflammatory imbalance for association with conversion to psychosis within 2 years.

Methods: A prospective case-control study was performed to assess the niacin response and interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α levels in 60 CHR individuals and 60 age- and sex-matched healthy controls (HC) from May 2019 to December 2021. Participants with CHR were identified using the Structured Interview for Prodromal Syndromes. The niacin-induced responses were measured using laser Doppler flowmetry. From the dose-response curves, the log-transferred concentration of methylnicotinate required to elicit a half-maximal blood flow response ($LogEC_{50}$) and maximal minus minimal blood flow response (Span) values were calculated for each subject. Serum cytokine levels were measured using enzyme-linked immunosorbent assay. Individuals with CHR were then divided into converters (CHR-C, n = 15) and non-converters (CHR-NC, n = 45) to psychosis based on their 2-year follow-up clinical status.

Results: The CHR group exhibited significantly higher $LogEC_{50}$ ($t = 3.650$, $P < .001$) and Span ($t = 2.657$, $P = .009$) values than the HC group. The CHR-C group exhibited a significantly shorter Span ($t = 4.027$, $P < .001$) than the CHR-NC group. The $LogEC_{50}$ showed a trend toward significance ($t = 1.875$, $P = .066$). None of the cytokine levels were significant. The conversion outcome can therefore be predicted by applying $LogEC_{50}$ ($P = .049$) and Span ($P < .001$). The regression model with variables of $LogEC_{50}$, Span, family history, and scores of positive symptoms showed good discrimination of subsequent conversion to psychosis and achieved a classification accuracy of 91.7%. The decreased $LogEC_{50}$ in the CHR-C group was significantly correlated with the increased IL-1β/IL-10 ratio (Spearman $\rho = -0.600$, $P = .018$), but this correlation was nonsignificant in the CHR-NC group.

Conclusions: Our findings indicate a significant association between niacin response and psychosis conversion outcomes in individuals with CHR. Compared with peripheral inflammatory cytokines, the niacin response can better predict conversion, although there may be an intersection between the two in biological mechanisms.

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Psychosis, mainly represented by schizophrenia, is among the top 25 leading disabilities worldwide, affecting approximately 1% of the population.[1] The early onset and incurable nature of this illness have led scientists to try to block the progress of its onset before it occurs.[2] Patients with psychosis generally undergo a prodromal stage before full-blown psychotic symptoms appear, during which individuals may experience attenuated symptoms,[3] mild cognitive decline,[4,5] and functional impairments.[6] Individuals in this phase are identified as clinically high risk (CHR), and knowledge of this is crucial for initiating precise prevention.

However, heterogeneity of psychosis, especially in the CHR population,[7] is one of the main difficulties of early identification and effective intervention. An alternative approach for treating this complex syndrome is to introduce biomarkers to identify subtypes based on specific biometrics.[8] An attenuated skin flush response to niacin has been widely replicated in schizophrenia,[9–11] is recognized as an endophenotype,[12] and is more prevalent in patients with schizophrenia and their family members than in healthy controls and patients with other mental disorders such as depression,[13] bipolar disorder,[14] and anxiety disorders.[15]

Unlike other etiologic hypotheses in psychosis, the biochemical basis of the attenuated niacin response is reasonably understood and is linked to prostaglandins in the cyclooxygenase pathway. Niacin activates a specific G-protein–coupled receptor (GPCR)[16] in response to skin contact. GPCR activation stimulates phospholipase A2 activation,[17] leading to release of arachidonic acid from cell membranes, followed by cyclooxygenase-mediated conversion to vasodilatory prostaglandins, mostly vasodilatory prostaglandins D2 and E2,[18] which promote vasodilation and skin flushing. However, it is still unclear how changes in the prostaglandin pathway are caused during psychosis. Previous studies in patients with schizophrenia have reported imbalances in $CD4^+$ T helper (Th)1/Th2 cytokines[19,20] and have suggested that the inflammatory imbalance may be related to an attenuated flush response.[21] A recent review by Ansarey[22] showed that inflammatory imbalance in schizophrenia plays an important role in regulating the flush response.

To date, no study has evaluated the association between niacin-induced response and inflammatory imbalance during the progression from CHR to full psychosis. The aim of this study was to examine the association of attenuated niacin response, as quantified using the volumetric niacin response obtained

Clinical Points

- Attenuated niacin response in individuals with clinical high risk is associated with an increased risk of developing psychosis.
- Inflammatory imbalance may represent an intersection between the biological mechanisms underlying attenuated niacin response and development of psychosis.
- Measurement of the niacin-induced response yields better predictive power than measurement of serum inflammatory cytokines.

through laser Doppler flowmetry, with a 2-year outcome of conversion to psychosis and with Th1/Th2 immune imbalance, measured using serum levels of interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF-α). We hypothesized that an attenuated niacin response would be observed in individuals with CHR, especially in those who converted to psychosis during the follow-up. We further hypothesized that the niacin response is related to Th1/Th2 immune imbalance.

METHODS

Participants

Participants with CHR were recruited and followed up with at the early psychosis service of the Shanghai Mental Health Center (SMHC) between May 2019 and December 2021. The ethics committee of the SMHC approved this study. All subjects gave written informed consent for the baseline clinical interviews, the niacin sensitivity skin test, blood sample collection, and the follow-up process. Participants younger than 18 years old had their consent forms signed by their guardians, and the adolescents gave verbal consent.

In total, 73 CHR participants were recruited through face-to-face interviews based on the Structured Interview for Prodromal Syndromes (SIPS).[23,24] Participants aged 14–35 years were naïve to psychotropics when they entered the study and had not received treatment for any psychiatric disorders. Notably, none of the participants had a history of substance abuse or dependence. In addition, all participants were required to confirm before the niacin test that they had not recently (within 2 weeks) used nonsteroidal anti-inflammatory drugs. A total of 60 CHR participants completed niacin tests, provided blood samples at baseline (2 of 73 did not complete baseline tests), and received face-to-face SIPS assessments at the 2-year follow-up (11 of 73 were lost during the follow-up period). Sixty healthy controls (HC) were recruited from the community during the same period. Clinical and cognitive assessments, niacin-sensitivity skin test, and blood sample collection from HC at baseline and follow-up were performed using consistent methods and conditions used with CHR individuals.

