Efficiency and Extent of Niacin-Induced Skin Flushing Patterns in Early Stages of Psychosis

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Abstract

Objective: Niacin-induced skin flushing response (NSFR) attenuation is a well-documented biomarker for psychosis and has also been used in studies of bipolar affective disorder. It appears not only in later stages but also in first episodes and in clinical high-risk (CHR) stages.

Methods: NSFR tests were conducted on healthy controls (HC), CHR individuals, and first-episode psychosis (FEP) patients from January 2019 to March 2024. The tests involved applying niacin patches at different concentrations and recording skin responses at multiple time points. A newly introduced slope variable was used to evaluate response efficiency. CHR participants were followed for 3 years to assess the predictive value of NSFR efficiency and attenuation degree for psychosis onset.

Results: This study included 98 CHR individuals (mean age: 18.4 years, 42.9% male), 54 FEP patients (24.7 years, 50% male), and 61 HC (25.8 years, 54.1% male). Over the 3-year follow-up, 23 (23.5%) CHR individuals converted to psychosis. CHR individuals showed NSFR attenuation levels between those of FEP patients and HC. Lower response efficiency was associated with a higher risk of developing psychosis, specifically at 10^{-4} M and 10^{-2} M concentrations ($P = .001$ and $P = .039$, respectively). The area under the curve for predicting psychosis onset using slope values at 10^{-2} M was 0.645 ($P = .034$). For discriminating CHR from HC, significant factors included slope at 10^{-3} M concentration ($P = .006$), total scores at 5 minutes ($P = .001$) and 15 minutes ($P = .005$), and total scores at 10^{-3} M ($P = .002$) and 10^{-2} M ($P = .001$). For discriminating FEP from HC, significant factors were the slope at 10^{-4} M concentration ($P = .023$), total score at 5 minutes ($P = .003$), and total score at 10^{-3} M concentration ($P = .040$).

Conclusions: NSFR efficiency is a sensitive marker for early psychosis risk, highlighting the need for precise and comprehensive detection methods.

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Existing evidence has established that attenuated niacin-induced skin flushing response (NSFR) is an important biomarker for psychosis. This characteristic not only appears in the later stages of psychosis[1,2] and in first-degree relatives of patients[3] but is also present at the onset of the first episode[4] and even during the clinical high-risk (CHR) stage. Attenuated NSFR may be associated with genetic markers or other phospholipid-related abnormalities in psychosis.[5,6] Research by Yao et al[7] found that this attenuation is a physiological subtype specific to psychosis when compared to the general population or those with bipolar disorder. A better understanding of this biomarker could eventually lead to the identification of a risk-conferring gene, be used to predict preferential response to treatment, or contribute to a rational deconstruction of the complex diagnosis of psychosis into biological subtypes.

Despite the aforementioned accumulation of evidence, the development of techniques for detecting NSFR has lagged behind. Historically, numerous methods have been employed to assess the niacin-induced response. Early NSFR detection methods involved applying niacin patches to the forearm for 1 minute and recording photographs at 5, 10, 15, and 20 minutes to assess the degree of response attenuation based on visual ratings by evaluators.[8,9] Another method used a laser Doppler flowmeter equipped with an integrating flow probe to measure cutaneous blood flow, analyzing dose-response data through nonlinear curve

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Clinical Points

- Niacin-induced skin flushing response attenuation can serve as a valuable early marker for psychosis.
- These authors are the first to introduce a slope variable to evaluate the response efficiency of the niacin-induced skin flushing response.
- Assessing the response efficiency of the niacin-induced skin flushing response can be a powerful strategy for predicting the risk of psychosis and identifying patients in the early stage.

fitting to calculate the NSFR values.[7] However, these are not the only approaches. Oral administration of niacin has also been used, followed by the measurement of skin or earlobe temperature as an indicator of the body's response to niacin. Additionally, optical reflection spectroscopy has been utilized to measure niacin-induced reactions. Both mainstream methods focus on measuring the degree of the NSFR but lack evaluation of the response efficiency over time.

In this study, we included 3 groups: healthy controls (HC), individuals at CHR, and first-episode psychosis (FEP) patients, all undergoing NSFR testing. We introduced a slope indicator to evaluate response efficiency and explored its role in distinguishing among the 3 groups. Additionally, CHR individuals were followed up for 3 years to assess the predictive value of NSFR efficiency and attenuation degree for the onset of psychosis.

METHODS

Sample and Procedures

This study enrolled 98 individuals identified as being at CHR for psychosis and followed them over a 3-year period. Additionally, 54 patients with FEP and 61 HC were included. Participants were recruited from the Shanghai At Risk for Psychosis-extended (SHARP-extended) cohort[10,11] between 2019 and 2024 at the Shanghai Mental Health Center (SMHC) in China, with ethics approval from the SMHC research committee (2019-19R). All participants provided informed consent; those under 18 years of age provided assent and had consent forms signed by their parents. Inclusion criteria were being between 15 and 45 years old, having at least 6 years of primary education, and being psychotropically naive. Exclusion criteria included severe somatic diseases, intellectual disability, a history of substance abuse, current inflammatory infections or recent use of anti-inflammatory drugs, and a history of niacin allergy.

