Utility of Negative Symptoms in Predicting Transition to Psychosis Among Individuals at Clinical High Risk

Mitchell D. Arnovitz[1,2,3*], R. E. Carrión[1,2,3], A. M. Auther[1,3], D. McLaughlin[3], J. Addington[4], C. E. Bearden[5], K. Cadenhead[6], T. Cannon[9], M. Keshavan[11], D. H. Mathalon[8], D. Perkins[10], W. Stone[11,12], M. T. Tsuang[13], E. F. Walker[14], S. W. Woods[9], J. M. Kane[1,2,3], & B. A. Cornblatt[1,2,3]

[1]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [2]The Feinstein Institute for Medical Research, Manhasset, NY; [3]Division of Psychiatry Research, The Zucker Hillside Hospital, Northwell Health, New York, NY; [4]University of Calgary, Calgary, AB, Canada; [5]University of California, Los Angeles, Los Angeles, CA; [6]University of California, San Diego, La Jolla, CA; [8]University of California, San Francisco, San Francisco, CA; [9]Yale University, New Haven, CT; [10]University of North Carolina at Chapel Hill, Chapel Hill, NC; [11]Harvard Medical School, Boston, MA; [12]Beth Israel Deaconess Medical Center, Boston, MA; [13]Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA; [14]Emory University, Atlanta, GA; *Presenting Author

BACKGROUND

- Schizophrenia is within the top 15 causes of global disability (GBD 2016), conferring an increased risk of premature mortality (Olfson et al., 2015), chronic medical conditions (Schoenbaum et al., 2017), and an exceedingly high economic burden (Kadakia et al., 2022).
- Schizophrenia has long been defined by **positive** and **negative** symptoms.
- Although positive symptoms are reliably attenuated by medication, negative symptoms have been harder to define and treat.
- Recent research supports the conceptualization of five core domains:

BLUNTED AFFECT | ALOGIA | AVOLITION | ASOCIALITY | ANHEDONIA

EXPRESSIVE | EXPERIENTIAL

- These are among the first symptoms reported in individuals who develop schizophrenia and are important prognostic factors.
- Negative symptoms are found in over 80% of individuals at clinical high risk for psychosis (CHR-P), (Piskulic et al., 2012) correlating with illness severity as well as both social and role functioning (Carrión et al., 2016).
- Despite the importance of negative symptoms, they are not utilized in algorithms to predict transition to psychosis in individuals at CHR-P.
- As such, there exists a critical gap in the recognition and prevention of schizophrenia.

METHODS

Subjects

- Data was collected as part of the third phase of the North American Prodromal Longitudinal Study, Phase 3 (NAPLS3), a consortium of nine programs focusing on the psychosis prodrome. (Addington et al., 2022) The sites are located at Emory University, Harvard University, University of Calgary, University of California at Los Angeles, University of California at San Diego, University of California at San Francisco, University of North Carolina at Chapel Hill, Yale University, and the Zucker Hillside Hospital at Northwell Health.
- Sample included Healthy Controls (HC, N=96), CHR-P individuals who transitioned to psychosis (CHR-T, N=70), and CHR-P individuals who did not transition to psychosis (CHR-NT, N=415).

Measures

- Participants were evaluated via Structured Interview for Psychosis-risk Syndromes (SIPS). (McGlashan, Walsh, & Woods, 2010)
- The SIPS was administered to participants at baseline, 2-, 4-, and 6-months follow up.
- CHR-P individuals met criteria for one of the established psychosis-risk syndromes:
  - Attenuated Positive Symptom Syndrome (APSS)
  - Brief Intermittent Psychotic Syndrome (BIPS)
  - Genetic Risk and Deterioration Syndrome (GRD)

Note that negative symptoms are not considered in diagnosing psychosis-risk syndromes

- Negative symptom total was established by adding Scale of Psychosis-Risk Symptoms (SOPS) N1-N5 ratings at each time point.

N1: Social Anhedonia | **N2**: Avolition | **N3**: Expression of Emotion | **N4**: Experience of Emotions & Self | **N5**: Ideational Richness

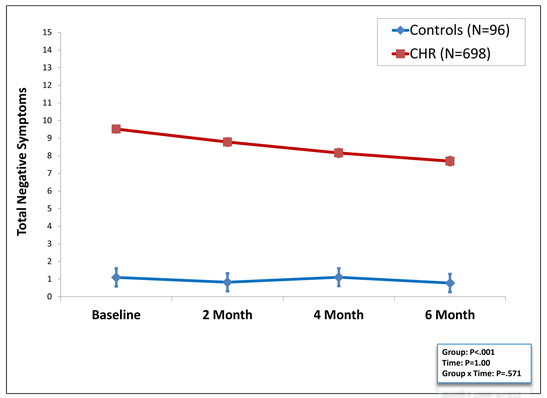
- Negative symptom subdomains were defined as follows, based on prior literature: Experiential = N1 + N2, Expressive = N3 + N4 + N5. (Giordano et al., 2022)
- Depression and positive symptom covariates were determined via the Calgary Depression Scale for Schizophrenia (CDSS) and SOPS P1-P5 ratings, respectively.
- Conversion to psychosis was confirmed via Structured Clinical Interview for DSM-IV (SCID-IV).