Clinical, Cognitive, and Outcome Assessments

The SIPS[23] was used to identify individuals with CHR who met 1 of the following prodromal syndrome criteria: (*a*) brief intermittent psychotic syndrome, (*b*) attenuated positive symptom syndrome, or (*c*) genetic risk and deterioration syndrome. The SIPS consists of 19 items that assess 4 symptom domains: positive (scale P1–P5: P1, unusual thought content; P2, suspiciousness; P3, grandiosity; P4, perceptual abnormalities; and P5, disorganized communication), negative (scale N1–N6: N1, social anhedonia; N2, avolition; N3, expression of emotion; N4, experience of emotions and self; N5, ideational richness; and N6, occupational functioning), disorganized (scale D1–D4: D1, odd behavior or appearance; D2, bizarre thinking; D3, trouble with focus and attention; and D4, impairment in personal hygiene), and general symptoms (scale G1–G4: G1, sleep disturbance; G2, dysphoric mood; G3, motor disturbances; and G4, impaired tolerance to normal stress). The Global Assessment of Functioning (GAF)[25] was used to measure the global psychological, social, and occupational functioning of the patients and to assess functional deterioration (score relative to 12 months prior) in the SIPS interview. Conversion to psychosis, determined using the criteria for Presence of Psychotic Symptoms[26] from the SIPS, was the major outcome of this study. Specifically, CHR converters (CHR-C) were defined by the presence of a level 6 positive symptom (the rating "6" refers to severe and psychotic) that was dangerous or disorganized or occurred at least an hour a day on average over 4 days a week, for at least 16 hours total. SIPS was performed at baseline and at the 2-year follow-up.

Neurocognitive performance was assessed using the Chinese version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB).[27] The MCCB was administered according to the standardized guidelines of the test manual. Consistent with the original version of the MCCB, the Chinese versions of the following 8 subtests were included in the present study: (1) part A of the Trail Making Test (Trail Making A), (2) symbol coding of the Brief Assessment of Cognition in Schizophrenia (BACS, BACS symbol coding), (3) Category Fluency Test (Category Fluency), (4) Continuous Performance Test-Identical Pairs (CPT-IP), (5) spatial span of the Wechsler Memory Scale-III (WMS-3 spatial span), (6) Revised Hopkins Verbal Learning Test (HVLT-R), (7) Revised Brief Visuospatial Memory Test (BVMT-R), and (8) Neuropsychological Assessment Battery: Mazes. The test-retest reliability in a previous Chinese psychosis sample ranged 0.73–0.94.[27] MCCB was performed at baseline and at the 2-year follow-up.

Quantification of Niacin Sensitivity

The cutaneous blood flow response to increasing concentrations of topical methyl nicotinate was measured according to the protocol of Messamore et al.[28] The log10 transformed $LogEC_{50}$ (the concentration of methyl nicotinate required to elicit a half-maximal blood flow [MBF] response) and Span (maximal minus minimal blood flow response) values from the dose-response curve

Table 1. Baseline Demographic, Clinical, and Cognitive Variables—Comparison Between CHR-C and CHR-NC

Variables	HC	CHR-Total	CHR-C	CHR-NC	Comparison $t/\chi^{2,a}$	Comparison P value[b]
Cases, n	60	60	15	45		
Age, mean (SD), y	20.8 (2.6)	19.7 (6.1)	19.5 (6.0)	19.8 (6.2)	0.145	.885
Male, n (%)	27 (45.0)	25 (41.7)	4 (26.7)	21 (46.7)	$\chi^2 = 1.851$	.174
Female, n (%)	33 (55.0)	35 (58.3)	11 (73.3)	24 (53.3)		
Education, mean (SD), y	12.4 (2.5)	11.6 (3.1)	11.8 (3.7)	11.6 (2.9)	0.236	.814
Family history, n (%)						
None	60	40 (66.7)	3 (20.0)	37 (82.2)	$\chi^2 = 21.621$	**<.001**
Low-risk[c]	0	19 (31.7)	12 (80.0)	7 (15.6)		
High-risk[d]	0	1 (1.7)	0 (0)	1 (2.2)		
Clinical variables, mean (SD)						
APSS	0	51 (85.0)	11 (73/3)	40 (88.9)	$\chi^2 = 1.608$	.447
GRDS	0	2 (3.3)	0 (0)	2 (4.4)		
BIPS	0	8 (13.3)	3 (20.0)	5 (11.1)		
Highest GAF in past year	80.4 (2.6)	77.8 (4.5)	78.0 (5.6)	77.8 (4.2)	0.179	.858
Current GAF	79.8 (2.8)	58.4 (8.4)	59.5 (8.9)	58.0 (8.3)	0.599	.552
GAF drop[e]	0.6 (2.3)	19.4 (7.2)	18.5 (7.3)	19.7 (7.3)	0.584	.561
Positive symptoms	0.8 (0.8)	9.0 (3.6)	10.9 (4.2)	8.4 (3.2)	2.389	**.020**
Negative symptoms	2.2 (1.1)	11.6 (5.8)	10.3 (6.4)	12.0 (5.7)	0.944	.349
Disorganization symptoms	1.3 (1.0)	4.4 (2.7)	4.6 (2.5)	4.3 (2.8)	0.329	.744
General symptoms	3.2 (1.4)	8.6 (3.5)	8.2 (4.1)	8.8 (3.4)	0.526	.601
SIPSTAL	7.6 (2.1)	33.6 (12.2)	34.0 (11.7)	33.4 (12.4)	0.152	.880
Cognitive variables, mean (SD)						
Trail Making A	27.9 (11.5)	30.6 (11.0)	31.1 (7.6)	30.4 (12.0)	0.201	.841
BACS symbol coding	68.4 (11.2)	56.0 (10.5)	56.2 (6.8)	56.0 (11.6)	0.077	.939
Category Fluency	23.0 (5.5)	19.8 (6.4)	19.3 (5.0)	20.0 (6.8)	0.371	.712
CPT-IP	3.0 (0.6)	2.4 (0.8)	2.8 (0.6)	2.3 (0.8)	1.982	.052
WMS-3 spatial span	17.1 (3.4)	14.9 (3.4)	13.7 (2.5)	15.2 (3.6)	1.517	.135
HVLT-R	27.2 (4.2)	24.5 (5.5)	26.0 (4.6)	24.0 (5.8)	1.250	.216
BVMT-R	29.8 (5.6)	25.8 (6.6)	26.8 (5.0)	25.4 (7.1)	0.698	.488
NAB mazes	19.3 (5.6)	17.4 (5.9)	15.4 (6.3)	18.0 (5.7)	1.527	.132