The research procedures were separate from routine clinical treatments at SMHC. CHR participants were reassessed annually using the Structured Interview for Prodromal Syndromes (SIPS)[12,13] throughout the follow-up period. Diagnoses of psychosis were confirmed according to the *International Classification of Diseases, 10th Revision* (*ICD-10*) criteria, conducted by an experienced psychiatrist with a minimum of 5 years of practice in psychiatry. For this study, FEP was operationally defined as the onset of nonaffective psychosis, with criteria including a duration of untreated psychosis of up to 2 years. Other inclusion and exclusion criteria were the same as those for the CHR group. HC participants were recruited from the local Shanghai community, matched to the FEP group by age, sex, and education, and had no family history of mental disorders. Detailed methodological information about the SHARP cohort is available in prior publications.[14–16]

Clinical Measurement and Outcome Criteria

The SIPS[12] was employed to identify individuals at CHR for psychosis. The SIPS includes 19 items across 4 symptom domains: positive symptoms (P1–P5: unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and disorganized communication), negative symptoms (N1–N6: social anhedonia, avolition, expression of emotion, experience of emotions and self, ideational richness, and occupational functioning), disorganized symptoms (D1–D4: odd behavior or appearance, bizarre thinking, trouble with focus and attention, and impaired personal hygiene), and general symptoms (G1–G4: sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to normal stress).

The primary outcome of this study was the conversion to psychosis. Among the 98 CHR individuals, 23 (23.5%) transitioned to full psychosis during 3 years of follow-up. Conversion was defined using the Presence of Psychotic Symptoms criteria within SIPS,[13,17] requiring at least 1 psychotic level symptom (rated "6" on the positive symptoms scale) that occurred with sufficient frequency or duration, specifically at least 1 hour a day on average over 4 days a week, totaling a minimum of 16 hours.

For patients with FEP, clinical psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS). The PANSS[18] comprises 30 items divided into 3 subscales: positive (P1–P7), negative (N1–N7), and general psychopathology (G1–G16). Each item is rated on a 7-point Likert scale ranging from 1 (absent) to 7 (extreme).

Previous studies by Zhang et al[19,20] have demonstrated the reliability and validity of the Chinese version of the SIPS, developed by the SHARP team.[21] This version showed good inter-rater reliability (intraclass correlation coefficient [ICC]: $r = 0.96$, $P < .01$) and validity, with 26.4% of subjects converting to psychosis within 2 years. The first author, certified in SIPS from Yale University-sponsored training, has substantial experience in Chinese

CHR research projects. The PANSS assessments were conducted by 2 senior psychiatrists who had completed the necessary training for this type of evaluation.

Measurement of the NSFR

A round filter paper patch was used to apply niacin as aqueous methylnicotinate (AMN). Four concentrations (10^{-1} M, 10^{-2} M, 10^{-3} M, and 10^{-4} M) of AMN solution were prepared on the test day. To set a reference distance, a sticky ruler was attached to the inner side of the participant's forearm. Four wet paper patches from each AMN concentration were applied to adjacent sites on the forearm for 1 minute and then removed. The NSFR was photographed from a fixed vertical view at 5, 10, 15, and 20 minutes after patch removal. The skin flush response was rated using the Berger Niacin Rating Scale[22]: 1 = no reaction; 2 = red spots covering less than 50% of the area, no edema; 3 = slight redness covering more than 50% of the area, no edema; 4 = moderate redness, homogeneous erythema, slight but not visible edema; 5 = redness spreading out, visible edema, sharp border; 6 = redness turns orange/yellow, clearly visible edema, diffuse border; 7 = severe redness and spreading edema, border barely recognizable. Each subject's flush response was rated by a research assistant and verified by a senior researcher, based on photos with anonymized file names. The raters were blind to the participants' group information, demographic and clinical details, and clinical outcomes. Details can be found in our previous publications.[23,24]

To ensure the consistency of scoring across raters, we implemented a comprehensive training program before the data collection phase. Our research team consisted of 2 trained raters who were all experienced in dermatological assessments. They participated in a series of training sessions that included both theoretical lectures and practical demonstrations. During the theoretical part, raters were educated on the NSFR scoring criteria in detail, which were based on well-established guidelines in the field. They learned about the different levels of skin flushing intensity at various concentrations and time points, and how to accurately assign scores. In the practical training, raters were presented with a set of standardized cases with known NSFR scores. They independently scored these cases, and then, the results were discussed in a group setting. Any discrepancies in scoring were thoroughly analyzed, and the correct scoring approach was reinforced. To further assess the inter-rater reliability, we conducted a pilot study on a subset of 28 participants. The raters scored the NSFR responses of these participants independently, and we calculated the inter-rater reliability using the ICC. The ICC value for our raters was 0.89, which indicates a high level of agreement among the raters. This result suggests that the scoring across raters was consistent and reliable.

Three methods were used to evaluate the efficiency and degree of the NSFR.