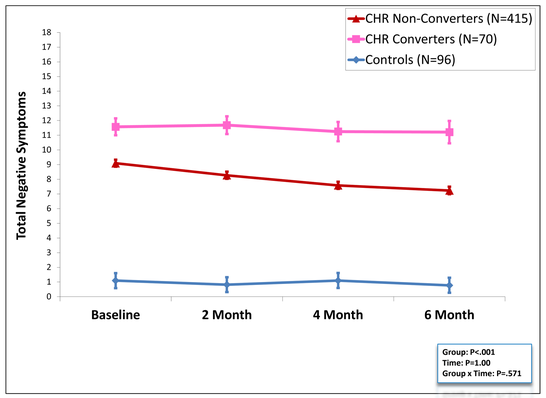
Statistical Analyses

- Linear mixed-effects models for repeated measures were used to evaluate group differences over time (SPSS v20).
- Follow-up analyses were conducted adjusting the models for depressive symptoms and attenuated positive symptoms (common sources of secondary symptoms) at the assessment.
- Cox proportional hazard regression models were used to examine the predictive associations between negative symptoms and transition to psychosis.

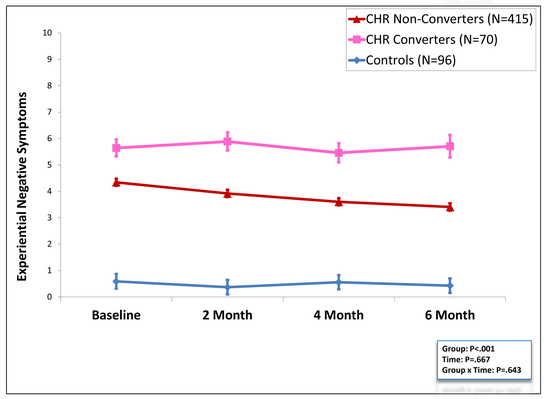
RESULTS

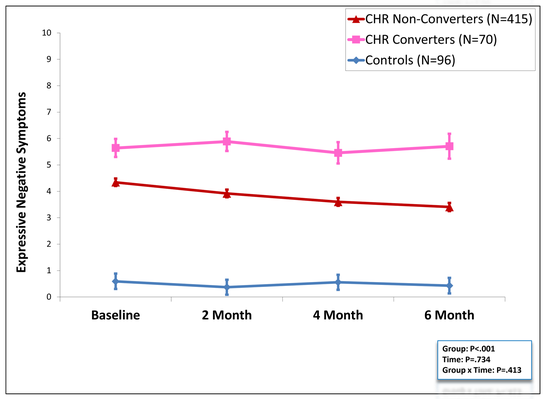
Total Negative Symptoms:



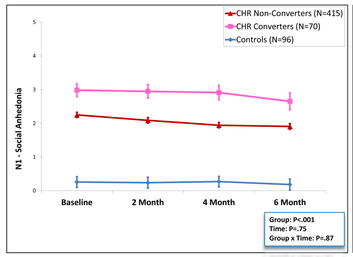


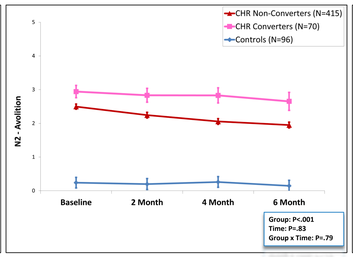
Experiential vs Expressive Negative Symptoms:

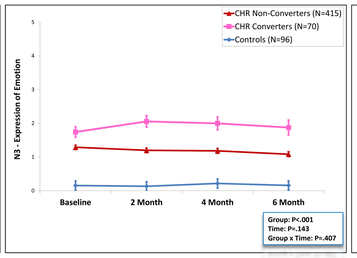


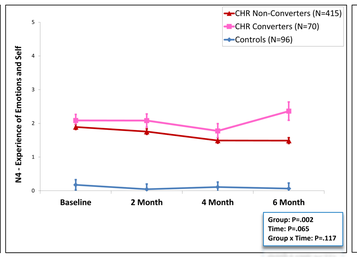


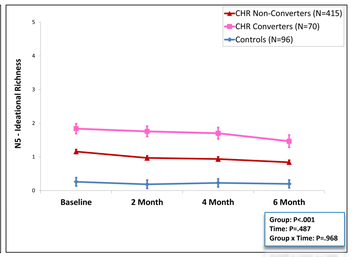
Individual Negative Symptoms:











- Mean baseline total negative symptoms were 1.09 for HCs (SE=0.510), 9.09 for CHR-NTs (SE=0.239), and 11.57 for CHR-Ts (SE=0.578).
- Total negative symptoms differed significantly between all three groups, such that CHR-Ts score significantly higher than CHR-NTs who score significantly higher than HCs (P<.001).
- CHR-T negative symptoms were stable over the six months; CHR-NT negative symptoms showed small improvements over six months but never reached those seen in HCs.
- This pattern remained even when adjusting for attenuated positive and depressive symptoms (P<0.001).
- Baseline negative symptom level predicted psychosis (P=0.006), even when including positive and depressive symptoms in the prediction model.
- This pattern holds true for Experiential (P=.025) and Expressive (P=0.014) subgroups as well as individual items separately.

CONCLUSIONS

- **Our findings reinforce the importance of negative symptoms in the prediction of psychosis in individuals considered to be at clinical high risk.**
- **Given the need for early recognition and treatment of psychosis, the data support inclusion of negative symptoms in predictive algorithms.**

ACKNOWLEDGEMENT

The authors would like to acknowledge the recent passing of Dr. Barbara Cornblatt, without whom this work would not be possible.

REFERENCES

Addington J, Liu L, Brummitt K, et al. North American Prodrome Longitudinal Study (NAPLS 3): Methods and baseline description. *Schizophr Res*. 2022;243:262-267. doi:10.1016/j.schres.2020.04.010
Carrión RE, Demmin D, Auther AM, et al. Duration of attenuated positive and negative symptoms in individuals at clinical high risk: Associations with risk of conversion to psychosis and functional outcome. *J Psychiatr Res*. 2016;81:95-101. doi:10.1016/j.jpsychires.2016.06.021
Giordano, GA, Palumbo, D, Pontillo, M, Mucci, A, Galderisi, S, Vicari, S. Negative symptom domains in children and adolescents at ultra-high risk for psychosis: association with real-life functioning. Schizophr Bull Open 2022; 3(1): sgac025
Kadakia A, Catillon M, Fan Q, et al. The Economic Burden of Schizophrenia in the United States. *J Clin Psychiatry*. 2022;83(6):22m14458. Published 2022 Oct 10. doi:10.4088/JCP.22m14458
Olfson M, Gerhard T, Huang C, Crystal S, Stroup TS. Premature Mortality Among Adults With Schizophrenia in the United States. *JAMA Psychiatry*. 2015;72(12):1172-1181. doi:10.1001/jamapsychiatry.2015.1737
PANDURANGI AK. The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-up. By T. H. McGlashan, B. C. Walsh and S. W. Woods. (Pp. 243; $54.95; ISBN 978 0199733316.) USA: Oxford University Press. 2010. *Psychological Medicine*. 2011;41(8):1785-1786. doi:10.1017/S0033291711000687
Piskulic D, Addington J, Cadenhead KS, et al. Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res*. 2012;196(2-3):220-224. doi:10.1016/j.psychres.2012.02.018
GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016 [published correction appears in Lancet. 2017 Oct 28;390(10106):e38]. *Lancet*. 2017;390(10100):1211-1259. doi:10.1016/S0140-6736(17)32154-2

DISCLOSURES

This study was supported by the National Institute of Mental Health (grant U01MH081984 to Dr Addington; grant U01MH081928 to Dr Stone; grant U01MH081944 to Dr Cadenhead; grant U01MH081902 to Drs Cannon and Bearden; grant U01MH082004 to Dr Perkins; grant U01MH081988 to Dr Walker; grant U01MH082022 to Dr Woods; grant U01MH076989 to Dr Mathalon; grant U01MH081857 to Dr Cornblatt). MDA is the recipient of the New Investigator Award from the International Society of CNS Clinical Trials and Methodology. JMK has received funds for research support from H. Lundbeck, Janssen, and Otsuka; has received consulting fees or honoraria for lectures from Alkermes, Biogen, Boehringer Ingelheim, Cerevel, Dainippon Sumitomo, H. Lundbeck, HLS, Indivior, Intra-Cellular Therapies, Janssen, Johnson and Johnson, Karuna, LB Pharmaceuticals, Merck, Minerva, Neurocrine, Neumora, Newron, Novartis, Otsuka, Reviva, Roche, Saladax, Sunovion, Takeda, and Teva; and has ownership interest in HealthRhythms, North Shore Therapies, LB Pharmaceuticals, Medincell, and the Vanguard Research Group. The rest of the authors declare no conflict of interest.

PRESENTER CONTACT

MArnovitz@Northwell.edu