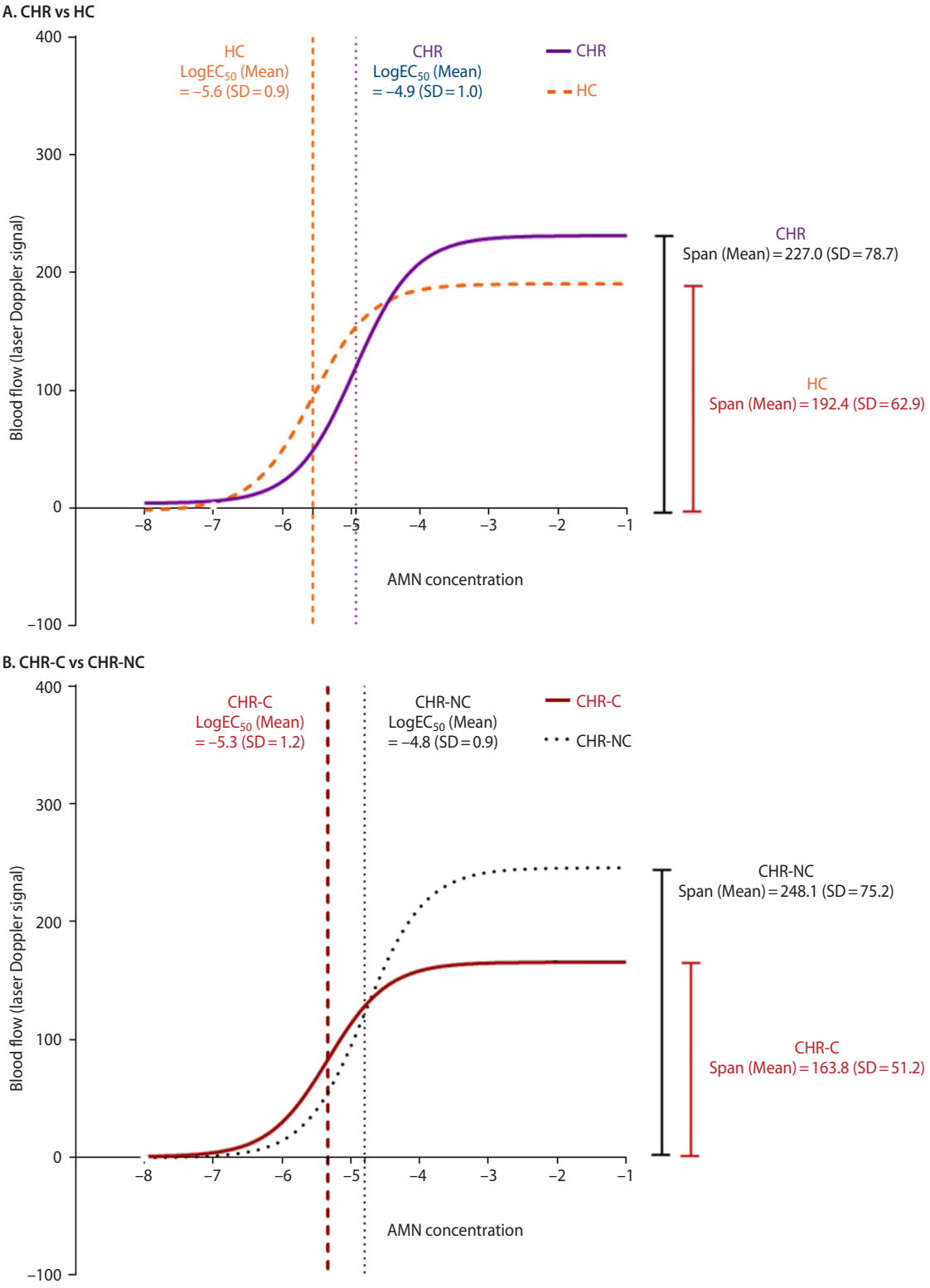
[a] $t/\chi^2 = t$ for independent t test and χ^2 for κ test.
[b] Boldface indicates significance.
[c] Low-risk family history = having any family members with mental disorders or a first-degree relative with non-psychotic disorders.
[d] High-risk family history = having at least 1 first-degree relative with psychosis.
[e] The highest GAF score in the past year minus the baseline GAF score.
Abbreviations: APSS = attenuated positive symptom syndrome, BACS = Brief Assessment of Cognition in Schizophrenia Symbol Coding, BIPS = brief intermittent psychotic syndrome, BVMT-R = Brief Visuospatial Memory Test–Revised, CHR = clinical high risk for psychosis, CHR-C = CHR individuals who converted to psychosis, CHR-NC = CHR individuals who did not convert to psychosis, CPT-IP = Continuous Performance Test–Identical Pairs, GAF = Global Assessment of Functioning, GRDS = genetic risk and deterioration syndrome, HC = healthy controls, HVLT-R = Hopkins Verbal Learning Test–Revised, NAB = Neuropsychological Assessment Battery, SIPSTAL= total score of the Structured Interview for Prodromal Syndromes, WMS-3 = Wechsler Memory Scale–Third Edition.

were applied to quantify the niacin sensitivity of each participant.[29] As LogEC_{50} values increased, Span values decreased, and niacin response attenuation was exacerbated. The cutaneous blood flow was measured using a laser Doppler flowmeter (PeriFlux System 5000). Laser Doppler signals from 8 recording sites on the anterior surface of the forearm (4 sites on each arm) were measured. To ensure a reliable comparison of the laser Doppler signals between participants, the instrument was regularly calibrated to the Brownian motion of latex particles in a standardized solution according to the manufacturer's instructions. EC_{50} values were obtained from nonlinear dose-response regression curves using Prism software (GraphPad Inc.).[28] The niacin response test was performed only at baseline.

Cytokine Measurement

Venous blood samples were drawn in the morning; the participants fasted for a minimum of 3 hours prior to blood collection. Blood samples were collected at the baseline time point. Ten milliliters of peripheral venous blood were drawn into anticoagulant-free tubes. The samples were kept for 1 hour, followed by centrifugation (1,710 g for 20 min at 4°C) for serum separation. Subsequently, the serum was separated and stored at −80°C until analysis. The serum levels of IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α in each sample were measured in duplicate using the enzyme-linked immunosorbent assay (ELISA) with the Human HS Cytokine Premixed Kit (catalog #: FCSTM09-10, USA). The concentration of cytokines was expressed as picograms of protein per milliliter of serum (pg/mL). All data were calibrated using standard curves generated for each cytokine. IL-1β, IL-2, and TNF-α were selected to represent Th1 cells, whereas IL-6 and IL-10 were selected to represent Th2 cells. The imbalance described in this study refers to the Th1/Th2 ratio relative to the ratio obtained from the HC group.