1. Efficiency dependence: linear regression was performed separately on the 4 concentrations (4 scores per concentration) and all 16 scores, with the x-axis corresponding to the time points of 5, 10, 15, 20 minutes, and the y-axis corresponding to the respective scores, from which the slope was calculated. The formula for calculating the slope m is:

$$m = \frac{N\sum(x_i y_i) - \sum x_i \sum y_i}{N\sum x_i^2 - (\sum x_i)^2}$$

   where: N is the number of data points. x_i is the time point (5, 10, 15, 20 minutes). y_i is the corresponding score.
2. Time dependence: The total scores at each time point (5, 10, 15, 20 minutes) were calculated. The total sum of all 20 scores was also calculated.
3. Concentration dependence: The total scores for each concentration (10^{-1} M, 10^{-2} M, 10^{-3} M, and 10^{-4} M) were calculated. The total sum of all 20 scores was also calculated.

Statistical Analysis

Demographic and baseline clinical features are presented separately. Quantitative variables are expressed as mean ± standard deviation (SD), while qualitative variables are presented as frequencies (%). Chi-square (χ^2) tests were used for comparisons of categorical variables. One-way analysis of variance (ANOVA) tests were used to compare the 3 groups (HC, CHR, and FEP) on continuous variables. The CHR individuals were further divided into converters and nonconverters based on the 3-year follow-up outcomes. The 2 groups (CHR-C and CHR-NC) were compared using independent t-tests. To enhance the comparability between groups, Z-score transformations were performed on the entire sample for the slope, total scores at each time point and each concentration, and the total score across all scores. Radar plots were generated using the Z-scores to provide a more intuitive understanding of the NSFR patterns in the different groups. Three logistic regression models (using the backward method) were constructed: (1) a CHR-C model to distinguish CHR-C from CHR-NC, (2) a CHR model to distinguish CHR from HC, and (3) an FEP model to distinguish FEP from HC. Individual probabilities were generated for these 3 models using the related variables of slope, total scores at each time point and each concentration, and total score across all scores, adjusted for sex, age, and education. Model performance was evaluated by plotting the receiver operating characteristic (ROC) curve and calculating the area under the ROC curve (AUC) for the probabilities and individual NSFR variables in 3 models.

Table 1.

Demographic and Clinical Variables, Comparison Among CHR, FEP, and HC Groups and CHR-C and CHR-NC

Variables	HC	CHR	FEP	Comparison[a]		CHR-C	CHR-NC	Comparison[a]	
				F/χ^2	*P*			t/χ^2	*P*
Cases, n	61	98	54	–	–	23	75	–	–
Age, mean (SD), y	25.82 (9.172)	18.41 (4.897)	24.70 (8.632)	$F = 23.608$	<.001	19.00 (5.108)	18.14 (4.700)	$t = 0.763$	.447
Male, n (%)	33 (54.1)	42 (42.9)	27 (50.0)	$\chi^2 = 2.033$	.362	13 (56.5)	29 (38.7)	$\chi^2 = 2.291$	.130
Female, n (%)	28 (45.9)	56 (57.1)	27 (50.0)			10 (43.5)	46 (61.3)		
Education, mean (SD), y	15.25 (5.700)	10.38 (2.852)	11.94 (3.253)	$F = 28.476$	<.001	11.30 (3.140)	10.10 (2.634)	$t = 1.855$	.067
SIPS variables, mean (SD)									
Positive symptoms	–	10.43 (3.482)	–	–	–	10.87 (3.584)	10.29 (3.463)	$t = 0.680$	.501
Negative symptoms	–	12.07 (5.676)	–	–	–	12.74 (5.667)	11.87 (5.700)	$t = 0.643$	.522
Disorganization symptoms	–	6.47 (2.752)	–	–	–	7.26 (2.864)	6.23 (2.689)	$t = 1.589$	.115
General symptoms	–	9.52 (2.755)	–	–	–	9.70 (2.055)	9.47 (2.947)	$t = 0.347$	.729
SIPS total score	–	38.04 (10.091)	–	–	–	40.74 (7.830)	37.26 (10.576)	$t = 1.330$	.187
PANSS variables, mean (SD)									
Positive symptom	–	–	22.79 (5.539)	–	–	–	–	–	–
Negative symptom	–	–	16.85 (8.110)	–	–	–	–	–	–
General psychopathology	–	–	44.15 (6.887)	–	–	–	–	–	–
Total score	–	–	83.79 (15.120)	–	–	–	–	–	–

[a]F/χ^2: F for 1-way analysis of variance test and χ^2 for κ test, t for independent t-test.
Abbreviations: CHR = clinical high risk for psychosis, CHR-C = individuals at CHR who converted to psychosis, CHR-NC = individuals at CHR who did not convert to psychosis, FEP = first-episode psychosis; HC = healthy controls; PANSS = Positive and Negative Syndrome Scale; SIPS = Structured Interview for Prodromal Symptoms.

RESULTS

Table 1 profiles and compares the demographic and clinical variables among HC, CHR, and FEP groups, as well as between CHR-C and CHR-NC. Significant differences were found in age ($F = 23.608$, $P < .001$) and education years ($F = 28.476$, $P < .001$) among HC, CHR, and FEP groups, with CHR individuals being younger and having fewer years of education compared to HC and FEP groups. No significant differences were observed in gender distribution across the groups. Within the CHR group, no significant differences were found between CHR-C and CHR-NC in terms of age, gender, education, and SIPS variables, including positive, negative, disorganization, and general symptoms, as well as the total SIPS score.

