

UC San Diego

UC San Diego Electronic Theses and Dissertations

Title

Do Early Risk Profiles Predict Short and Long-Term Outcomes of Persons at Clinical High-Risk for Psychosis?

Permalink

<https://escholarship.org/uc/item/7kj9v58c>

ISBN

9798190926279

Author

Kennedy, Leda

Publication Date

2026-09-11

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA SAN DIEGO
SAN DIEGO STATE UNIVERSITY

Do Early Risk Profiles Predict Short and Long-Term Outcomes of Persons at Clinical High-Risk
for Psychosis?

A dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Clinical Psychology

by

Leda Kennedy

Committee in charge:

University of California San Diego

Professor Kristin Cadenhead, Chair

Professor Colin Depp

San Diego State University

Professor Miguel Villodas

Professor Scott Roesch

Professor Nader Amir

©

Leda Kennedy, 2026

All rights reserved.

The Dissertation of Leda Kennedy is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California San Diego
San Diego State University

TABLE OF CONTENTS

DISSERTATION APPROVAL PAGE	iii
TABLE OF CONTENTS.....	iv
LIST OF TABLES.....	vi
LIST OF FIGURES	viii
ACKNOWLEDGEMENTS.....	ix
VITA.....	xi
ABSTRACT OF THE DISSERTATION	xvi
1. INTRODUCTION	1
1.1 Early risk factors known to influence conversion to psychosis in CHR.....	1
1.2 Risk factors related to clinical symptom severity in CHR.....	5
1.3 Risk factors related to functional outcomes in CHR	7
1.4 Factors that are predictive of future diagnosis in early psychosis	9
1.5 Interaction of risk factors in CHR.....	11
1.6 A methodological shift towards elucidating early risk profiles in CHR.....	13
1.7 Comparable models in the literature	14
1.8 Emergence of long-term follow-up studies in psychosis and CHR.....	15
1.9 Gaps in the literature regarding the long-term course of CHR and the potential role of risk profiles in the prediction of long-term outcomes.....	19
2. PURPOSE AND SPECIFIC AIMS	21
3. METHODS	24
3.2 Statistical Plan.....	30
4. RESULTS	34
4.1 Study characteristics: baseline sample.....	34
4.2 Development of early risk profiles through latent class analysis (LCA).....	37
4.2.1 Selection of indicator variables and description of data	37
4.2.2 Missing data analysis	39
4.2.4 Sensitivity analyses using internal imputation via FIML	43
4.2.5 LCA-Without GCI	47
2-Year Follow-Up.....	53
4.3.1 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA With GCI and covariates for complete cases	54
4.3.2 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA Without GCI (complete case data).....	57

4.3.3 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA Without GCI and covariates with internally imputed data by FIML	63
Long Term (5-20 year) Follow-Up (LTF)	68
4.4 Study characteristics: Long-term (5-20 year) follow-up (LTF) sample	68
4.5 Prediction of long-term (5-20 year) outcomes by early risk profiles (LCA-With GCI and LCA-Without GCI)	71
4.5.1 Logistic regressions of CCS and GAF at LTF predicted by LCA With GCI and covariates	71
4.5.2 Logistic regressions of CCS and GAF at LTF predicted by LCA Without GCI and covariates	76
4.5.3 Binomial logistic regressions of affective versus non-affective psychosis diagnosis at LTF among converters predicted by LCA with and without GCI and covariates	80
5. DISCUSSION	83
5.1 Distinct latent classes or risk profiles with and without GCI	84
5.1.1 Comparable findings regarding latent subgroups of CHR in the literature	88
5.2 Early risk profiles and prediction of 2-year outcomes	93
5.3. Early risk profiles and prediction of LTF (5-20 year) outcomes	97
5.4 Early risk profiles among individuals who converted to psychosis and prediction of lifetime diagnostic outcomes	104
5.5 Study Limitations and Future Directions	107
5.6 Summary and Clinical Implications	112
Appendix A. Assumption testing for 2-year follow-up logistic regressions (ggplot2, GGalley)	142
Appendix B. Assumption testing for 5–20-year long-term follow-up (LTF) logistic regressions (ggplot2, GGalley)	149
Appendix C. Assumption testing for 5-20 year follow-up (LTF) psychosis diagnosis (affective vs. non-affective) logistic regressions (ggplot2, GGalley)	157

LIST OF TABLES

Table 1: Assessments by timepoints (months).....	25
Table 2: Baseline characteristics of NAPLS 1-3 total sample	35
Table 3: Baseline characteristics by parent study	36
Table 4: Baseline characteristics of NAPLS 1-3 by site	36
Table 5: LCA-With GCI with 2-class solution incorporating complete cases only (stepmixr)...	43
Table 6: LCA-With GCI with 2-class solution with missing data using FIML (stepmixr).....	45
Table 7: LCA-Without GCI with 2-class solution incorporating complete cases only (stepmixr)	50
Table 8: Without GCI with 2-class solution with missing data using FIML (stepmixr)	52
Table 9: Clinical and functional status at 2-year follow-up.....	54
Table 10: Ordinal logistic regression of GAF at 2-years predicted by LCA-With GCI, age, and years of education (complete case data)	56
Table 11: Ordinal logistic regression of GAF at 2-years predicted by LCA-Without GCI, age, and years of education (complete case data).....	58
Table 12: Multinomial and binomial logistic regressions of CCS at 2-years predicted by LCA- With GCI (internally imputed cases by FIML).....	61
Table 13: Ordinal logistic regression of GAF at 2-years predicted by LCA-With GCI, age, and years of education (internally imputed data by FIML).....	63
Table 14: Multinomial and binomial logistic regressions of CCS at 2-years predicted by LCA- Without GCI (internally imputed cases by FIML)	64
Table 15: Ordinal logistic regression of GAF at 2-years predicted by LCA-Without GCI, age, and years of education (internally imputed data by FIML)	66
Table 16: Demographics, clinical status, functioning, cannabis use, and treatment profiles of 5- 20 year LTF participants	69
Table 17: Multinomial logistic regression of CCS (3-level) at 5-20 year LTF predicted by LCA- With GCI controlling for medication history, cannabis use frequency at LTF, and total years to LTF	73
Table 18: Binomial logistic regression of CCS (2-level) at 5-20 year LTF predicted by LCA- With GCI controlling for medication history, total years to LTF, and sex.....	74

Table 19: Ordinal logistic regression of GAF at LTF predicted by LCA-With GCI controlling for medication history, age at LTF, years of education at LTF, cumulative lifetime cannabis use, total years of cannabis use	75
Table 20: Multinomial logistic regression of CCS (3-level) at 5-20 year LTF predicted by LCA-Without GCI controlling for medication history, cannabis use frequency at LTF, and total years to LTF	77
Table 21: Binomial logistic regression of CCS (2-level) at 5-20 year LTF predicted by LCA-Without GCI controlling for medication history, total years to LTF, and sex.....	78
Table 22: Ordinal logistic regression of GAF at LTF predicted by LCA-Without GCI controlling for medication history, age at LTF, years of education at LTF, cumulative lifetime cannabis use, total years of cannabis use	79
Table 23: Binomial logistic regression of LTF conversion diagnosis predicted by LCA-With GCI, psychotherapy history, total years of cannabis use, and sex	81
Table 24: Binomial logistic regression of LTF conversion diagnosis predicted by LCA-Without GCI, psychotherapy history, total years of cannabis use, and sex	82

LIST OF FIGURES

Figure 1: Etiological model of psychosis from Cornblatt et al., 2003	2
Figure 2: Distributions of continuous potential indicator variables.....	37
Figure 3: Correlation matrices of potential indicator variables for LCA	39
Figure 4: Histogram of missing data for final selected indicator variables	40
Figure 5: 2-class solution for complete cases LCA-With GCI (poLCA)	42
Figure 6: Distribution of GCI, FH, and CT in LCA with 2-class solution for complete cases.....	47
Figure 7: 2-class solution for complete cases LCA- Without GCI (poLCA)	49
Figure 8: Predicted probability of GAF at 2-years by LCA- With GCI	57
Figure 9: Predictive probability of conversion at 2-years by LCA- With GCI class membership and 95% CI (internally imputed data by FIML)	62
Figure 10: Predictive probability of conversion at 2-years by LCA- Without GCI class membership and 95% CI (internally imputed data by FIML)	65
Figure 11: Holistic Screening Model for LCA-With GCI.....	113
Figure 12: Assumption Testing for Appendices A-C	142

ACKNOWLEDGEMENTS

I would like to acknowledge the unparalleled mentorship and guidance provided to me by my advisor Dr. Kristin Cadenhead, without which the present project nor my career in general would be possible. Throughout my doctoral training, Dr. Cadenhead has nurtured all elements of my professional development and has encouraged me to follow my instincts and to be confident in myself as a person and scientist. Dr. Cadenhead is also, above all, a role model for me and any other female clinician researcher who wishes to pave a path in the competitive field of clinical research in psychiatry. Uniquely, she has taught me to do so with an emphasis on showcasing personal authenticity and kindness, establishing real relationships with others in the field, and never taking oneself too seriously. While this chapter together has come to a close, I am grateful that this is just the beginning of what will be a long and treasured relationship.

I would also like to acknowledge the members of the UCSD Cognitive Assessment and Risk Evaluation (CARE) Program for their support and community throughout these last several years, and to Dr. Helene Mirzakhania for her endless education, advice, and for modeling what an ideal life as a clinical psychologist looks like. Critically, I would like to thank the individuals who participated in research within the CARE program for sharing their lives and experiences with our group 5-20 years ago, and for their willingness to pick up the phone or to answer a letter asking them to do it all over again. Without these individuals, many of whom have experienced significant challenges throughout their lives, this research would not be possible. I would like to give special thanks to the members of my guidance committee and dissertation committee. I have been fortunate to have had Drs. Colin Depp, Nader Amir, Miguel Villodas, and Scott Roesch be essential figures in my clinical training, personal growth, and education, and I also look forward to leaning on their guidance for many years to come.

Lastly, I dedicate this dissertation to my husband Nicky who never doubted me and who continuously supported me even when my career took us across the country and world. Thank you for your love, encouragement, and sacrifice. I further dedicate this project to my sisters Cardin and Fiona, and to my mother Bernadette, the female scientist who embodied the concept that a fulfilling career where one's mind is challenged and where one can continually learn is a career worth working for. Without my family I would not have been able to navigate the challenges and the accomplishments that come with pursuing a doctorate degree and I thank them for their continuous love and support.

VITA

EDUCATION

- Ph.D., *Clinical Psychology*** 2021- 2026
**San Diego State University/University of California San Diego
Joint Doctoral Program (JDP)**
San Diego, California
Advisor: Dr. Kristin Cadenhead
Major Area of Study: Experimental Psychopathology
Proposed Dissertation: *Do Early Risk Profiles Predict Short and Long-Term Outcomes of
Persons at Clinical High-Risk for Psychosis?*
- M.S., *Clinical Psychology*** 2021-2023
San Diego State University
San Diego, California
Thesis: *Cannabis-use Frequency and Associated Neurocognition Among Youth at
Clinical High-Risk (CHR) for Psychosis: Emergence of a Distinct Subgroup Predicted by
Premorbid Functioning*
- M.Sc., *Psychiatric Research*** 2020-2021
**The Institute of Psychiatry, Psychology, and Neuroscience (IoPPN)
Department of Psychosis Studies
King's College London**
London, United Kingdom
Thesis: *Associations of Cortical and Subcortical Brain Morphometry with Positive
Schizotypy: An ENIGMA Consortium Meta-Analysis*
Awarded: *Distinction*
- B.A., *Anthropology*** 2012-2015
**The American University
Washington, District of Columbia**

AWARDS

- Schizophrenia International Research Society (SIRS) Early Career Award for Academic Excellence (2025)
- Schizophrenia International Research Society (SIRS) Poster Award Finalist (2023, 2025)
- Dorothea Frick Memorial Scholarship- SDSU/UCSD Joint Doctoral Program in Clinical Psychology (2023)
- Graduate Student Travel Award- University of California San Diego 2021, 2022, 2023
- Society of Biological Psychiatry Predoctoral Travel Fellowship Award (2022)
- Institute of Psychiatry, Psychology, and Neuroscience (IoPPN) Taught Postgraduate Scholarship, King's College London (2020)
- U.S Fulbright Scholar Research Semifinalist (2018)

PEER REVIEWED PUBLICATIONS

1. **Kennedy, L.**, Lin, J., Meetra, V., Villodas, M., & Cadenhead, K. (2025). Socioenvironmental and developmental predictors of cannabis initiation and use in psychosis: a systematic scoping review. *Current Addiction Reports*. doi: <https://doi.org/10.1007/s40429-025-00654-7>
2. **Kennedy, L.**, Ku.,B., Bearden, C., Amir, C., Woods, S., Cannon, T., Perkins, D., Carrion, R., Cornblatt, B., Stone, W., Mathalon, D., Keshavan, M., Waker, E., & Cadenhead, K. (2024). Occasional cannabis use is associated with higher premorbid functioning and IQ in youth at clinical high-risk (CHR) for psychosis: parallel findings to psychosis cohorts. *Schizophrenia Research*, doi:<https://doi.org/10.1016/j.schres.2024.07.032>
3. **Kennedy, L.**, Holt, T., Hunter, A., Golshan, S., Cadenhead, K., & Mirzakhani, H. (2024). Development of an anti-inflammatory diet for first-episode psychosis (FEP): A feasibility study protocol. *Frontiers in Nutrition*, 11. <https://doi.org/10.3389/fnut.2024.1397544>
4. Jacobs, G. R., Coleman, M. J., Lewandowski, K. E., Pasternak, O., Cetin-Karayumak, S., Meshulam-Gately, R. I., Wojcik, J., **Kennedy, L.**, Knyazhanskaya, E., Reid, B., Swago, S., Lyons, M. G., Rizzoni, E., John, O., Carrington, H., Kim, N., Kotler, E., Veale, S., Haidar, A., ... Shenton, M. E. (2024). An Introduction to the Human Connectome Project for Early Psychosis. *Schizophrenia Bulletin*, sbae123. <https://doi.org/10.1093/schbul/sbae123>
5. Caballero, N., Machiraju, S., Diomino, A., **Kennedy, L.**, Kadivar, A., & Cadenhead, K. S. (2023). Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis. *Current Psychiatry Reports*, 25(11), 683–698. <https://doi.org/10.1007/s11920-023-01456-2>
6. Amir, C. M., Kapler, S., Hoftman, G. D., Kushan, L., Zinberg, J., Cadenhead, K. S., **Kennedy, L.**, Cornblatt, B. A., Keshavan, M., Mathalon, D. H., Perkins, D. O., Stone, W., Tsuang, M. T., Walker, E. F., Woods, S. W., Cannon, T. D., Addington, J., & Bearden, C. E. (2023). Neurobehavioral risk factors influence prevalence and severity of hazardous substance use in youth at genetic and clinical high risk for psychosis. *Frontiers in Psychiatry*, 14, 1143315. <https://doi.org/10.3389/fpsyt.2023.1143315>
7. Hesson, H. M., Shea, E. A., Appelbaum, P. S., Dishy, G., Cohen-Romano, C., **Kennedy, L.**, Bornico, M., Lee, K., Pia, T., Syed, F., Villalobos, A., Lieberman, J. A., Wall, M. M., Brucato, G., & Girgis, R. R. (2023). Victimology of Mass Shootings and Mass Murders Not Involving Firearms. *Violence and Victims*, 38(1), 15–24. <https://doi.org/10.1891/VV-2022-0051>

8. Woodberry, K. A., Powers, K. S., Bryant, C., Downing, D., Verdi, M. B., Elacqua, K. M., Reuman, A. R. L., **Kennedy, L.**, Shapiro, D. I., West, M. L., Huang, D., Crump, F. M., Grivel, M. M., Blasco, D. A., Herrera, S. N., Corcoran, C. M., Seidman, L. J., Link, B. G., McFarlane, W. R., & Yang, L. H. (2021). Emotional and stigma-related experiences relative to being told one is at risk for psychosis. *Schizophrenia Research*, 238, 44–51. <https://doi.org/10.1016/j.schres.2021.09.017>
9. Jutla, A., Califano, A., Dishy, G., Hesson, H., **Kennedy, L.**, Lundgren, B., Pia, T., Veenstra-VanderWeele, J., Brucato, G., & Girgis, R. R. (2020). Neurodevelopmental predictors of conversion to schizophrenia and other psychotic disorders in adolescence and young adulthood in clinical high risk individuals. *Schizophrenia Research*, 224, 170–172. <https://doi.org/10.1016/j.schres.2020.10.008>
10. **Kennedy, L.**, Brucato, G., Lundgren, B., Califano, A., Dishy, G., Hesson, H., Masucci, M. D., Pia, T., Goldberg, P. H., Xu, Q., Wall, M. M., & Girgis, R. R. (2021). Thematic content of obsessive and compulsive symptoms and conversion to psychosis in a clinical high-risk cohort. *Early Intervention in Psychiatry*, 15(5), 1423–1428. <https://doi.org/10.1111/eip.13057>
11. Dishy, G., **Kennedy, L.**, Lundgren, B., Xu, Q., Masucci, M. D., Califano, A., Hesson, H., Cohen-Romano, C., Pia, T., & Brucato, G. (2020). Temporal relationship between onset of positive and negative symptoms in the course of attenuated psychotic illness. *Psychiatry Research*, 293, 113439. <https://doi.org/10.1016/j.psychres.2020.113439>
12. **Kennedy, L.**, Johnson, K. A., Cheng, J., & Woodberry, K. A. (2020). A Public Health Perspective on Screening for Psychosis Within General Practice Clinics. *Frontiers in Psychiatry*, 10. <https://doi.org/10.3389/fpsyt.2019.01025>

MANUSCRIPTS UNDER REVIEW

1. Du, A., **Kennedy, L.**, Bearden, C., Woods, S., Cannon, T., Perkins, D., Carrion, R., Cornblatt, B., Stone, W., Mathalon, D., Keshavan, M., Waker, E., Cadenhead, K. (2025) Victimization and engagement with the legal system among individuals at clinical high risk (CHR) for psychosis. *Schizophrenia Research*. Under Review..
2. Kirschner, Matthias *, Hodzic-Santor, Benazir, * **Kennedy, L** *, ... Modinos, Gemma ^ for the *ENIGMA Schizotypy Working Group*. (2024) Multiscale characterization of cortical signatures in positive and negative schizotypy: A worldwide ENIGMA study. *Nature: Mental Health*. Under secondary review. ***equal contributions to manuscript/co-first authors**
3. Pham, D., **Kennedy, L.**, Bearden, C., Woods, S., Cannon, T., Perkins, D., Carrion, R., Cornblatt, B., Stone, W., Mathalon, D., Keshavan, M., Waker, E., Cadenhead, K. (2024). Exploring group differences in attenuated symptoms and functioning between clinical

high-risk individuals with and without posttraumatic stress disorder. *Early Intervention in Psychiatry*. Under review.

POSTER PRESENTATIONS/ PUBLISHED ABSTRACTS

1. **Kennedy, L.**, Addington, J., Bearden, C., Cannon, T., Cornblatt, B., Keshavan, M., Mathalon, D., Perkins, D., Stone, W., Woods, S., Walker, E., Cadenhead, K. (2025, March 30-April 2nd). *Clinical and functional characteristics of individuals at clinical high-risk (CHR) for psychosis at 5-20 year follow-up: Insights into the interactions and impacts of cannabis use and early life adversity on lifetime outcomes*. [Poster Presentation]. Schizophrenia International Research Society Annual Meeting 2025, Chicago, IL.
2. **Kennedy, L.**, Cadenhead, K. (2024, August 8-10) *Continuity of psychological intervention across 10-20 years following a first-episode of psychosis (FEP): insights into outcomes and treatment patterns across the lifespan from a small cohort* [Poster Presentation]. American Psychological Association Annual Meeting 2024, Seattle, WA.
3. **Kennedy, L.**, Cadenhead, K. (2024, May 9-11). *Cannabis use, neurocognition, and associated clinical factors in early psychosis: a multi-level modeling approach* [Poster Presentation and Abstract]. Society of Biological Psychiatry Annual Congress 2024, “*Is the Translational Medicine Approach Living Up to its Promise in Psychiatry?*” Austin, TX. *Biological Psychiatry*, Vol. 95, Issue 10, S271: <https://doi.org/10.1016/j.biopsych.2024.02.917>
4. **Kennedy, L.**, Holt, T., Morrel, A., Golshan, S., Cadenhead, K., Mirzakhani, H. (2023, July 10-12) *Dietary habits and eating pathology in First Episode Psychosis (FEP): Preliminary descriptive findings from a pilot study* [Poster Presentation]. International Early Psychosis Association 14th Annual Congress, “*Early Intervention in a Changing World,*” Lausanne, Switzerland.
5. **Kennedy, L.**, Addington, J., Bearden, C., Cannon, T., Cornblatt, B., Keshavan, M., Mathalon, D., Perkins, D., Stone, W., Woods, S., Walker, E., Cadenhead, K. (2023, April 27-29). *Frequency of Cannabis-Use, Neurocognitive Performance and Functioning in Clinical High-Risk Participants From the NAPLS-3 Cohort: Moderate Use is Associated With Better Performance and Functioning* [Poster Presentation and Abstract]. Society of Biological Psychiatry Annual Meeting, San Diego, CA, *Biological Psychiatry*, 93(9), S99. <https://doi.org/10.1016/j.biopsych.2023.02.254>
6. Kirschner, M., Hodzic-Santor, B., **Kennedy, L.**, Erp, T. van, Turner, J., Thompson, P. M., Aleman, A., Dagher, A., Kaiser, S. (2023). *Cortical Signatures of Positive and Negative Schizotypy: A Worldwide Enigma Study* [Abstract]. *Biological Psychiatry*, 93(9), S290–S291. DOI: <https://doi.org/10.1016/j.biopsych.2023.02.725>
7. **Kennedy, L.**, Holt, T., Hunter, A., Golshan, S., Shekhtman, T., Sugathan, R., Cadenhead, K., Mirzakhani, H. (2022, April 26). *Design of an anti-inflammatory diet for First-Episode Psychosis: Developmental and Formative Phases* [Poster Presentation]. 17th

Annual Lewis L. Judd Young Investigators Symposium, UCSD Department of Psychiatry, San Diego, CA.

8. **Kennedy, L.**, Twamley, E., Fuente-Sandoval, C. D. la, Wykoff, J., Kelsven, S., Reyes-Madrigal, F., Kelly, M., Robles-Guerrero, C., Cadenhead, K. (2022, April 28-30). *Compensatory Cognitive Training (CCT) Among Latinx Youth at Clinical High-Risk (CHR) for Psychosis: An Analysis of the Feasibility of a Collaborative United States and Mexico Randomized Controlled Trial (Progresar)*[Poster Presentation and Abstract]. Society of Biological Psychiatry Annual Meeting, New Orleans, LA, *Biological Psychiatry*, 91(9), S297. <https://doi.org/10.1016/j.biopsych.2022.02.753>
9. Nehneh-Sissoho, A., **Kennedy, L.**, Kegeles, L.S. (2019) *The relationship between dopamine levels determined by the dopamine depletion 2-scan method and baseline binding potential* [Poster Presentation]. New York State Psychiatric Institute, Columbia Irving Medical Center, New York, NY.
10. Woodberry, K.A., Powers, K.S., Bryant, C., Downing, D., Verdi, M., **Kennedy, L.**, Shapiro, D.I., Girgis, R., Brucato, G., Huang, D., Crump, F.M., Corcoran, C.M., Seidman, L.J., Link, B., McFarlane, W.R., Yang, L. (2019, April 10-14). *Identifying Youth at Clinical High Risk: What's the Emotional Impact?* [Poster Presentation] Schizophrenia International Research Society, Orlando, Florida.
11. Yang, L., MacFarlane, W., Seidman, L., Corcoran, C., Bruce Link, Bryant, C., Kline, E.R., Cloutier, A., Woodberry, K., **Kennedy, L.** (2017). *Predictors of Being 'Most Impacted' by Psychosis in Self-Identity Among Individuals at Clinical High Risk for Psychosis* [Abstract]. Schizophrenia Bulletin, Volume 43, Pages S96. doi: 10.1093/schbul/sbx021.258
12. **Kennedy, L.**, Cheng, J., Hendel, V., Kline, E., Li, H., Mesholam-Gately, R., Wojcik, J., McCarley, R., Goldstein, J.M., Shenton, M.E., Seidman, L., Srihari, V., Keshavan, M., Woodberry, K.A. (2018). *Screening for psychosis in primary care: a new frontier for early detection and intervention?* [Poster Presentation] Harvard Medical School Department of Psychiatry Mysell Research Day, Boston, MA.
13. **Kennedy, L.**, Kline, E., Chokran, C., Rodenhiser-Hill, J., Seidman, L., Woodberry, K. (2017). *Identifying community readiness to make referrals for emerging psychosis* [Poster Presentation]. Harvard Medical School Department of Psychiatry Research Day, Boston, MA.

ABSTRACT OF THE DISSERTATION

Do Early Risk Profiles Predict Short and Long-Term Outcomes of Persons at Clinical High-Risk for Psychosis?

by

Leda Kennedy

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2026
San Diego State University, 2026

Professor Kristin Cadenhead, Chair

Risk factors related to short-term (2-year) outcomes among youth at clinical high-risk for psychosis (CHR) include severity of attenuated psychosis symptoms, cannabis use, early life adversity, and functional impairment. Given known interactions between these and other risk factors, distinct “risk-profiles” may be present and may predict longer-term outcomes. Few studies have followed CHR youth beyond 2 years, limiting understanding of the lifetime impact of these collective factors.

Latent class analyses (LCA) were employed to isolate risk-profiles from existing data of CHR youth ($N = 1846$). Two LCA were conducted; one including baseline global cognitive

index (GCI) as an indicator variable (LCA-With GCI), and one without GCI (LCA-Without GCI). Risk-profiles were then used as predictors of 2-year outcomes in logistic regressions. Aim 2: Risk-profiles from a subset of these individuals ($n = 419$) who were reassessed after 5-20 years were employed as predictor variables of clinical and functional outcomes in a series of logistic regressions. Aim 3: Risk-profiles were tested as predictors of long-term diagnosis among those who converted to psychosis in exploratory analyses.

Aim 1: Both LCA produced risk-profiles with 2 classes (LCA-With GCI: Class 1=60% of estimated population shares, Class 2=40% of estimated population shares; LCA-Without GCI: Class 1=38% Class 2= 62%) corresponding to a “Lower-Risk” and “Higher-Risk” class. Being in both “Lower-Risk” classes was associated with decreased odds of conversion ($ps<.05$) and low functioning ($ps<.001$) at 2-years. Aim 2: Only LCA-Without GCI predicted clinical status at trend-level ($p=.06$) and significantly predicted global functioning ($p=.03$) at 5–20-year long-term follow-up (LTF); being in the “Lower-Risk” class was associated with decreased odds of conversion and increased odds of higher functioning at LTF. Aim 3: Being in the Lower-Risk (LCA-Without GCI) Class was associated at trend-level ($p=.08$) with an affective psychosis diagnosis at LTF, however other relevant covariates more significantly predicted later diagnosis ($ps<.05$).

Early risk-profiles are present in CHR youth that have predictive value for long-term clinical and functional outcomes. Better understanding of baseline risk-profiles can inform the development of interventions that specifically target underlying disease mechanisms and that are effective across the lifespan.

1. INTRODUCTION

The past three decades have seen a significant interdisciplinary push geared towards elucidating risk factors for psychotic disorders, conditions typically marked by profound individual disability and that contribute to high societal and economic cost.^{1,2} Researchers through this initiative have isolated the presence of the clinical high-risk for psychosis (CHR) state, the prodromal period prior to the onset of psychotic illness in which youth experience subthreshold hallucinations, delusions, and functional decline.³ This period has been identified as a critical window for targeted intervention aimed at reducing symptoms, improving functioning, and ultimately preventing the onset of chronic psychiatric illness.^{4,5} The ability to predict later conversion to psychosis as well as symptomatic, functional, and diagnostic outcomes in this population is limited however due an emphasis on cross-sectional risk factors for these domains; there is little understanding of how risk factors interact in the early phase of illness. Further, the short time window in which these outcomes are studied in CHR (typically within a span of 2 years)^{3,4} hinders the ability to evaluate the impact of these early collective risk factors on outcomes across the lifespan. In response to this, the proposed dissertation aims to evaluate the interactive nature of risk factors for multidimensional outcomes in CHR, with the objective of capturing distinct early risk profiles that map onto clinical and functional outcomes across the early illness phase. In a novel approach for this population, the proposed dissertation aims to then determine if these early risk profiles are predictive of long-term (5-20 year) conversion to psychosis, clinical symptom severity, functioning, and diagnosis.

1.1 Early risk factors known to influence conversion to psychosis in CHR

Through investigations in CHR, an etiological model of psychosis has been theorized in which genetic vulnerability interacts with environmental precursors, leading to emerging

psychiatric symptoms, cognitive deficits, and functional decline that collectively interact with environmental “triggers” (e.g. stress, cannabis use) to initiate the onset of psychosis (**Figure 1**).⁶ Available evidence to date from pioneering large-scales studies in CHR has suggested that approximately 20-30% of CHR youth convert to a psychotic disorder within 2 years following the onset of attenuated psychosis symptoms.^{7,8} These early findings created the methodological blueprint for studying CHR, with international research groups designing comparable longitudinal frameworks to investigate the psychosis-risk-conversion paradigm.^{7,9}

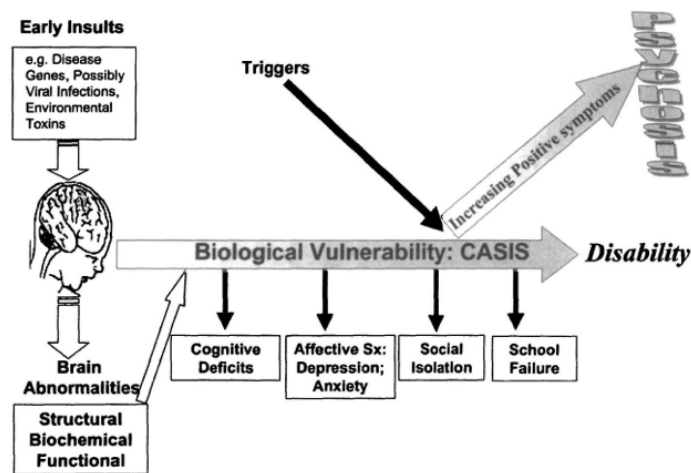


Figure 1: Etiological model of psychosis from Cornblatt et al., 2003

The North American Prodromal Longitudinal Study (NAPLS-1) was one of the earliest multi-site initiatives aimed at prospectively investigating the CHR state, which included diagnostic standardization, exploration of naturalistic factors that contributed to conversion, as well as collection of specific risk factors for functional decline and attenuated symptoms in this population.¹⁰ Early investigations in this consortium identified five baseline factors associated with a later conversion to psychosis within a 2-year time period: having a first-degree relative with psychosis accompanied by a recent decline in global functioning, higher levels of unusual thought content, higher levels of suspiciousness/paranoia, more severe impairment in social

functioning, as well as a history of substance abuse (any substances).¹¹ This foundational initiative confirmed the presence of unique CHR sequelae that differentiated CHR youth from healthy controls and that comprised specific risk for conversion to a psychotic disorder.