Figure 1. Dose Effect Curve for Niacin-Induced Response Expressed as $LogEC_{50}$ and Span Values in (A) CHR vs HC and (B) CHR-C vs CHR-NC



Abbreviations: AMN = aqueous methylnicotinate, CHR = clinical high risk for psychosis, CHR-C = CHR individuals who converted to psychosis, CHR-NC = CHR individuals who did not convert to psychosis, HC = healthy controls.

Table 2. Inflammatory Cytokines and Th1/Th2 Ratios—Comparisons Between CHR and HC and Between CHR-C and CHR-NC

			Comparison				Comparison	
Variables	CHR-Total	HC	*t*	*P*	CHR-C	CHR-NC	*t*	*P*
Cases	60	60			15	45		
LnIL-1β	−0.8 (0.7)	−0.9 (0.9)	0.598	.551	−1.1 (0.7)	−0.7 (0.7)	1.673	.100
LnIL-2	−0.9 (0.7)	−1.0 (1.2)	0.643	.522	−0.6 (0.4)	−1.0 (0.8)	1.614	.885
LnIL-6	0.2 (0.4)	0.2 (0.8)	0.784	.434	0.4 (0.5)	0.2 (0.3)	1.671	.100
LnIL-8	2.3 (0.6)	2.3 (0.6)	0.288	.774	2.1 (0.5)	2.3 (0.6)	1.395	.168
LnIL-10	−1.1 (0.9)	−0.8 (0.9)	1.165	.247	−0.9 (0.7)	−1.1 (1.0)	0.819	.417
LnTNF-α	2.4 (0.2)	2.4 (0.3)	0.180	.857	2.3 (0.2)	2.4 (0.2)	1.417	.162
Th1/Th2 ratio								
LnIL-1β/LnIL-10	2.5 (9.7)	0.8 (2.3)	1.079	.283	0.8 (4.5)	3.1 (11.1)	0.761	.450
LnIL-2/LnIL-10	3.0 (13.1)	1.6 (1.9)	0.719	.474	1.3 (1.8)	3.7 (15.5)	0.509	.614
LnTNF-α/LnIL-10	−7.3 (30.2)	−1.8 (5.4)	1.228	.222	−5.9 (12.8)	−7.8 (34.6)	0.200	.842
LnIL-1β/LnIL-6	−1.9 (24.9)	−5.5 (30.5)	0.683	.496	0.7 (9.8)	−2.7 (28.4)	0.457	.650
LnIL-2/LnIL-6	−9.8 (39.7)	−7.3 (36.4)	0.306	.760	0.3 (5.1)	−13.8 (46.3)	1.000	.324
LnTNF-α/LnIL-6	17.9 (66.0)	11.3 (55.9)	0.580	.563	0.3 (19.1)	23.7 (74.7)	1.195	.237

Abbreviations: CHR = clinical high risk, CHR-C = CHR individuals who converted to psychosis, CHR-NC = CHR individuals who did not convert to psychosis, HC = healthy controls, IL = interleukin, Ln = transformed values of inflammatory cytokine concentrations, TNF-α = tumor necrosis factor-α.

Data Analysis

The demographic, clinical, and cognitive characteristics of the CHR-Total, CHR-C, and CHR nonconverter (CHR-NC) participants are presented as descriptive statistics and expressed as percentages and means (standard deviation, SD). Variables were compared across groups using independent-sample *t* tests (for continuous variables) or χ^2 tests (for categorical variables). The Ln transform for values of inflammatory cytokine concentrations was performed, making the data conform to a normal distribution. The niacin responses are expressed as $LogEC_{50}$ and Span in a dose-effect curve, and cytokine levels and Th1/Th2 ratios were compared between CHR-Total and HC and between CHR-C and CHR-NC using independent-sample *t* tests. The predictive performance of the niacin response variables in discriminating CHR-C from CHR-NC was evaluated using receiver operating characteristic (ROC) curve analysis. The discriminative ability of $LogEC_{50}$ and Span was evaluated using the area under the ROC curve (ROC-AUC) for the conversion outcome. According to an optional classification, the AUC can be defined as follows: 0.9–1, excellent; 0.8–0.9, good; 0.7–0.8, fairly good; 0.6–0.7, weak; and 0.5–0.6, useless.[30] The optimal cutoff point was detected by maximizing the Youden index, which is calculated as the sum of the true positive and true negative rates minus 1. The subgroup was defined as having a value below the optimal cutoff point of the $LogEC_{50}$ value and lower than the Span value. A small group of patients with CHR was identified using a scatter diagram. Considering that differences between CHR-C and CHR-NC groups in family history and positive symptom scores were found at baseline, these variables with predictive values were entered into the multivariate model. A Hosmer-Lemeshow goodness-of-fit test was performed to assess the calibration of the predictive logistic regression model. The Wald χ^2 statistic was used to test the significance of individual variables in the model. Finally, we calculated Spearman rank correlations between the niacin response and Th1/Th2 ratios for CHR-Total, CHR-C, and CHR-NC.

RESULTS

Demographic, Clinical, and Cognitive Characteristics

The baseline characteristics of the participants are summarized in Table 1. The CHR-C group was more likely to have relatives with a psychiatric family history ($P < .001$) and a higher severity of positive symptoms than the CHR-NC group ($P = .020$). In the HC group, the mean age was 20.8 ± 2.6 years, 27 (45.0%) of the patients were men, and they received education for 12.4 ± 2.5 years, which are comparable to the CHR group (age: $t = 1.201$, $P = .232$; sex: $\chi^2 = 0.136$, $P = .713$; education: $t = 1.555$, $P = .123$). Participant follow-up characteristics are summarized in Supplementary Table 1.

Niacin-Induced Responses

The distributions of the $LogEC_{50}$ and Span values for the CHR vs HC and CHR-C vs CHR-NC groups are shown in Figure 1. The CHR group exhibited significantly higher $LogEC_{50}$ ($t_{118} = 3.650$, $P < .001$) and Span ($t_{118} = 2.657$, $P = .009$) values than the control group (Figure 1A). The CHR-C group exhibited a significantly lower Span ($t_{58} = 4.027$, $P < .001$) than the CHR-NC group. $LogEC_{50}$ showed a trend toward significance ($t_{58} = 1.875$, $P = .066$) (Figure 1B).