Figure 1 illustrates the dependency of efficiency, time, and concentration on the skin flush response induced by AMN among 3 groups: CHR (in red), FEP (in black), and HC (in green). Panel A shows that the slope values differ significantly across the groups, with the most notable difference between FEP and HC ($P = .020$) at 10^{-4} M concentration of AMN solution. Panel B highlights time dependence, indicating that the total score varies over time, with significant differences particularly at the 5-minute mark ($P = .021$) between FEP and HC. Panel C demonstrates the concentration dependence of the response, revealing significant differences between FEP and HC ($P = .014$) at 10^{-4} M concentration and between CHR and HC ($P = .003$), between FEP and HC ($P = .043$) at 10^{-1} M concentration.

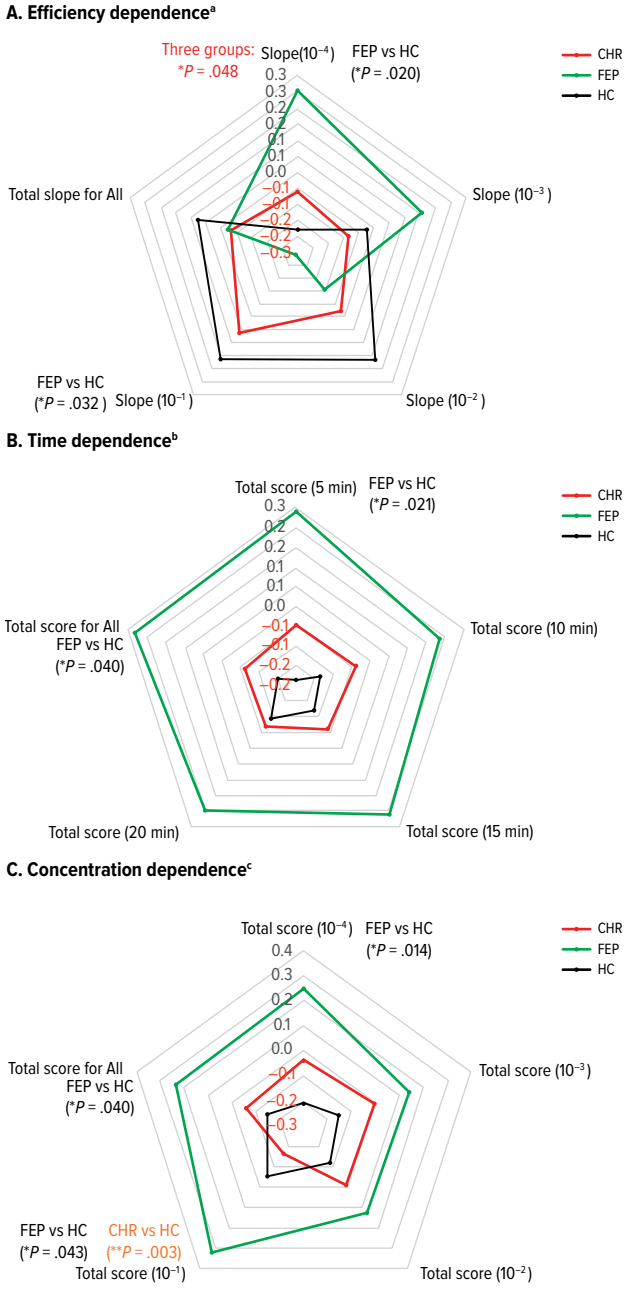
Figure 2 shows the radar plots comparing the efficiency, time, and concentration dependencies of skin flush response between 2 groups: CHR-C (in red) and CHR-NC (in black). Panel A illustrates significant differences in efficiency dependence between the 2 groups, with notable differences in slope values ($P = .001$) at 10^{-4} M concentration and ($P = .039$) at 10^{-2} M concentration. Panels B and C demonstrate time and concentrations dependence, showing attenuated response patterns generally in the CHR-C group compared with CHR-NC at various time points (10, 15, and 20 minutes) and concentrations (10^{-1} M, 10^{-2} M, 10^{-3} M, and 10^{-4} M), although these differences are not statistically significant.

Table 2 presents the results of the logistic regression analysis (backward) to identify the factors influencing the prediction of CHR-C within the CHR group, as well as the discrimination of CHR and FEP from HC. For predicting CHR-C in the CHR group, model predictors included gender, the slope at 10^{-4} M ($P = .030$) and 10^{-2} M ($P = .033$), and total score of 10^{-4} M concentrations. For discriminating CHR from HC, significant factors included the intercept, slope at 10^{-3} M concentration ($P = .006$), total scores at 5 minutes ($P = .001$) and 15 minutes ($P = .005$), total scores at 10^{-3} M ($P = .002$) and 10^{-2} M ($P = .001$), and age ($P < .001$). For discriminating FEP from HC, significant factors were the intercept, slope at 10^{-4} M concentration ($P = .023$), total score at 5 minutes ($P = .003$), and total score at 10^{-3} M concentration ($P = .040$).