The second iteration of the NAPLS study (NAPLS-2) built upon these findings in a multi-site investigation specifically aimed at exploring mechanisms of conversion to psychosis in CHR.¹² Referencing findings from the broader international CHR literature on factors that had been historically associated with conversion,^{4,13–16} these investigators developed a “psychosis risk calculator (PRS)” to isolate distinct subgroups of those most at risk for developing psychosis over time.^{13,17} The PRS included pre-selected risk-factors known to influence conversion in CHR samples: age at onset of symptoms, attenuated psychosis symptom severity, verbal learning and processing speed, level of social functioning, exposure to childhood trauma and stressful life events, and family history of a psychotic disorder.¹⁷ This PRS performed at a level comparable to other clinical predictive models outside of psychiatry, and found that those with the highest level of unusual thought content and persecutory ideas, the steepest decline in social functioning, the lowest performance in verbal learning, memory and processing speed, as well as a younger age of onset of psychosis-risk symptoms comprised the highest risk for conversion to psychosis.¹⁷ Of note, analyses of the PRS found that childhood trauma, early life stress, and family history of psychosis were not predictive of conversion to psychosis within the NAPLS-2 sample, however these factors have independently been linked with increased risk for psychosis in other studies.^{18,19} Age of onset of symptoms has been found to be a less robust predictor in several studies and is highly correlated with age in general.²⁰ This model has been replicated and validated well-outside of the NAPLS consortium and has been applied to predictive modeling of psychosis-risk in research and clinical samples across the globe.^{21–23}

The development of the PRS highlighted the importance of exploring risk levels in CHR given that this is a highly heterogeneous psychiatric population with significant variation in risk exposure and overall outcome. Importantly however, predictive models in CHR, including the PRS, are limited in that they only reflect risk factors known to influence conversion within the traditional 2-year study period in which CHR youth are typically observed. Further, while the impact of substance use on CHR conversion in early studies was broadly explored and ultimately unclear, the last several decades have seen a significant increase in more focused investigations of substances in the attenuated psychosis context, specifically zeroing in on cannabis use as an important risk factor in the evolution of CHR.^{17,24}

As is observed in chronic psychosis populations, CHR youth have been shown to use cannabis at alarmingly high rates compared to other psychiatric groups and healthy populations, spurring global research projects aimed at understanding how cannabis use interacts with risk for developing psychosis.^{25–29} Findings from recent reviews and meta-analyses evaluating the association between cannabis use and conversion to psychosis in CHR have been mixed; while some individual studies have found that cannabis use is associated with conversion to psychosis,^{27–33} findings from several studies in CHR do not support this relationship.^{25,27,29,34–40} The strongest evidence for an association between cannabis use and psychosis-risk appears to be highly dependent on use-factors such as chronology of cannabis use (age of first use of cannabis), as well as frequency of cannabis use.^{30,41} This is widely reported in retrospective studies of first-episode psychosis (FEP). A review by Bagot and colleagues⁴² highlighted that adolescent cannabis initiation (initiation before age 18) is commonly reported in established psychosis cohorts, and is associated in these groups with earlier conversion and more severe psychosis symptoms. Use frequency and age of initiation have been shown across studies to

moderate the effect of cannabis use on risk for developing psychosis where heavier use and younger age of initiation are associated with an increased risk for psychosis.^{33,43} A single meta-analysis by Kraan and colleagues found that among available studies in CHR that explored this paradigm, cannabis abuse or dependence (not just reported use) was associated with conversion to psychosis, furthering substantiating a “dose-response” relationship between cannabis use and risk for psychosis that is contingent on frequency and initiation age.^{24,44,45} Importantly however, these findings are primarily reflective of retrospective studies among individuals who have already developed psychosis, and more investigations are needed in CHR which prospectively observe the dynamic nature of these relationships.

1.2 Risk factors related to clinical symptom severity in CHR

Much attention has been given to predictors of conversion to psychosis in CHR, however few studies have explored specific predictors of clinical symptom severity in this population. Severity of clinical symptoms are strongly correlated with overall functioning in CHR,⁴⁶ and can have a unique impact on one’s ability to access appropriate care, perception of themselves within their environment, and overall sense of well-being.⁴⁷ Waford and colleagues,⁴⁸ for example, found that demographic correlates such as age, sex, and education level predicted scores of attenuated psychosis symptoms in which older individuals displayed more suspiciousness, and female CHR youth displayed more severe unusual thought content and less severe perceptual abnormalities. Falukozi and Addington⁴⁹ found that experiencing trauma before the age of 16 was associated with higher incidences of persecutory ideas and grandiosity, and lower incidences of hearing “non-negative” voices as well negative self-cognitions in a sample of CHR youth. Some independent studies and reviews in CHR have reported that regular cannabis use is also associated with exacerbation of attenuated psychosis symptoms, however the causal interpretation of this relationship is limited by mostly cross-sectional design as well as a

confluence of risk factors that could impact this paradigm.^{29,40,50,51} Our own group found that among CHR youth who use cannabis daily, grandiose symptoms and perceptual abnormalities (visual, tactile, auditory hallucinations) were more severe compared to less frequent users.⁵¹ These findings have not been consistent however across CHR contexts, with several studies reporting no differences in symptom severity between users and non-users.^{29,52–55} Dragt and colleagues⁵⁶ conducted one of the only studies to date that included a discussion of age of cannabis use and found that a younger age of cannabis abuse or dependence was associated with an earlier onset of attenuated psychosis symptoms among a large cohort of CHR individuals.

While knowledge regarding specific predictors of clinical symptomatology is relatively limited in CHR, there is some understanding of the general course of symptom severity in this population. In the NAPLS-2 study, Addington and colleagues²⁰ reported on clinical symptom presentations across the entire sample as well as how symptoms transformed over the 2-year study period. Investigators in this study found that across the study duration, severity of all 19 attenuated psychosis symptoms reflective of positive, negative, disorganized, and general symptom categories improved over time, with the most significant improvement occurring within the first 6 months following identification as CHR.²⁰ When comparing 2-year outcomes, these investigators also chose to evaluate not only the baseline symptom profiles of those who converted but also of those who were in remission of attenuated psychosis and those who were still experiencing persistent attenuated psychosis symptoms. They found that lower baseline levels of suspiciousness and total positive symptoms significantly differentiated individuals who were in remission of symptoms at 2-year follow up, however no specific baseline symptoms predicted persistent attenuated symptoms.²⁰ A recent meta-analysis by Beck and colleagues⁵⁷ of clinical symptom severity outcomes among CHR youth followed for at least 2 years found that,

at follow-up, between 28%-71% of CHR participants had not remitted from CHR symptoms. These preliminary findings suggest that there could be specific factors that predict sustained symptoms in CHR groups, however (and as these authors argue) more studies that elucidate long-term risk profiles are needed which capture collective risk factors for symptom severity over time rather than just observing baseline risk factors in isolation. This may provide insight into the early course of symptoms and related risk factors so that targeted interventions can be developed to address or reduce symptom severity in real-time.

1.3 Risk factors related to functional outcomes in CHR

Functional impairment has a significant impact on quality of life among CHR youth as well as the ability of these young people to maintain employment, remain enrolled in school, and form meaningful social connections.⁵⁸ Several risk factors for functional impairment in CHR have been identified across the traditional 2-year study period. Neurocognitive deficits have been widely linked to functional impairment in CHR, with several studies reporting that domain-impairments in areas such as processing speed, verbal learning, attention, and executive functioning are related to deficits in social, global and role functioning.⁵⁹⁻⁶² Attenuated negative symptoms have also been mechanistically implicated in functional impairments among CHR studies. A recent meta-analysis by Devoe and colleagues⁴⁶ demonstrated that across studies that explored the relationship between CHR symptomatology and functional outcomes, total negative symptom scores were strongly correlated with poorer role, social, and global functioning. Within predictive models, this review found that negative symptoms significantly contributed to the variance in functional outcomes in all studies compared to other relevant risk factors.⁴⁶ Carrión⁶² and colleagues also found that disorganized symptom levels and motor disturbances significantly predicted later impaired social and role functioning respectively.

Cannabis use has also been linked to functional outcomes in CHR populations. While deficits in functioning are a hallmark symptom in CHR, several studies have interestingly found that CHR cannabis users have higher social and global functioning compared to non-users however these effects are typically not sustained over time (in the few studies that have explored this longitudinally).^{36,59} Findings from this group within the NAPLS-3 study found that CHR youth who used cannabis at a moderate level (compared to a heavy or minimal/no use level) had higher social functioning and premorbid functioning.⁵¹ This is a trend that has been reported on in FEP contexts^{63–65}, and it has been theorized that perhaps higher premorbid functioning may lead to higher social functioning which, in turn, predicts cannabis use rather than cannabis use itself having an impact on functional outcomes. The impact of cannabis use on long-term (past 2-year) functional outcomes however has not been explored in CHR, limiting understanding of how this phenomenon may change with more sustained lifetime use.

Premorbid functioning has also typically been considered a harbinger for future functioning in CHR cohorts, and is correlated with negative symptoms.^{46,66} Within a large sample of CHR youth, Lyngberg and colleagues⁶⁶ explored patterns of premorbid adjustment as they pertained to functional and clinical outcomes and found that lower premorbid functioning was associated with more severe negative symptoms and worse social functioning. Using cluster-analyses, these investigators also found that specific levels of premorbid functioning across the three premorbid domains (childhood, early adolescence, late adolescence) corresponded to functional and clinical “profiles” in CHR: “deteriorating”, “stable-intermediate”, and “stable-good.” These profiles were reflective of baseline data and were comprised of measures of social functioning and attenuated positive and negative symptoms.⁶⁶

Importantly, in a review discussed previously, Beck and colleagues⁵⁷ also found that across longitudinal studies of CHR nearly 50% of CHR patients reported poor psychosocial functioning at long term (at least 2 year) follow-up, signaling that CHR youth are vulnerable to long-term functional impairment, particularly within their social contexts. Given that higher social and global functioning and associated characteristics such as increased social support, education, and employment have been correlated with improved outcomes across the psychosis spectrum⁶⁷⁻⁷⁰, it is critical to identify early and perhaps modifiable mechanisms of long-term functional impairment in CHR.

1.4 Factors that are predictive of future diagnosis in early psychosis

CHR youth demonstrate significant psychiatric comorbidity at baseline, with other common diagnoses being major depressive disorder, anxiety disorders, developmental disorders, and to a smaller degree, post-traumatic stress disorder.⁷¹ There is little known however regarding what shapes diagnoses over time, a question most salient with regards to conversion to psychosis. CHR youth who convert to psychosis may develop either a non-affective (schizophrenia) or affective (bipolar disorder with psychotic features, schizoaffective disorder) psychosis diagnosis.^{72,73} Given that outcomes and treatment needs differ between these two diagnostic groups,^{74,75} it is critical to identify early risk profiles that predict either an affective or a non-affective psychosis lifetime course. Much of the available information regarding risk factors for either diagnostic course is from retrospective analyses in FEP however, not from prospective studies in CHR, and no studies to our knowledge have explored predictors of diagnostic course among converters in CHR. Comparisons of FEP individuals with affective and non-affective psychosis have highlighted that factors such as female sex, higher premorbid and global functioning, better neurocognition, the presence of specific mood symptoms, higher exposure to early life trauma, and less severe positive and negative symptomatology are more

predictive of an affective psychosis presentation than a non-affective presentation in FEP.^{76–80} Factors such as poorer premorbid and global functioning, more pronounced neurocognitive deficits, and more severe negative symptoms have been acknowledged as risk factors for a non-affective psychosis presentation.^{81–84} While neurocognitive deficits are present in both affective and non-affective psychosis presentations^{85–87}, comparisons between these diagnostic groups have been disparate. Lewandowski and colleagues⁸⁸ compared neurocognitive functioning across individuals with schizophrenia, schizoaffective disorder, and bipolar disorder with psychotic features and found that neurocognitive performance did not differ across diagnostic groups. Torrent and colleagues⁸⁹ alternatively found that among a FEP sample, the affective group displayed better neurocognition (executive functioning) and less severe clinical symptoms at baseline compared to the non-affective group; however, this was not sustained over time. No studies, however, have explored how profiles of prodromal neurocognitive performance may predict either diagnosis.

Findings regarding cannabis use slightly confound existing evidence regarding known substance use behaviors between these two groups. While rates of substance use are generally thought to be higher among those who develop a non-affective psychosis diagnosis, small studies in established psychosis cohorts have indicated that cannabis use specifically may be associated with an increased risk for mania and/or affective psychotic disorders (bipolar or depression), indicating a need for further investigation of this relationship in the attenuated psychosis context.^{26,90,91}

These findings collectively indicate that even in the prodromal phase of illness, these interacting risk factors may be present and could be indicative of future CHR converters most likely to transition to an affective or non-affective psychosis diagnosis. Importantly, determining

if early risk profiles predict later psychosis diagnosis could improve precision of interventions focused on subthreshold affective or non-affective presentations while still in the attenuated illness phase.

1.5 Interaction of risk factors in CHR

Several risk factors have been identified among CHR youth that are related to conversion to psychosis as well as to the general clinical and functional well-being of CHR individuals in the short-term. While many of these risk factors have unique independent effects on outcomes such as conversion, symptom severity, functioning, and potentially diagnosis (among converters), they have demonstrated associations with one another. Cannabis use specifically has been discussed in the previous sections as being directly related to these outcomes, however it is critical to note that cannabis use has also been shown to interact synergistically with several other risk factors. Several studies in FEP, for example, have reported that rates of cannabis use are significantly higher among those who have a history of childhood trauma, and that cannabis use in adolescence may be associated with an increased risk for psychosis among those who have experienced early-life trauma.^{14,43,92} Importantly, research by Trotta and colleagues⁹³ found in a large sample of FEP patients that cannabis use mediated the effect of “early household discord” on later risk for psychosis, and several emerging studies in FEP have found that cannabis and early life trauma have an interactive and additive effect on risk for psychosis.^{94,95} In CHR, the interactive relationship between cannabis, childhood adversity, and clinical outcomes has barely been explored prospectively, however there may be more evidence to suggest that cannabis use and early adverse events have less of an impact on conversion to psychosis than they do on attenuated symptom severity. Recent findings from Lu and colleagues⁹⁶ for example reported that perceptual abnormalities (hallucinations) are more common among those who currently use cannabis and who have also experienced childhood trauma.

Neurocognitive functioning also appears to have a complex interplay with cannabis use in early psychosis. Some studies have found specific domain-impairments among cannabis users compared to non-users, while others have reported better neurocognition in users or no differences between users and non-users.^{59,97–99} Consistent with findings in FEP,^{63,100–102} there is some evidence that cannabis use is associated with higher premorbid IQ and global neurocognition^{34,103} in CHR cohorts. Findings regarding cannabis use and premorbid functioning are mixed, with contrasting evidence in FEP supporting that both higher and lower premorbid functioning is associated with cannabis use.^{63,102,104} Some studies have delved deeper into different domains of premorbid functioning and found that specifically lower academic premorbid functioning is associated with higher rates of cannabis use later in life among psychosis cohorts.^{16,104} This relationship is less clear in CHR however these authors found that better overall premorbid functioning predicted higher premorbid IQ which, in turn, predicted a moderate cannabis use pattern in CHR.⁵¹ These findings could signify that better premorbid functioning is related to better cognition and social functioning, perhaps predicting a more moderate (less severe) cannabis use pattern in a social context specifically.⁵¹ Critically, these findings represent cross-sectional data and do not make inferences about how this paradigm transforms over time.

In addition to the interaction between cannabis use and known risk factors in CHR, it is well documented that functioning, symptoms, neurocognition, early life events, and genetic risk have their own associations in this population.¹³ Much of the available studies exploring these risk factors however are centered on “snapshots” in time, using baseline measurements of these markers to predict outcomes rather than painting a holistic picture of the interrelated nature of risk factors and their impact on outcomes in the early stages of CHR pathology. It is plausible

that capturing profiles of these collective risk factors could elucidate groups of CHR youth with varying degrees of risk and resilience for future outcomes, a cornerstone of improving efficacy of early interventions for psychosis.

1.6 A methodological shift towards elucidating early risk profiles in CHR

Considering known interactions between several risk factors for later clinical, functional, and diagnostic outcomes in CHR discussed above, it is important to observe how these collective factors impact outcomes. A review of the literature in this section, considering previous risk models, has isolated distinct risk-factor “motifs” that appear to both interact with one another and be important prognostic indicators of outcomes in CHR: attenuated psychosis symptoms, verbal learning, memory, and processing speed, social and global functioning, a family history of psychosis, cannabis use behaviors (age of initiation, frequency/severity), premorbid functioning and IQ, and exposure to childhood trauma and adverse life events. These findings suggest that distinct subgroups, or profiles, of CHR youth may be present that reflect the variation in how these risk factors relate to one another and that these profiles may be viable multidimensional predictors for outcomes across the initial illness stage.

CHR youth are a highly heterogeneous group who display significant variation in risk factors at baseline.^{3,7} To date, most studies that observe these factors do so parsimoniously, using analysis of variance (ANOVA) to study changes in individual variables over time typically comparing outcomes between CHR youth and healthy controls.^{4,105} The PRS utilized survival analyses/regressions such as the Cox Proportional Hazard model to risk prediction for conversion across levels of baseline independent variables.^{17,106} In a recent review by Addington and colleagues regarding the future of disease conceptualization and prediction in CHR¹⁰⁵, authors argued for a shift away from more simplistic univariate analyses of risk factors and conversion

towards longitudinal analyses that can capture the heterogeneity of these groups and how different profiles can predict later outcomes.

1.7 Comparable models in the literature

Importantly, developing holistic profiles of CHR (regardless of how they map onto specific outcomes) is a relatively novel concept in this population.¹⁰⁵ Only a select few studies have used more advanced methodologies such as latent growth-class analysis (LGCA) or latent profile analyses (LPA) in large samples of CHR, which have just begun to highlight that specific profiles/classes are even present in these groups.^{107,108} Most recently, Berge¹⁰⁹ and colleagues utilized LPA to isolate profiles from the same risk factors that comprise the original PRS from the NAPLS study, and detected two distinct profiles based on these collection of risk factors. These profiles did not differentiate those who converted to psychosis, however the profile that represented those who were older, had better neurocognition, more trauma, a greater decline in functioning, and who were at higher genetic risk for psychosis displayed more severe symptoms and more frequent cannabis and alcohol use over the 2-year study period.¹⁰⁹ Healey¹¹⁰ and colleagues similarly utilized LPA to identify three distinct clinical classes in a moderately sized CHR sample (n=171). These investigators found that baseline scores on the Scale of Prodromal Symptoms (SOPS), Calgary Depression Scale for Schizophrenia (CDSS), as well as scores on several neurocognitive tests differentiated a mild class (low conversion rate, low symptoms, intact neurocognition), a more “paranoid-affective class” (moderate conversion rate, higher suspiciousness, moderate symptoms and neurocognitive impairment, and a “negative-neurocognitive” class (highest conversion rate, most severe symptoms and neurocognitive impairment as well as highest impairment in social functioning.¹¹⁰ Allswede and colleagues¹¹¹ expanded on this by employing longitudinal LPA to identify trajectories of symptoms and functioning within a select group (those which sufficient follow-up data) from the NAPLS 1-2

consortia (N=422). These analyses isolated three distinct groups who 1) displayed improvement in symptoms and functioning across 2 years, or 2) had moderate impairments in symptoms and functioning or 3) displayed consistent impairment in functional and clinical domains across time.¹¹¹ Of note, no studies that have utilized this type of modeling in CHR have incorporated cannabis use patterns or behaviors into the formation of profile trajectories, despite the symbiotic relationship between cannabis use and known risk factors in this population discussed previously.

These emerging findings emphasize that not only do distinct multidimensional profiles exist in CHR, but that they have differential effects on outcomes within the typical 2-year longitudinal study period. While observing how these profiles influence outcomes across 2-years is consistent with the longitudinal framework used in CHR studies across the world, contemporary research initiatives emphasizing a lifespan approach to understanding psychosis suggest it is also critical to explore multidimensional profiles well beyond the early phase of illness. In addition to a field-wide shift towards diversifying and improving our understanding of the interactive nature of risk factors in psychosis, a select few initiatives across the psychosis spectrum have begun to evaluate the trajectories of psychosis phenomenology across the lifespan, paving the way to explore the long-term naturalistic course of CHR.

1.8 Emergence of long-term follow-up studies in psychosis and CHR

Given that the field of early intervention for psychosis is somewhat still in its infancy, it has only recently been possible to evaluate longer-term outcomes of individuals on the psychosis spectrum spanning from the early phases of illness into older adulthood.^{9,112} Some international research groups have begun to follow-up participants who were originally identified as being FEP nearly a decade prior. In Denmark, the OPUS trial has employed longitudinal LPA to explore long-term trajectories of positive and negative symptoms in FEP 10 years following

initial identifications and detected distinct profile trajectories of relapse and recovery.^{113,114} The AESOP-10 consortium in the United Kingdom has followed FEP individuals for 10 years employing growth mixture modeling to identify distinct classes that captured clinical changes over time post FEP; researchers in this study identified a remitting-improving group, a late decline, a late improvement, and a persistent symptom group.¹¹⁵ In more progressed psychosis, these studies have elucidated that the course of psychotic disorders over time, once typically believed to be marked by predominantly progressive decline, is much more nuanced and punctuated by periods of recovery especially immediately after the FEP. These formative long-term studies in FEP have provided methodological templates for observing naturalistic trajectories of attenuated psychosis.

A primary limitation of large-studies in CHR across the globe is the typical timeframe in which risk factors are studied, generally 2 years from baseline coinciding with traditional longitudinal designs of CHR that are informed by timeline of known conversion rates which has been discussed previously.^{4,8,116} Some available studies have followed CHR youth beyond this period however and have begun to isolate unique trends in CHR pathology that directly provide insight into how the clinical and functional course of CHR transforms over a longer period as well as how CHR youth respond to certain interventions. Cornblatt and colleagues¹¹⁷ conducted one of the earlier longer-term investigations of CHR, following subjects for 5 years with the aim of determining risk factors for conversion beyond 2 years as well as identifying subgroups of CHR with different intervention needs. Investigators in this study re-established a conversion rate of 28% and found that disorganized symptoms, persecutory ideas, deficits in verbal memory and social function were the most accurate predictors of conversion at 5-year follow up. These authors also identified that CHR youth have varying degrees of risk level corresponding with

needing minimal treatment, supportive care, or more aggressive treatment.¹¹⁷ Of relevance, emerging intervention studies that had longer-term follow-up periods in CHR have found that cognitive behavioral therapy for psychosis (CBT-p) over the course of 4 years was more effective at preventing a FEP than treatment as usual¹¹⁸, and that omega-3 supplementation in a randomized controlled trial was associated with lower rates of transition to psychosis and better functional outcomes at 6 year follow-up.¹¹⁹

Select studies have also explored long-term clinical, functional, and diagnostic outcomes among CHR youth, specifying differences between those who convert and those who do not go on to convert to psychosis. An early study by Lin and colleagues¹²⁰ followed up with CHR subjects who participated in research 2-14 years (mean=6.9 years) prior with the aim of examining diagnostic outcomes for non-converters over the course of illness and at long-term follow-up. Researchers in this study found that nearly 30% of CHR participants reported persistent attenuated psychosis symptoms at follow-up. During the long-term follow up period in this study, most of this sample reported comorbid diagnoses such as major depressive disorders, anxiety disorders, and substance use disorders which were present at baseline. Only a small portion of individuals in this study reported having full remission of any disorders at follow-up, indicating that regardless of psychotic conversion, CHR youth are at considerable risk for long-term psychiatric illness.¹²⁰ This study highlighted that diagnostic heterogeneity was considerable at baseline and at follow-up, and that baseline predictors such as sex, attenuated psychosis symptoms (negative symptoms), global functioning, IQ, and age significantly predicted certain diagnostic courses.¹²⁰

Michel and colleagues¹²¹ were also interested in exploring long-term outcomes in addition to conversion in CHR, with an emphasis on understanding diagnostic and functional

outcomes. Investigators re-evaluated subjects between 1-10 years (mean= 4 years) and found that CHR symptoms remitted among one-third of participants. Over half of participants who did not convert to psychosis met criteria for an Axis-1 disorder at follow up, primarily an affective or anxiety disorder and displayed persistent functional impairment. In this study, baseline risk factors did not significantly predict specific diagnostic or level of functional impairment at follow-up.¹²¹ Critically, similar to findings by Lin and colleagues,¹²⁰ risk for long-term outcomes was based on individual baseline risk factors and trajectories of early illness were not ascertained given that only two timepoints were included in this study. Additionally, these researchers only focused on how early symptom and functional presentation impacted later diagnosis and patient characteristics were limited to age, sex, education, occupation, marital status, family history of psychosis, and medication status with no consideration of the impact of cannabis use on the course of illness.¹²¹

These trends have been echoed in a recent study by Beck and colleagues⁵⁷ in which investigators re-evaluated 75 CHR subjects who participated in research 16 years prior. Unique to other long-term follow-up studies in CHR, this study both recontacted participants and, for those who were not recontacted, conducted estimations of transition rates across the 16 year period based on baseline symptom severity and functional status.⁵⁷ These researchers found that of the original 255 CHR youth that participated at baseline, it was estimated that nearly 40% of those subjects transitioned to psychosis at either the 3, 5, 10, or 16 year follow-up period. Of those recontacted and re-evaluated, baseline social functioning significantly predicted remission at 16 year follow-up; baseline cannabis use, age, sex, attenuated psychosis symptom severity did not significantly predict long-term functional outcomes.⁵⁷ Less than 30% of the long-term follow-up sample achieved recovery or remission from psychiatric illness in general, again

underscoring that long-term investigations of CHR are needed to understand the true risk these youth face for a variety of psychiatric outcomes.⁵⁷

1.9 Gaps in the literature regarding the long-term course of CHR and the potential role of risk profiles in the prediction of long-term outcomes

Collectively, emerging evidence of the long-term course of CHR signifies that rates of conversion to psychosis vary in the years following the traditional 2-year conversion period, and diagnostic outcomes, functional status, and symptom severity at long-term follow-up are also highly heterogeneous. Several important gaps remain however in the understanding of the long-term course of CHR, as well as the ability of early risk factors to predict specific lifetime outcomes, a central goal of early intervention for psychosis.

While baseline variables in isolation of one another may have predictive value for future outcomes, they provide little insight into early disease course or how interventions can best be tailored in the years following identification as being at CHR. Additionally, given the known interaction of cannabis use with early CHR symptomatology, it is important to detect profiles that incorporate different facets of cannabis use in addition to other known risk factors for later outcomes. It is plausible then that these risk profiles, capturing the heterogeneity of early CHR, could act as holistic predictors for early (2-year) and lifetime outcomes. Second, long-term follow-up studies of CHR should endeavor to explore multidimensional outcomes in both those who converted past the original study period as well as those who did not convert at long-term follow up. While available life-time studies in CHR are quite limited, significant focus has been placed on exploring diagnostic outcomes among those who have not converted.^{57,120} While incredibly important as these findings elucidate the true general psychiatric risk that CHR youth comprise, it is equally critical to identify risk profiles associated with the development either affective or non-affective lifetime psychosis diagnoses among those who convert to psychosis

across the lifespan as these illnesses require different treatments and have been shown to have differing outcomes.⁷⁶

2. PURPOSE AND SPECIFIC AIMS

As was outlined in the previous section, significant research emphasis over the last 2+ decades has been placed on identifying risk factors for conversion to psychosis among youth identified as being at clinical high-risk for psychosis (CHR), with the aim of establishing targets for early intervention and preventing debilitating chronic illness.^{3,8,122} In addition to widely reported clinical, neurocognitive, and functional deficits in the CHR population, there are disproportionately high rates of cannabis use in this group, higher reported use frequency, and a younger onset of cannabis initiation that are associated with more severe symptoms.^{25,36,38,44,123,124} Importantly, little is known about course of illness beyond 2 years past identification as well as the impact of early risk profiles on outcomes across the psychosis lifespan.^{8,116} Additionally, CHR youth are clinically heterogeneous with significant psychiatric comorbidity at baseline, and there is a dearth in scientific understanding of how interactions between known prognostic factors in CHR influence already ambiguous long-term clinical, functional, and diagnostic outcomes.^{25,26,90,122,125} The overarching research question that guided the proposed study is as follows: *Do CHR youth populations display distinct risk profiles that predict outcomes in the early course of illness, and are these profiles related to/predictive of long-term (5-20 year) outcomes?* To address these questions, the proposed dissertation involved secondary analysis of data collected through the parent study “Predictors and Moderators of Long-Term Outcome of Persons at Clinical High-Risk for Psychosis,” a multi-site initiative that has involved re-contacting and re-evaluating a large and diverse ($N=1846$) cohort of CHR youth initially evaluated 5-20 years ago. Results from this study elucidated unique risk profiles incorporating cannabis use, clinical symptoms, functioning, neurocognition, and other early facets of CHR, and identified the long-term impact of these profiles on multidimensional outcomes. The aims of this study were:

Aim 1: Isolate and characterize risk profiles for short-term (2-year) outcomes among CHR youth through latent class analysis. *Hypothesis 1a.* Distinct risk profiles will emerge from baseline data, informed by age at first cannabis use, use frequency/severity, genetic risk for psychosis, early attenuated psychosis symptoms, exposure to childhood trauma and adverse events, premorbid, social, and global functioning, IQ, verbal learning, memory, and processing speed. *Hypothesis 1b.* Profiles from *1a* will be viable predictors of clinical status and functioning across the initial 2-year study period. Profiles that capture heaviest cannabis use, younger age of cannabis initiation, more severe symptoms, higher genetic-risk for psychosis, higher exposure to early adverse life events, lower premorbid, social, and global functioning, and lower IQ, verbal learning, memory, and processing speed will be predictive of conversion and functional impairment in the initial 2-year parent study period.

Aim 2: Evaluate long-term (5-20 year) outcomes (conversion, symptom severity, functioning) based on early risk profiles. *Hypothesis 2.* Risk profiles identified in **Aim 1** that capture consistent heaviest cannabis use, younger age of cannabis initiation, more severe symptoms, higher genetic-risk for psychosis, higher exposure to early adverse life events, lower premorbid, social, and global functioning, and lower IQ, verbal learning, memory, and processing speed will be predictive of conversion and functional impairment at 5-20 year follow up.

Aim 3: Explore whether early risk-profiles are predictive of a non-affective versus affective psychosis diagnosis at 5-20 year follow-up among converters.

Hypothesis 3. Among converters, we hypothesized that risk profiles reflective of consistent but moderate cannabis use, older age of initiation, less severe symptoms, higher global and social functioning, higher premorbid functioning, better neurocognition (IQ, verbal learning, memory,

processing speed) and higher exposure to early adverse life events will be associated with an affective psychosis diagnosis at long-term (5-20 year) follow-up.