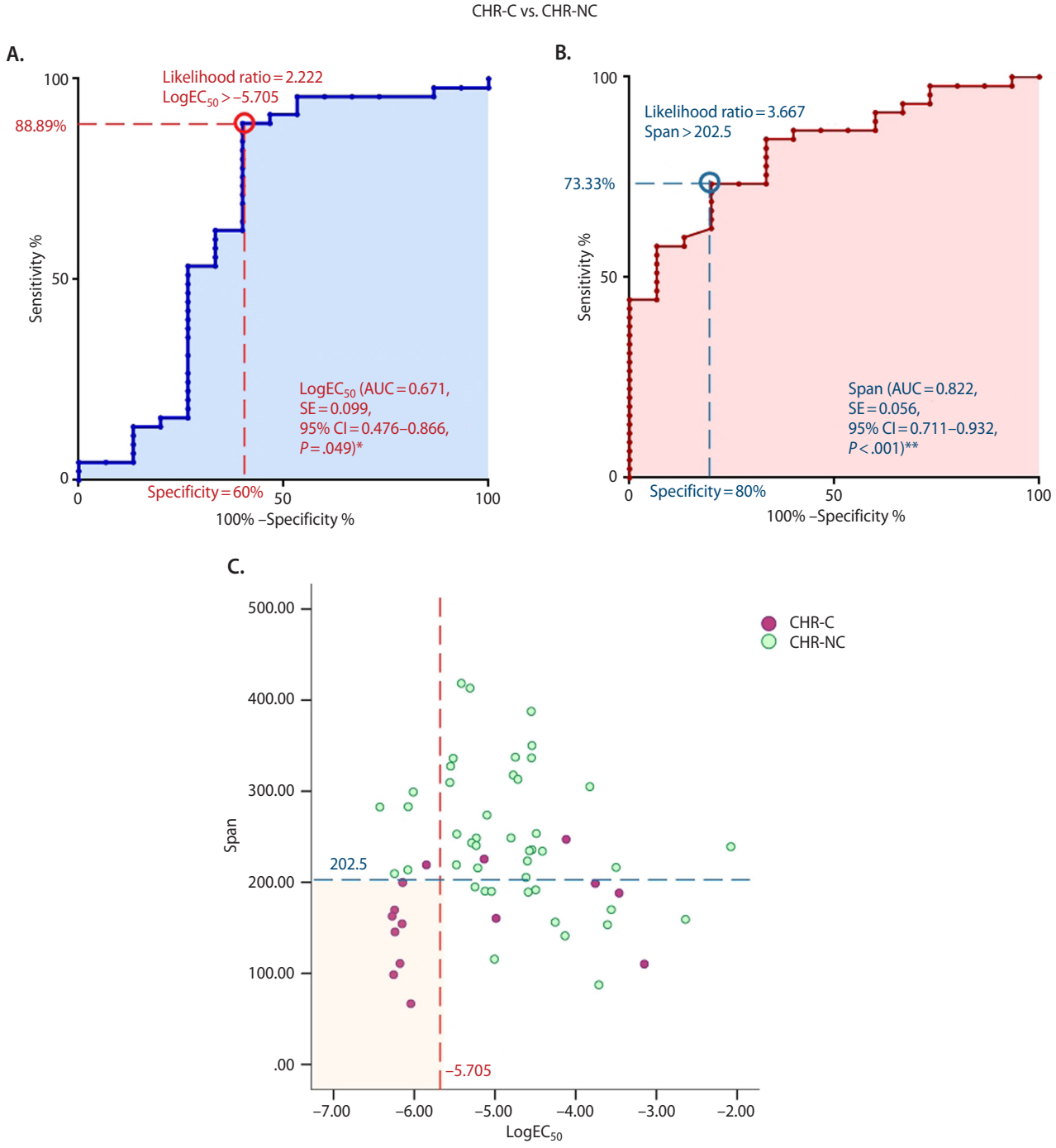
Inflammatory Cytokines

We compared the Ln-transformed levels of inflammatory cytokines between HC and CHR patients with conversion and non-conversion outcomes; none of them was significant (Table 2).

Validity of Niacin Response Predictors

Figure 2A and 2B show the ability of the niacin response to predict conversion. The ROC curve shows that the $LogEC_{50}$ (AUC = 0.671, SE = 0.099, 95% CI = 0.476–0.866, $P = .049$) and Span (AUC = 0.822, SE = 0.056, 95% CI = 0.711–0.932, $P < .001$) can distinguish CHR-C from CHR-NC. The cutoff points for $LogEC_{50}$ and Span were determined to be −5.705 and 202.5, respectively. The sensitivities for $LogEC_{50}$

Figure 2. (A) ROC Curve and LogEC$_{50}$ Cutoff Points, With Relative Sensitivity and Specificity to Predict Conversion; (B) ROC Curve and Cutoff Points of the Span, With Relative Sensitivity and Specificity to Predict Conversion; (C) Bivariate Plot of LogEC$_{50}$ and Span in CHR-C and CHR-NC



Abbreviations: AUC = area under the curve, CHR = clinical high risk for psychosis, CHR-C = CHR individuals who converted to psychosis, CHR-NC = CHR individuals who did not convert to psychosis, CI = confidence interval, ROC = receiver operating characteristic, SE = standard error.

and Span were 0.889 and 0.733, and the specificities were 0.600 and 0.800, respectively. Figure 2C shows, using the cutoff criteria, a bivariate plot of LogEC$_{50}$ and Span with stratification of conversion and non-conversion. Eight of the 15 CHR-Cs and none of the CHR-NCs in the lower left quadrant were predicted to be conversions. ROC analysis revealed that LogEC$_{50}$ (AUC = 0.670, SE = 0.049, 95% CI = 0.574–0.766, P = .001) and Span (AUC = 0.637, SE = 0.051, 95% CI = 0.537–0.736, P = .010) could distinguish CHR from HC (Supplementary Figure 1).