Figure 3 presents the ROC curves evaluating the predictive performance of different models for distinguishing between groups based on the skin flush

Figure 1.

Radar Plots Showing the Dependence of Efficiency, Time, and Concentration on the Skin Flush Response Induced by AMN Among 3 Groups: CHR, FEP, and HC

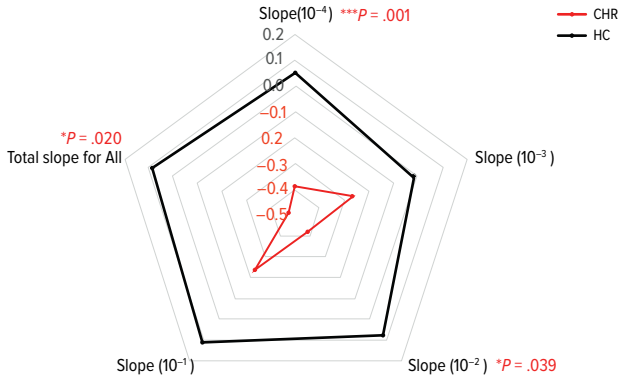


[a]Panel A: The radar plot illustrates the slope for 3 groups, facilitating the comparison of response efficiency among CHR, FEP, and HC.
[b]Panel B: This radar plot shows the total score of the skin flush response at different time points (5, 10, 15, and 20 min) after the removal of AMN patches, clearly presenting the impact of time on the skin flush response of each group.
[c]Panel C: The radar plot demonstrates the total score of the skin flush response at various concentrations of AMN (10^{-1} M, 10^{-2} M, 10^{-3} M, and 10^{-4} M), effectively reflecting the relationship between AMN concentration and the skin flush response.
Abbreviations: AMN = aqueous methylnicotinate, CHR = clinical high risk for psychosis, FEP = first-episode psychosis, HC = healthy controls.

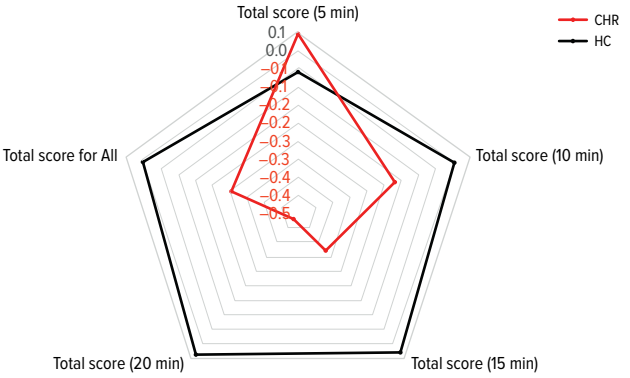
Figure 2.

Radar Plots Comparing the Dependence of Efficiency, Time, and Concentration on the Skin Flush Response Induced by AMN Between 2 Groups: CHR-C and CHR-NC

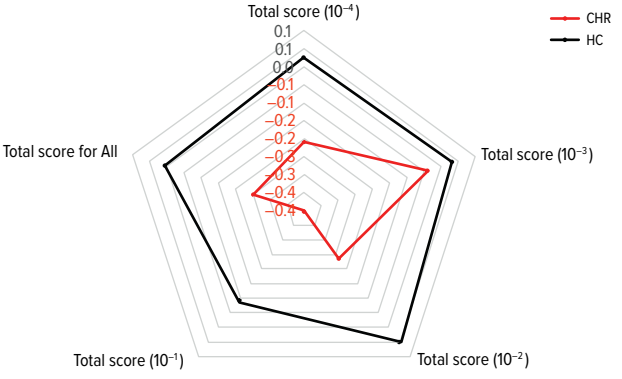
A. Efficiency dependence[a]



B. Time dependence[b]



C. Concentration dependence[c]



[a]Panel A: The radar plot illustrates the slope for the 2 groups, enabling an easy comparison of their response efficiency in relation to the AMN-induced skin flush response.
[b]Panel B: This radar plot shows the total score of the skin flush response at different time points (5, 10, 15, and 20 min) after the removal of AMN patches. It helps to clearly observe how the time factor affects the skin flush response of the CHR-C and CHR-NC groups.
[c]Panel C: The radar plot demonstrates the total score of the skin flush response at various concentrations of AMN (10^{-1} M, 10^{-2} M, 10^{-3} M, and 10^{-4} M). This effectively reflects how the concentration of AMN influences the skin flush response in the 2 groups.
Abbreviations: AMN = aqueous methylnicotinate, CHR-C = individuals at CHR who converted to psychosis, CHR-NC = individuals at CHR who did not convert to psychosis,

Table 2.