3. METHODS

At baseline assessment, as part of participation in one of three (NAPLS1, NAPLS2, AND NAPLS3) CHR parent studies, subjects received comprehensive interviews with symptom, functioning, and neurocognitive assessments spanning across 2 years.^{12,126,127} Of the original 1846 participants, approximately 300 subjects converted to psychosis during the initial follow-up periods and will be incorporated into analyses involving converters only (see **Measures and Statistical Plan**). Follow-up data at 5-20 years included diagnostic, clinical, functional, and cannabis-related assessment (see **Measures**). Participants from the parent studies were recruited to 9 representative sites across North America between 1999-2018 from community mental health centers, schools, private providers, as well as through self-referrals from community advertising campaigns.^{12,126,127} Participants were admitted into the parent studies if they met diagnostic criteria for Attenuated Psychosis Syndrome (APS) based on the Structured Interview for Psychosis-Risk Syndrome (SIPS)/ Scale of Prodromal Symptoms (SOPS).⁵ As part of the long-term follow-up study (LTF), participants were relocated using tiered recruitment strategies outlined by UCSD researcher Dr. Marc Shuckit (mass-mailing followed by phone-call followed by medical records search followed by use of social media e.g. Facebook, Been Verified).¹²⁸ To date, 419 participants from the parent studies have been identified across sites and re-interviewed.

Inclusion/Exclusion Criteria: CHR subjects from the original parent studies met the following inclusion criteria: (1) male or female, age 12 and 30 years; (2) understood and signed an informed consent (or assent for minors) document in English; (3) met diagnostic criteria for a CHR as per the SIPS. Eligible CHR subjects did not meet criteria for current or lifetime Axis 1 psychotic disorder, including affective psychoses. Full inclusion and exclusion criteria have been reported on extensively from the parent studies.^{126,127,129}

Participants completed baseline clinical and functional assessments, and neurocognitive testing. Participants in the parent studies were followed for 2 years, with clinical and functional, and neurocognitive measures administered every 6 months. As part of this 5-20 year follow-up, participants were recontacted and subsequently scheduled to be reinterviewed in person, via remote capabilities such as video conferencing (Zoom) or via telephone to accommodate geographic relocation over time, modalities which have been shown across clinical settings in the context of the COVID-19 pandemic to be effective means of collecting clinical data.^{130,131} The baseline neurocognitive battery (see **Measures**) administered in the parent studies was not readministered at 5-20 year follow-up (**Table 1**).

Table 1: Assessments by timepoints (months)

Assessments	BSL	6	12	18	24	5-20 Year F.U.
Demographics	X					X
Clinical Assessment	X	X	X	X	X	X
Diagnostic Assessment	X					X
Functional Assessment	X	X	X	X	X	X
Cannabis Use Assessment (CUQ)	X					
Cannabis Use Assessment (AUS/DUS)	X	X	X	X	X	X
IQ Estimate (WRAT) and Neurocognitive Measures of PS, VL, Memory (MATRICS-MCCB)	X	X	X	X	X	

3.1 Measures

Aim 1: Developing short-term risk profiles and relationships to 2-year outcomes

Development of short-term latent profiles through LCA was based on these measures from the initial parent studies (**Aim 1**):

Cannabis use: The Cannabis Use Questionnaire (CUQ), developed as part of the parent NAPLS 1-3 studies, was to ascertain age at first use of cannabis at baseline.¹²⁷ The Alcohol Use/Drug

Use Scale (AUS/DUS) measured cannabis use frequency/severity and delineated participants with no reported use, use without impairment, and either cannabis abuse or dependence. This scale was administered at baseline and at each follow-up period across the initial 2 year study period (**Table 2**).

Premorbid IQ: At baseline in the initial parent studies, premorbid IQ was estimated via the Wide Range Achievement Test- Four Reading (WRAT-4); this assessment produced both a continuous raw score and a continuous standard score.^{132,133}

Verbal Learning, Memory, and Processing Speed: Subtests of the MATRICS Consensus Cognitive Battery (MCCB)¹³⁴ were administered in the parent studies that assessed verbal learning and processing speed. The Brief Assessment of Cognition in Schizophrenia- Symbol Coding (BACS Symbol Coding) assessed performance in processing speed by asking the respondent to quickly copy a set of symbols on a blank sheet considering time and order in which the symbols were displayed.¹³⁵ The Hopkins Verbal Learning Test- Revised (HVLT-R) assessed verbal learning and memory performance by assessing the participant's ability to recall various words following three separate learning trials.¹³⁶ The Letter Number Span (LNS) test assessed verbal memory by evaluating the participant's ability to correctly re-order letter and number sequences spoken aloud to them by the administrator.¹³⁷ All tests produced continuous total scores which were systematically adjusted into z-scores. These values were then transformed into a Global Cognitive Index (GCI) score by averaging the z-score values of each test into one continuous GCI score.

APS Symptoms: APS criteria was assessed at baseline through the SIPS/SOPS based on 5 positive symptom domains (P1=unusual thought content, P2=suspiciousness, P3=grandiosity, P4=perceptual abnormalities, and P5=disorganization) on a scale from 0 (Absent) to 6 (Psychotic

Severity) with a score of 3 indicating the presence of subthreshold psychosis/APS criteria.⁵ This scale also included measures of attenuated negative, disorganized, and general symptoms rated on the same 0-6 scale. For each symptom category, a total score was produced.⁵

Premorbid Functioning: Premorbid functioning was ascertained via the Premorbid Adjustment Scale (PAS) at baseline in the initial studies.¹³⁸ The PAS evaluated academic and social functioning for distinct developmental domains: childhood, early and late adolescence, and early adulthood. Total premorbid functioning was calculated by averaging the scores received in each domain, with final scores ranging from 0.0-1.0 producing a cumulative score to reflect all collective premorbid domains where a higher score indicates lower premorbid functioning.¹³⁸

Global Functioning and Social Functioning: The Global Assessment of Functioning (GAF) provided a total functioning score ranging from 0-100 in which 0 represents complete inability to function, and 100 represents excellent global functioning.¹³⁹ The Global Functioning Role and Social scales (GF-R+S), two distinct measures of social and role functioning designed specifically for CHR youth in the context of the NAPLS 1-3 parent studies, assessed domains of functioning separately from the impact of psychiatric symptoms.^{140,141} In addition to total GAF score, GF-R+S scales ranged from 1-10 with 1 representing severe disability in role functioning/inability to maintain social functioning, 10 representing excellent/superior social/functioning, and there was one total score (continuous variable) for each scale/domain.¹⁴¹

Participant Characteristics: The baseline dataset from the parent studies included basic demographic information such as number of early adverse life events from the Childhood Trauma Questionnaire¹⁻ and the Peri Life Events scale,² family history of psychosis, as well as extensive assessment of comorbid diagnoses at baseline.

For all continuous indicator variables, total scores on the corresponding measure were categorized into ordinal variables reflecting low, moderate, and high functioning groups based on responses within the 25th, 50th, and 75th quantiles of functioning.

Aim 2: Using profiles from Aim 1 to predict long-term (5-20 year) outcomes

Conversion and clinical symptom severity: Participants were evaluated at 5-20 year follow up as to whether they met criteria for conversion to psychosis during the initial 2-year study period or between the initial participation in research and the 5-20 year follow up. Conversion status and clinical symptom severity were ascertained via the SIPS/SOPS, and participants were assigned membership to either 1) in remission of attenuated psychosis symptoms, 2) symptomatic or prodromal progression, or 4) conversion. Remission status was defined as all psychosis-risk diagnostic criteria (PDC)¹⁴⁴ in remission, with all attenuated positive symptom categories (P1-P5) on the SIPS/SOPS rated < 3 (no longer meeting attenuated psychosis syndrome).

Symptomatic status was defined as all PDC in remission, but 1 or more P1-P5 symptoms on the SIPS/SOPS are rated 3-5 within the previous month **with no increase** in the past year. Prodromal progression status was defined as currently meeting one of the PDC and a score of 3 or higher on P1-P5 of the SIPS/SOPS. Conversion status was defined as ever having a score of 6 on P1-P5 of the SIPS/SOPS and meeting conversion criteria based on the PDC.

Functioning: Functional outcomes at 5-20 years were measured via the GAF and the GF-R+S in separate analyses of global, role, and social functioning respectively. These measures are described in the previous section. For each functional domain, total scores on the corresponding measure were categorized into ordinal variables reflecting low, moderate, and high functioning groups based on responses within the 25th, 50th, and 75th quantiles of functioning.

Aim 3: Explore whether early risk-profiles are predictive of a non-affective versus affective psychosis diagnosis at 5-20 year follow-up among converters

Diagnosis: At 5–20-year follow-up, long-term primary diagnosis were confirmed via the SCID-5 and will be employed as a dichotomous outcome variable in regression analyses (affective or non-affective psychosis diagnosis) described in **Aim 3**. For individuals who converted to psychosis **during or following** the initial parent study period, analyses will be conducted to observe how early risk profiles predicted later transition to an affective (Bipolar, Major Depressive or Schizoaffective Disorder) vs. non-affective (Schizophrenia, Schizophreniform, Delusional disorder) psychotic disorder.

Covariates

For regression analyses outlined in **Aims 2 and 3**, the following variables were utilized as covariates if between-group differences were detected and they were linearly related to outcome variables through backwards selection (see **Statistical Plan**):

Participant characteristics: Demographic characteristics not included in the formation of risk profile trajectories were compared between profiles following completion of **Aim 1** to determine relevant covariates for regression analyses in **Aim 2 and Aim 3**. For regression analyses for 2-year outcomes, covariates were sex, age, and lifetime years of education. For 5-20 year outcomes, in addition to the aforementioned covariates, time to LTF, lifetime cannabis use (frequency and cumulative use), total years of cannabis use, medication history and psychotherapy history were employed as additional covariates. For exploratory analyses of affective versus non-affective psychosis diagnosis outcomes among converters, duration of untreated psychosis (DUP) was also included as a covariate.

3.2 Statistical Plan

R version 2024.12.1+563 was used for all statistical analyses. Latent class analyses (LCA) were the primary method of modeling interrelated baseline risk factors in this study and for developing early risk profiles central to this project. This approach was appropriate to address missing data at random (MAR) and used Full Information Maximum Likelihood (FIML) to allow for inclusion of cases in which some data may be missing.¹⁴⁵ LCA was employed to identify profiles of risk factors from baseline data of the parent studies (**Aim 1**), and logistic regressions were then employed to determine if certain profiles were predictive of clinical and functional status at 2 years. Logistic regressions were then employed with those same risk profiles as predictors for long term (5-20 year) outcomes.^{107,146,147} In all statistical tests, alpha was set at $\alpha=.05$. There was substantial statistical power for analyses conducted in **Aims 1-2** given the large baseline sample ($N=1846$) and LTF sample ($n=419$), as well as the use of FIML to estimate values for incomplete cases. Exploratory **Aim 3** which included a small sample ($n=66$) of converters was underpowered which will be discussed below.

Hypothesis 1a. Distinct risk profiles will emerge from baseline data, informed by age at first cannabis use, use severity/frequency, genetic risk for psychosis, early attenuated psychosis symptoms, exposure to early childhood trauma and adverse events, premorbid, social, and global functioning, IQ, verbal learning, memory, and processing speed.

For Hypothesis 1a, development of the LCA followed a stepped approach outlined by Sinha and colleagues,¹⁴⁷ in which indicator variables were carefully evaluated and selected a priori, missing data structures were analyzed, model assumptions were tested, model fit was established and model performance were compared leading to optimal model selection. Sensitivity analyses using complete and missing case data through FIML were conducted as follow-up analyses of LCA. In the indicator variable selection process, multicollinearity was

assessed between indicator variables, and correlation matrices of $r \geq .7$ were evaluated and indicator variables were removed from the final LCA if correlations were too high/if certain variables were composites of other variables.¹⁴⁷ Included continuous indicator variables were transformed to discrete three-level categorical variables representing values in the 25th, 50th, and 75th quantiles (low, moderate, high values) and categorical variables remained unadjusted. R package “poLCA” was used to test 2, 3, and 4 class solutions. Maximum-likelihood estimation was replicated for 20 test models in each tested class number, and the number of appropriate classes for the selected data was determined by consistent replication of these test models and comparison of fit indices. While little consensus exists in the literature about factors influencing statistical power to differentiate profiles in LCA, common indices of model fit tested through simulation studies are Akaike Information Criterion (AIC), Bayesian information criteria (BIC), Lo-Mendel-Rubin and Vuong-Lo-Mendel-Rubin (LMR/VLMR) tests and these were collectively presented for the LCA and used for model comparison.^{147–149} To conduct sensitivity analyses on the final solutions, R package “stepmixr” was utilized to replicate the solutions developed via “poLCA” and to test model viability for both incomplete and complete case data. Multiple imputation methods were considered iteratively based on missing data structures with a preference for employing internal imputation.

Hypothesis 1b. Profiles from 1a will be viable predictors of clinical symptoms and functioning at the end of the initial 2-year study period. Profiles that capture heaviest cannabis use, younger age of cannabis initiation, more severe symptoms, higher genetic-risk for psychosis, higher exposure to early adverse life events, lower premorbid, social, and global functioning, and lower IQ, verbal learning, memory, and processing speed will be predictive of conversion and functional impairment in the initial 2-year parent study period. For Hypothesis 1b, profile

membership from profiles developed in *Hypothesis 1a* were used as a two-level nominal independent variable in binomial, multinomial, and ordinal logistic regressions with clinical, conversion, and functional status at 2-year follow-up as the dependent variables following regression steps outlined below in **Aims 2 and 3**.

*Hypothesis 2. Short-term risk profiles identified in **Aim 1** that capture consistent heaviest cannabis use, younger age of cannabis initiation, more severe symptoms, higher genetic-risk for psychosis, higher exposure to early adverse life events, lower premorbid, social, and global functioning, and lower IQ, verbal learning, memory, and processing speed will be predictive of conversion and functional impairment at 5-20 year follow up.*

Hypothesis 3. Among converters, we hypothesize that risk profiles reflective of consistent but moderate cannabis use, older age of cannabis initiation, less severe symptoms, higher global and social functioning, higher premorbid functioning, better neurocognition (IQ, verbal learning, memory, processing speed) and lower exposure to early adverse life events will be associated with an affective psychosis diagnosis at long-term follow-up.

For hypotheses in **Aim 2**, established risk profiles developed in **Aim 1** served as predictor variables in separate binomial, multinomial, and ordinal logistic regressions with outcomes being 1) conversion and clinical symptom severity (binary and nominal variables) and 3) global functioning (ordinal variables). For Hypothesis 3 in exploratory **Aim 3**, the risk profiles from **Aim 1** were again employed as predictor variables with affective or non-affective psychosis diagnosis at the dependent variable (dichotomous) in a binomial logistic regression. Preliminary power analyses suggested that a sample of 270 would allow for significant statistical power of .8, however in this study there were significantly fewer converters available than this ($n=66$). Given this, results should be interpreted with caution. Risk profiles were formatted as a nominal

independent variable with number of levels dependent on profiles detected in **Aim 1** to evaluate effects on the dependent variable.^{150,151} A priori theorized covariates (see **Covariates** above) were entered into univariate analyses with risk profile as the grouping variable. Covariates significant at $\alpha=.1$ remained in the logistic models, and through an iterative backwards selection process those not significant at this level were removed initially then readded one at a time until only significant variables remained in the model.¹⁵⁰ Assumptions of multicollinearity, independence of observation, and linearity between continuous predictors and dependent variables were evaluated, which are outlined in **Appendices A-C**.¹⁵² The primary index of goodness of fit for regression models was the change in AIC as well as Nagelkerke R^2 (pseudo- R^2).^{153,154} Results were interpreted using odds ratios (OR) (binary logistic regressions), proportional OR (ordinal logistic regressions) with 95% confidence intervals, and relative-risk ratios (multinomial logistic regression) .^{152,155}

4. RESULTS

4.1 Study characteristics: baseline sample

CHR participants from the collective parent studies NAPLS 1-3 ($N=1846$) varied in age, sex, racial, and ethnic backgrounds, and were representative of 10 distinct sites across North America (**Tables 2-4**). Diagnostic comorbidity was considerable across the total parent study sample (**Table 2**), with the most frequent comorbid diagnosis being major depressive disorder.

Table 2: Baseline characteristics of NAPLS 1-3 total sample

Characteristic	NAPLS 1-3 (N = 1,846 ¹)
Age (years)	18.3 (4.3)
Sex	
Female	884 / 1,846 (48%)
Male	962 / 1,846 (52%)
Race	
Asian	101 / 1,843 (5.5%)
Black	76 / 1,843 (4.1%)
Multiracial	289 / 1,843 (16%)
Native American/First Nation	27 / 1,843 (1.5%)
Not Specified	5 / 1,843 (0.3%)
Pacific Islander	27 / 1,843 (1.5%)
White	1,318 / 1,843 (72%)
Missing	3
Ethnicity	
Hispanic	343 / 1,842 (19%)
Non-Hispanic	1,499 / 1,842 (81%)
Missing	4
Years of Education	11.0 (3.0)
Missing	330
MDD Diagnosis	
Not Present	1,090 / 1,736 (63%)
Present	646 / 1,736 (37%)
Missing	110
Bipolar Diagnosis	
Not Present	1,681 / 1,733 (97%)
Present	52 / 1,733 (3.0%)
Missing	113
GAD Diagnosis	
Not Present	1,473 / 1,723 (85%)
Present	250 / 1,723 (15%)
Missing	123
OCD Diagnosis	
Not Present	1,623 / 1,731 (94%)
Present	108 / 1,731 (6.2%)
Missing	115
PTSD Diagnosis	
Not Present	1,369 / 1,447 (95%)
Present	78 / 1,447 (5.4%)
Missing	399
ADHD Diagnosis	
Not Present	1,241 / 1,446 (86%)
Present	205 / 1,446 (14%)
Missing	400

¹ Mean (SD); n / N (%)

Table 3: Baseline characteristics by parent study

Characteristic	NAPLS 1 (N = 372 ¹)	NAPLS 2 (N = 764 ¹)	NAPLS 3 (N = 710 ¹)
Age (years)	18.2 (4.7)	18.5 (4.2)	18.2 (4.0)
Sex			
Female	231 / 372 (62%)	328 / 764 (43%)	325 / 710 (46%)
Male	141 / 372 (38%)	436 / 764 (57%)	385 / 710 (54%)
Race			
Asian	26 / 372 (7.0%)	26 / 763 (3.4%)	49 / 708 (6.9%)
Black	34 / 372 (9.1%)	20 / 763 (2.6%)	22 / 708 (3.1%)
Multiracial	22 / 372 (5.9%)	131 / 763 (17%)	136 / 708 (19%)
Native American/First Nation	0 / 372 (0%)	13 / 763 (1.7%)	14 / 708 (2.0%)
Not Specified	0 / 372 (0%)	3 / 763 (0.4%)	2 / 708 (0.3%)
Pacific Islander	1 / 372 (0.3%)	15 / 763 (2.0%)	11 / 708 (1.6%)
White	289 / 372 (78%)	555 / 763 (73%)	474 / 708 (67%)
Missing	0	1	2
Ethnicity			
Hispanic	56 / 369 (15%)	142 / 763 (19%)	145 / 710 (20%)
Non-Hispanic	313 / 369 (85%)	621 / 763 (81%)	565 / 710 (80%)
Missing	3	1	0
Years of Education	9.4 (2.5)	10.9 (2.9)	11.3 (3.1)
Missing	320	7	3

¹ Mean (SD); n / N (%)

Table 4: Baseline characteristics of NAPLS 1-3 by site

Characteristic	Calgary (N = 248 ¹)	Emory (N = 177 ¹)	Harvard (N = 117 ¹)	Toronto (N = 39 ¹)	UCLA (N = 232 ¹)	UCSD (N = 215 ¹)	UCSF (N = 82 ¹)	UNC-CH (N = 226 ¹)	Yale (N = 303 ¹)	ZHH (N = 207 ¹)
Age (years)	17.6 (3.7)	20.9 (5.2)	18.8 (3.7)	19.8 (4.2)	17.8 (4.0)	18.7 (4.0)	17.7 (3.6)	20.4 (3.8)	17.1 (4.6)	16.5 (2.7)
Sex										
Female	123 / 248 (50%)	89 / 177 (50%)	52 / 117 (44%)	25 / 39 (64%)	104 / 232 (45%)	92 / 215 (43%)	39 / 82 (48%)	109 / 226 (48%)	151 / 303 (50%)	100 / 207 (48%)
Male	125 / 248 (50%)	88 / 177 (50%)	65 / 117 (56%)	14 / 39 (36%)	128 / 232 (55%)	123 / 215 (57%)	43 / 82 (52%)	117 / 226 (52%)	152 / 303 (50%)	107 / 207 (52%)
Race										
Asian	10 / 248 (4.0%)	6 / 177 (3.4%)	8 / 117 (6.8%)	4 / 39 (10%)	24 / 231 (10%)	12 / 214 (5.6%)	14 / 82 (17%)	6 / 225 (2.7%)	4 / 303 (1.3%)	13 / 207 (6.3%)
Black	9 / 248 (3.6%)	7 / 177 (4.0%)	6 / 117 (5.1%)	2 / 39 (5.1%)	3 / 231 (1.3%)	6 / 214 (2.8%)	2 / 82 (2.4%)	8 / 225 (3.6%)	16 / 303 (5.3%)	17 / 207 (8.2%)
Multiracial	38 / 248 (15%)	23 / 177 (13%)	12 / 117 (10%)	2 / 39 (5.1%)	62 / 231 (27%)	49 / 214 (23%)	20 / 82 (24%)	13 / 225 (5.8%)	30 / 303 (9.9%)	40 / 207 (19%)
Native Amer.	5 / 248 (2.0%)	0 / 177 (0%)	3 / 117 (2.6%)	0 / 39 (0%)	1 / 231 (0.4%)	14 / 214 (6.5%)	2 / 82 (2.4%)	1 / 225 (0.4%)	1 / 303 (0.3%)	0 / 207 (0%)
Not Specified	0 / 248 (0%)	0 / 177 (0%)	1 / 117 (0.9%)	0 / 39 (0%)	3 / 231 (1.3%)	1 / 214 (0.5%)	0 / 82 (0%)	0 / 225 (0%)	0 / 303 (0%)	0 / 207 (0%)
Pacific Isl.	5 / 248 (2.0%)	2 / 177 (1.1%)	3 / 117 (2.6%)	0 / 39 (0%)	5 / 231 (2.2%)	4 / 214 (1.9%)	1 / 82 (1.2%)	2 / 225 (0.9%)	3 / 303 (1.0%)	2 / 207 (1.0%)
White	181 / 248 (73%)	139 / 177 (79%)	84 / 117 (72%)	31 / 39 (79%)	133 / 231 (58%)	128 / 214 (60%)	43 / 82 (52%)	195 / 225 (87%)	249 / 303 (82%)	135 / 207 (65%)
Missing	0	0	0	0	1	1	0	1	0	0
Ethnicity										
Hispanic	9 / 248 (3.6%)	14 / 177 (7.9%)	13 / 117 (11%)	1 / 39 (2.6%)	77 / 229 (34%)	73 / 214 (34%)	21 / 82 (26%)	20 / 226 (8.8%)	61 / 303 (20%)	54 / 207 (26%)
Non-Hispanic	239 / 248 (96%)	163 / 177 (92%)	104 / 117 (89%)	38 / 39 (97%)	152 / 229 (66%)	141 / 214 (66%)	61 / 82 (74%)	206 / 226 (91%)	242 / 303 (80%)	153 / 207 (74%)
Missing	0	0	0	0	3	1	0	0	0	0
Years of Ed.	10.8 (2.5)	10.2 (3.5)	11.9 (3.1)	NA (NA)	10.7 (2.9)	11.4 (2.8)	11.1 (2.7)	13.5 (2.5)	10.0 (3.0)	10.2 (2.4)
Missing	0	3	1	39	3	60	0	55	125	44

¹ Mean (SD); n / N (%)

4.2 Development of early risk profiles through latent class analysis (LCA)

The presentation of the development of early risk profiles through LCA will follow the following format: 1) descriptive statistics of a priori selected indicator variables and correlation matrices, 2) variable selection and transformation of indicator variables to discrete variables, 3) exploration of missing data structures, 4) LCA analysis of complete data (complete case analysis with R package ‘poLCA’), 5) sensitivity analyses and internal imputation using R package ‘stepmixr’ with missing data and FIML.

4.2.1 Selection of indicator variables and description of data

Continuous a priori selected indicator variables generally followed normal distribution patterns with no significant outliers (**Figure 2**).

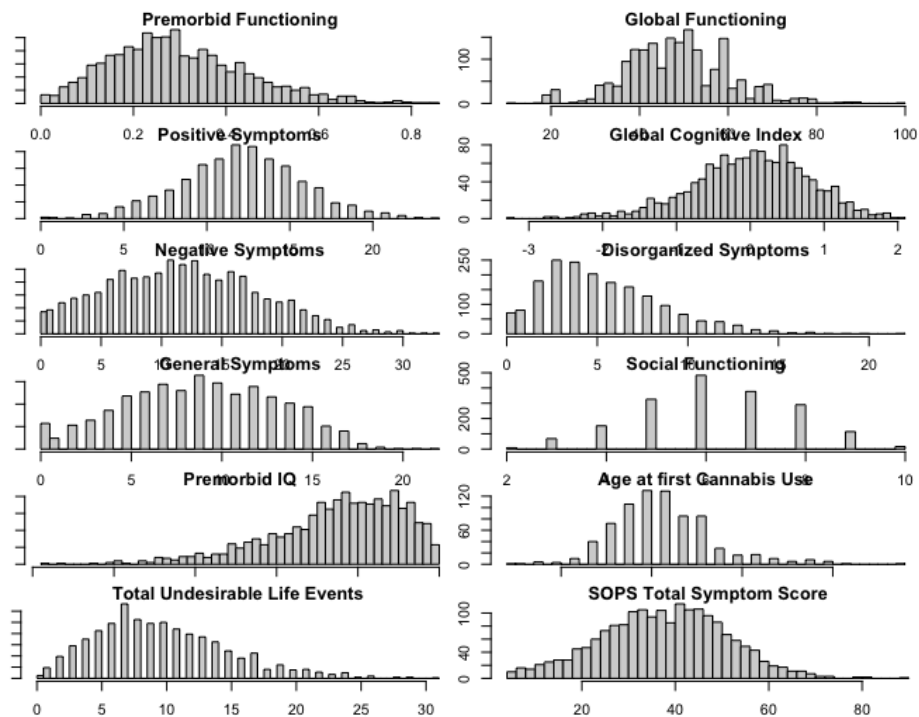
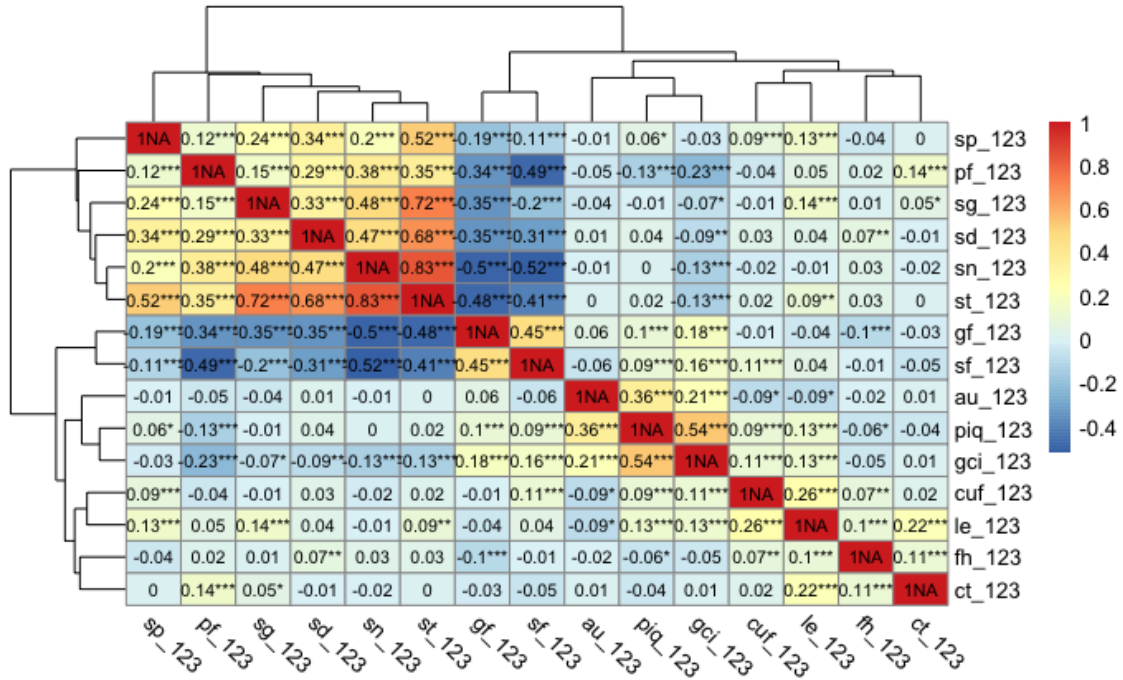


Figure 2: Distributions of continuous potential indicator variables

Breakdown of categorical variables showed that $n=436$ participants reported a family history of psychosis ($n=1345$ denied a family history), and $n=1190$ participants reported a history of childhood trauma ($n=210$ denied a history of childhood trauma). $N=1300$ participants reported no cannabis use, $n=341$ reported use without impairment, and $n=137$ met criteria for cannabis use disorder.

Indicator variables that were highly intercorrelated ($r>.7$) and that were composites of other indicator variables were removed where appropriate in accordance to steps outlined by Sinha and colleagues¹⁴⁷. Positive, negative, disorganized, and general symptom scores were removed as indicators for the LCA in favor of including total symptom score. Global functioning was a composite score including social functioning and total symptoms, so investigators removed global functioning. Social functioning was also moderately correlated with total premorbid functioning ($r=.5$, $p<.001$), and given that total premorbid functioning includes measures of premorbid social functioning, total social functioning was eliminated as an indicator variable for the LCA. Based on a priori hypotheses suggesting risk profiles with and without baseline neurocognitive measures should be evaluated, GCI was included together in one LCA model and GCI was removed in the other (see **Results**). Correlations between all indicator variables is demonstrated in **Figure 3**.



*sp_123=SOPS Positive Symptoms, pf_123=Total Premorbid Functioning, sg_123=SOPS General Symptoms, sd_123=SOPS Disorganized Symptoms, sn_123=SOPS Negative Symptoms, st_123=SOPS Total Symptoms, gf_123=Global Functioning, sf_123= Social Functioning, au_123=Age at First Cannabis Use, piq_123= Premorbid IQ, gci_123= Global Cognitive Index, cuf_123= Cannabis Use Severity, le_123=Undesirable Life Events, fh_123= Family History of Psychosis, ct_123=Childhood Trauma

Figure 3:Correlation matrices of potential indicator variables for LCA

Following inspection of collinearity between indicator variables, the remaining selected indicator variables to be included in the LCA were total premorbid functioning, total symptom score, age of first cannabis use, premorbid IQ, global cognitive index, cannabis use severity, undesirable life events, family history of psychosis, and history of childhood trauma. Final selected continuous indicator variables were transformed to discrete ordinal variables representing participant data falling into the 25th, 50th, or 75th quantiles. Across all selected indicator variables, each quantile comprised >10% ($n=185$) of the total sample.