Predictive Model and Performance

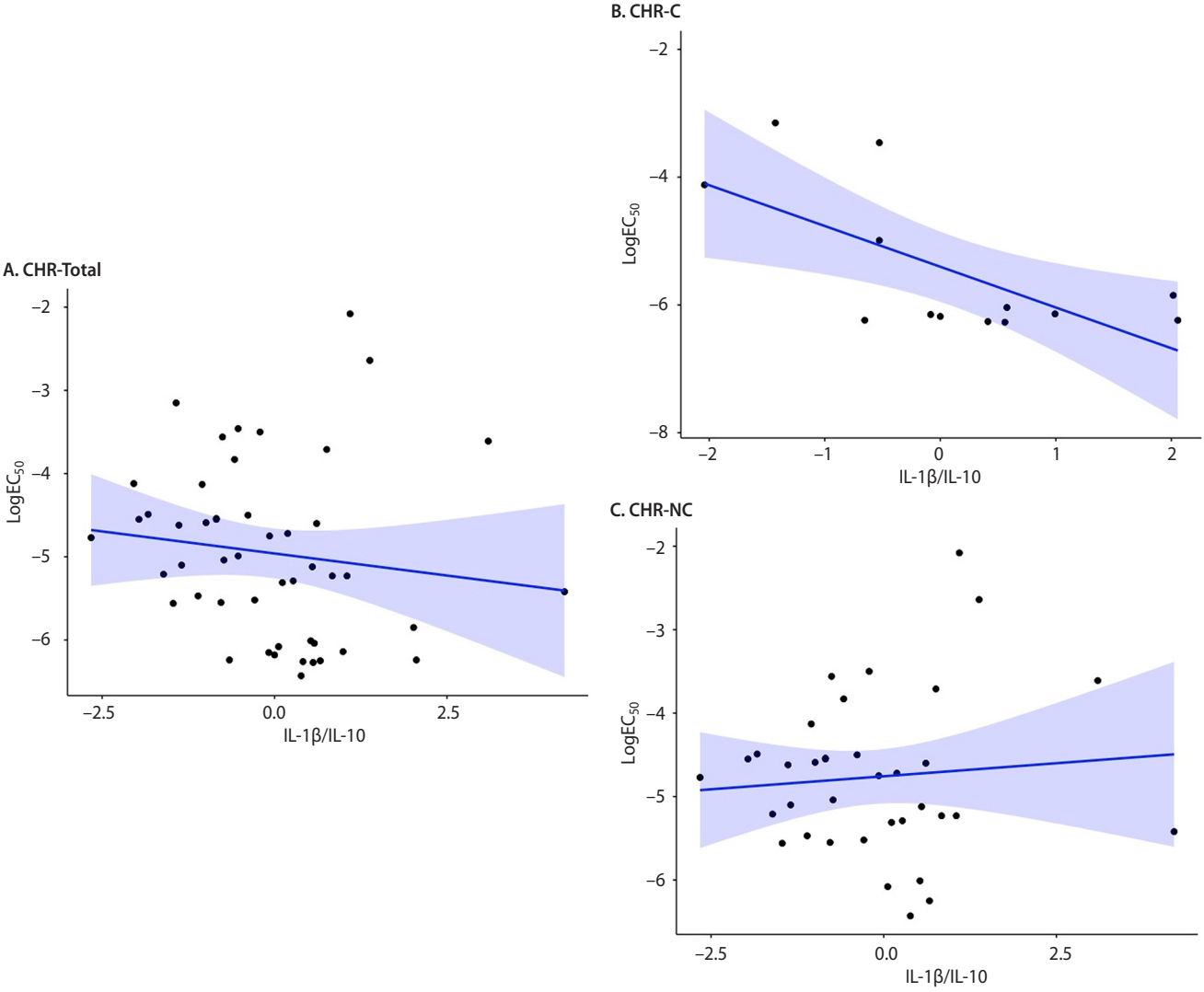
Multiple logistic regression analysis was conducted to predict conversion using estimated niacin response

Table 3. Logistic Regression for Predicting Conversion to Psychosis, Adjusted by Family History and SIPS Score of Positive Symptoms[a]

Predictor factors	β[a]	SE	β(OR)[b]	95% CI for β	Wald statistic	*P* value[c]
Factors of niacin response						
$LogEC_{50}$	0.858	0.485	2.359	0.912–6.106	3.130	.077
Span	0.020	0.007	1.020	1.006–1.035	7.466	**.006**
Family history	2.454	0.940	11.634	1.843–73.459	6.812	**.009**
Positive symptoms	−0.298	0.151	0.742	0.552–0.997	3.917	**.048**
Factors of inflammatory cytokines						
Family history	−3.065	1.364	0.047	0.003–0.676	5.047	**.025**
Positive symptoms	−0.228	0.185	0.796	0.554–1.144	1.517	.218
LnIL-1β	1.378	1.010	3.968	0.548–28.723	1.862	.172
LnIL-2	−0.887	1.426	0.412	0.025–6.734	0.387	.534
LnIL-6	0.978	1.594	2.659	0.117–60.498	0.376	.540
LnIL-8	0.000	1.230	1.000	0.090–11.157	0.000	1.000
LnIL-10	−0.143	0.740	0.866	0.203–3.693	0.038	.846
LnTNF-α	3.693	4.103	40.157	0.013–124,918.938	0.810	.368

[a]Beta is the regression coefficient.
[b]β(OR) = standardized regression coefficient.
[c]Boldface indicates significance.
Abbreviations: 95% CI = estimated 95% confidence interval for the corresponding parameter, IL = interleukin, SE = standard error, SIPS = Structured Interview for Prodromal Syndromes, TNF-α = tumor necrosis factor-α.

Figure 3. Correlations Between $LogEC_{50}$ and LnIL-1β/LnIL-10 Ratio in (A) CHR-Total, (B) CHR-C, and (C) CHR-NC



Abbreviations: CHR = clinical high risk for psychosis, CHR-C = CHR individuals who converted to psychosis, CHR-NC = CHR individuals who did not convert to psychosis, IL = interleukin, Ln = Ln-transformed values of inflammatory cytokine concentrations.

variables as predictors, adjusting for family history and SIPS score of positive symptoms that were significantly different between the CHR-C and CHR-NC groups (Table 1). The Hosmer-Lemeshow test showed good calibration for the model ($\chi^2 = 6.124$, $P = .633$). The overall model achieved a classification accuracy of 91.7%. The OR for a conversion outcome for Span was robust and statistically significant (OR = 1.020, $P = .006$, 95% CI = 1.006–1.035), and a trend toward significance was found for $LogEC_{50}$ (OR = 2.359, $P = .077$, 95% CI = 0.912–6.106) (Table 3). None of the cytokines or the Th1/Th2 ratio were significant in the predictive model. The values of the risk probabilities were generated in the regression model for each case and then used for ROC analysis. Discrimination for the conversion outcome was better for risk probabilities (AUC = 0.938, 95% CI = 0.869–1, $P < .001$) than for each cytokine and the Th1/Th2 ratio (AUC = 0.502–0.665, $P > .05$).