Logistic Regression Analysis (Backward) to Ascertain the Factors That Impact the Prediction of CHR-C in CHR, Discrimination of CHR in HC, and FEP in HC[a]

Variables	β	SE	Ward	*P* value	VIF
Prediction of CHR-C in CHR group (N = 98)					
(Intercept)	3.632	1.890	3.694	.055	–
Slope (10^{-4})	57.051	26.296	4.707	.030	1.341
Slope (10^{-2})	8.186	3.841	4.541	.033	1.006
Total score (10^{-4})	−0.756	0.445	2.889	.089	1.341
Gender (1 = male, 2 = female)	−0.940	0.531	3.134	.077	1.008
Discrimination of CHR from HC (CHR, N = 92; HC, N = 53)					
(Intercept)	−9.148	1.816	25.369	<.001	–
Slope (10^{-3})	15.124	5.506	7.546	.006	2.452
Total score (5 min)	0.657	0.204	10.356	.001	4.425
Total score (10 min)	0.368	0.236	2.422	.12	7.551
Total score (15 min)	0.683	0.245	7.801	.005	8.752
Total score (10^{-3})	−0.623	0.198	9.911	.002	6.658
Total score (10^{-2})	−0.731	0.224	10.631	.001	7.806
Age	0.236	0.048	24.252	<.001	1.073
Discrimination of FEP from HC (FEP, N = 54; HC, N = 53)					
(Intercept)	−2.086	0.813	6.589	.010	–
Slope (10^{-4})	10.673	4.697	5.163	.023	1.472
Slope (10^{-3})	9.235	4.796	3.708	.054	2.264
Total score (5 min)	0.465	0.157	8.781	.003	3.158
Total score (10^{-3})	−0.299	0.146	4.207	.040	4.824

[a]β denotes the regression coefficient.
Abbreviations: CHR = clinical high risk for psychosis, CHR-C = individuals at CHR who converted to psychosis, FEP = first-episode psychosis; HC = healthy controls, VIF = variance inflation factor.

response. Panel A compares the CHR-C prediction model probabilities and individual concentration slopes, showing that the CHR-C model probability achieves an AUC of 0.772 ($P < .001$) and slope at 10^{-2} M concentration achieves an AUC of 0.645 ($P = .034$). Panel B displays the performance of the CHR discrimination model across various slopes, time points, and concentrations, with the CHR model probability achieving the highest AUC of 0.906 ($P < .001$) and the total score for 5 minutes and 20 minutes, 10^{-1} M concentration, and total score for all achieving the significant AUC. Panel C assesses the FEP discrimination model, highlighting the slopes and total scores for different concentrations and time points, with the FEP model probability achieving the highest AUC of 0.729 ($P < .001$) and the slope at 10^{-1} M concentration; the total score for 5 minutes, 15 minutes, and 20 minutes; 10^{-1} M concentration and 10^{-4} M concentration; and total score for all achieving the significant AUC.

In terms of sensitivity and specificity, the ROC curves for the CHR-C and CHR-NC subgroups revealed important differences in their ability to predict psychosis onset. The CHR-C Prediction Model showed moderate sensitivity (73.91%) and specificity (71.60%) at the optimal cutoff (probability = 0.754), which demonstrates its ability to distinguish individuals who converted to psychosis. In comparison, the CHR Discrimination Model performed better overall, with higher sensitivity (81.63%) and specificity (88.68%) at an optimal cutoff (probability = 0.305), making it a valuable tool for discriminating between CHR individuals at risk for psychosis. The FEP Discrimination Model, while effective, had a slightly lower AUC (0.729) with sensitivity (70.37%) and specificity (73.58%) at an optimal cutoff (probability = 0.476), indicating its reliability in distinguishing FEP cases.

DISCUSSION

Key Findings

This study presents several key strengths, including the inclusion of samples from both CHR and FEP populations, and the comprehensive 3-year follow-up of CHR individuals. This allows for an in-depth examination of the significance of NSFR characteristics in the progression and development of psychosis, a topic not previously reported in the literature. Additionally, this study is the first to introduce the variable of NSFR efficiency, which can enhance the clinical applicability of the NSFR test. Our key findings are as follows: (1) NSFR efficiency, rather than the response intensity, is more closely associated with the conversion of CHR to psychosis. Lower efficiency indicates a higher risk of developing psychosis. (2) The degree of attenuation in NSFR can effectively differentiate between CHR and HC, showing good discriminative power. (3) Both the efficiency and intensity of the NSFR can help distinguish FEP from HC. These findings highlight the potential clinical utility of NSFR tests in predicting and differentiating stages of psychosis, thereby offering valuable insights into early detection and intervention strategies.

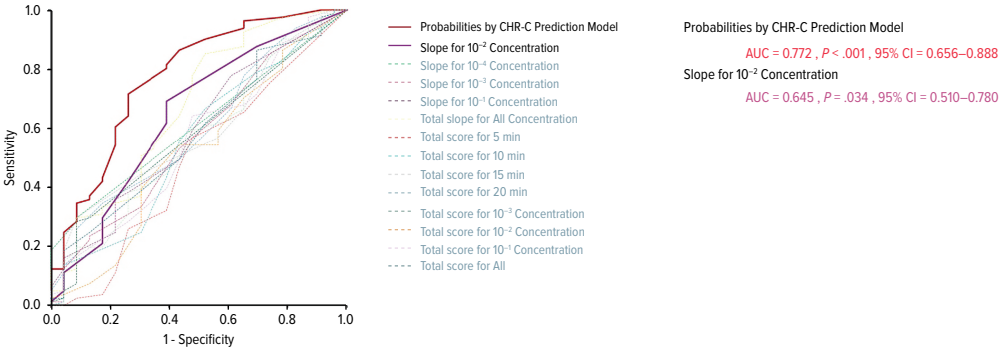
CHR-C vs CHR-NC. Our study found that within the CHR group, the efficiency of the NSFR, rather than the intensity, is a more crucial factor in predicting the conversion to psychosis. Specifically, lower efficiency in the NSFR was associated with a higher risk of conversion to psychosis. This finding is significant as it highlights a potential biomarker that could improve the prediction of individuals at high risk. Previous studies have produced mixed results regarding the NSFR in CHR individuals, with some reporting attenuated responses[23,25,26] and others noting increased responses.[22] Our study contributes to this debate by suggesting that the efficiency of the response—how quickly and effectively the skin reacts to niacin—might be more important than the mere presence or absence of an attenuated reaction.