4.2.2 Missing data analysis

Final selected indicator variables had relatively consistent levels of missing data, with most indicator variables having less than 30% of data missing. Age at cannabis initiation, total

undesirable life events, and global cognitive index were the three variables with the highest proportion of missing data (**Figure 4**). Based on high levels of missing data in these key indicator variables, investigators systematically decided to proceed with LCA on the complete cases ($n=673$) and to display sensitivity analyses with missing data, or internal imputation, as adjunctive tests of the viability models considering complete and missing/internally imputed data.

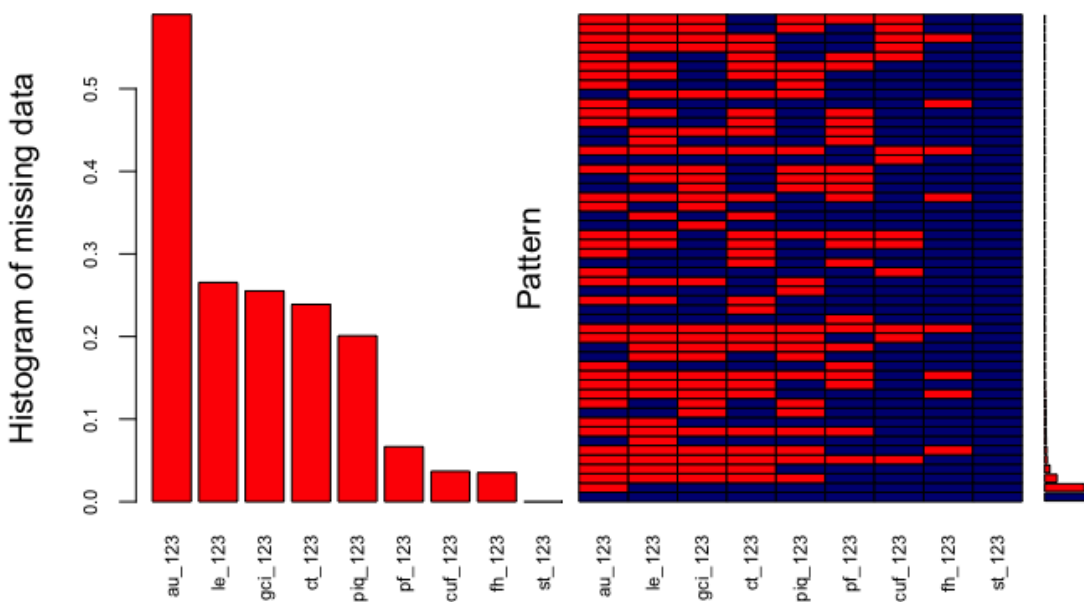
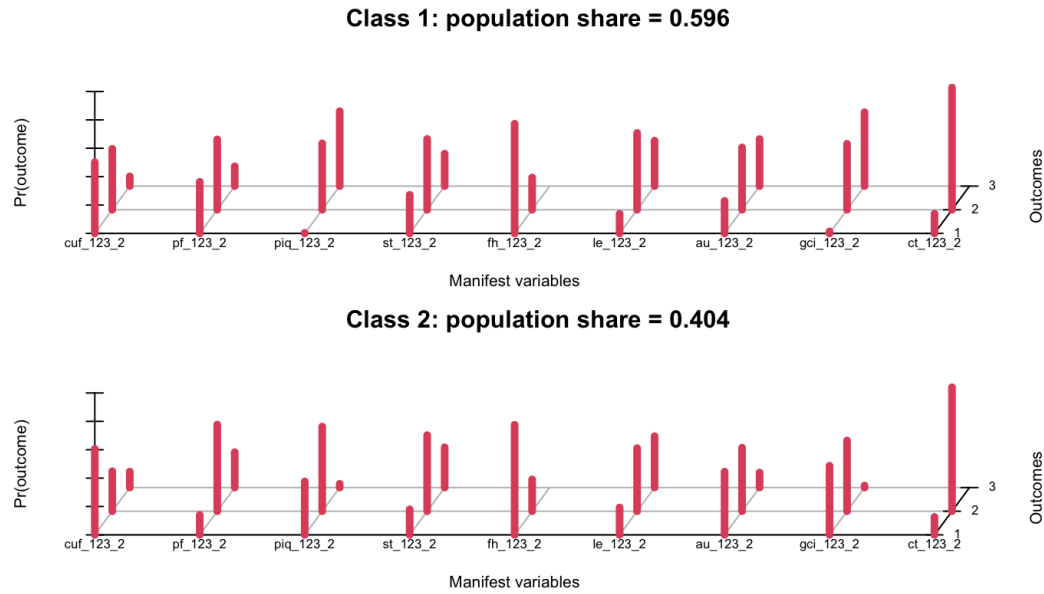


Figure 4: Histogram of missing data for final selected indicator variables

4.2.3 LCA with all indicator variables

R package ‘poLCA’ was utilized to conduct LCA. Baseline LCA from NAPLS 1-3 including a prior selected indicator variables (total premorbid functioning, total symptom score, age of first cannabis use, premorbid IQ, global cognitive index, cannabis use severity, undesirable life events, family history of psychosis, and history of childhood trauma) were conducted in a stepped-format for 2, 3, and 4-class models. For the first iteration **with complete**

cases ($n=673$), the 2-class model demonstrated a maximum likelihood (ML= -5228.943) value that was successfully replicated across 20 test iterations. In this 2-class model, 60% of the estimated population share was in class 1 and 40% of the estimated population share was in class 2 ($AIC_2=10523.89$, $BIC_2=10672.77$). The 3 and 4 class models did not show successful replication of the maximum likelihood value, and fit indices worsened with each additional class ($AIC_3=10474.09$, $BIC_3=10699.68$; $AIC_4=10452.25$, $BIC_4=10754.53$). Therefore, overall best-fitting model for the complete case data was a 2-class solution ($AIC_2=10523.89$, $BIC_2=10672.77$) (**Figure 5**). Of note, Lo-Mendel-Rubin and Vuong-Lo-Mendel-Rubin (LMR/VLMR) tests were conducted comparing 2 and 3-class solutions (LMR LR ($df=17$)=79.71 LR=83.80, $p<.001$) and the 3 and 4-class solutions (LMR LR ($df=17$)=53.12, LR=55.84, $p<.001$) and were both statistically significant suggesting a 4-class solution may be appropriate. Considering that log-likelihood and AIC/BIC were not improving and models were not consistently replicating, we chose to rely on fit indices such as maximum-likelihood, AIC, and BIC and continue with the 2-class solution.



* *pf_123*=Total Premorbid Functioning, *st_123*=SOPS Total Symptoms, *au_123*=Age at First Cannabis Use, *piq_123*= Premorbid IQ, *gci_123*= Global Cognitive Index, *cuf_123*= Cannabis Use Severity, *le_123*=Undesirable Life Events, *fh_123*= Family History of Psychosis, *ct_123*=Childhood Trauma

Figure 5: 2-class solution for complete cases LCA-With GCI (poLCA)

Class 1, or the “Lower-Risk Class,” was characterized by predominantly moderate-low rates of cannabis use (~43% of individuals were within the “use without impairment” category, ~50% were in the “no use” category, 7% were within the “cannabis use disorder” category), higher premorbid functioning (~96% within the top two quantiles), higher premorbid IQ (~99% within the top two quantiles), less severe total attenuated psychosis symptoms (~77% in the bottom two quantiles), low rates of reported family history of psychosis (~77% reported no family history), moderate-high levels of undesirable life events (~86% in the top two quantiles), older age of cannabis initiation (~77% in the top two quantiles), better global cognition (~98% in

the top two quantiles), and high rates of reported childhood trauma (86% reported a history of childhood trauma).

Class 2, or the “Higher-Risk Class,” was characterized by a slightly higher proportion of individuals reporting a cannabis use disorder (11%) (~28% were within the “use without impairment” category, and ~60% were in the “no use” category), lower premorbid functioning (~86% in the bottom two quantiles), lower premorbid IQ (~98% in the bottom two quantiles), more severe total attenuated psychosis symptoms (~82% in the top two quantiles), low rates of reported family history of psychosis (~78% reported no family history), moderate-high undesirable life events (~80% in the top two quantiles), younger age of cannabis initiation (~90% in the bottom two quantiles), poorer global cognition (~99% in the bottom two quantiles), high rates of reported childhood trauma (~87% reported a history of childhood trauma).

4.2.4 Sensitivity analyses using internal imputation via FIML

Separate sensitivity analyses were conducted using the R ‘stepmixer’ package to evaluate patterns of missing data in both complete cases ($n=673$) (**Table 5**) and cases including missing data, or internal imputation, via full information maximum likelihood (FIML) ($N=1846$) (**Table 6**).

Table 5: LCA-With GCI with 2-class solution incorporating complete cases only (stepmixr)

Variable Name	Class 2	Class 1
Age at first cannabis use (25 th Quantile)	0.4458	0.2290
Age at first cannabis use (50 th Quantile)	0.4479	0.4393
Age at first cannabis use (75 th Quantile)	0.1063	0.3317
Childhood trauma (Not present=0)	0.1263	0.1388
Childhood trauma (Present=1)	0.8737	0.8612
Cannabis use severity (No use=0)	0.6060	0.5018
Cannabis use severity (Use without impairment=2)	0.2816	0.4298
Cannabis use severity (Abuse or Dependence=3)	0.1124	0.0685

Table 5: LCA-With GCI with 2-class solution incorporating complete cases only (stepmixr),continued

Family history of psychosis (Not present=0)	0.7759	0.7730
Family history of psychosis (Present=1)	0.2241	0.2270
Global cognitive index (25 th Quantile)	0.4873	0.0140
Global cognitive index (50 ^h Quantile)	0.0143	0.4649
Global cognitive index (75 th Quantile)	0.0143	0.5211
Undesirable life events (25 th Quantile)	0.1933	0.1382
Undesirable life events (50 th Quantile)	0.4443	0.5414
Undesirable life events (75 th Quantile)	0.3624	0.3203
Total Premorbid Functioning (25 th Quantile)	0.1396	0.3640
Total Premorbid Functioning (50 th Quantile)	0.6108	0.4960
Total Premorbid Functioning (75 th Quantile)	0.2496	0.5276
Premorbid IQ (25 th Quantile)	0.3763	0.0044
Premorbid IQ (50 ^h Quantile)	0.5969	0.4680
Premorbid IQ (75 th Quantile)	0.0267	0.5276
Total Attenuated Psychosis Symptoms (25 th Quantile)	0.1800	0.2719
Total Attenuated Psychosis Symptoms (25 th Quantile)	0.5362	0.4991
Total Attenuated Psychosis Symptoms (25 th Quantile)	0.2838	0.2290
Class Weights	.40	.60
Estimation Method	1-step	
Number of Observations		
Number of Latent Classes		
Number of Estimated Parameters		
Log-Likelihood (LL)		
-2LL		
Average LL		
AIC		
BIC		
Sample-Size Adjusted BIC		
Entropy		
Scale-Related Entropy		

Rerunning the LCA with the “stepmixr” program successfully replicated the complete cases model developed through “poLCA”.

Table 6: LCA-With GCI with 2-class solution with missing data using FIML (stepmixr)

Variable Name	Class 2	Class 1
Age at first cannabis use (25 th Quantile)	0.4380	0.2268
Age at first cannabis use (50 th Quantile)	0.4576	0.4522
Age at first cannabis use (75 th Quantile)	0.1044	0.3210
Childhood trauma (Not present=0)	0.1453	0.1605
Childhood trauma (Present=1)	0.8547	0.8395
Cannabis use severity (No use=0)	0.7794	0.6767
Cannabis use severity (Use without impairment=2)	0.0901	0.2610
Cannabis use severity (Abuse or Dependence=3)	0.1306	0.0624
Family history of psychosis (Not present=0)	0.7273	0.7861
Family history of psychosis (Present=1)	0.2727	0.2139
Global cognitive index (25 th Quantile)	0.4914	0.0152
Global cognitive index (50 th Quantile)	0.4880	0.5109
Global cognitive index (75 th Quantile)	0.0206	0.4739
Undesirable life events (25 th Quantile)	0.3499	0.2038
Undesirable life events (50 th Quantile)	0.4507	0.5465
Undesirable life events (75 th Quantile)	0.1995	0.2497
Total Premorbid Functioning (25 th Quantile)	0.1747	0.3343
Total Premorbid Functioning (50 th Quantile)	0.4944	0.5056
Total Premorbid Functioning (75 th Quantile)	0.3309	0.1601
Premorbid IQ (25 th Quantile)	0.4660	0.0128
Premorbid IQ (50 th Quantile)	0.5034	0.5283
Premorbid IQ (75 th Quantile)	0.0307	0.4588
Total Attenuated Psychosis Symptoms (25 th Quantile)	0.2329	0.2964
Total Attenuated Psychosis Symptoms (50 th Quantile)	0.4859	0.5009
Total Attenuated Psychosis Symptoms (75 th Quantile)	0.2812	0.2027

Table 6: LCA-With GCI with 2-class solution with missing data using FIML (stepmixr), continued

Class Weights	.53	.47
Estimation Method	1-step	
Number of Observations	1846	
Number of Latent Classes	2	
Number of Estimated Parameters	51	
Log-Likelihood (LL)	-11557.4680	
-2LL	23114.9360	
Average LL	-6.2608	
AIC	23216.94	
BIC	23498.50	
Sample-Size Adjusted BIC	23720.03	
Entropy	633.5574	
Scale-Related Entropy	.5049	

Internal estimation with missing data via FIML showed stable replication of the original model with minor variations in proportional shares of individuals in each class across variables, particularly in the case of the undesirable life events variable (**Table 6**). Given the significant reduction in model fit (AIC=23216, BIC=23498) when employing FIML compared to the complete case LCA, analyses that include complete case data were more appropriate however classes developed using FIML were employed in regression analyses to account for reduction in sample size that occurred when comparing baseline data to 2-year and 5-20-year outcomes.

4.2.5 LCA-Without GCI

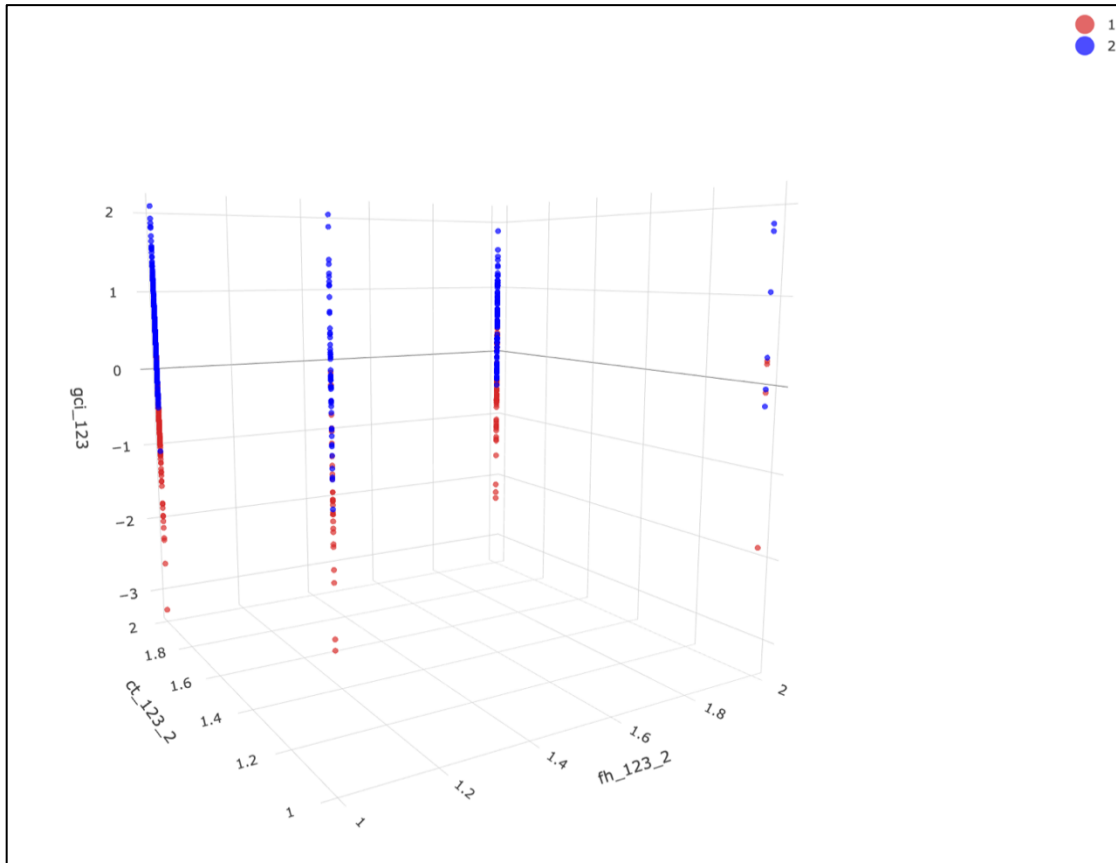


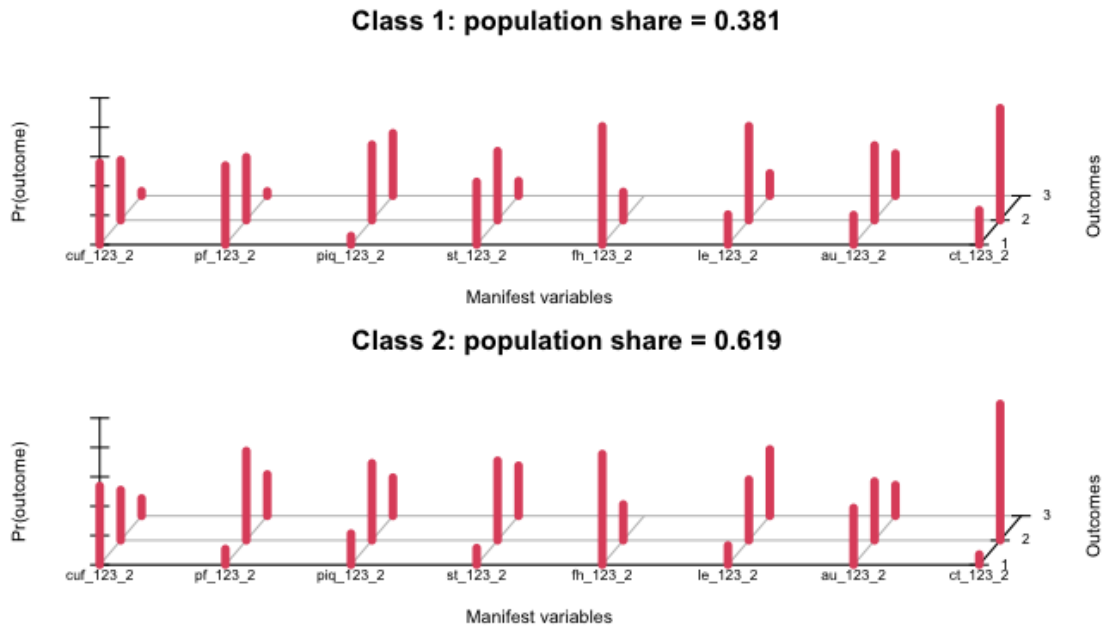
Figure 6: Distribution of GCI, FH, and CT in LCA with 2-class solution for complete cases

When evaluating relationships between indicator variables as was described in section 3.2.1, it was discovered that the addition of the variable representing global cognitive index (GCI) (gci_123_2) significantly impacted the clustering of data by the variables representing family history of psychosis (fh_123_2) and history of childhood trauma (ct_123_2). GCI was not significantly associated with family history ($X^2 = .56, p = .76$) or childhood trauma ($X^2 = .25, p = .88$) but was rather completely independent of these two variables (**Figure 6**).

Improved selection criteria via log-likelihood in models including GCI compared to those without GCI suggested that GCI, when included with the other selected indicator variables, better differentiated the classes as compared to family history and childhood trauma. Consistent with a priori hypotheses discussed in the **Methods** section related to theoretical concerns

regarding availability of cognitive testing at baseline in investigations of CHR as well as high levels of missing data/inconsistent neuropsychological testing across parent studies, investigators conducted follow-up LCA without the GCI variable.

Again, baseline LCA from NAPLS 1-3 including a prior selected indicator variables (total premorbid functioning, total symptom score, age of first cannabis use, premorbid IQ, cannabis use severity, undesirable life events, family history of psychosis, and history of childhood trauma) were conducted in a stepped-format for 2, 3 and 4-class models. Using complete case analyses ($n=673$), the 2-class model demonstrated a maximum likelihood (ML= -4622.488) value that was successfully replicated across 20 test iterations. In this 2-class model, 38% of the estimated population share was in class 1 and 62% of the estimated population share was in class 2 ($AIC_2=9302.977$, $BIC_2=9433.904$). The 3 and 4 class models did not show successful replication of the maximum likelihood value, and fit indices worsened with each additional class ($AIC_3=9267.069$, $BIC_3=9465.717$; $AIC_4=9239.792$, $BIC_4=9506.161$). Therefore, overall best-fitting model for the complete case data was a 2-class solution ($AIC_2=9302.977$, $BIC_2=9433.904$) (**Figure 7**). Again, we found that although Lo-Mendel-Rubin and Vuong-Lo-Mendel-Rubin (LMR/VLMR) tests were all significant ($ps<.001$) across class solutions, other fit indices collectively captured consistency of model replication and model improvement.



* *pf_123*=Total Premorbid Functioning, *st_123*=SOPS Total Symptoms, *au_123*=Age at First Cannabis Use, *piq_123*= Premorbid IQ, *cuf_123*= Cannabis Use Severity, *le_123*=Undesirable Life Events, *fh_123*= Family History of Psychosis, *ct_123*=Childhood Trauma

Figure 7: 2-class solution for complete cases LCA- Without GCI (poLCA)

Class 1, or the “Lower-Risk Class- Without GCI,” was characterized by predominantly moderate-low rates of cannabis use (~41% of individuals were within the “use without impairment” category, ~56% were in the “no use” category, 3% were within the “cannabis use disorder” category), higher premorbid functioning (~96% within the top two quantiles), higher premorbid IQ (~94% within the top two quantiles), less severe total attenuated psychosis symptoms (~89% in the bottom two quantiles), low rates of reported family history of psychosis (~81% reported no family history, ~19% reported a family history), moderate-low levels of undesirable life events (~84% in the bottom two quantiles), older age of cannabis initiation

(~80% in the top two quantiles), and moderate-high rates of reported childhood trauma (~76% reported a history of childhood trauma).

Class 2, or the “Higher-Risk Class-Without GCI”, was characterized by a slightly higher proportion of individuals reporting a cannabis use disorder (11%) (~34% were within the “use without impairment” category, and 54% were in the “no use” category), lower premorbid functioning (~88% in the bottom two quantiles), lower premorbid IQ (~73% in the bottom two quantiles), more severe total attenuated psychosis symptoms (~88% in the top two quantiles), low rates of reported family history of psychosis but higher than in the Lower Risk Class-Without GCI” (~75% reported no family history, ~24% reported a family history), moderate-high undesirable life events (~86% in the top two quantiles), younger age of cannabis initiation (~89% in the bottom two quantiles), and higher rates of reported childhood trauma compared to the Lower-Risk Class-Without GCI (~93% reported a history of childhood trauma).

Sensitivity analyses involving the use of ‘stepmixr’ to replicate this 2-class solution and to employ internal imputation via FIML as outlined in **3.2.4** were conducted which demonstrated successful model replication with complete cases and missing data (**Tables 7-8**). Based on model fit indices, again the complete case 2-class solution was selected as the best overall model for future analyses.

Table 7: *LCA-Without GCI with 2-class solution incorporating complete cases only (stepmixr)*

Variable Name	Class 1	Class 2
Age at first cannabis use (25 th Quantile)	0.2022	0.3880
Age at first cannabis use (50 th Quantile)	0.5101	0.4015
Age at first cannabis use (75 th Quantile)	0.2876	0.2106
Childhood trauma (Not present=0)	0.2358	0.0700
Childhood trauma (Present=1)	0.7642	0.9300

Table 7: LCA-Without GCI with 2-class solution incorporating complete cases only (stepmixr), continued

Cannabis use severity (No use=0)	0.5582	0.5372
Cannabis use severity (Use without impairment=2)	0.4101	0.3435
Cannabis use severity (Abuse or Dependence=3)	0.0318	0.1194
Family history of psychosis (Not present=0)	0.8068	0.7550
Family history of psychosis (Present=1)	0.1932	0.2450
Undesirable life events (25 th Quantile)	0.2055	0.1319
Undesirable life events (50 th Quantile)	0.6413	0.4139
Undesirable life events (75 th Quantile)	0.1532	0.4542
Total Premorbid Functioning (25 th Quantile)	0.5392	0.1078
Total Premorbid Functioning (50 th Quantile)	0.4302	0.6091
Total Premorbid Functioning (75 th Quantile)	0.0306	0.2831
Premorbid IQ (25 th Quantile)	0.0589	0.2129
Premorbid IQ (50 th Quantile)	0.5149	0.5256
Premorbid IQ (75 th Quantile)	0.4262	0.2615
Total Attenuated Psychosis Symptoms (25 th Quantile)	0.4279	0.1143
Total Attenuated Psychosis Symptoms (50 th Quantile)	0.4712	0.5430
Total Attenuated Psychosis Symptoms (75 th Quantile)	0.1009	0.3427
Class Weights	.40	.60
Estimation Method	1-step	
Number of Observations		
Number of Latent Classes		
Number of Estimated Parameters		
Log-Likelihood (LL)		
-2LL		
Average LL		
AIC		
BIC		
Sample-Size Adjusted BIC		
Entropy		
Scale-Related Entropy		

Table 8: Without GCI with 2-class solution with missing data using FIML (stepmixr)

Variable Name	Class 1	Class 2
Age at first cannabis use (25 th Quantile)	0.2512	0.3571
Age at first cannabis use (50 th Quantile)	0.4855	0.4323
Age at first cannabis use (75 th Quantile)	0.2633	0.2106
Childhood trauma (Not present=0)	0.2229	0.0652
Childhood trauma (Present=1)	0.7771	0.9348
Cannabis use severity (No use=0)	0.8650	0.5749
Cannabis use severity (Use without impairment=2)	0.1204	0.2751
Cannabis use severity (Abuse or Dependence=3)	0.0146	0.1500
Family history of psychosis (Not present=0)	0.8308	0.6662
Family history of psychosis (Present=1)	0.1692	0.3338
Undesirable life events (25 th Quantile)	0.4622	0.0418
Undesirable life events (50 th Quantile)	0.5378	0.4509
Undesirable life events (75 th Quantile)	0.0000	0.5074
Total Premorbid Functioning (25 th Quantile)	0.3074	0.1837
Total Premorbid Functioning (50 th Quantile)	0.4594	0.5465
Total Premorbid Functioning (75 th Quantile)	0.2332	0.2698
Premorbid IQ (25 th Quantile)	0.2654	0.2312
Premorbid IQ (50 th Quantile)	0.5267	0.5009
Premorbid IQ (75 th Quantile)	0.2079	0.2679
Total Attenuated Psychosis Symptoms (25 th Quantile)	0.3313	0.1825
Total Attenuated Psychosis Symptoms (50 th Quantile)	0.4521	0.5408
Total Attenuated Psychosis Symptoms (75 th Quantile)	0.2166	0.2767
Class Weights	.54	.46

Table 8: Without GCI with 2-class solution with missing data using FIML (stepmixr), continued

Estimation Method	1-step
Number of Observations	1846
Number of Latent Classes	2
Number of Estimated Parameters	45
Log-Likelihood (LL)	-10268.4368
-2LL	20536.8735
Average LL	-5.5625
AIC	20626.87
BIC	20875.31
Sample-Size Adjusted BIC	21070.78
Entropy	747.9307
Scale-Related Entropy	.4155

In summary and confirmatory to our hypotheses in **Hypothesis 1a: Aim 1**, two separate LCA (with and without GCI) were conducted with complete case data and replicated with internal imputation using FIML. These two 2-class solutions were selected as the final models to be transformed into predictor variables in follow-up regression testing.

2-Year Follow-Up

4.3 Study characteristics: 2-year follow-up

From the NAPLS 1-3 parent studies, current clinical status (CCS) was collected for $n=1206$ individuals and global assessment of functioning (GAF) was collected for $n=1571$ participants who had at least one follow-up throughout the course of the study. Last observation carried forward (LOCF) was used to ascertain the last available value for both CCS and GAF.

Table 9 displays clinical and functional status at 2-year follow-up.

Table 9: Clinical and functional status at 2-year follow-up

Characteristics 2-Year Follow Up	Total Follow-Up Sample
Average follow-up time (years)	1.09 (.90)
Current Clinical Status	
In remission	302 / 1206 (25%)
Symptomatic or Prodromal Progression	650/ 1206 (53.9%)
Conversion	254/1206 (21.1%)
Global Assessment of Functioning	
Low (25 th Quantile)	396/ 1571 (25.2%)
Moderate (50 th Quantile)	795/1571 (51%)
High (75 th Quantile)	380/1571 (24.1%)
Characteristics 2-Year Follow Up	Complete case data (only those included in LCAs)
Current Clinical Status	
In remission	109 / 452 (24%)
Symptomatic	110 / 452 (24%)
Prodromal Progression	154/ 452 (34%)
Conversion	79/ 452 (17%)
Global Assessment of Functioning	
Low (25 th Quantile)	180 / 625 (28.8%)
Moderate (50 th Quantile)	290/ 625 (46.4%)
High (75 th Quantile)	155/ 625 (24.8%)

[†] Mean (SD); n / N (%)

4.3.1 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA With GCI and covariates for complete cases

Assumption testing was conducted for multinomial, ordinal, and binary logistic regression. Dependent variables were either nominal, ordinal or binary in nature with a combination of continuous and categorical predictors. Independence of observation between variables was observed by visually inspecting plots of residuals against factors. Multicollinearity was tested between predictor variables and those that were highly correlated ($r > .7$) were re-evaluated/removed as covariates. Linear relationships were confirmed between continuous predictors and the logit transformation of the dependent variable, with significance set at $p = .05$. Full results of assumption testing for 2-year logistic regressions can be found in **Appendix A**. In

this multivariable model of 452 observations, LCA-With GCI was included as the primary predictor variable for CCS and GAF at 2-year follow-up. A priori selected covariates included sex, age at baseline, and years of education. For analyses where CCS was the dependent variable, univariate chi-square tests showed no significant association between CCS and sex ($\chi^2 = 1.17$, $p = .56$), and Kruskal Wallis Rank Sum tests showed no significant association between CCS and age ($\chi^2 = .43$, $p = .81$) nor years of education ($\chi^2 = 2.19$, $p = .35$). We then included all confounders in the model and used backward selection with the exclusion p-value set to $p = .1$ to determine whether any covariates should remain. All covariates (sex, age, years of education) were not statistically significant predictors of CCS at 2-years ($p > .10$) following backwards selection indicating that covariates were not appropriate for this analysis. Direct multinomial logistic regression analyses demonstrated no linear association between LCA-With GCI and 2-year CCS ($p > .10$). When CCS was transformed into a two-level dependent variable, conversion or no conversion, binomial logistic regression similarly reflected that LCA-With GCI class was not a viable predictor of CCS at 2-year follow-up ($B = .26$, $p = .30$).