Correlation Analysis

We analyzed whether niacin responses were correlated with the Th1/Th2 ratio. $LogEC_{50}$ was correlated with the LnIL-1β/LnIL-10 ratio in CHR-Total (Spearman $\rho = -0.280$, $P = .040$) (Figure 3A). The decreased $LogEC_{50}$ in the CHR-C group was significantly correlated with the increased LnIL-1β/LnIL-10 ratio (Spearman $\rho = -0.600$, $P = .018$) (Figure 3B). However, in the CHR-NC group, this negative correlation was not significant (Spearman $\rho = -0.027$, $P = .870$) (Figure 3C). Other correlations were not significant between niacin responses and the ratios of IL-2/IL-10, TNF-α/IL-6, and IL-2/IL-6.

DISCUSSION

Key Findings

The attenuated niacin response is a useful endophenotype in patients with psychosis. In this study, we found that a significantly diminished niacin response can be applied to identify a subgroup of "real" CHR individuals and serve as a good predictor of conversion to psychosis. Our findings provide valuable information that the association between niacin response and immune imbalance appears to be more specific to CHR-C than to CHR-NC individuals. From the perspective of clinical application in the early identification of psychosis, the measurement of niacin-induced response has a better predictive attribute than the measurement of serum inflammatory cytokines and Th1/Th2 ratios.

Niacin Response Abnormality

Individuals with CHR may develop various mental disorders. The attenuated niacin response can serve as a biomarker to detect a subgroup of real risk for psychosis with aberrant phospholipid signaling. The niacin response was significantly different between the CHR-C and CHR-NC groups, with CHR-C showing a lower response to niacin than CHR-NC. This result is consistent with previous studies that reported a blunted niacin response in patients with schizophrenia, with the application of various niacin measurements using laser Doppler flowmetry,[9,31] visual semiquantitative analysis,[13,32] optical reflection spectroscopy,[33] and oral measurements.[14]

Although the results of the attenuated niacin response in patients with schizophrenia compared with HC were relatively consistent, the results in the CHR population varied. Berger et al[34] compared the niacin response between adolescents with CHR and HC using a visual semiquantitative method and found that the niacin response was significantly increased in the CHR group. Additionally, it was reported that there was no difference between CHR-C and CHR-NC after a 1-year follow-up period. In contrast, Langbein et al[35] measured the niacin response using an optical reflection spectroscopy method and compared CHR individuals and patients with first-episode psychosis. Similar blunted niacin-induced skin flush reactions were found in both groups. Our previous study[11] used a visual semiquantitative method to compare the niacin response among CHR individuals, patients with first-episode schizophrenia, and HC. The niacin response in the CHR samples was characterized by modest levels, which were intermediate between HC individuals and patients with schizophrenia. In combination with the findings of this study, we believe that the phenomenon of attenuated niacin response is more obvious in the CHR-C subgroup than in the CHR-NC subgroup, which is consistent with the findings on schizophrenia. However, in the entire CHR population, the results may be unstable owing to the heterogeneity of the samples and the varied detection methods.

Immunity Imbalance

This study failed to find the specific value of peripheral inflammatory cytokines and Th1/Th2 ratios in distinguishing CHR from HC and CHR-C from CHR-NC. A previous review[36] explored potential inflammatory biomarkers for conversion to psychosis; however, it failed to confirm whether inflammatory cytokines are state or trait indicators for conversion to psychosis. Significant heterogeneity of CHR and CHR-C populations as well as methodological factors, such as blood sample processing and cytokine measurements, can affect the results. In this study, we failed to replicate the previous findings[37–39] that found significant differences in cytokine levels and Th1/Th2 ratios in individuals with CHR versus patients with psychosis and HC, mainly because of our conception of CHR or CHR-C as a homogeneous group, whereas it exists as a heterogeneous population with distinct subtypes.[40] Several confounding factors have been reported to influence serum cytokine levels, including sex,[41,42] smoking,[43] and psychiatric medications.[44] In this study, there were no sex differences between the CHR and HC groups, and none of the participants in our study had smoked or previously taken psychiatric medications.

Variables for Prediction

The niacin response has been described as a promising trait marker of schizophrenia since its response was found to be significantly lower in patients with schizophrenia at different stages of the disease and in their first-degree

relatives[45] in comparison with HC.[13] Our findings add new value for applying the niacin test in predicting psychosis. The two variables $LogEC_{50}$ and Span, generated by quantifying the blood flow response to niacin, contributed significantly to the prediction of conversion, especially Span, which mainly reflects the degree of response. Notably, the finding that the lower the $LogEC_{50}$, the higher the risk for conversion to psychosis in this study is inconsistent with previous studies, which found that patients with schizophrenia had higher values of $LogEC_{50}$ than HC had.[31] The $LogEC_{50}$ value is derived from the dose-response curve, which can be significantly affected by MBF. In this study, CHR-C individuals had a significantly lower MBF than CHR-NC individuals, resulting in a reduction in the concentration of methyl nicotinate required to elicit a half-MBF response.

Correlations Between Niacin Response and Immunity

A new contribution from this study to the current research field of early identification of psychosis is that we found that the association between the niacin response and the Th1/Th2 balance was only significant in the IL-1β/IL-10 ratio in CHR-C individuals. The Th1/Th2 imbalance is a classic immune response pattern in patients with schizophrenia. Schwarz et al[46,47] proposed that there may be a bio-subtype of schizophrenia (one-third) characterized by a Th1/Th2 imbalance and predominantly negative symptoms. This hypothesis agrees with the findings by Yao et al of a similar percentage of patients with first-episode psychosis characterized by an attenuated niacin response. Our data support that the niacin response may be a useful biomarker for the selection of a more homogeneous subgroup of CHR. Our recent study[48] investigated niacin-induced responses in 240 patients with first-episode psychosis and found that an attenuated niacin response is likely to be associated with a subtype of psychosis characterized by serious negative symptoms. The diagnostic criteria for CHR are based on positive symptoms. However, even in the prodromal phase, negative symptoms are common. Some studies[5,49,50] have found that negative symptoms during CHR status are more effective than positive symptoms in predicting late-onset psychosis. For this subgroup, immune-imbalanced-phenotype individuals with CHR may be potentially relevant in the implementation of more specific strategies (for example, celecoxib, a cyclooxygenase-2 inhibitor[51,52]; *N*-acetyl-L-cysteine[53,54]; and sulforaphane[55]) for early prevention.