Mechanistically, reduced efficiency may be a more sensitive indicator than the degree of attenuation. Existing studies that focus solely on response intensity may not fully capture the value of NSFR testing, as reduced efficiency could lead to the same level of attenuation over a prolonged observation period. However, efficiency allows for earlier detection of

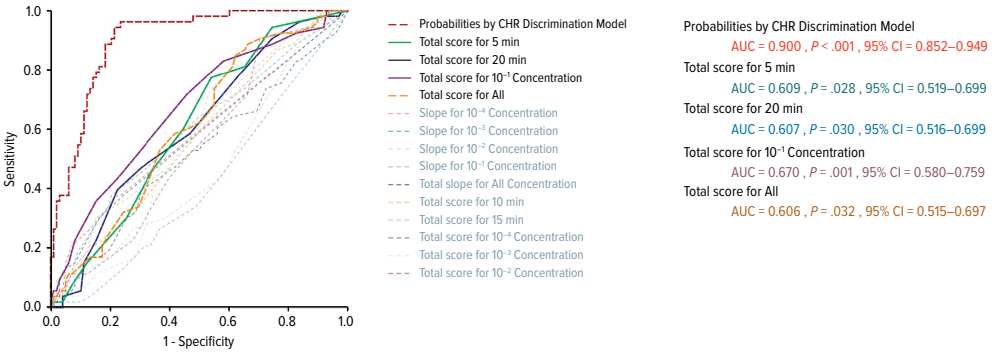
Figure 3.

ROC Curves Are Used to Assess the Predictive Performance of Diverse Models for Differentiating Among Groups According to the Skin Flush Response to AMN

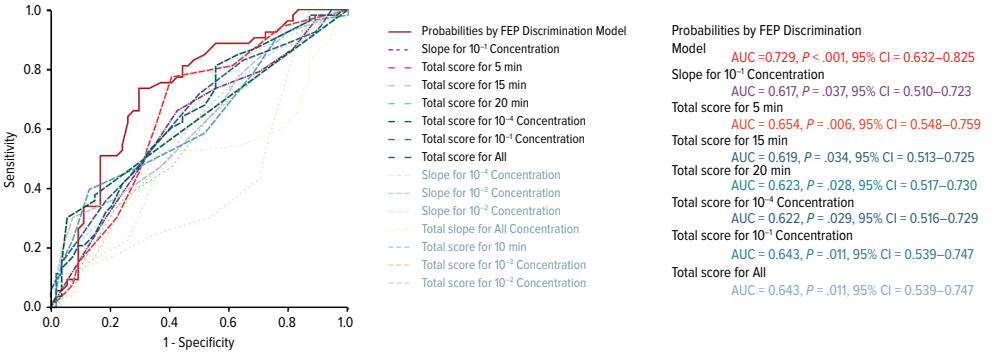
A. CHR-C prediction model[a]



B. CHR discrimination model[b]



C. FEP discrimination model[c]



[a]Panel A: The ROC curves juxtapose the probabilities forecasted by the CHR-C model with various slopes, time points, and AMN concentrations. The optimal ROC curve (probabilities by CHR-C Prediction Model) has an AUC of 0.772 ($P < .001$, 95% CI, 0.656–0.888). At a particular optimal cutoff ($P = .754$), its sensitivity is 73.91%, and specificity is 71.60%, indicating its discriminatory ability for the CHR-C group. This shows how well the CHR-C model can distinguish the CHR-C group based on the skin flush response parameters.

[b]Panel B: The ROC curves contrast the probabilities predicted by the CHR model with different slopes, time points, and AMN concentrations. The best-performing ROC curve (probabilities by CHR Discrimination Model) has an AUC of 0.900 ($P < .001$, 95% CI, 0.852–0.949). At an optimal cutoff ($P = .305$), the corresponding sensitivity and specificity are 81.63% and 88.68%, respectively. These values are crucial for differentiating CHR individuals, highlighting the effectiveness of the CHR model in separating CHR cases from others.

[c]Panel C: The ROC curves compare the probabilities predicted by the FEP model with different slopes, time points, and AMN concentrations. The top-performing ROC curve (probabilities by FEP Discrimination Model) has an AUC of 0.729 ($P < .001$, 95% CI, 0.632–0.825). At an optimal cutoff ($P = .476$), the sensitivity and specificity are 70.37% and 73.58%, respectively, demonstrating its effectiveness in discriminating FEP cases. This indicates how accurately the FEP model can identify FEP cases based on the skin flush response data.