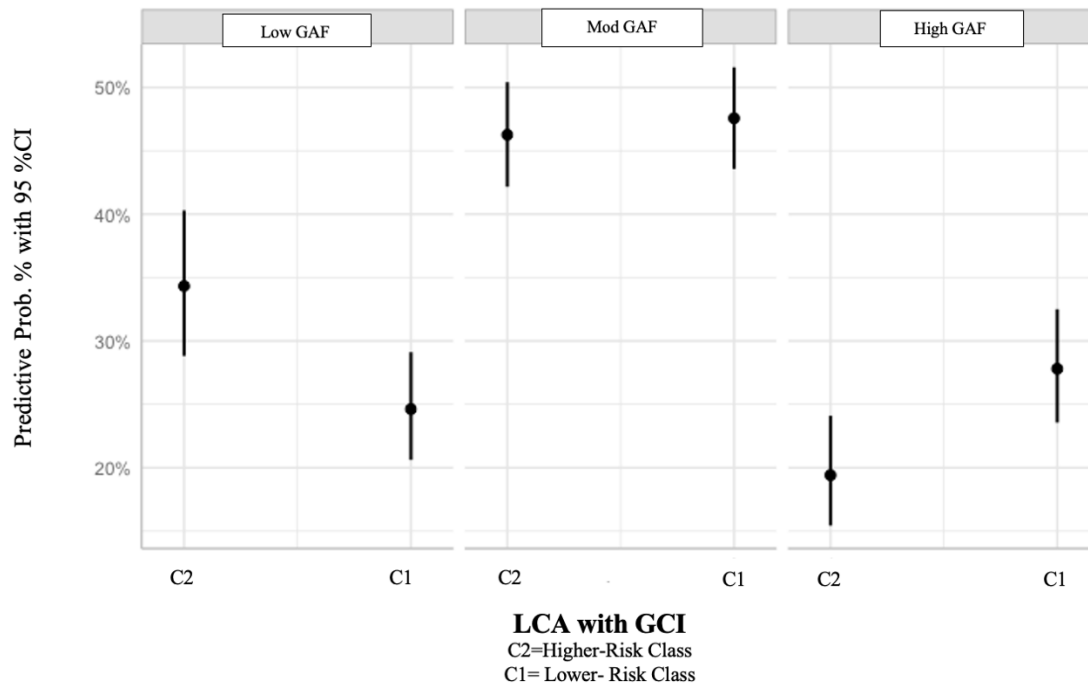
For analyses where GAF was the dependent variable, univariate chi-square tests showed no significant association between GAF and sex ($\chi^2 = 3.07$, $p = .22$), and Kruskal Wallis Rank Sum tests showed no significant association between GAF and age ($\chi^2 = 1.39$, $p = .50$). Years of education however was associated with GAF below the threshold of $p = .10$ ($\chi^2 = 4.08$, $p = .09$). Again, we employed backwards selection including all confounders in the model with GAF as the dependent variable with the exclusion p-value set to $p = .1$. In this approach, sex was removed from the model ($p > .10$) and both age ($p < .003$) and years of education ($p < .003$) remained as viable covariates. Results are displayed in **Table 10**.

Table 10: Ordinal logistic regression of GAF at 2-years predicted by LCA-With GCI, age, and years of education (complete case data)

GAF at 2 Years	Parameter Estimate	Standard Error	p-value	Prop. Odds Ratio (95%CI)
Intercept (Low to Mod GAF)	-1.13	.41	.006	
Intercept (Mod to High GAF)	.94	.41	.02	
LCA- With GCI- Class 1/Lower-Risk Class	.47	.17	.005	1.6 (1.15-2.31)
Age at baseline	-.09	.03	<.001	.91 (.86-.96)
Years of education	.11	.04	.01	1.12 (1.02-1.22)
AIC: 1313.135				
Nagelkerke R ² =.04				
Number of Observations: 625				

Out of 625 observations, results from ordinal logistic regression showed that if assigned to LCA With GCI- Class 1 or the Lower-Risk Class the odds of being in the higher functioning groups (e.g. moderate or high functioning versus low functioning groups) at 2-years are 1.6 times higher than those in the LCA-With GCI-Class 2, or Higher-Risk Class, holding age and years of education constant. For every one-year increase in baseline age, the odds of having higher functioning decreased by .91, holding other variables constant. Additionally, with every one-year increase in years of education, the odds of being in the higher functioning groups (e.g. moderate or high functioning versus low functioning groups) increases by 1.12 holding constant all other variables. In summary, those who are in the LCA With GCI- Class 1 or the Lower-Risk Class are more likely to be in the top two quantiles of functioning at 2-year follow-up controlling for baseline age and years of education (**Figure 8**). Additionally, those who are older at baseline are less likely to be in the moderate-high functioning group at 2-year follow-up however those with more reported education at baseline are more likely to be in the moderate-high functioning group

at 2-year follow-up. This model with covariates also demonstrated marginally improved model fit compared to the intercept only model ($AIC_1=1329.74$, Nagelkerke $R^2=.04$) however overall did not significantly improve the null model.



**Points correspond to predictive probabilities and bars correspond to 95% CI.*

Figure 8: Predicted probability of GAF at 2-years by LCA- With GCI

4.3.2 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA Without GCI (complete case data)

For analyses of CCS at 2-years predicted by LCA- Without GCI, covariates were not included in the model based on previous analyses in 3.3.1. Similarly, direct regression analyses demonstrated no linear association between LCA-Without GCI and 2-year CCS ($p>.10$). When the CCS variable was transformed to a two-level dependent variable, binomial logistic regression demonstrated no linear relationship between LCA-Without GCI class and 2-year CCS ($B=-.27$, $p=.32$). In analyses where GAF at 2-years was the dependent variable, there were statistically significant group differences in GAF by LCA-Without GCI group membership ($\chi^2=36.93$,

$p < .001$). Again, backwards selection was used with all confounders in the model with GAF as the dependent variable leading to removal of sex as a covariate ($p > .10$) and both age ($p < .003$) and years of education ($p < .05$) remained as viable covariates. Results are displayed in **Table 11**.

Table 11: Ordinal logistic regression of GAF at 2-years predicted by LCA-Without GCI, age, and years of education (complete case data)

GAF at 2 Years	Parameter Estimate	Standard Error	p-value	Prop. Odds Ratio (95%CI)
Intercept (Low to Mod GAF)	-.09	.41	.006	
Intercept (Mod to High GAF)	1.20	.41	.02	
LCA- With GCI- Class 1/Lower-Risk Class	.86	.16	.005	2.34 (1.71-3.26)
Age at baseline	-.07	.03	<.001	.93 (.87-.98)
Years of education	.09	.04	.01	1.10 (1.01-1.19)
AIC: 1297.64				
Nagelkerke R ² =.07				
Number of Observations: 625				

Out of 625 observations, results from ordinal logistic regression showed that if assigned to LCA With GCI- Class 1 or the Lower-Risk Class the odds of being in the higher functioning groups (e.g. moderate or high functioning versus low functioning groups) at 2-years are 2.34 times higher than those in the LCA-With GCI-Class 2, or Higher-Risk Class, holding age and years of education constant. For every one-year increase in baseline age, the odds of having higher functioning are .93, meaning there is a 7% decrease in odds of having higher functioning, holding other variables constant. Additionally, with every one-year increase in years of education, the odds of being in the higher functioning groups (e.g. moderate or high functioning versus low functioning groups) increases by, 1.10, or a 10% increase in odds, holding constant

all other variables. In summary, the those who are in the LCA With GCI- Class 1 or the Lower-Risk Class are more likely to be in the top two quantiles of functioning at 2-year follow-up controlling for baseline age and years of education, parallel to trends visualized in **Figure 8**. Additionally, those who are older at baseline are less likely to be in the moderate-high functioning group at 2-year follow-up however those with more reported education at baseline are more likely to be in the moderate-high functioning group at 2-year follow-up. This model with covariates also demonstrated marginally improved model fit compared to the intercept only model ($AIC_1=1333.75$, Nagelkerke $R^2=0$) however overall did not significantly improve from the null model.

Preliminary longitudinal regression analyses of both LCA-With GCI and LCA-Without GCI using **complete case data only** demonstrated that these two 2-class solutions do not appear to be viable linear predictors of clinical status at 2-year follow-up, however, are significant predictors of global functioning at 2-year follow-up, holding age and years of education constant.

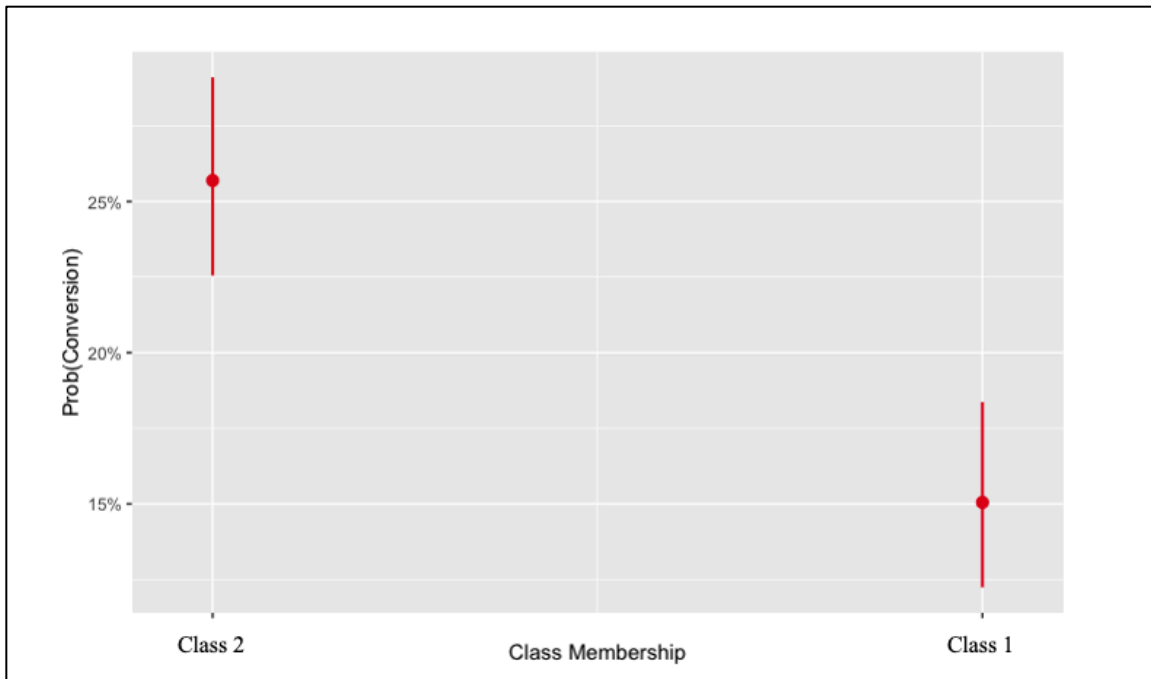
*4.3.3 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA With GCI and covariates with **internally imputed data by FIML***

For analyses of CCS and GAF at 2-year follow-up predicted by LCA-With GCA (internally imputed cases), preliminary univariate chi-square tests demonstrated statistically significant group differences between CCS group based on class membership ($\chi^2=25.56$, $p<.0001$), with Class 2 or the Higher-Risk Class-With GCI demonstrating higher rates of individuals in the symptomatic/progression and conversion groups. Univariable analyses with 1206 observations demonstrated that the log-odds of being in the symptomatic and/or progression group compared to the remission group increased by .32 if assigned to Class 1 or the Lower-Risk-With GCI class, meaning that this class membership was associated with persistent

attenuated psychosis rather than remission at 2-year follow-up. Inversely, the log-odds of being in the conversion group compared to the remission group decreased by .44 if assigned to Class 1 or the Lower-Risk-With GCI class, signifying that conversion status at 2-years was less related to lower-risk class membership and more related higher-risk class membership. Follow-up univariable binomial logistic regressions transforming CCS into a 2-level dependent variable representing non-conversion and conversion demonstrated that for individuals in Class 1 or the Lower-Risk-With GCI class the odds of converting to psychosis at 2-year follow-up was multiplied by a factor of $\exp(-.67) = .51$ compared to those in Class 2, or the Higher-Risk with GCI class. In other words, the odds of converting to psychosis for those in Class 1 are .51 times less than the odds for those in Class 2. Results of both the univariable multinomial regression and the univariable binomial regression for CCS at 2-years (LCA-With GCI) are outlined in **Table 12**. These models (multinomial and binomial) with covariates also demonstrated marginally improved model fit compared to the intercept only models ($AIC_1=2435.17$, Nagelkerke $R^2=0$; $AIC_1=1243.6$, Nagelkerke $R^2=0$) however overall did not significantly improve from the null model. Predicted probabilities of non-conversion vs. conversion and 95% confidence intervals are displayed in **Figure 9**.

Table 12: Multinomial and binomial logistic regressions of CCS at 2-years predicted by LCA-With GCI (internally imputed cases by FIML)

CCS- Remission, Symptomatic/Progression, or Conversion	<i>Symptomatic/Progression vs. Remission</i>	<i>Conversion vs. Remission</i>
Intercept	.62 (.09); 1.86	-.01 (-.45); .99
LCA- With GCI- Class 1	.32 (.14); 1.38*	-.44 (.18); .67*
AIC: 2413.106		
Nagelkerke R ² =.02		
Number of Observations: 452		
Standard errors are reported in parentheses, <i>bolded</i> refers to Relative Risk Ratio, * refers to $p < .05$		
CCS- Non-Conversion vs. Conversion	<i>Non-Conversion vs. Conversion</i>	
	B (S.E)	OR
Intercept	1.05 (.09)	
LCA-With GCI-Class 1	-.67 (.15)	.51***
AIC: 1224.9		
Nagelkerke R ² =.03		
Number of Observations: 452		
Standard errors are reported in parentheses, *** refers to $p < .001$		



**Points correspond to predictive probabilities and bars correspond to 95% CI.*

Figure 9: Predictive probability of conversion at 2-years by LCA- With GCI class membership and 95% CI (internally imputed data by FIML)

Ordinal logistic regression of GAF at 2-years with 625 observations predicted by LCA- With GCI (internally imputed cases) again controlling for age and years of education demonstrated that if assigned to the Class 1 or “Lower-Risk Class” the odds of being higher functioning increased by 1.77 compared to the Class 2 or “Higher-Risk Class.” In other words, being in the Class 1 was associated with higher odds of being in the highest two functioning quantiles. Similar trends of older age being associated with reduced odds of higher functioning and more years of education being associated with increased odds of higher functioning holding class membership constant persisted in this model (**Table 13**). Again, this model with covariates also demonstrated marginally improved model fit compared to the intercept only model ($AIC_1=3257.07$, Nagelkerke $R^2=0$) however overall did not significantly improve from the null model.

Table 13: Ordinal logistic regression of GAF at 2-years predicted by LCA-With GCI, age, and years of education (internally imputed data by FIML)

GAF at 2 Years	Parameter Estimate	Standard Error	p-value	Prop. Odds Ratio (95%CI)
Intercept (Low to Mod GAF)	-1.16	.22	<.001	
Intercept (Mod to High GAF)	1.13	.22	<.001	
LCA- With GCI- Class 1/Lower-Risk Class	.57	.11	<.001	1.77 (1.44-2.18)
Age at baseline	-.07	.02	<.001	.93 (.89-.97)
Years of education	.09	.03	<.001	1.09 (1.03-1.16)
AIC: 3199.08				
Nagelkerke R ² =.04				
Number of Observations: 625				

4.3.3 Logistic regressions of CCS and GAF at 2-year follow up predicted by LCA Without GCI and covariates with *internally imputed data by FIML*

Univariable multinomial logistic regression of CCS at 2-years predicted by LCA Without GCI (internally imputed cases) with 452 observations were conducted. In these analyses only the log-odds change between the conversion and remission group were statistically significant between class groups; there was a decrease of .36 in the odds of being in the conversion group versus the remission group if assigned to Class 1 or the Low-Risk-without GCI class. Follow-up univariable binomial logistic regressions transforming CCS into a 2-level dependent variable representing non-conversion and conversion demonstrated that for individuals in Class 1 or the Lower-Risk-Without GCI class the odds of converting to psychosis at 2-year follow-up was multiplied by a factor of $\exp(-.29) = .74$ compared to those in Class 2, or the Higher-Risk without GCI class. In other words, the odds of converting to psychosis for those in Class 1 are .74 times

lower than the odds for those in Class 2. Results of both the univariable multinomial regression and the univariable binomial regression for CCS at 2-years (LCA-With GCI) are outlined in **Table 14**. Critically, the multinomial model demonstrated virtually no improvement in model fit compared to the intercept only model ($AIC_1=2453.17$, Nagelkerke $R^2=0$), whereas the binomial model only showed a moderate improvement in model fit compared to the intercept only model ($AIC_1=1243.6$, Nagelkerke $R^2=0$). Predicted probabilities of non-conversion vs. conversion and 95% confidence intervals are displayed in **Figure 10**.

Table 14: Multinomial and binomial logistic regressions of CCS at 2-years predicted by LCA-Without GCI (internally imputed cases by FIML)

CCS- Remission, Symptomatic/Progression, or Conversion	Symptomatic/Progression vs. Remission	Conversion vs. Remission
--	--	-----------------------------

Intercept	.81(.09); 2.24	-.03 (.11); .97
LCA- Without GCI- Class 1	-.10 (.14); .91	-.36 (.18); .68*

AIC: 2434.59

Nagelkerke $R^2=.004$

Number of Observations: 452

Standard errors are reported in parentheses, Bolded refers to Relative Risk Ratio,
* refers to $p<.05$

CCS- Non-Conversion vs. Conversion	Non-Conversion vs. Conversion
---------------------------------------	----------------------------------

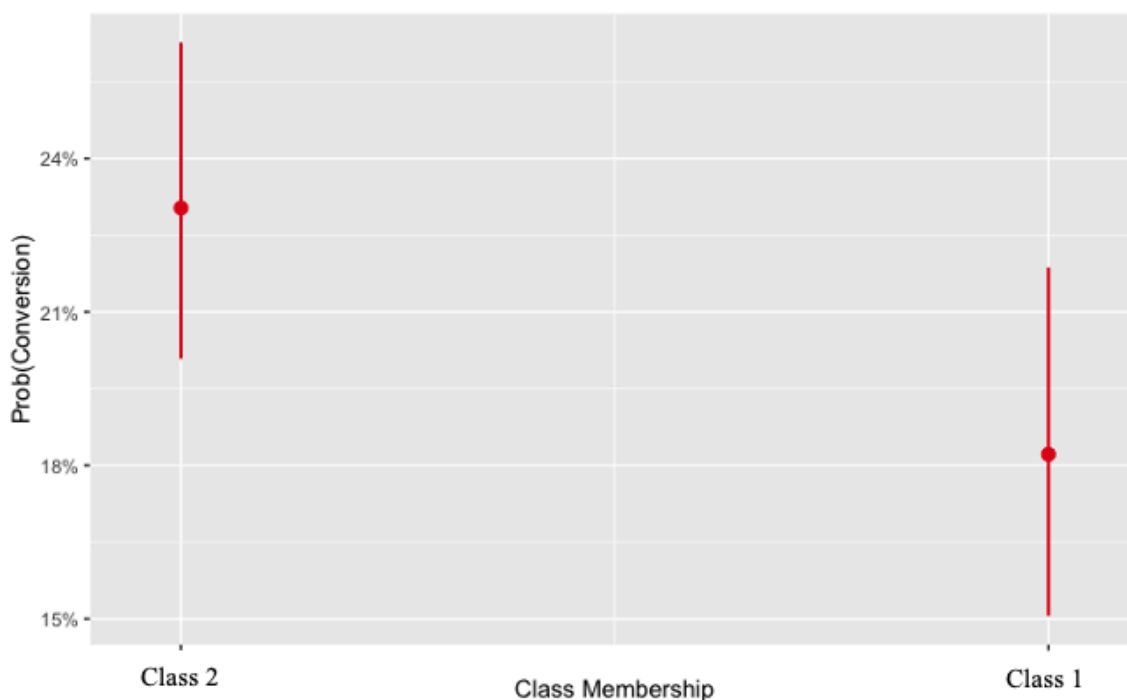
	B (S.E)	OR
Intercept	-1.21 (.09)	
LCA-Without GCI-Class 1	-.29 (.15)	.74*

AIC: 1224.9

Nagelkerke $R^2=.005$

Number of Observations:452

Standard errors are reported in parentheses, * refers to $p<.05$



**Points correspond to predictive probabilities and bars correspond to 95% CI.*

Figure 10: Predictive probability of conversion at 2-years by LCA- Without GCI class membership and 95% CI (internally imputed data by FIML)

Ordinal logistic regression of GAF at 2-years with 625 observations predicted by LCA- With GCI (internally imputed cases) again controlling for age and years of education demonstrated that if assigned to the Class 1 or “Lower-Risk Class” the odds of being higher functioning were 2.81 times the odds for Class 2 or “Higher-Risk Class.” In other words, being in the Class 1 was associated with higher odds of being in the highest two functioning quantiles. Similar trends of older age being associated with reduced odds of higher functioning and more years of education being associated with increased odds of higher functioning holding class membership constant persisted in this model (**Table 15**). This model, compared those presented previously, shows a modestly improved model fit however still does not greatly improve the intercept only model ($AIC_1=3257.07$, Nagelkerke $R^2=0$).

Table 15: Ordinal logistic regression of GAF at 2-years predicted by LCA-Without GCI, age, and years of education (internally imputed data by FIML)

GAF at 2 Years	Parameter Estimate	Standard Error	p-value	Prop. Odds Ratio (95%CI)
Intercept (Low to Mod GAF)	-0.77	.22	<.001	
Intercept (Mod to High GAF)	1.61	.22	<.001	
LCA- Without GCI- Class 1/Lower-Risk Class	1.03	.11	<.001	2.81 (2.30-3.44)
Age at baseline	-.05	.02	<.001	.95 (.91-.99)
Years of education	.08	.03	<.001	1.08 (1.02-1.15)
AIC: 3123.90				
Nagelkerke R ² =.1				
Number of Observations: 625				

In summary, we tested whether the two 2-class solutions (LCA-With GCI and LCA-Without GCI) developed as part of **Aim 1** were significant predictors of 2-year CCS (both three-level and binary outcomes) and GAF analyzing LCA developed with complete case data as well as internally imputed case data by FIML. In these multinomial, ordinal, and binomial logistic regression analyses, we also tested whether sex, age, and years of education were viable covariates. In analyses of 2-year CCS, LCA With GCI and LCA Without GCI utilizing complete cases only were not linearly associated with CCS. When these analyses were repeated utilizing internally imputed data by FIML thus significantly increasing sample size, both 2-class solutions were significant linear predictors of CCS when CCS represented a three-level outcome (remission vs. symptomatic or progression vs. conversion) as well as a dichotomous outcome (non-conversion vs. conversion). In both analyses of CCS with imputed data and consistent with **Hypothesis 1b:Aim 1**, Class 1 or the Lower-Risk Class (with and without GCI) was associated

with a slightly increased odds of being in the symptomatic/progression group compared to the remission group and significantly decreased odds of being in the conversion group versus the remission group. This was echoed in both binomial regressions of CCS (predicted by LCA with and without GCI); Class 1 demonstrated significantly lower probability of conversion compared to Class 2 or the Higher-Risk Class (with and without GCI). These analyses suggest that internally imputed LCA-With and Without GCI may be preferential to complete case LCA for regression analyses.

Results from the 2-year multivariable analyses of GAF predicted by LCA-With GCI and LCA-Without GCI covarying for age and years of education with complete case data as well as internally imputed data by FIML suggest these variables are statistically viable linear predictors of 2-year global functioning. In analyses of GAF with complete case data for LCA-With and Without GCI, being in Class 1 or the Lower-Risk class in both contexts was associated with increased odds of being higher functioning at 2-years controlling for confounders. Similarly, in analyses with imputed LCA data, being in Class 1 or the Lower-Risk class in both contexts was associated with increased odds of being higher functioning at 2-years controlling for confounders. These analyses collectively suggest, considering complete case data and imputed case data, that individuals in Class 1- With and Without GCI have higher global functioning at 2-year follow-up, and individuals in Class 2- With and Without GCI have lower global functioning at 2-year follow-up, confirming **Hypothesis 1b: Aim 1**. Patterns of older baseline age being associated with incrementally lower functioning and more years of education being associated with higher functioning at 2-years were surprising. A potential hypothesis regarding this trend may be that individuals who entered the parent studies later may have had more progressed illness and subsequent functional decline that continued for 2-years. Additionally, those with

more years of education at baseline may have had higher sustained academic functioning at 2-years, which is a component of global functioning. Trends in these covariates will be examined further in the **Discussion** section.

The next phase of analyses, consistent with **Aims 2-3**, focused on testing whether LCA-With GCI and LCA-Without GCI predicted long-term (5-20 year) CCS, GAF, and among those who converted to psychosis in the LTF study period, affective or non-affective psychosis diagnosis considering adjunctive effects of other relevant covariates known to impact lifetime outcomes. In analyses of 5–20-year outcomes, we chose to focus on LCA-With GCI and LCA-Without GCI with **internally imputed data by FIML** given that this method may allow for better categorization of CCS at 5-20 years and may help to statistically account for significant loss of attrition across the 5–20-year study period.

Long Term (5-20 year) Follow-Up (LTF)

4.4 Study characteristics: Long-term (5-20 year) follow-up (LTF) sample

Of the original 1846 CHR individuals who participated in NAPLS 1-3 studies, 419 LTF individuals were recontacted and re-evaluated with the aim of determining current clinical status, lifetime diagnosis, functioning, as well as related factors that impacted their trajectories since initial research participation. LTF participants represented a diverse population across racial and ethnic lines, socioeconomic status, employment and academic history, and life experiences. While beyond the scope of the present project to explore these in detail, individuals recontacted as part of this project represented a broad spectrum of lived experience with no psychiatric symptoms, chronic mental illness, sustained recovery, and periods of relapse and remission. While there were many individuals who were not able to be recontacted for a variety of reasons, through public records or family member testimony for $n=62$ participants from the parent

studies we were able to ascertain that of these individuals $n=40$ had died (5 of which were known suicides), $n=14$ were currently incarcerated, $n=6$ had developed psychosis, $n=3$ were in active military service, and $n=1$ was in long-term residential care for psychiatric reasons.

On average, LTF participants had a follow-up time of approximately 10 years. Surprisingly, the LTF sample was predominantly female and, on average, under the age of 30. The highest proportion of LTF individuals were still either symptomatic or met criteria for attenuated psychosis progression at 5–20-year follow-up. Among those who converted to psychosis, the majority of LTF individuals were re-diagnosed with an affective psychosis condition. At LTF, over three quarters of the sample displayed moderate to low global functioning. Rates of current and cumulative lifetime cannabis use patterns were varied and followed a bimodal distribution with the highest proportion of individuals reporting no cannabis use and the second highest group reporting weekly to daily use. Nearly three quarters of the sample endorsed using cannabis at least once in their lifetime. Treatment histories were also highly heterogenous, however nearly three quarters of the LTF sample reported receiving at least one trial of psychiatric medication and at least one trial of engagement with psychotherapy in the LTF time window (following initial research participation) (**Table 16**).

Table 16: *Demographics, clinical status, functioning, cannabis use, and treatment profiles of 5-20 year LTF participants*

Characteristic	NAPLS 1-3 LTF (N = 419 ¹)
Average age at LTF (years) <i>Range 17-59 years old</i>	28.79 (6.27)
Average time to LTF (years) <i>Range 4-26 years</i>	10.36 (4.61)
Years of Education	14.78 (2.44)
Sex	
Female	211 / 419 (50.4%)
Male	208 / 419 (49.6%)
Race	
Asian	34 / 419 (8.1%)

Table 16: Demographics, clinical status, functioning, cannabis use, and treatment profiles of 5-20 year LTF participants, continued

Black	46 / 419 (11%)
Multiracial	54/ 419 (12.9%)
Native American/First Nation	9 / 419 (4.5%)
Pacific Islander	0/ 419 (0%)
Central or South American	24/419 (5.7 %)
White	242 / 419 (57.8%)
Current Clinical Status (CCS)	
In remission	167/ 415 (40.2%)
Symptomatic or prodromal progression	179 / 415 (43.1%)
Conversion	69/ 415 (16.6%)
Missing	4
Global Assessment of Functioning	
Low (25 th Quantile)	110 / 415 (27%)
Moderate (50 th Quantile)	209/ 415 (50.4%)
High (75 th Quantile)	92/ 415 (22%)
Missing	4
Conversion Diagnoses	
Affective Psychosis	37 (50.7)
Non-Affective Psychosis	29 (39.1 %)
Duration of Untreated Psychosis (DUP) in Days for Converters	102.58 (361.52)
Ever Used Cannabis at LTF	301/405 (74.3%)
Cannabis Use Severity at LTF	
Low Use: <i>No Use-2-4 times per year</i>	141/272 (51.8%)
Moderate Use: <i>6 times per year-3 times per month</i>	26/272 (9.6%)
High Use: <i>Weekly-Daily</i>	105/272 (38.6%)
Cumulative Lifetime Cannabis Use at LTF	
1-100 times	108/272 (39.7%)
101-1000 times	66/272 (24.3 %)
1001-10,000 times	98/272 (36%)
Total Years of Cannabis Use at LTF	7.5 (6.07)
Received Psychiatric Medication Treatment in LTF period	
No medication	103/ 412 (25%)
At least one trial of psychiatric medication	309 /412 (75%)

Table 16: Demographics, clinical status, functioning, cannabis use, and treatment profiles of 5-20 year LTF participants, continued

Received Psychotherapy in LTF period

No psychotherapy	112/411 (27.3%)
At least one period of engagement in psychotherapy	299/411 (72.7%)

¹ Mean (SD); n / N (%); 15 subjects were controls from the parent studies who converted. These subjects were not included in LTF analyses however are reflected in the counts above.

4.5 Prediction of long-term (5-20 year) outcomes by early risk profiles (LCA-With GCI and LCA-Without GCI)

In this phase of analyses, LCA- With GCI and LCA-Without GCI incorporating internally imputed cases by FIML were employed as predictor variables in multinomial and binomial logistic regressions of CCS at LTF (3-level and 2-level dependent variables), as well as in ordinal logistic regression of GAF at LTF (3-level dependent variable). Among a subset of those individuals who converted to psychosis in the LTF study period, these two 2-class solutions were employed as predictor variables in binomial logistic regressions employing lifetime psychosis diagnosis as the outcome variable (2-level dependent variable).