Limitations

The main limitation of the present study was that only the baseline niacin response and inflammatory cytokine levels were measured. There would be stronger evidence if we had measured these variables at the 2-year follow-up. Second, whereas cutaneous blood flow and serum cytokine levels were measured in both the CHR and HC groups, body mass index (BMI) and other metabolic markers were not assessed. As a result, whether these variables can be confounders when analyzing the niacin response and Th1/Th2 balance remains unknown. Third, the sample size in the CHR-C group was small.

CONCLUSION

Our study provides evidence for an association between niacin response in individuals with CHR and later development of psychosis. The present findings suggest that niacin response tests should be considered in psychosis identification and prediction. This will help improve the accuracy of psychosis prediction and deepen our understanding of membrane phospholipid-arachidonic acid-prostaglandin pathways that may be relevant for at least a subgroup of CHR individuals characterized by immune imbalance, which in turn would support more tailored intervention and prevention in the CHR population.

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Author Contributions: Drs Zhang, Xiao, and H. Wu and Prof Wang designed the study. Drs Zeng, Ye, Gao, and Xu and Profs H. Liu and Chen analyzed the data. Drs Zhang, X. Wu, and Zhou drafted the first version of the manuscript. Drs Hu, X. Liu, Wei, Li, and Tang performed a literature search and reviewed the revised manuscript. All authors contributed substantially to the manuscript and approved the final version for submission. All authors are responsible for the integrity, accuracy, and presentation of data.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Association of Attenuated Niacin Response With Inflammatory Imbalance and Prediction of Conversion to Psychosis From Clinical High-Risk Stage

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

1. Table 1 Two-year Follow-up Clinical and Cognitive Variables, Comparison Between CHR-C and CHR-NC
2. Figure 1 ROC Curve and Cut-off Points of the LogEC50 and Span With Relative Sensitivity and Specificity to Discriminate CHR From HC

DISCLAIMER

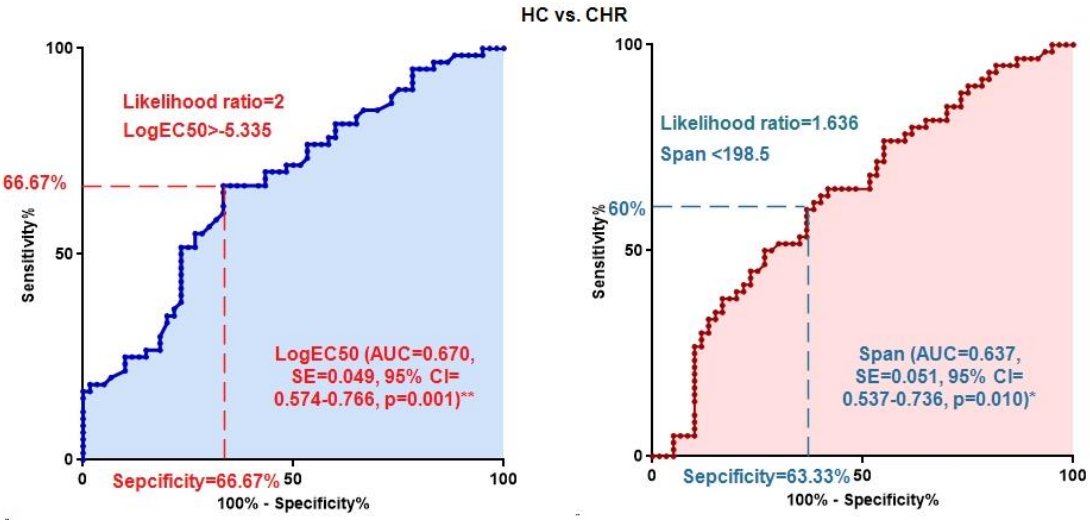
This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Two-year Follow-up clinical and cognitive variables, comparison between CHR-C and CHR-NC.

Variables	CHR- total	CHR-C	CHR-NC	Comparison	
				t	*P* value
Cases(n)	60	15	45	-	-
Clinical variables					
Follow-up GAF	64.2(9.4)	58.2(7.7)	66.2(9.1)	3.047	**0.003**
Positive symptoms	6.0(4.5)	9.7(4.5)	4.8(3.8)	4.176	**<0.001**
Negative symptoms	8.8(4.9)	11.3(7.3)	7.9(3.6)	1.766	0.096
Disorganization symptoms	4.3(2.6)	4.4(2.2)	4.3(2.8)	0.170	0.865
General symptoms	8.3(3.7)	9.8(3.4)	7.8(3.7)	1.854	0.069
SIPSTAL	27.4(10.2)	35.3(11.1)	24.7(8.5)	3.863	**<0.001**
Cognitive variables [Mean (SD)]					
Trail Making A	31.9(12.5)	41.5(10.7)	28.6(11.4)	3.855	**<0.001**
BACS symbol coding	56.1(12.0)	51.1(13.1)	57.8(11.2)	1.931	0.058
Category Fluency	19.1(5.8)	16.8(4.7)	19.8(5.9)	1.775	0.081
CPT-IP	2.6(0.8)	2.7(0.9)	2.6(0.8)	0.127	0.900
WMS-3 spatial span	16.4(2.9)	15.3(3.9)	16.8(2.4)	1.400	0.179
HVLT-R	23.1(5.8)	22.8(6.4)	23.1(5.7)	0.190	0.850
BVMT-R	26.3(6.3)	22.4(6.5)	27.6(5.7)	2.924	**0.005**
NAB mazes	18.0(6.5)	13.0(5.1)	19.8(6.1)	3.858	**<0.001**

Note. Abbreviations: BACS, Brief Assessment of Cognition in Schizophrenia symbol coding; BVMT-R, Brief Visuospatial Memory Test–Revised; CPT-IP, Continuous Performance Test–Identical Pairs; HVLT-R, Hopkins Verbal Learning Test–Revised; NAB, Neuropsychological Assessment Battery mazes; WMS-3, Wechsler Memory Scale–Third Edition spatial span. GAF, Global Assessment of Functioning; CHR, clinical high risk for psychosis. *t*: *t* for independent t-test.

Supplementary Figure 1. ROC curve and cut-off points of the LogEC50 and Span with relative sensitivity and specificity to discriminate CHR from HC.



Note. Area under Curve (AUC), Receiver Operating Characteristic (ROC), Standard error (SE), Confidence interval (CI), CHR, clinical high risk; HC, Healthy control.