Abbreviations: AMN = aqueous methylnicotinate, AUC = area under the curve, CHR = clinical high risk for psychosis, CHR-C = individuals at CHR who converted to psychosis, FEP = first-episode psychosis, ROC = receiver operating characteristic.

changes in this biological marker. This suggests that evaluating the speed and effectiveness of the NSFR can provide an earlier and possibly more accurate indication of psychosis risk, reflecting subtle dysfunctions in the prostaglandin pathway involved in vasodilation and inflammatory responses.[25,27,28] Thus, the efficiency of the NSFR could serve as a valuable tool in early clinical assessments and interventions.[10]

CHR vs HC. For the degree of NSFR, our study reveals that the attenuation level in CHR individuals lies between that of FEP patients and HC, with consistent differences in attenuation levels when comparing CHR to HC and FEP in both time and concentration dependences. Although our CHR model achieved a high discrimination accuracy of 90%, this may be partially attributed to age differences between the CHR and HC groups, potentially enhancing the model's performance. Overall, the attenuation severity degrees of the NSFR in CHR individuals are less pronounced than in FEP patients but more marked than in HC.

For NSFR efficiency, a particularly interesting finding is the differential slope values, reflecting NSFR efficiency across the 3 groups. At lower concentrations (10^{-4} M and 10^{-3} M), HCs exhibit the highest slope values. However, as the concentration increases (10^{-2} M and 10^{-1} M), the slope values for FEP patients become larger. This phenomenon could be explained by the rapid initial reaction to high niacin concentrations in HC, which quickly reaches a peak and then maintains a high level, resulting in a lower slope. In contrast, FEP and CHR individuals show a continued increase in response during the later stages, leading to higher slope values. Thus, the slope variable at lower concentrations may be particularly valuable in distinguishing CHR from HC, highlighting its potential as a sensitive marker for early psychosis risk. This underscores the importance of not only measuring the degree of attenuation but also assessing the efficiency of the NSFR, especially at low niacin concentrations.

FEP vs HC. Our study found that the attenuation of NSFR in FEP patients is the most pronounced, consistent with previous findings that patients with psychosis often display reduced NSFR.[1,4,29] This characteristic is also observed in their nonpsychotic relatives,[3] supporting the hereditary nature of this response. Further supporting our findings, Lien et al[30] identified a significant linkage peak at chromosomal region 14q32.12 influencing the NSFR in schizophrenia. This locus is distinct from those previously linked to schizophrenia, suggesting the presence of modifier genes for schizophrenia-related attenuation of the NSFR. Additionally, our previous research has demonstrated that NSFR is prevalently blunted in patients with schizophrenia or affective disorders, highlighting its potential as an auxiliary diagnostic marker.[24] The observed niacin-blunted subgroup suggests a common biological basis in these disorders, which could provide new insights into their pathological mechanisms.[31]

Limitations

This study has several limitations. First, while the HC group was matched to the FEP group in terms of demographic characteristics, the CHR individuals were younger than those in the FEP group,[32] resulting in an age mismatch between the HC and CHR groups. This could introduce an age bias when comparing CHR and HC. Second, clinical symptoms in FEP were assessed using the PANSS, while CHR individuals were evaluated with the SIPS, making direct comparisons of clinical symptoms between these groups difficult. Third, the NSFR was only assessed at baseline, and not re-evaluated during follow-up, preventing the analysis of longitudinal changes in NSFR. Furthermore, our inclusion and exclusion criteria did not account for the use of supplements such as omega-3 fatty acids or dietary supplements containing niacin.[33] These substances could potentially affect the NSFR results. Omega-3 fatty acids have been shown to modulate inflammatory responses and vascular function, which might interact with the physiological mechanisms underlying the NSFR. Similarly, niacin-containing supplements could directly confound the test results. Future research should consider controlling for these factors to improve the accuracy and reliability of NSFR-based assessments. The relatively small sample size of CHR-C converters may have introduced selection bias and reduced the precision of our estimates, potentially affecting the strength and reliability of the associations observed between the predictors and the conversion to psychosis. Lastly, the CHR follow-up was conducted in a real-world setting without intervening in the clinicians' treatment decisions. Consequently, some CHR individuals may have received medication during the 3-year follow-up period, potentially influencing their clinical outcomes.[34,35]

CONCLUSION

This study highlights that the degree of NSFR attenuation in CHR individuals lies between that of FEP patients and HC, with CHR exhibiting more marked attenuation compared to HC. Importantly, lower response efficiency, rather than attenuation degree, is more relevant to psychosis risk in CHR individuals, suggesting its potential as a sensitive early marker. Given the importance of response efficiency, future research should focus on improving the accuracy and objectivity of NSFR assessments. Current visual rating methods are subjective and do not effectively capture the response efficiency, leading to imprecise efficiency measurements. Advanced technologies such as AI and computer vision could be utilized to develop more precise

and comprehensive methods for assessing NSFR.[36] This approach could enhance the clinical utility of NSFR testing in predicting and managing psychosis.

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