4.5.1 Logistic regressions of CCS and GAF at LTF predicted by LCA With GCI and covariates

Assumption testing was conducted for multinomial, ordinal, and binary logistic regression. Dependent variables were either nominal, ordinal or binary in nature with a combination of continuous and categorical predictors. Independence of observation between variables was observed by visually inspecting plots of residuals against factors. Multicollinearity was tested between predictor variables and those that were highly correlated ($r > .7$) were re-evaluated/removed as covariates if needed. Linear relationships were confirmed between continuous predictors and the logit transformation of the dependent variable, with significance set at $p = .05$. Full results of assumption testing can be found in **Appendix B**.

For analyses of CCS at LTF predicted by LCA-With GCA, backwards selection was utilized to determine appropriate covariates. All confounders were entered into the regression with CCS as the dependent variable, and covariates were removed incrementally using a p-value threshold of .1 until only significant covariates remained. In the final model of CCS at LTF (3-level dependent variable) LCA-With GCI was added as a predictor variable controlling for history of medication use, cannabis use frequency at LTF, and total years to LTF. Multivariable analyses with 397 observations demonstrated that the log-odds of being in the symptomatic and/or progression group compared to the remission group increased by .12 if assigned to Class 1 or the Lower-Risk-With GCI class, meaning that this class membership was associated with persistent attenuated psychosis rather than remission at 2-year follow-up. Inversely, the log-odds of being in the conversion group compared to the remission group decreased by .12 if assigned to Class 1 or the Lower-Risk-With GCI class, signifying that conversion status at 2-years was less related to lower-risk class membership and more related higher-risk class membership. Importantly, neither of these relationships with LCA-With GCI and CCS (3-level) were statistically significant when controlling for covariates. Having a history of a medication trial in the LTF period significantly increased the odds of being in the conversion group compared to the remission group at LTF, and having a current frequent cannabis use pattern increased the odds of being in the symptomatic group versus the remission group at LTF. Additionally, more years to LTF was associated with decreased odds of being in the symptomatic group versus the remission group as well as increased odds of being in the conversion group versus the remission group, however this relationship was non-significant. This model moderately improved overall model fit compared to the intercept only model ($AIC_1=819.39$, Nagelkerke $R^2=0$). **Table 17** outlines these analyses with associated relative-risk ratios. In summary, when considering important covariates,

LCA-With GCI was not a significant predictor of CCS at LTF (3-level), whereas factors related to medication exposure, cannabis use, and total follow-up years were more significant drivers of this outcome.

Table 17: Multinomial logistic regression of CCS (3-level) at 5-20 year LTF predicted by LCA-With GCI controlling for medication history, cannabis use frequency at LTF, and total years to LTF

CCS- Remission, Symptomatic/Progression, or Conversion	<i>Symptomatic/Progression vs. Remission</i>	<i>Conversion vs. Remission</i>
Intercept	.40 (.52); 1.50	-2.64 (.76); .07
LCA- With GCI- Class 1	.12 (.29); 1.13	-.12 (.37); .88
Medication History (present)	.46 (.32); 1.58	1.47 (.57); 4.35*
Current cannabis use frequency (moderate)	.72 (.49); 2.05	-.32 (.84); .72
Current cannabis use frequency (frequent)	.61 (.31); 1.84*	.54 (.40); 1.72
Total years to LTF	-.11 (.04); .90**	.04 (.04); 1.04
AIC: 519.97		
Nagelkerke R ² = .14		
Number of Observations: 397		

Standard errors in parentheses, bolded numbers refer to Relative Risk Ratio, *refers to <.05, ** refers to <.006

Backwards selection was again employed to determine appropriate covariates. Follow-up multivariable binomial logistic regressions with 397 observations transforming CCS into a 2-level dependent variable representing non-conversion and conversion demonstrated that for individuals in Class 1 or the Lower-Risk With GCI Class the odds of converting to psychosis at 2-year follow-up was multiplied by a factor of $\exp(-.55) = .58$ compared to those in Class 2, or the Higher-Risk with GCI class holding other variables constant. In other words, the odds of converting to psychosis for those in Class 1 were .58 times less than the odds for those in Class 2. These relationships were significant at trend-level. Exposure to medication within the LTF period and more years to LTF were significantly associated with an increased odds of conversion at LTF and sex was not a significant predictor of CCS in this model. This model moderately

improved overall model fit compared to the intercept only model ($AIC_1=359.21$, Nagelkerke $R^2=0$). Full results including odds ratios are outlined in **Table 18**.

Table 18: Binomial logistic regression of CCS (2-level) at 5-20 year LTF predicted by LCA-With GCI controlling for medication history, total years to LTF, and sex

CCS- Non-Conversion vs. Conversion	Non-Conversion vs. Conversion	
	B (S.E)	OR
Intercept	-3.81 (.66)	
LCA-With GCI-Class 1	-.55 (.30)	.58*
Medication History (present)	1.88 (.54)	6.54***
Total years to LTF	.10 (.03)	1.11***
Sex (female)	-.51 (.29)	.60
AIC: 323.7		
Nagelkerke $R^2=.16$		
Number of Observations:397		
Standard errors in parentheses, *refers to $p<.06$, *** refers to $p<.001$		

Following backwards selection of covariates, multivariable ordinal analyses with 396 observations of GAF at LTF predicted by LCA-With GCI demonstrated that when controlling for other covariates, LCA With GCI membership was not a significant predictor of LTF GAF. Instead, GAF at LTF appeared to be more strongly influenced by medication history, age at LTF, lifetime cumulative cannabis use, and total years of cannabis use. Individuals with a medication trial history, who were older at LTF, and who reported moderate-frequent cumulative lifetime cannabis use had decreased odds of higher functioning at LTF, or were generally lower functioning at LTF. Those with more years of education as well as more years of total cumulative cannabis use had increased odds of being higher functioning at LTF, highlighting a somewhat paradoxical findings regarding cannabis use and functioning. This model moderately improved overall model fit compared to the intercept only model ($AIC_1=821.75$, Nagelkerke $R^2=0$). Full results are outlined including proportional odds ratios in **Table 19**.

Table 19: Ordinal logistic regression of GAF at LTF predicted by LCA-With GCI controlling for medication history, age at LTF, years of education at LTF, cumulative lifetime cannabis use, total years of cannabis use

GAF at LTF (Low, Mod, High)	Parameter Estimate	Standard Error	p-value	Prop. Odds Ratio (95%CI)
Intercept (Low to Mod GAF)	-.69	.94		
Intercept (Mod to High GAF)	1.75	.95		
LCA- With GCI- Class 1/Lower-Risk Class	.01	.26	.97	1.01 (.61-1.68)
Medication history (present)	-1.09	.29	<.001	.33 (.19-.59)
Age at LTF	-.057	.03	.04	.94 (.89-1.0)
Years of education at LTF	.20	.06	<.001	1.22 (1.08-1.37)
Cumulative lifetime cannabis use (moderate)	-.66	.33	.05	.52 (.27-.99)
Cumulative lifetime cannabis use (heavy)	-.94	.32	.003	.38 (.21-.72)
Total years of cannabis use	.07	.03	.009	1.07 (1.02-1.13)
AIC: 502.73				
Nagelkerke R ² =.17				
Number of Observations: 396				

In summary, analyses of LTF outcomes demonstrated that LCA-With GCI predicted only CCS (2-level) at trend level significance when controlling for other confounders, suggesting that individuals from Class 1 or the Lower-Risk class had lower odds of converting to psychosis by LTF compared to those in Class 2 or the Higher-Risk class. In analyses of CCS (3 and 2-level) aspects of cannabis use severity, medication exposure, and total years to LTF were more statistically influential in the prediction of LTF clinical status than LCA-With CGI membership.

Medication history, years of education, cumulative lifetime cannabis use, and total years of cannabis use were stronger predictors of GAF at LTF than LCA-With GCI membership.

4.5.2 Logistic regressions of CCS and GAF at LTF predicted by LCA Without GCI and covariates

Multinomial, binomial, and ordinal regressions were repeated incorporating LCA-Without GCI as a predictor variable. Identical assumption testing outlined in the previous section was conducted for all regressions and their predictor variables. For analyses of LTF CCS (3-level) with 397 observations predicted by LCA-Without GCI, nearly identical patterns as were observed in analyses of LCA-With GCI emerged (**Table 20**). LCA-Without GCI membership was not a significant predictor of LTF CCS (3-level) when controlling for relevant covariates. Individuals with medication exposure had increased odds of being in the conversion group compared to the remission group at LTF, and those with high cannabis use frequency patterns at LTF had increased odds of being in the symptomatic/prodromal progression group versus the remission group. Those with more years of follow-up again had decreased odds of being in the symptomatic /prodromal progression group compared to those in remission however those with more years to LTF had increased odds of being in the conversion group compared to the remission group, however this was not statistically significant. This model demonstrated moderately improved model fit compared to the intercept only model ($AIC_1=819.39$, Nagelkerke $R^2=0$).

Table 20: Multinomial logistic regression of CCS (3-level) at 5-20 year LTF predicted by LCA-Without GCI controlling for medication history, cannabis use frequency at LTF, and total years to LTF

CCS- Remission, Symptomatic/Progression, or Conversion	<i>Symptomatic/Progression vs. Remission</i>	<i>Conversion vs. Remission</i>
Intercept	.36 (.49); 1.43	-2.80 (.74); .06
LCA- Without GCI- Class 1	.44 (.29); 1.55	.31 (.38); 1.34
Medication History (present)	.46 (.32); 1.58	1.48 (.57); 4.39*
Current cannabis use frequency (moderate)	.78 (.49); 2.18	-.30 (.84); .74
Current cannabis use frequency (frequent)	.60 (.31); 1.82*	.54 (.39); 1.72
Total years to LTF	-.11 (.04); .89**	.04 (.04); 1.04
AIC: 519.97		
Nagelkerke R ² =.14		

Number of Observations: 397

Standard errors in parentheses, bolded numbers refer to Relative Risk Ratio, *refers to <.05, ** refers to <.006

Follow-up multivariable binomial logistic regressions transforming LTF CCS into a 2-level dependent variable representing non-conversion and conversion demonstrated that for individuals in Class 1-Without GCI or the Lower-Risk class the odds of converting to psychosis at 2-year follow-up was again multiplied by a factor of $\exp(-.55)=.58$ compared to those in Class 2-With GCI, or the Higher-Risk class, holding other variables constant. In other words, the odds of converting to psychosis for those in Class 1 were .58 times less than the odds for those in Class 2. In these analyses however these relationships were not statistically significant. Again, exposure to medication within the LTF period and more years to LTF were significantly associated with an increased odds of conversion at LTF, and sex was again not a significant predictor of CCS in this model. This model demonstrated moderately improved model fit compared to the intercept only model ($AIC_1=359.21$, Nagelkerke $R^2=0$). Full results including odds ratios are outlined in **Table 21**.

Table 21: Binomial logistic regression of CCS (2-level) at 5-20 year LTF predicted by LCA-Without GCI controlling for medication history, total years to LTF, and sex

CCS- Non-Conversion vs. Conversion	Non-Conversion vs. Conversion	OR
	B (S.E)	
Intercept	-4.33 (.65)	
LCA-Without GCI-Class 1	-.55 (.30)	.58
Medication History (present)	1.88 (.54)	6.57***
Total years to LTF	.10 (.03)	1.11***
Sex (female)	-.51 (.29)	.60
AIC: 324.79		
Nagelkerke R ² =.16		
Number of Observations:397		
Standard errors in parentheses, *** refers to $p < .001$		

Interestingly, in multivariable ordinal regressions of GAF at LTF with 396 observations, LCA Without GCI was a significant predictor of LTF GAF controlling for relevant covariates. For those in Class 1-Without GCI or the Lower-Risk class, there was a significant increase in the odds of being higher functioning at LTF holding medication history, age at LTF, cumulative lifetime cannabis use, and total years of cannabis use constant. Identical trends that were observed in analyses of LTF With GCI regarding relationships between individual covariates and GAF at LTF remained consistent in this model. This model demonstrated modest improvements in model fit compared to the intercept only model ($AIC_1=821.73$, Nagelkerke $R^2=0$). Full results including proportional odds ratios are outlined in **Table 22**.

Table 22: Ordinal logistic regression of GAF at LTF predicted by LCA-Without GCI controlling for medication history, age at LTF, years of education at LTF, cumulative lifetime cannabis use, total years of cannabis use

GAF at LTF (Low, Mod, High)	Parameter Estimate	Standard Error	p-value	Prop. Odds Ratio (95%CI)
Intercept (Low to Mod GAF)	--1.01	.95		
Intercept (Mod to High GAF)	1.50	.95		
LCA- Without GCI- Class 1/Lower-Risk Class	.55	.26	.03	1.74 (1.05-2.91)
Medication history (present)	-1.12	.29	<.001	.33 (.19-.57)
Age at LTF	-.04	.03	.12	.96 (.91-1.01)
Years of education at LTF	.18	.06	<.003	1.19 (1.06-1.34)
Cumulative lifetime cannabis use (moderate)	-.70	.33	.04	.49 (.25-.94)
Cumulative lifetime cannabis use (heavy)	-.94	.32	.003	.39 (.21-.73)
Total years of cannabis use	.06	.03	.02	1.07 (1.01-1.13)
AIC: 498.08				
Nagelkerke R ² =.2				
Number of Observations: 396				

Multinomial, binomial, and ordinal regression analyses were conducted to determine if early risk-profiles from the parent studies of CHR youth (LCA-With GCI and LCA-Without GCI) had predictive value for lifetime (5-20) outcomes. While estimated profile membership to either 2-class solution was linearly related to CCS (3 and 2-level) in isolation, and in one context being in the Class 1-With GCI or Lower-Risk class was associated with a trend-level decreased odds of conversion at LTF controlling for confounders, critical covariates known to influence long-term clinical and functional outcomes were ultimately stronger statistical predictors than

estimated class membership. This ultimately contradicted hypotheses (based on trend-level significant findings for CCS 2-level) related to clinical outcome based on class membership proposed in **Hypothesis 2: Aim 2**. Regarding GAF at LTF, LCA-Without GCI was a significant predictor of later global functioning, specifically highlighting that those in the Class 2-Without GCI, or Higher-Risk class, had lower odds of higher functioning at LTF, confirming proposed hypotheses related to functioning in **Hypothesis 2: Aim 2**. These findings may suggest that the addition of indicator variables related to global cognition in the development of early-risk profiles may not be as statistically related to later global functioning compared to classifying subjects based on only clinical and functional characteristics.

4.5.3 Binomial logistic regressions of affective versus non-affective psychosis diagnosis at LTF among converters predicted by LCA with and without GCI and covariates

Exploratory binomial logistic regressions among those who converted to psychosis in either the parent studies or in the LTF period ($n=66$) were conducted. LTF with and without GCI were employed as predictor variables in separate analyses. Assumption testing outlined in previous sections for binomial logistic regressions was conducted; full results can be found in **Appendix C**. Backwards selection was again utilized to identify significant covariates including the a priori hypothesized covariates (age at LTF, sex, years to LTF, years of education at LTF, current cannabis use frequency at LTF, cumulative cannabis use in lifetime, exposure to a medication trial in the LTF period, and engagement in psychotherapy throughout the LTF period). Duration of untreated psychosis (DUP) was added in the backwards selection process following confirmation that the addition of this variable did not violate the assumption of multicollinearity and was linearly related to the logit odds of the dependent variable.

In analyses of affective versus non-affective diagnosis at LTF, LCA with GCI was not a significant predictor of diagnostic outcome. Sex, exposure to psychotherapy in the LTF period,

and total years of cannabis use were all significant predictors of diagnosis at LTF among those who converted to psychosis. Females, those who had at least one period of engagement with psychotherapy, and those with more years of cannabis use had significantly higher odds of developing an affective psychosis diagnosis at 5-20 years compared to males with no treatment history and less years of cannabis use. Critically, this model demonstrated substantial improvement in model fit compared to the intercept only model ($AIC_1=92.52$, Nagelkerke $R^2=0$). Full results including odds ratios are outlined in **Table 23**.

Table 23: Binomial logistic regression of LTF conversion diagnosis predicted by LCA-With GCI, psychotherapy history, total years of cannabis use, and sex

Affective vs. Non-Affective Psychosis Diagnosis		
	B (S.E)	OR
Intercept	-3.08 (1.34)	
LCA-With GCI-Class 1	-1.60 (1.02)	.20
Engagement with psychotherapy in LTF period	2.03 (1.04)	7.65**
Total years of cannabis use	.17 (.08)	1.18**
Sex (female)	3.62 (1.28)	37.62***
AIC: 42.87		
Nagelkerke $R^2=.60$		
Number of Observations:66		
Standard errors in parentheses, *refers to $p<.05$, *** refers to $p<.001$		

Identical analyses employing the LCA-Without GCI predictor variable demonstrated identical predictive trends among covariates and later psychosis diagnosis, however LCA-Without GCI appeared to be significantly associated with later diagnosis at trend-level. Holding other covariates constant, being in the Class 1-Without GCI or the Lower-Risk class was associated with an increased odds of developing an affective psychosis diagnosis at 5–20-year LTF (**Table 24**). This model similarly demonstrated substantial improvement in model fit compared to the intercept only model ($AIC_1=92.52$, Nagelkerke $R^2=0$).

Table 24: Binomial logistic regression of LTF conversion diagnosis predicted by LCA-Without GCI, psychotherapy history, total years of cannabis use, and sex

Affective vs. Non-Affective Psychosis Diagnosis		
	B (S.E)	OR
Intercept	-4.98 (1.7)	
LCA-Without GCI-Class 1	1.85 (1.07)	6.35*
Engagement with psychotherapy in LTF period	2.03 (.99)	7.64**
Total years of cannabis use	.22 (.09)	1.24**
Sex (female)	2.98 (1.08)	19.80***
AIC: 42.33		
Nagelkerke R ² =.60		

Number of Observations:66

Standard errors in parentheses, *refers to $p < .08$, ** refers to $p < .05$, *** refers to $p < .005$

These exploratory analyses, particularly those involving LCA-Without GCI, are in part consistent with our initial hypothesis outlined in **Hypothesis 3: Aim 3** that “risk profiles reflective of consistent but moderate cannabis use, older age of cannabis initiation, less severe symptoms, higher global and social functioning, higher premorbid functioning, better neurocognition (IQ, verbal learning, memory, processing speed) and lower exposure to early adverse life events will be associated with an affective psychosis diagnoses at long-term follow-up.” Importantly however, and in contrasts to elements of the initial hypothesis, it appeared when comparing the two analyses with LCA-With GCI and LCA-Without GCI that the addition of global cognition in early risk profiles may not be an important classifier for later diagnosis among those who convert to psychosis.

5. DISCUSSION

This study sought to explore whether distinct “risk-profiles” capturing latent constructs of risk were present in a large sample ($N=1846$) of CHR youth. This population is hallmarked by significant heterogeneity in both baseline clinical presentation and illness course, often complicating risk prediction as well as precision of early intervention. Specifically, this project examined through LCA the interactive nature of baseline factors known to impact early clinical and functional outcomes (cannabis use, attenuated psychosis symptom severity, history of childhood trauma, adverse life experiences, family history of psychosis, functioning, and global cognition) and identified distinct profiles based on these factors. The isolation of such risk profiles through LCA, a scantily employed statistical strategy in this population, provided valuable insight into naturalistic subgroups in CHR that were categorized by varying levels of both exposure to environmental and genetic factors as well as symptom severity, functioning, and neurocognition.

Following the identification of latent risk profiles within this group, profiles representing “higher” and “lower” risk subgroups were evaluated in regression analyses to determine if particular profiles were statistically predictive of 2-year clinical and functional outcomes. In a novel opportunity for CHR research, this group also examined whether baseline risk profiles had predictive value for long-term (5-20 year) outcomes among a small subset of participants who were re-evaluated later in life ($n=419$). The first sets of longitudinal analyses were critical in validating the use of risk profiles as predictive variables for outcomes within the traditional 2-year study period in CHR and highlighted key statistical relationships between risk profile types and early clinical and functional outcome. Analyses of long-term follow-up outcomes confirmed similar trends observed across the initial 2-year period and consideration of relevant covariates known to impact long-term illness trajectory provided a more holistic insight into the

relationships between estimated baseline risk profile membership and lifetime outcomes.

This study also aimed to determine if baseline risk profiles of individuals who ultimately transitioned to psychosis differentiated those who would go on to develop an affective versus non-affective psychosis. The affective versus non-affective psychosis outcome is a largely understudied research question with potentially significant implications for early intervention strategies as well as for increasing scientific knowledge regarding naturalistic outcomes of diverse diagnostic presentations in early psychosis.

The present dissertation not only identified subtypes of risk using latent classification methods within one of the largest consortia of CHR youth in the world, but also examined how these groupings mapped onto outcomes within and far beyond the early illness period. Findings from this project mark an exciting development in the growing body of research aimed at elucidating the psychosis-risk paradigm in the immediacy and across the lifespan, with particular attention to informing early interventions that address disease mechanism and multidimensional risk and resilience factors. The motivation for developing baseline risk profiles and determining their predictive value for long-term clinical status and functioning was primarily to address the overarching research and clinical question, “what factors are present and potentially modifiable in the earliest phase of illness that will be important to address to improve lifetime outcomes?”

5.1 Distinct latent classes or risk profiles with and without GCI

The first primary aim of this study was to determine whether distinct latent classes would emerge based on a priori hypothesized indicator variables in a large cohort of CHR youth. We chose to develop two separate latent class models, LCA-With GCI and LCA-Without GCI, based on both theoretical questions regarding availability of neuropsychological testing at baseline, as well as a significant missing amount of neurocognitive data and inconsistent neuropsychological

tests administered across the parent studies. Systematically evaluating 2, 3, and 4-class solutions, 2-class solutions were preferable given selected fit indices for LCA-With GCI and LCA-Without GCI with both complete cases and internally imputed data. Consistent with interpretation guidelines outlined by Weller and Sinha ^{147,156} interpretation of classes based on subtle differences in multiple indicator variables was of less importance, meaning that it was expected latent classes differed across levels of indicator variables.

To best categorize and understand the phenotypes of each class, variables that demonstrated the most significant variation between classes were the most revealing. For the 2-class solution of LCA-With GCI, Class 1 (Lower-Risk Class) and Class 2 (Higher-Risk Class), most estimated population shares were in Class 1, indicating that in these subgroups the Lower-Risk subtypes represented the majority of the estimated sample. We chose to use terminology such as “lower and higher” risk to underscore that both classes comprised an inherent non-zero level of risk given that specific levels of the indicator variables were known risk-factors for outcomes in CHR. Classes were not considerably different with regards to levels of cannabis use, adverse life events, presence of family history of psychosis, nor exposure to childhood trauma. Minor variations were detected between classes in levels of cannabis use severity, such that a slightly larger number of individuals estimated to be in Class 2 met criteria for a cannabis use disorder, however Class 1 had more estimated individuals who reported regular use without impairment. These findings may be consistent with previous trends reported by this group and others which suggested that CHR youth with moderate cannabis use patterns also appear to have higher premorbid functioning compared to those with no use and frequent use patterns, meaning that moderate use is not always associated with parallel deficits in functioning or cognition⁵¹. Class 1 and Class 2 (with GCI) were instead most strongly differentiated by global cognitive

index, premorbid functioning, premorbid IQ, age of onset of cannabis use, and attenuated psychosis symptom severity.

For the 2-class solution of LCA-Without GCI, again similar classes emerged that were analogous to Class 1 (Lower-Risk Class) and Class 2 (Higher-Risk Class) in the previously discussed model. With the exclusion of GCI as an indicator variable, classes were mostly differentiated by exposure to childhood trauma, having a family history of psychosis, premorbid functioning, premorbid IQ, age of onset of cannabis use, and attenuated psychosis symptom severity. Again, classes were only marginally differentiated by levels of cannabis use severity and adverse life events. As was discussed in the **Results** section, the removal of GCI as an indicator variable strengthened the differentiation between classes by family history of psychosis and exposure to childhood trauma, most likely due to the estimation parameters employed in LCA given that GCI was shown to be completely independent from childhood trauma and family history in univariate analyses. Developing and analyzing both LCA-With GCI and LCA-Without GCI proved to be a critical process to not only improve predictive validity of profiles, which will be discussed in the following sections, but also to strengthen clinical utility of these risk profiles in practice.

Inclusion of neuropsychological batteries in research of CHR is commonplace due to widely reported neurocognitive deficits among CHR youth.¹⁵⁷ In a recent review and meta-analysis of neurocognitive functioning among 5162 CHR youth by Catalan and colleagues¹⁵⁸ authors reconfirmed that not only do CHR youth display distinct neurocognitive deficits compared to healthy controls across nearly all primary domains of cognition, but that baseline neurocognitive impairments in verbal learning, visual memory, processing speed, attention, and IQ were all independently associated with a later conversion to psychosis. These findings assert

that considering baseline neurocognitive performance within these domains, as was done in this study in the development of the LCA-With GCI model, may be an essential component of improving risk-prediction longitudinally in CHR. Importantly however, some considerations are warranted when improving accessibility and clinical practicality of neuropsychological testing in CHR.

One argument for developing models with and without measures of global cognition in this study was that selection of neuropsychological tests varies significantly across CHR studies as well as in the present project, potentially impacting replicability of latent classes. Across the parent studies of NAPLS 1-3, we selected scores from three tests (HVLIT, BACS, LNS) that represented important cognitive risk domains shown to play a role in psychosis outcomes and developed a global index based on these tests, despite significant amounts of missing data and that one of the parent studies (NAPLS-1) did not administer some of these tests. Global cognitive indices could theoretically be developed from many other neurocognitive tests, and in the present study, may have captured a narrow and non-universal construct of global cognition. Another limitation to depending on neurocognitive information in latent class development is related to clinical practicality. Most studies in CHR (including the parent studies in this project) employ lengthy testing batteries such as the MATRICS Consensus Cognitive Battery (MCCB) that measure these and other domains with the aim of collecting a myriad of neurocognitive information.¹³⁴ Perhaps instead of this “kitchen sink” approach which is time-consuming and resource-demanding, future studies can investigate differences in how individual neurocognitive tests distinguish latent risk classes in CHR to improve hypotheses related to neurocognitive profiles in this population. Once individual tests that are critical to neurocognitive profiles are identified, researchers in CHR can strive to increase accessibility and ease of administration of

shorter, more “bedside” neurocognitive tests that measure specific domains.

Additionally, some CHR individuals who are only seeking clinical evaluation and care (versus participating in research) may never receive any neuropsychological evaluation, potentially limiting the clinical utility of latent risk profiles that depend on neurocognitive information.¹⁵⁹ Importantly, for those who do receive neuropsychological testing, interpretation of common neuropsychological batteries also are often constrained by issues of norming, cultural responsiveness, and longitudinal validity.¹⁶⁰ Findings from a recent systematic review of neuropsychological measures in research of psychosis-spectrum groups by Mwesiga and colleagues¹⁶¹ demonstrated that typical neurocognitive measures used in research within these populations have poor clinical utility outside of high-income countries as well as a dearth of proven reliability and validity among participants in low-middle income countries. Given that the primary goal of developing risk profiles in this study was to, through understanding distinct subgroups of risk, improve clinical identification and intervention in CHR broadly, it was important to also develop risk profiles that were not reliant on neuropsychological tests that are subject to these limitations.

LCA-Without GCI in this study may serve as a more clinically adaptable risk profile template for CHR clinical settings that have access to psychosis-risk assessment, functional assessment, basic demographic information, substance use information, and brief cognitive screenings however who may not have the resources to provide comprehensive neuropsychological testing.

5.1.1 Comparable findings regarding latent subgroups of CHR in the literature

As has been mentioned in this study, use of latent analyses to detect subgroups in CHR has been historically limited and these approaches are emerging as innovative statistical methods

to address heterogeneity and improve individualization of risk prediction and subsequent intervention. To date, most (out of the few available) LCA or LPA approaches have focused on isolating unilateral or bilateral constructs such as identifying baseline symptom, functioning, or cognitive (or combination of these factors) dimensions in CHR and their univariate relationships to demographics, clinical, and functional outcomes.^{162–165} Two studies have broadened this approach to include adding transition rates as indicator variables along with symptom or cognitive measures, to develop classes that include outcomes as well as baseline predictors.^{110,162} Bjornestad and colleagues¹⁶⁶ took the opposite approach of developing latent classes based on clinical status at 2-years (poor chance at remission, early, and later remission), and using univariate analyses to detect differences between outcome classes and baseline predictor variables.

Across studies in CHR that have used latent analyses, which have taken varying approaches, a few themes have emerged. Namely, and unlike the latent classes developed in this study, important parallel risk factors such as substance use, family history of psychosis, exposure to childhood trauma and adverse life experiences, were not entered into the development of classes but were (in only a few studies) explored as covariates for univariate analyses of clinical and functional outcomes.^{121,162,163} Moreover, all studies that used latent analyses in CHR mentioned above compared their developed classes via univariate ANOVA rather than regression modeling, limiting the ability to explore the predictive value of classes and their contribution to model fit, as well as the variance in outcome by class membership. Most of these studies also ranged significantly in the number of identified classes based on selected indicator variables, however among those that observed unilateral constructs like symptom or cognitive dimensions they showed consistency in themes of distinct symptom subgroups reflective of low,

moderate, and high-risk profiles.^{110,162–165,167} While studies that combined baseline and longitudinal clinical and/or functional outcomes as predictor variables in LCA captured classes that represented illness trajectories, the combination of these variables in the latent class development significantly limited the prospective use of baseline risk profiles alone to predict later outcomes and reduced potential clinical utility.

Only Bergé and colleagues,¹⁰⁹ who employed LPA within the NAPLS-3 baseline dataset, developed latent profiles based on risk-variables from the NAPLS psychosis-risk calculator (age, symptoms, aspects of cognition, childhood trauma, social functioning, and family history of psychosis). This study interestingly found slightly different characteristics compared to the classes developed in the present study; in their 2-class solution their “higher-risk” class was categorized by older age, better cognition, more exposure to undesirable life events and childhood trauma, more severe symptoms, poorer functioning, and higher rates of family history of psychosis. Unlike the LCA-With GCI and LCA-Without GCI models developed in this study, these investigators employed substance use disorder and conversion to psychosis as the primary outcomes of which to compare classes, and found that the “higher-risk” class had more rates of substance use however there was no significant association with conversion to psychosis.¹⁰⁹ Interestingly, Bergé and colleagues utilized LPA, which included a combination of continuous and categorical indicator variables. In their classes including both measures of cognition (continuous), childhood trauma (continuous), and family history of psychosis (dichotomous), all three of these variables significantly differentiated classes unlike the LCA results from this study. It is possible that classes developed in the present project were potentially limited by the categorical nature of variables, particularly in the context of childhood trauma as this variable only distinguished between whether any type of childhood trauma was present, rather than

distinguishing between types of childhood trauma or total number of exposures to childhood trauma as Bergé and colleagues¹⁰⁹ demonstrated. This is particularly relevant in studies of CHR due to previous evidence suggesting certain types of childhood trauma, particularly sexual and physical abuse and emotional neglect are closely associated with more severe symptoms and in some studies conversion to psychosis.¹⁶⁸ Moreover, findings from Loewy and colleagues¹⁶⁹ demonstrated that the number of instances of childhood trauma was associated with more severe CHR symptoms and reduced functioning, suggesting that significant nuance of risk may be lost when childhood trauma is defined as a binary construct.

While there is no “optimal” method for selecting indicator variables in LCA as this is typically hypothesis driven¹⁴⁷, one advantage of the profiles developed as part of our study is that they incorporated an updated collection of diverse risk factors, beyond those included in the original psychosis risk-calculator by Cannon and colleagues¹¹, known to impact conversion in CHR. Additionally, to our knowledge, this is the first study to employ LCA in CHR considering specific factors related to baseline cannabis use specifically, building on Bergé and colleagues¹⁰⁹ emphasis on exploring how multi-dimensional latent subgroups in CHR differ in substance use-behaviors. In this study, we did not find that cannabis use severity substantially distinguished latent classes, which was surprising given previous robust findings related to the interaction between frequent/more severe cannabis use patterns and higher attenuated psychosis symptoms.²⁴ These known relationships led us to spuriously anticipate that Class 2 or the Higher-Risk class (with and without GCI) might be categorized by a higher proportion of estimated individuals in the most “severe” category of cannabis use. We believe these findings may be, in part, due the cannabis use severity variable itself given that this variable did not necessarily capture frequency of use, but rather categorized individuals as no use, use without

impairment, or abuse/dependence consistent with DSM criteria.¹⁷⁰ Importantly, the other cannabis related variable included in the development of our latent classes, age at first cannabis use, was a strong determinant of estimated class membership specifically demonstrating that in both 2-class models older age of initiation was associated with membership in the Lower-Risk classes. This is consistent with existing knowledge related to age of cannabis initiation and other risk symptoms in CHR,⁵⁶ and reinforced the role of cannabis use factors as critical risk variables that should be included in holistic latent class development for CHR.

Overall, our phenotypic classification for both 2-class solutions (LCA-With GCI and LCA Without GCI) as being comprised of “Lower-Risk” and “Higher-Risk” classes is consistent with theoretical background regarding relationships between these risk-factor variables and with their independent effects on clinical and functional outcomes in CHR. Levels of premorbid functioning were directionally consistent with levels of global cognition and premorbid IQ in both Lower and Higher-risk classes, which is observed in the broader CHR literature.⁵⁹ Higher attenuated symptoms were expectedly associated with the Higher-Risk classes, and expectedly inverse to measures of premorbid functioning, premorbid IQ, global cognition, and age at first use of cannabis.^{24,26,27,59} These classes representing multiple domains of risk are consistent with the field-wide assertion that dimensional approaches to understanding psychiatric conditions are more informative than, say, a singular categorial approach (e.g. symptom, cognition, functioning).¹⁷¹ This holistic approach is particularly important for early psychosis populations, given that these conditions are multifactorial in etiology, presentation, and course with strong genetic, neurobiological, and environmental influences.¹⁷² Excitingly, these class structures were also stable across replications with complete case data and internally imputed cases, signaling the need for further replication and reliability testing in other cohorts of CHR youth.

5.2 Early risk profiles and prediction of 2-year outcomes

Our second hypothesis within the first primary aim was that early risk-profiles representing the “Higher-Risk” subtype (LCA-With GCI and LCI-Without GCI) would be predictive of 2-year conversion to psychosis and lower global functioning among a subset of CHR youth who had completed at least one-follow-up in the original parent studies ($n=625$). Findings from regression analyses were somewhat inconsistent when comparing LCA-With GCI and LCA-Without GCI using complete case data and internally imputed data due to a smaller sample size for those with complete case data only, so findings from internally imputed cases will be discussed here. LCA-With GCI and LCA-Without GCI significantly predicted CCS at 2-years, both when CCS was reflective of remission versus symptomatic/prodromal progression versus conversion as well as when CCS was simply reflective of non-conversion versus conversion. Being in the Lower-Risk class (for both LCA-With GCI and LCA-Without GCI) was associated with slightly decreased odds of being in the remission group compared to the symptomatic group, and significantly reduced odds of being in the conversion group compared to the remission group. Interestingly, the Lower-Risk class in both models was not associated with being in the remission group at 2-year follow-up but was rather more associated with the symptomatic/prodromal progression group. Given that the Lower and Higher-risk classes in both models had considerable shares of estimated participants in the moderate to high total symptom severity groups, there is an inherent assumption that both risk classes have substantial shares of individuals with symptoms that may continue to meet criteria for attenuated psychosis at 2-years. These findings are consistent with studies in CHR that report high rates of persistent attenuated psychosis symptoms at 2-year follow-up.

A recent meta-analysis by Salazar de Pablo and colleagues¹⁷³ of short-term outcomes

from 75 prospective studies in CHR demonstrated that at 12-month follow-up, remission from attenuated psychosis symptoms occurred in only 33% of subjects and at 24-month follow-up approximately 41% of subjects achieved remission status. In this study's sample, 24% of individuals achieved remission status at 2-years while 58% were still in the symptomatic/prodromal progression group. The reduced odds of both Lower and Higher-risk groups of being in the remission group in this study leaves much to be understood regarding what early baseline risk profiles may be predictive of clinical remission at 2-years. One of the few studies that employed latent analysis to study remission characteristics at 2-years in CHR youth demonstrated that for those who achieve some level of symptomatic remission, it was a multi-phase process.¹⁶⁶ In this study, Bjornestad and colleagues¹⁶⁶ identified that at 2-year follow up, individuals were classified into three remission classes: poor chance of remission, later remission, and early remission. Both the early remission and later remission classes were significantly predicted by baseline global functioning and premorbid academic functioning, however baseline age, attenuated psychosis symptoms, substance use, years of education, and sex were not significant predictors of remission.¹⁶⁶ Perhaps in the present study, delineation of academic and social premorbid functioning instead of total premorbid functioning in the development of baseline risk profiles may have better delineated remission from the other clinical statuses (symptomatic/progression or conversion) at 2-year follow up.

In analyses of non-conversion versus conversion at 2-year follow-up, those in the Lower-Risk class had significantly reduced odds of being in the conversion group compared to the Higher-Risk class for both models. This was consistent with available literature on latent classes in CHR representing similar levels of indicator variables. Stübke and colleagues¹⁶², in their 3-class solution of CHR risk factors, found that classes with the lowest symptoms, highest

functioning, and highest neurocognitive performance were associated with the lowest transition to psychosis rates, parallel findings to our Lower-Risk class in LCA-With GCI. The other available studies that explored latent classes and later transition to psychosis in CHR delineated dimensions of symptoms as part of class development, finding that variation in levels of positive, negative, or disorganized symptoms had distinct effects on conversion outcomes.^{110,164,165} In the development of latent classes in this study, attenuated psychosis symptoms were captured by a total score including all types of psychosis-risk symptoms, limiting the ability to explore effects on conversion by specific symptom type.

An updated umbrella review by Andreou and colleagues¹⁷⁴ demonstrated that the strongest meta-analytic evidence for predictors of conversion in 2 years supports the role of attenuated positive and negative symptoms, functioning, and deficits in verbal memory in a later conversion to psychosis. This study also cited significant but weak associations between childhood trauma, cannabis dependence, sex, age, living situation, disorganized symptoms, and certain electrophysiological markers and transition to psychosis.¹⁷⁴ These recent findings fortunately confirm appropriateness of indicator variables selected for analyses of our multi-dimensional latent classes, as well as relevance to 2-year conversion outcomes examined in this study. Our approach however provided insight into the interactive nature of these risk factors as a singular baseline profile of risk, reducing heterogeneity of the baseline sample and painting a holistic picture of 2-year risk for conversion.

Analyses in this study also demonstrated that both LCA-With GCI and LCA-Without GCI, covarying for age and education, were significant predictors of GAF at 2-year follow-up with both Lower-Risk classes being associated with increased odds of being in the higher functioning groups. No other studies to our knowledge that have employed latent analyses in

CHR to predict outcomes have reported on functional outcomes at follow-up specifically but rather have included baseline functioning as a selected indicator variable. Known independent predictors of functional outcome at 2-years in CHR are baseline neurocognition (verbal memory, verbal fluency, processing speed), baseline disorganized symptoms, baseline social functioning, and motor functioning, however these factors are deeply understudied in comparison to clinical outcomes.^{62,175} Elements of both LCA-With GCI and LCA-Without GCI shed new insight onto the role of additional factors such as childhood trauma, family history, premorbid functioning, adverse life events in the prediction of later functioning. Surprisingly, LCA-Without GCI more strongly predicted 2-year GAF (higher odds ratios, modest improvement in model fit) than LCA-With GCI, paradoxical findings based on the same neurocognitive domains in GCI (verbal learning, memory, processing speed) being cited as strong predictors of later functioning in the current literature.^{61,62,175}

The only covariates included in regressions of 2-year outcomes were sex, age, and years of education. Sex was not linearly associated with either CCS or GAF, which is generally consistent with a lack of consistent findings on the role of sex for either outcome.^{62,176} In analyses of 2-year GAF, older baseline age was associated with lower odds of being in the high functioning groups, whereas more years of baseline education was associated with higher odds of being in high functioning groups. Given that these variables were accounting for each other in analyses, it could mean that in this sample individuals who were older at baseline (and subsequently lower functioning at 2-years) may have had less years of education due to underlying academic functional decline at baseline, a common area where functional decline is observed in youth at CHR.¹⁷⁷ Additionally, perhaps those who had more years of education at baseline also had higher academic functioning at baseline which is a component of global

functioning, indicating a subgroup of people who had an education level commensurate with their age.

5.3. Early risk profiles and prediction of LTF (5-20 year) outcomes

For our second primary aim, we hypothesized that developed latent classes/risk profiles from the first aim would be predictive of 5-20-year outcomes at LTF among a subset of individuals from the parent studies who were recontacted and re-evaluated ($n=419$). Specifically, we hypothesized that the Higher-Risk classes would be predictive of psychotic conversion and low global functioning at LTF. Given the substantial follow-up period ($M=10.36$ years) in the LTF study, it was critical to include a more thorough collection of covariates in regression analyses of outcomes that may also have influenced long-term clinical status and functioning. In the few comparable long-term follow-up analyses of CHR in the literature, colleagues have included aspects of lifetime cannabis use, treatment history within the LTF period, years of education, and time to follow-up as important covariates given that these aspects appear to affect longitudinal outcomes within FEP studies.^{57,121} Analyses of CCS at LTF when CCS was defined by remission versus symptomatic/prodromal progression versus conversion demonstrated that baseline risk profile membership (LCA with and without GCI) was not a significant predictor of CCS, but rather critical covariates such as current cannabis use frequency, having engaged in at least one medication trial, and total years to follow-up were significant predictors of this outcome. In analyses where CCS delineated non-conversion versus conversion, LCA-With GCI predicted CCS only at trend-level significance, with trend-level patterns indicating that estimated membership in the Lower-Risk class was associated with a decreased odds of conversion at LTF. Again however, it was the critical covariates such as exposure to medication and years to LTF (cannabis use was not a covariate in these analyses) that were the strongest drivers of non-

conversion versus conversion.

These findings broadly suggested that multidimensional baseline profiles, capturing several domains of risk, may not be as robust regarding their predictive value of long-term clinical status when controlling for covariates that are more related to factors that occur within the long-term study period. Given that there are so few studies that have explored the role of baseline characteristics in the prediction of long-term outcomes in CHR, it is difficult to comment on whether these findings are consistent with the literature. Importantly however, of the few available LTF studies in CHR, some researchers have employed regression modeling to investigate these relationships.^{57,178} Beck and colleagues⁵⁷ followed a sample of 255 CHR subjects for an average of 4 years (range 0-16 years) and found, through regression analyses in a similar format to the present study, that only higher baseline psychosocial functioning was associated with remission at LTF. Baseline characteristics such as age, sex, positive and negative attenuated psychosis symptoms, and cannabis use were not associated with any long-term clinical outcome.⁵⁷ A recent study by Tognin and colleagues¹⁷⁸ fascinatingly found through multilevel logistic regression that specific types of adverse childhood experiences (ACES) were associated with different clinical outcomes at 5-year follow-up. In this study, investigators found that baseline physical abuse was associated with a reduced likelihood of remission, and that death of a parent was associated with an increased likelihood of conversion to psychosis, controlling for sex, age, race, IQ, and site.¹⁷⁸ Interestingly, these investigators also found that separation from a parent was associated with an increased likelihood of remission, hypothesizing that this could be due to removing a child from a negative home environment.¹⁷⁸ Evidence from this study again asserts that perhaps, when developing latent classes in CHR, delineating types of childhood trauma may lead to the elucidation of more specific classes but also may have a

stronger predictive value for long-term outcomes.

Collectively, this evidence supports what we were not able to confirm in the present LTF study, that specific baseline characteristics not only distinguish those still symptomatic from conversion at LTF, but that there are also baseline characteristics that are specifically associated with remission at LTF. A select few studies have specifically tried to better understand this remission group by only analyzing those who do not convert to psychosis at LTF. For example, Lin and colleagues¹⁷⁹ in 5-year follow-up sample of CHR found that females were less like to be in remission at LTF, and that meeting criteria at baseline for brief intermittent psychotic symptoms was associated with a lower risk of persistent attenuated psychosis symptoms at LTF. In the present study, we did not complete analyses for remission versus symptomatic/prodromal progression only, which may have elucidated whether baseline risk profiles differentiated the two groups.

The non-significant associations between baseline risk profiles and CCS at LTF in this study point to an important question regarding grouping individuals by shared risk factors versus examining independent variables' predictive value on long-term outcomes in CHR. No LTF studies in CHR to date, except for the present study, have used baseline latent classes involving multidimensional risk factors to predict long-term outcomes. The nature of varying levels of risk factors in predictive latent classes, while potentially a better real-world representation of the heterogeneity of CHR individuals at baseline, may dilute the strength of singular factors that are most predictive of later clinical outcome. Additionally, it is also possible that in this new terrain of long-term follow-up studies in CHR, participants have significantly changed and/or too much time has passed from baseline to follow-up and there is another critical time window in the illness course in which certain levels of risk factors are better statistical harbingers for later

clinical outcomes. It is plausible that given early risk profiles in this study appeared to be predictive of 2-year outcomes, specifically conversion, that there may be another conversion-risk period following the early phase of illness however it may be significantly before the long-term follow-up period (average of 10 years). Ideally, future studies that can follow individuals estimated to be in certain baseline risk profiles prospectively would utilize trajectory modeling with shorter follow-up periods within the LTF study window to observe changes in risk for certain clinical outcomes over time. This method would elucidate whether level of risk for certain outcomes plateaus over time based on one's estimated class membership.

Regarding the important covariates in analyses of LTF CCS, findings that those who displayed the most frequent cannabis use at LTF were also less likely to be in the remission of attenuated psychosis symptoms was largely consistent with known relationships between current cannabis use frequency and exacerbation of attenuated psychosis symptoms.²⁴ This use frequency did not appear to comprise increased risk for conversion at LTF, also consistent with the literature regarding a lack of a clear association between cannabis use and conversion to psychosis in CHR.²⁴ This covariate also tells us little about cannabis use behaviors across the LTF study period, however studies of cannabis use patterns in CHR suggest that predictors of current cannabis use patterns are, unsurprisingly, past cannabis use patterns, suggesting these current LTF patterns of use may have been sustained over the LTF study period.¹⁸⁰ In our analyses we also found that more time to LTF was associated with a decreased likelihood of being in the symptomatic/prodromal progression group compared to the remission group, indicating that more years to LTF was more closely related to remission status at LTF. In the context of our study, we hypothesize that perhaps these findings are indicative of individuals who may be easier to contact, especially following a long period of time since their original

participation. We further suggest that perhaps the ability to be contacted, especially in psychiatric populations, could be a proxy for higher functioning or less severe symptomatology as individuals are still connected with their primary contact method or family members who were able to get them reconnected to the study.

The additional finding that exposure to at least one psychiatric medication trial is associated with an increased risk of being in the conversion group at LTF was unsurprising; studies in CHR suggest that those who require medication intervention, specifically antipsychotic medication, at some point during illness course may be more likely to have a later diagnosis of psychosis.^{181,182} Researchers posit this may be a proxy variable for more severe symptoms or more resource utilization and may not be reflective of the overall efficacy of medication to treat attenuated psychosis symptoms.¹⁸¹ More precise studies have delineated individual efficacy of specific psychotropic medication for attenuated psychosis symptoms and comorbid conditions which shed light onto current scientific findings that common psychiatric medications such as benzodiazepine or low dose antipsychotics do little to prevent psychosis onset or treat CHR symptoms in isolation compared to a combined psychotherapy/psychiatry approach.¹⁸³ Critically in this study however we did not distinguish between types of psychiatric medication exposure.

Findings regarding global functioning via the GAF at LTF in this study were unexpected. Controlling for age, years of education, medication exposure in the LTF period, cumulative lifetime cannabis use, and total years of cannabis use, LCA-Without GCI was a significant predictor of LTF GAF. Being in the Class 2 or Higher-Risk class was associated with decreased odds of being in the higher functioning groups at LTF. While these findings are confirmatory to our hypotheses, it was unexpected that the latent classes without primary baseline measures of neurocognition (LCA-Without GCI), one of the most robust predictors of later functional status

in CHR,⁶² appeared to significantly predict LTF GAF when classes without primary baseline neurocognition did not (LCA-With GCI). One theory is that following a certain longitudinal follow-up time, neurocognitive deficits simply improve and no longer impact associated functional outcomes in CHR youth. Meta-analytic evidence of neurocognitive trajectories within the traditional 2-year study period in CHR suggests that while neurocognitive performance is variable among CHR youth over time, there is a general trend of deficits becoming less pronounced across time, and in some domains, substantial improvements occur in neurocognition naturalistically in this population.^{184,185} While this has not been demonstrated in long-term studies of CHR, it is possible that similar trends persist over time, especially among those who are at lower risk of converting to psychosis. Thus, it is possible that the classification of individuals as part of LCA-With GCI, in which individuals were distinguished based on neurocognitive performance at baseline, can be interpreted as arbitrary when comparing these profiles to long-term global functioning. Importantly, LCA-Without GCI still included baseline measures of premorbid functioning and IQ, which are also known predictors for later functional outcomes in CHR, and may be more stable early predictors of long-term functioning than global neurocognition which we understand changes substantially over time.⁶²

Other strong predictors of GAF at LTF were age and years of education at LTF, medication exposure in LTF period, cumulative lifetime cannabis use, and total years of cannabis use. Identical trends regarding age and years of education that were observed in analyses of 2-year follow up were repeated at LTF; individuals who were older at LTF had decreased odds of being in the higher functioning groups, and individuals who had more years of education at LTF had increased odds of being in the higher functioning groups. From a recovery-oriented framework, this trend was critical to replicate in the context of lifetime outcomes in CHR. As

will be discussed in the **Summary and Clinical Implications** portion of this section, engagement in education appears to be a protective factor for functional decline across the lifespan. It is also possible that the inverse is true, that individuals who are generally doing better clinically are more likely to engage in education. In studies of functioning in CHR youth, it is often challenging to ascertain the true impact of educational years on outcomes as many are younger and still in primary educational years or have taken substantial breaks in their academic journey due to emerging mental health concerns.^{177,186} It is possible that by LTF, we may be able to observe a more stable measure of years of education (despite gaps) given that participants are older and have had more opportunities to re-engage with education in the LTF study period.

Findings regarding cumulative lifetime cannabis use and total years of cannabis used at LTF underscore the unfolding mystery related to how cannabis use is paradoxically related to both higher and lower areas of functioning across the psychosis spectrum.^{51,52,93,100,102} Findings from the present study indicated that higher cumulative use of cannabis over the lifespan is associated with decreased odds of higher functioning at LTF, which is an important addition to limited evidence of long-term functional outcomes among CHR individuals who use cannabis. Based on the available evidence regarding the relationship between cannabis and functioning across the psychosis spectrum, the general consensus remains that among CHR populations cannabis use has marginally been associated with improved social functioning which is also observed in FEP populations,^{51,63,100} however in more progressed psychosis there is more evidence to support that frequent cannabis use is associated with global functional issues.²⁴ Importantly, no studies to our knowledge have compared cannabis use patterns across a LTF study period in CHR to later functional outcomes, limiting our understanding of whether these findings are consistent with other groups. As has been discussed previously, the present group

replicated previous findings in FEP that individuals with higher premorbid functioning also had higher social functioning, which in turn led to more moderate (but still consistent) cannabis use patterns.^{51,102} In the present study and leaning on this theoretical background, we hypothesize that perhaps the findings of more total years of cannabis use being associated with higher functioning are an example of how sustained cannabis use in isolation (not taking into account frequency or potency) could be a proxy for higher premorbid and social functioning. Essentially, perhaps those who can sustain cannabis use over time have a level of social functioning that allows them to obtain cannabis, potentially use at a moderate level, and maintain high functioning. More studies are needed which explore the interplay between cannabis use behaviors and functioning across a long-term period in CHR however to clarify these trends.

Lastly in analyses of GAF at LTF, we found that having at least one trial of psychiatric medication over the study period was associated with a significant reduction in the odds of being in the higher functioning groups. Similarly to findings regarding medication exposure and clinical outcomes in CHR, it has been widely reported that exposure to specifically antipsychotic medications is a “negative prognostic indicator” and has been associated with functional deficits at both baseline and follow-up.^{187,188}

5.4 Early risk profiles among individuals who converted to psychosis and prediction of lifetime diagnostic outcomes

Our third primary aim in this study was to investigate, among those who converted to psychosis across the entire study period ($n=69$), whether baseline risk profiles predicted either an affective or non-affective psychosis diagnosis at LTF. We hypothesized that individuals estimated to be in the Lower-Risk classes, who ultimately converted to psychosis, would be more likely to develop an affective psychosis diagnosis at LTF, covarying for factors known to

influence long-term illness course. As was discussed in the introduction, this hypothesis was also driven by findings that report individuals diagnosed with bipolar disorder with psychotic features and other mood disorders with psychosis tend to display better long-term global outcomes than individuals with schizophrenia diagnoses.^{74,79,89}

We found that controlling for sex, total years of cannabis used, duration of untreated psychosis (DUP), and a history of at least one period of engagement in psychotherapy, LCA-Without GCI was a trend-level significant predictor of an affective diagnosis at LTF. Small-scale studies in FEP have found that individuals who go on to develop an affective psychosis diagnosis were more likely to be female, had shorter durations of untreated psychosis, and demonstrated higher premorbid functioning and lower rates of substance use compared to those who go on to develop a non-affective psychosis diagnosis.^{76,77,79} Studies have also found that baseline mood instability and certain types of attenuated psychosis symptoms such as grandiosity and religious delusions, are also most predictive of an affective, however most are dependent on retrospective accounts of symptoms.⁷⁹ Unfortunately in the present study, we did not include any measures of baseline comorbid affective symptoms or specify by content of attenuated positive symptoms.

In the present study, we confirmed that some of these risk factors discussed in the literature were indeed consistent with those who developed an affective psychosis condition. In addition to the Lower-Risk class at trend-level (consisting of individuals estimated to have higher premorbid functioning and moderate cannabis use patterns) being more predictive of an affective course, females were more likely than males to develop an affective psychosis diagnosis at LTF. More total years of cannabis use was also associated with an affective psychosis diagnosis, again leading us to hypothesize that perhaps this variable is a distant proxy for intact social functioning given that no other aspects of cannabis use were related to this

outcome. Given that a longer DUP is typically correlated with a more severe outcome¹⁸⁹ and in some studies with a development of schizophrenia¹⁹⁰, it was surprising that DUP was not a significant predictor of diagnostic outcome in this study.

Interestingly, having been engaged with at least one period of psychotherapy was also predictive of an affective course. While the definition of psychotherapy was incredibly broad in this study and could have encapsulated supportive counseling, group therapy, psychodynamic intervention, dialectical behavioral therapy (DBT), and cognitive behavioral therapy (CBT), we hypothesize that engagement in psychotherapy could be an extension of higher functioning and better overall treatment adherence among those with an affective illness. This is reported in the literature in studies comparing treatment adherence between diagnostic subtypes in psychosis; while treatment adherence across the spectrum of affective to non-affective psychosis is a significant issue, individuals with a diagnosis of schizophrenia have higher rates of treatment non-adherence in comparison to individuals with affective psychosis diagnoses such as bipolar disorder or schizoaffective disorder.¹⁹¹ Typically individuals across the psychosis spectrum receive front-line treatment in the form of psychiatric intervention rather than psychotherapeutic intervention,¹⁹² leading us to hypothesize that perhaps those in this sample who received psychotherapy comprised a subgroup who were more engaged in treatment overall or more able to access secondary intervention.

The motivations to explore how baseline characteristics among converters may be predictive of long-term diagnosis were twofold in this study. First, little is known about collective baseline features of converters in CHR. The assessment of risk for conversion in this population is typically based on primary clinical, functional, and genetic factors such as severity of psychosis risk symptoms, level of functional decline, and genetic risk for psychosis.

Development of latent risk profiles in this study have elucidated that among those who eventually convert to psychosis, levels of baseline characteristics vary considerably and in our previous analyses we have outlined that certain profiles comprise a higher level of risk for conversion in general. Given that affective and non-affective psychoses are characterized by distinct clinical and functional sequelae, the relationship between certain baseline characteristics and the development of either diagnostic pathway elucidates early factors that may warrant specific intervention, which will be discussed further in the **Summary and Clinical Implications** section.

Our second motivation was due to a novel aspect of the LTF study design; many individuals who converted to psychosis during the parent studies received provisional diagnoses such as psychosis not otherwise specified (NOS), schizophreniform, or delusional disorders. It is widely understood that provisional diagnoses from the FEP period shift over time due to both changes in diagnostic accuracy and the naturalistic evolution of psychosis symptoms.^{75,79,182,193} In this study, trained clinical assessors across the LTF sites readministered extensive diagnostic assessment with participants, and through an intensive consensus process, reformulated diagnoses for all participants. This process allowed for the re-evaluation of predictors of conversion diagnoses even among those who converted in the original studies, subsequently refining understanding of how baseline characteristics may map onto authentic diagnostic subtypes in psychosis as they potentially transform over time or as diagnostic assessment improves.

5.5 Study Limitations and Future Directions

The present study had several important limitations to consider when interpreting findings. Firstly, there were several limitations specific to latent class approaches in general.

Risk profiles or latent classes developed as the primary aim of this study were inherently limited in their direct interpretation of the given sample, due to the fact that distinct classes do not represent actual membership to subgroups, but rather estimated membership to subgroups.^{147,194} It is important that the latent classes developed as part of this study are not automatically interpreted as literal subgroups within this sample, but rather as theoretical insights regarding trends/varying levels of risk factors within a heterogeneous population. As Lanza described in a review of LCA for developmental psychological research, latent classes can be thought of as a “heuristic” for further understanding trends within a diverse patient population. This can be problematic when inferring that similar latent subgroups may be present outside of this sample, in the broader CHR phenotype for example, as subgroups observed in this study could be representations of trends in the NAPLS1-3 studies only. This highlights the importance of repeating identical methodology for the purposes of replication in other samples. Given that the use of LCA is a burgeoning strategy in studies of CHR, projects that aim to replicate these and other findings should exercise caution to ensure they follow similar multi-step procedures of variable selection, missing data analyses, ensure they replicate models on complete and FIML estimated cases, and most importantly, publish these processes to build a foundation for best practices of latent analysis in psychosis populations.

There are also inherent limitations to interpreting latent classes in the context of clinical adaptability. Importantly, there is an assumption of conditional independence in LCA that difference among the levels of indicator variables is due to the latent class estimations only.¹⁹⁵ Given that indicator variables selected in this study to develop the latent risk profiles were hypothesized a priori based on existing literature regarding risk factors in CHR, it is possible that there are other indicator variables that could alter the composition of estimated classes, and it is

possible (if not likely) that factors outside of the latent class structures themselves could impact the association between variables. While we did our best to control for multicollinearity between indicator variables in this study, there is unclear guidance in the literature as to what degree of collinearity will impact the interpretation of the LCA parameters.^{147,195} It is possible in these regards that our threshold of $r=.7$ was too high and could have impacted the structure of classes and the interpretation of related variables. Additionally, although FIML has been shown to be a robust estimation method for managing missing data and is more reflective of the present sample given that it uses information from complete and missing cases, it may be a factor that influences reproducibility in other samples. Given that FIML is computationally demanding, studies that aim to replicate the findings of the present study should be consistent in use of statistical software packages and methodology of data presentation.¹⁴⁷

Regarding interpretation of latent classes in this study the labels of “lower and higher-risk” do not perfectly capture the clinical and functional phenotypes of the classes, which is a common challenge in the description of latent classes.^{147,194} In this study, this may have been due to the categorical structure of many of the selected indicator variables, specifically the continuous variables that were transformed to represent values via quantiles. “Higher and lower” levels of a specific variable in each class were interpreted by whether an estimated class had values in either the top two (50th, 75th) or bottom two (50th, 25th) quantiles of each variable. In many cases, both classes had comparable values in the middle quantile but had marginally larger proportion of values in the bottom or top quantiles, potentially indicating that nuance related to those who scored in the moderate levels of certain variables may be somewhat lost. Future projects that employ LCA within the NAPLS 1-3 dataset may consider transforming continuous variables into binary constructs of low and high scores, or even (where possible) test a mixed

variable approach with LPA to see if classes differ when continuous and categorical data can remain untransformed in the model. This strategy however is computationally difficult with inconsistent guidelines regarding model fit, and is typically more challenging to describe and interpret.¹⁹⁶ Overall, LCA is an exciting analytical approach to explore subgroups in heterogenous populations, however given its relative novelty in psychiatric populations and particularly among psychosis-risk groups, results should be interpreted with caution as well as from a theoretical perspective.

Second, there were important limitations related to regression analyses, covariates, and outcomes within this study. In this study we included three types of logistic regression analyses, ordinal, binomial, and multinomial logistic regressions. Both ordinal and binomial logistic regressions in the 2-year and LTF regressions were interpreted with proportional odds ratios and standard odds ratios respectively. Multinomial logistic regressions in this study however employed relative risk ratios to describe findings. It is important to emphasize that these measurements are not analogous to probabilities of an event occurring, which is a common misconception when interpreting these measures, and odds ratios should be interpreted slightly differently compared to relative risk ratios. Odds ratios in this study referred to the odds of being in the conversion group versus the non-conversion group as well as being in the low versus moderate versus high functioning groups. Relative-risk ratios in this study however calculated the probability of being all CCS groups (remission, symptomatic/prodromal progression, conversion) and then compared likelihood of being one group compared to the other based on this probability.^{197,198} Interpretation of relative risk-ratios in this study was more cumbersome than interpretation of odds ratios, given that this process required the constant comparison to the reference group (remission status). This drew attention to the potential limitations of the three-

level CCS outcome variable, given that comparisons between the symptomatic/progression group and remission group as well as the comparisons between the conversion group and remission group did not provide much insight on the remission group itself. Future studies may want to change the order of the reference group for CCS to learn more about relative-risk of this outcome or perhaps reconsider this variable altogether. Analyses of conversion versus non-conversion were more statistically robust given that latent class membership was generally a significant predictor of this outcome, specifically at 2-year follow-up.

Lastly, regarding regression analyses, the exploratory binomial logistic regressions employed in aim three of this study should be interpreted with caution given the notably small sample size ($n=66$). While there is no written rule regarding minimum sample size for binomial logistic regressions, smaller sample sizes will lead to significantly underpowered results as was the case in these analyses.¹⁹⁹ Power estimates in this study suggested that a sample size of closer to 270 would lead to a power estimate of .80, indicating that trends observed must be re-evaluated in a larger sample of converters. Given that the broader LTF study is still ongoing, it's likely that more individuals who converted to psychosis will be recruited and these analyses can be re-performed.

In analyses of 2-year outcomes, selection of covariates was limited to age, sex, and years of education. Our motivation for reducing the included covariates in these analyses was to prioritize using these analyses as “test” models to evaluate whether baseline risk profiles were linearly related to identical outcomes that would be tested at LTF. It is possible that other important covariates such as exposure to medication, psychotherapy, and comorbid substance use may be important factors that could influence short-term outcomes controlling for estimated risk profile membership. Similarly, covariates included in analyses of LTF were not exhaustive

regarding factors that may have impacted long-term outcomes and were heavily reliant on retrospective accounts over extended time periods. Although we were able to corroborate testimony with medical records and informant accounts in some cases, these assessments of treatment history, previous substance use, reporting of symptoms for diagnostic assessment, and information regarding duration of untreated illness (among converters) were all heavily subject to self-report and recall bias.

5.6 Summary and Clinical Implications

Collectively, findings from this study confirmed that distinct risk profiles are present in CHR based on gradation of levels of diverse risk factors, and that these baseline risk profiles influenced 2-year clinical and functional outcomes as well as 5-20-year functional outcome. Results of this study, which utilized a novel approach to understanding overlapping risk factors in CHR and their effect on short and long-term (5-20 year) illness course, not only serve to increase scientific understanding regarding the heterogeneity of prodromal psychosis but also inform how we can direct knowledge of risk profiles towards improving early intervention strategies.

It is not a novel concept in the clinical care of CHR youth that certain individuals have different levels of risk factors. Once an individual is deemed at CHR for psychosis, it is the core component of case conceptualization and treatment planning to establish potential baseline factors that may put someone at increased risk for psychosis, focusing on family history for psychosis, substance use, and changes in academic and social functioning. What can be challenging however when multiple risk factors are present is to identify specific overlapping areas where intervention is needed and most effective, where certain strengths should be emphasized, and how we can communicate level of risk to patients leaning on evidence-based

information. Although latent risk profiles developed as part of this study are estimations of theoretical trends within a particular sample and have not been further evaluated in a clinical care setting, the idea of developing dimensional approaches to risk identification and treatment in CHR is considered gold-standard of care for this heterogenous population that often requires multiple levels of intervention. Given findings that individuals estimated to be in the Lower-Risk Class (with and without GCI), for example, have reduced odds of developing psychosis and have higher functioning by 2-year follow-up, it could be clinically advantageous during the initial screening process to “designate” participants to either class based on their responses to risk categories as an early phase of treatment planning. One can imagine a checklist approach at baseline, in which subjects are clinically classified as being in the Higher or Lower-Risk class through a holistic screening process (**Figure 11**).

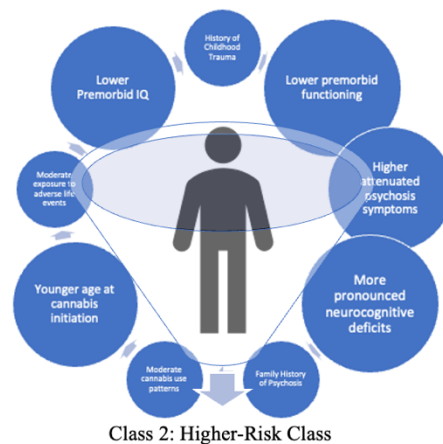


Figure 11: Holistic Screening Model for LCA-With GCI

Expanding on the psychosis-risk calculator from the parent studies¹⁷, which produced a total “risk score”, these latent classes instead provide critical information on subtypes of CHR youth who may have moderate exposure to one risk factor while having high exposure to another

related risk factor. Considering the interaction between baseline risk factors, treatment planning should involve a discussion of this co-occurrence and should emphasize psychoeducation and integrated evidence-based interventions. From a patient-centered perspective, use of latent risk profiles to improve precision of early intervention could follow a stepped-model, prioritizing the most distressing or impactful aspect of a patient's risk profile and addressing other areas of risk simultaneously or in successive format.

For example, referencing the LCA-Without GCI model, endorsement of childhood trauma at baseline could indicate that a trauma-informed cognitive behavioral therapy such as cognitive processing therapy (CPT) may be appropriate to address cognitive distortions stemming from trauma and simultaneously teach skills to manage thoughts and experiences related to attenuated psychosis symptoms, drawing from elements of cognitive behavioral therapy for psychosis (CBT-p).¹¹⁸ In this approach, information from latent risk profiles considers that this individual may also have had compounded exposure to adverse life experiences following childhood, important information for application of therapeutic skills to recent life events. Membership to the Higher-Risk class in this model would suggest that this individual may be at increased risk for an earlier initiation of cannabis use as well as moderate to frequent cannabis use patterns if cannabis has not already been initiated. From a trauma-informed lens, this information can assist in providing tangible examples in cognitive therapy of maladaptive coping and avoidance strategies involving substance use. Additionally, when coupled with psychoeducation regarding the interplay between trauma, cannabis use, and attenuated psychosis symptoms, more informed wellness and relapse prevention plans can be developed. In clinical applications of the LCA-With GCI model, perhaps individuals estimated to be in the Higher-Risk class may benefit from cognitive remediation strategies within the first 2-

years to improve functional outcomes, however findings from the present study suggest that neurocognitive deficits observed in the early course of illness may not have much relevance to long-term (5-20 year) functional outcomes, so the impact of cognitive remediation interventions in CHR beyond this early period remains to be determined.

Early risk profiles may also highlight areas of resilience in CHR subtypes that would be important to emphasize in clinical care. While the opposite of a risk factor is not inherently a resilience factor²⁰⁰, information from variables comprising the Lower-Risk classes in both models and their relationship to outcomes could inform how potentially modifiable influences may shield someone from the negative effects of a risk-factor over time. For example, given that across models in this study the Lower-Risk class was defined by better premorbid functioning and older age of cannabis initiation, clinicians can work to ascertain what were the components of better premorbid functioning (e.g. family networks, psychosocial support from peers, higher engagement in school due to close relationships with educators) and (for those who endorsed trying cannabis) what led them to delay onset of initiation (e.g. peer-to-peer support regarding substance use, negative view of substance use, strong emotion regulation skills). This information can be used to bolster intervention across the short and/or long-term span of illness.

In short, information from early risk profiles can serve to improve the individualized integrated treatment model that is emerging as the standard of care for not only CHR youth but for youth with a wide range of emerging psychiatric concerns.²⁰¹ Importantly, individuals estimated to be in the Lower and Higher risk groups can equally benefit from early intervention services however class membership may indicate those with more immediate needs and/or more acute presentations.

It is also critical to discuss the implications of early risk profiles and covariates on

specific types of outcomes in this study. Across the initial 2-year study period, class membership revealed important baseline predictors of clinical and functional status, in addition to the effects of age and years of education at baseline. Findings that the Higher-Risk classes were associated with higher odds of conversion to psychosis as well as lower functioning at 2-years indicated that interventions addressing clinical symptoms and functional recovery are important even in the short-term, regardless of whether individuals transition to a psychotic disorder. This is well-reported in the literature in established psychosis, as recovery-oriented frameworks that emphasize restoration of academic and social functioning are a hallmark of coordinated specialty care (CSC) programs dedicated to early psychosis treatment in the United States.²⁰² Importantly, one area for improvement for early intervention in CHR is the development of standardized evidence based interventions for substance use, particularly cannabis use. As was outlined in a recent review by this author²⁰³, cannabis initiation and use in early psychosis groups is heavily influenced by peer attitudes towards substance use, and there is a dearth of established cannabis use interventions for youth at risk for mental health concerns. This author proposed that peer-based interventions for cannabis use and initiation may be an important next frontier to address high rates of use in CHR and early age of initiation, a factor shown in the present study to be associated with poorer outcomes across the lifespan.²⁰³

Perhaps the most compelling findings from this study, given the unprecedented opportunity to explore 5-20 year outcomes in CHR, were that certain baseline risk profiles predicted long-term functional outcomes. In this study, individuals in the Higher-Risk class at baseline had lower global functioning at long-term follow-up, potentially speaking to the enduring impact of functional deficits prior to and throughout the duration of one's illness. Coupled with the findings that heavy lifetime cannabis use and exposure to psychiatric

medication were also associated with poorer long-term global functioning, and that years of education was inversely associated with functioning, these results appear to strengthen the argument for recovery-oriented intervention across the lifespan for CHR individuals.

There is often an overemphasis in clinical care on symptom reduction and an underemphasis on long-term functional or cognitive intervention for psychiatric populations.²⁰⁴ Findings from the present study underscore the persistence of functional issues in prodromal psychosis far beyond the early illness period, and as robust evidence in psychosis spectrum populations demonstrates, functional deficits reduce the likelihood of recovery, contribute to the maintenance of social fragmentation and isolation, are associated with poorer quality of life, and are also associated with increased resource utilization and burden on individuals and care systems.^{205,206} While the recovery-oriented framework in psychosis has been widely studied and implemented for first-episode and more progressed psychotic disorders^{202,204,207}, it has not been widely evaluated through randomized controlled trials in the CHR context. The emphasis of this treatment orientation on functional recovery through peer and community engagement, group and individual psychotherapy, goal-setting, social-skills training, cognitive rehabilitation, and family engagement may serve to address and potentially prevent chronic functional issues even among youth with subthreshold psychosis.²⁰⁴ Early risk profiles from this study offer insight into a potential time window for functional intervention specifically, now bolstered by lifetime evidence of a link between baseline and long-term global functioning.

REFERENCES

1. Kadakia, A., Catillon, M., Fan, Q., Williams, G. R., Marden, J. R., Anderson, A., Kirson, N., & Dembek, C. (2022). The Economic Burden of Schizophrenia in the United States. *The Journal of Clinical Psychiatry*, 83(6), 43278. <https://doi.org/10.4088/JCP.22m14458>
2. Fusar-Poli, P., McGorry, P. D., & Kane, J. M. (2017). Improving outcomes of first-episode psychosis: An overview. *World Psychiatry*, 16(3), 251–265. <https://doi.org/10.1002/wps.20446>
3. Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L. J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., ... Yung, A. (2013). The psychosis high-risk state: A comprehensive state-of-the-art review. *JAMA Psychiatry*, 70(1), 107–120. <https://doi.org/10.1001/jamapsychiatry.2013.269>
4. Caballero, N., Machiraju, S., Diomino, A., Kennedy, L., Kadivar, A., & Cadenhead, K. S. (2023). Recent Updates on Predicting Conversion in Youth at Clinical High Risk for Psychosis. *Current Psychiatry Reports*. <https://doi.org/10.1007/s11920-023-01456-2>
5. McGlashan, T. H., Walsh, B., & Woods, S. W. (2010). *The Psychosis-risk Syndrome: Handbook for Diagnosis and Follow-Up*. Oxford University Press.
6. Cornblatt, B. A., Lencz, T., Smith, C. W., Correll, C. U., Auther, A. M., & Nakayama, E. (2003). The Schizophrenia Prodrome Revisited: A Neurodevelopmental Perspective. *Schizophrenia Bulletin*, 29(4), 633–651. <https://doi.org/10.1093/oxfordjournals.schbul.a007036>
7. Fusar-Poli, P., Bonoldi, I., Yung, A. R., Borgwardt, S., Kempton, M. J., Valmaggia, L., Barale, F., Caverzasi, E., & McGuire, P. (2012). Predicting Psychosis: Meta-analysis of Transition Outcomes in Individuals at High Clinical Risk. *Archives of General Psychiatry*, 69(3), 220–229. <https://doi.org/10.1001/archgenpsychiatry.2011.1472>
8. Salazar de Pablo, G., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., Soardo, L., Cabras, A., Fortea, L., Catalan, A., Vaquerizo-Serrano, J., Coronelli, F., Kaur, S., Da Silva, J., Shin, J. I., Solmi, M., Brondino, N., Politi, P., McGuire, P., & Fusar-Poli, P. (2021). Probability of Transition to Psychosis in Individuals at Clinical High Risk: An Updated Meta-analysis. *JAMA Psychiatry*, 78(9), 970–978. <https://doi.org/10.1001/jamapsychiatry.2021.0830>
9. Fusar-Poli, P., Salazar de Pablo, G., Correll, C. U., Meyer-Lindenberg, A., Millan, M. J., Borgwardt, S., Galderisi, S., Bechdolf, A., Pfennig, A., Kessing, L. V., van Amelsvoort, T., Nieman, D. H., Domschke, K., Krebs, M.-O., Koutsouleris, N., McGuire, P., Do, K. Q., & Arango, C. (2020). Prevention of Psychosis: Advances in Detection, Prognosis, and

- Intervention. *JAMA Psychiatry*, 77(7), 755–765.
<https://doi.org/10.1001/jamapsychiatry.2019.4779>
10. Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M., Walker, E. F., Woods, S. W., Heinssen, R., & for the NAPLS group. (2007). North American Prodrome Longitudinal Study: A Collaborative Multisite Approach to Prodromal Schizophrenia Research. *Schizophrenia Bulletin*, 33(3), 665–672. <https://doi.org/10.1093/schbul/sbl075>
 11. Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., Seidman, L. J., Perkins, D., Tsuang, M., McGlashan, T., & Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: A multisite longitudinal study in North America. *Archives of General Psychiatry*, 65(1), 28–37.
<https://doi.org/10.1001/archgenpsychiatry.2007.3>
 12. Addington, J., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Addington, J. A., & Cannon, T. D. (2012). North American Prodrome Longitudinal Study (NAPLS 2): Overview and recruitment. *Schizophrenia Research*, 142(1–3), 77–82.
<https://doi.org/10.1016/j.schres.2012.09.012>
 13. Addington, J., Farris, M., Stowkowy, J., Santesteban-Echarri, O., Metzack, P., & Kalathil, M. S. (2019). Predictors of Transition to Psychosis in Individuals at Clinical High Risk. *Current Psychiatry Reports*, 21(6), 39. <https://doi.org/10.1007/s11920-019-1027-y>
 14. Coughlan, H., & Cannon, M. (2017). Does childhood trauma play a role in the aetiology of psychosis? A review of recent evidence. *BJPsych Advances*, 23(5), 307–315.
<https://doi.org/10.1192/apt.bp.116.015891>
 15. Kraan, T., Velthorst, E., Smit, F., de Haan, L., & van der Gaag, M. (2015). Trauma and recent life events in individuals at ultra high risk for psychosis: Review and meta-analysis. *Schizophrenia Research*, 161(2), 143–149.
<https://doi.org/10.1016/j.schres.2014.11.026>
 16. Kline, E. R., Ferrara, M., Li, F., D’Souza, D. C., Keshavan, M., & Srihari, V. H. (2022). Timing of cannabis exposure relative to prodrome and psychosis onset in a community-based first episode psychosis sample. *Journal of Psychiatric Research*, 147, 248–253.
<https://doi.org/10.1016/j.jpsychires.2022.01.039>
 17. Cannon, T. D., Yu, C., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Heinssen, R., Jeffries, C. D., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Kattan, M. (2016). An Individualized Risk Calculator for Research in Prodromal Psychosis. *The American Journal of Psychiatry*, 173(10), 980–988. <https://doi.org/10.1176/appi.ajp.2016.15070890>

18. Holtzman, C. W., Shapiro, D. I., Trotman, H. D., & Walker, E. F. (2012). Stress and the prodromal phase of psychosis. *Current Pharmaceutical Design*, 18(4), 527–533. <https://doi.org/10.2174/138161212799316280>
19. Sullivan, P. F. (2005). The Genetics of Schizophrenia. *PLoS Medicine*, 2(7), e212. <https://doi.org/10.1371/journal.pmed.0020212>
20. Addington, J., Liu, L., Buchy, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Bearden, C. E., Mathalon, D. H., & McGlashan, T. H. (2015). North American Prodrome Longitudinal Study (NAPLS 2): The Prodromal Symptoms. *The Journal of Nervous and Mental Disease*, 203(5), 328–335. <https://doi.org/10.1097/NMD.0000000000000290>
21. Carrión, R. E., Cornblatt, B. A., Burton, C. Z., Tso, I. F., Auther, A. M., Adelsheim, S., Calkins, R., Carter, C. S., Niendam, T., Sale, T. G., Taylor, S. F., & McFarlane, W. R. (2016). Personalized Prediction of Psychosis: External Validation of the NAPLS-2 Psychosis Risk Calculator With the EDIPPP Project. *The American Journal of Psychiatry*, 173(10), 989–996. <https://doi.org/10.1176/appi.ajp.2016.15121565>
22. Fusar-Poli, P., Rutigliano, G., Stahl, D., Davies, C., Bonoldi, I., Reilly, T., & McGuire, P. (2017). Development and Validation of a Clinically Based Risk Calculator for the Transdiagnostic Prediction of Psychosis. *JAMA Psychiatry*, 74(5), 493–500. <https://doi.org/10.1001/jamapsychiatry.2017.0284>
23. Oliver, D., Wong, C. M. J., Bøg, M., Jönsson, L., Kinon, B. J., Wehnert, A., Jørgensen, K. T., Irving, J., Stahl, D., McGuire, P., Raket, L. L., & Fusar-Poli, P. (2020). Transdiagnostic individualized clinically-based risk calculator for the automatic detection of individuals at-risk and the prediction of psychosis: External replication in 2,430,333 US patients. *Translational Psychiatry*, 10(1), 1–10. <https://doi.org/10.1038/s41398-020-01032-9>
24. West, M. L., & Sharif, S. (2023). Cannabis and Psychosis. *Child and Adolescent Psychiatric Clinics of North America*, 32(1), 69–83. <https://doi.org/10.1016/j.chc.2022.07.004>
25. Farris, M. S., Shakeel, M. K., & Addington, J. (2020). Cannabis use in individuals at clinical high-risk for psychosis: A comprehensive review. *Social Psychiatry and Psychiatric Epidemiology*, 55(5), 527–537. <https://doi.org/10.1007/s00127-019-01810-x>
26. Sideli, L., Quigley, H., La Cascia, C., & Murray, R. M. (2020). Cannabis Use and the Risk for Psychosis and Affective Disorders. *Journal of Dual Diagnosis*, 16(1), 22–42. <https://doi.org/10.1080/15504263.2019.1674991>
27. Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H. K., Berg, D. van den, Haan, L. de, & Gaag, M. van der. (2016). Cannabis use and transition to psychosis in individuals at ultra-high risk: Review and meta-analysis. *Psychological Medicine*, 46(4), 673–681. <https://doi.org/10.1017/S0033291715002329>

28. Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia Bulletin*, 42(5), 1262–1269. <https://doi.org/10.1093/schbul/sbw003>
29. van der Meer, F. J., Velthorst, E., Meijer, C. J., Machielsen, M. W. J., & de Haan, L. (2012). Cannabis use in patients at clinical high risk of psychosis: Impact on prodromal symptoms and transition to psychosis. *Current Pharmaceutical Design*, 18(32), 5036–5044. <https://doi.org/10.2174/138161212802884762>
30. Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., Marconi, A., La Cascia, C., Reis Marques, T., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A. S., Morgan, C., Stahl, D., ... Murray, R. M. (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin*, 40(6), 1509–1517. <https://doi.org/10.1093/schbul/sbt181>
31. Kristensen, K., & Cadenhead, K. S. (2007). Cannabis abuse and risk for psychosis in a prodromal sample. *Psychiatry Research*, 151(1), 151–154. <https://doi.org/10.1016/j.psychres.2006.10.001>
32. Valmaggia, L. R., Day, F. L., Jones, C., Bissoli, S., Pugh, C., Hall, D., Bhattacharyya, S., Howes, O., Stone, J., Fusar-Poli, P., Byrne, M., & McGuire, P. K. (2014). Cannabis use and transition to psychosis in people at ultra-high risk. *Psychological Medicine*, 44(12), 2503–2512. <https://doi.org/10.1017/S0033291714000117>
33. van der Steur, S. J., Batalla, A., & Bossong, M. G. (2020). Factors Moderating the Association between Cannabis Use and Psychosis Risk: A Systematic Review. *Brain Sciences*, 10(2), Article 2. <https://doi.org/10.3390/brainsci10020097>
34. Amir, C. M., Kapler, S., Hoftman, G., Kushan, L., Zinberg, J., Cadenhead, K. S., Kennedy, L., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., Perkins, D. O., Stone, W., Tsuang, M. T., Walker, E. F., Woods, S. W., Cannon, T. D., Addington, J., & Bearden, C. E. (2022). *Substance use in youth at genetic and clinical high risk for psychosis* (p. 2022.12.01.22282991). medRxiv. <https://doi.org/10.1101/2022.12.01.22282991>
35. Addington, J., Case, N., Saleem, M. M., Auther, A. M., Cornblatt, B. A., & Cadenhead, K. S. (2014). Substance use in clinical high risk for psychosis: A review of the literature. *Early Intervention in Psychiatry*, 8(2), 104–112. <https://doi.org/10.1111/eip.12100>
36. Auther, A. M., McLaughlin, D., Carrión, R. E., Nagachandran, P., Correll, C. U., & Cornblatt, B. A. (2012). Prospective study of cannabis use in adolescents at clinical high risk for psychosis: Impact on conversion to psychosis and functional outcome. *Psychological Medicine*, 42(12), 2485–2497. <https://doi.org/10.1017/S0033291712000803>

37. Buchy, L., Perkins, D., Woods, S. W., Liu, L., & Addington, J. (2014). Impact of substance use on conversion to psychosis in youth at clinical high risk of psychosis. *Schizophrenia Research*, 156(2), 277–280. <https://doi.org/10.1016/j.schres.2014.04.021>
38. Carney, R., Cotter, J., Firth, J., Bradshaw, T., & Yung, A. R. (2017). Cannabis use and symptom severity in individuals at ultra high risk for psychosis: A meta-analysis. *Acta Psychiatrica Scandinavica*, 136(1), 5–15. <https://doi.org/10.1111/acps.12699>
39. Phillips, L. J., Curry, C., Yung, A. R., Yuen, H. P., Adlard, S., & McGorry, P. D. (2002). Cannabis use is not associated with the development of psychosis in an ‘ultra’ high-risk group. *Australian and New Zealand Journal of Psychiatry*, 36(6), 800–806. <https://doi.org/10.1046/j.1440-1614.2002.01089.x>
40. Santesteban-Echarri, O., Liu, L., Miller, M., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Stone, W. S., Tsuang, M. T., Walker, E. F., Woods, S. W., & Addington, J. (2022). Cannabis use and attenuated positive and negative symptoms in youth at clinical high risk for psychosis. *Schizophrenia Research*, 248, 114–121. <https://doi.org/10.1016/j.schres.2022.08.005>
41. Ganesh, S., & D’Souza, D. C. (2022). Cannabis and Psychosis: Recent Epidemiological Findings Continuing the “Causality Debate.” *American Journal of Psychiatry*, 179(1), 8–10. <https://doi.org/10.1176/appi.ajp.2021.21111126>
42. Bagot, K. S., Milin, R., & Kaminer, Y. (2015). Adolescent Initiation of Cannabis use and Early-Onset Psychosis. *Substance Abuse*, 36(4), 524–533. <https://doi.org/10.1080/08897077.2014.995332>
43. Kiburi, S. K., Molebatsi, K., Ntlantsana, V., & Lynskey, M. T. (2021). Cannabis use in adolescence and risk of psychosis: Are there factors that moderate this relationship? A systematic review and meta-analysis. *Substance Abuse*, 42(4), 527–542. <https://doi.org/10.1080/08897077.2021.1876200>
44. Colizzi, M., & Murray, R. (2018). Cannabis and psychosis: What do we know and what should we do? *The British Journal of Psychiatry: The Journal of Mental Science*, 212(4), 195–196. <https://doi.org/10.1192/bjp.2018.1>
45. D’Souza, D. C., Radhakrishnan, R., Sherif, M., Cortes-Briones, J., Cahill, J., Gupta, S., Skosnik, P. D., & Ranganathan, M. (2016). Cannabinoids and Psychosis. *Current Pharmaceutical Design*, 22(42), 6380–6391. <https://doi.org/10.2174/1381612822666160826105628>
46. Devoe, D. J., Braun, A., Seredynski, T., & Addington, J. (2020). Negative Symptoms and Functioning in Youth at Risk of Psychosis: A Systematic Review and Meta-Analysis. *Harvard Review of Psychiatry*, 28(6), 341–355. <https://doi.org/10.1097/HRP.0000000000000273>

47. Fusar-Poli, P., Carpenter, W. T., Woods, S. W., & McGlashan, T. H. (2014). Attenuated psychosis syndrome: Ready for DSM-5.1? *Annual Review of Clinical Psychology*, 10, 155–192. <https://doi.org/10.1146/annurev-clinpsy-032813-153645>
48. Waford, R. N., MacDonald, A., Goines, K., Novacek, D. M., Trotman, H. D., Elaine F., W., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R., Mathalon, D. H., Tsuang, M. T., Perkins, D. O., Seidman, L. J., Woods, S. W., & McGlashan, T. H. (2015). Demographic correlates of attenuated positive psychotic symptoms. *Schizophrenia Research*, 166(1), 31–36. <https://doi.org/10.1016/j.schres.2015.04.035>
49. Falukozi, E., & Addington, J. (2012). Impact of Trauma on Attenuated Psychotic Symptoms. *Psychosis*, 4(3), 203–212. <https://doi.org/10.1080/17522439.2011.62686712>
50. Nieman, D. H., Dragt, S., van Duin, E. D. A., Denneman, N., Overbeek, J. M., de Haan, L., Rietdijk, J., Ising, H. K., Klaassen, R. M. C., van Amelsvoort, T., Wunderink, L., van der Gaag, M., & Linszen, D. H. (2016). COMT Val158Met genotype and cannabis use in people with an At Risk Mental State for psychosis: Exploring Gene x Environment interactions. *Schizophrenia Research*, 174(1), 24–28. <https://doi.org/10.1016/j.schres.2016.03.015>
51. Kennedy, L., Ku, B., Addington, J., Amir, C., Bearden, C. E., Cannon, T., Carrión, R., Cornblatt, B. A., Keshavan, M. S., Perkins, D. O., Stone, W., Walker, E., Woods, S. W., & Cadenhead, K. S. (2023). *Cannabis-Use Frequency and Associated Neurocognition Among Youth at Clinical High-Risk (CHR) for Psychosis: Emergence of a Distinct Subgroup Predicted by Premorbid Functioning* (SSRN Scholarly Paper No. 4570266). <https://doi.org/10.2139/ssrn.4570266>
52. Carrión, R. E., Auther, A. M., McLaughlin, D., Adelsheim, S., Burton, C. Z., Carter, C. S., Niendam, T., Ragland, J. D., Sale, T. G., Taylor, S. F., Tso, I. F., McFarlane, W. R., & Cornblatt, B. A. (2023). Recreational Cannabis Use Over Time in Individuals at Clinical High Risk for Psychosis: Lack of Associations with Symptom, Neurocognitive, Functioning, and TreatmentPatterns. *Psychiatry Research*, 115420. <https://doi.org/10.1016/j.psychres.2023.115420>
53. Gill, K. E., Poe, L., Azimov, N., Ben-David, S., Vadhan, N. P., Girgis, R., Moore, H., Cressman, V., & Corcoran, C. M. (2015). Reasons for cannabis use among youths at ultra high risk for psychosis. *Early Intervention in Psychiatry*, 9(3), 207–210. <https://doi.org/10.1111/eip.12112>
54. Mizrahi, R., Kenk, M., Suridjan, I., Boileau, I., George, T. P., McKenzie, K., Wilson, A. A., Houle, S., & Rusjan, P. (2014). Stress-induced dopamine response in subjects at clinical high risk for schizophrenia with and without concurrent cannabis use. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 39(6), 1479–1489. <https://doi.org/10.1038/npp.2013.347>

55. McHugh, M. J., McGorry, P. D., Yung, A. R., Lin, A., Wood, S. J., Hartmann, J. A., & Nelson, B. (2017). Cannabis-induced attenuated psychotic symptoms: Implications for prognosis in young people at ultra-high risk for psychosis. *Psychological Medicine*, 47(4), 616–626. <https://doi.org/10.1017/S0033291716002671>
56. Dragt, S., Nieman, D. H., Becker, H. E., van de Fliert, R., Dingemans, P. M., de Haan, L., van Amelsvoort, T. A., & Linszen, D. H. (2010). Age of onset of cannabis use is associated with age of onset of high-risk symptoms for psychosis. *Canadian Journal of Psychiatry. Revue Canadienne De Psychiatrie*, 55(3), 165–171. <https://doi.org/10.1177/070674371005500308>
57. Beck, K., Studerus, E., Andreou, C., Egloff, L., Leanza, L., Simon, A. E., Borgwardt, S., & Riecher-Rössler, A. (2019). Clinical and functional ultra-long-term outcome of patients with a clinical high risk (CHR) for psychosis. *European Psychiatry*, 62, 30–37. <https://doi.org/10.1016/j.eurpsy.2019.08.005>
58. Fulford, D., Niendam, T. A., Floyd, E. G., Carter, C. S., Mathalon, D. H., Vinogradov, S., Stuart, B. K., & Loewy, R. L. (2013). Symptom Dimensions and Functional Impairment in Early Psychosis: More to the Story than Just Negative Symptoms. *Schizophrenia Research*, 147(1), 125–131. <https://doi.org/10.1016/j.schres.2013.03.024>
59. Mensi, M. M., Orlandi, M., Casini, E., Catalan, A., de Pablo, G. S., Fusar-Poli, P., & Borgatti, R. (2023). Neurocognition and functioning in adolescents at clinical high risk for psychosis. *Child and Adolescent Psychiatry and Mental Health*, 17(1), 22. <https://doi.org/10.1186/s13034-023-00567-1>
60. Squarcina, L., Kambeitz-Ilankovic, L., Bonivento, C., Prunas, C., Oldani, L., Wenzel, J., Ruef, A., Dwyer, D., Ferro, A., Borgwardt, S., Kambeitz, J., Lichtenstein, T. K., Meisenzahl, E., Pantelis, C., Rosen, M., Upthegrove, R., Antonucci, L. A., Bertolino, A., Lencer, R., ... PRONIA consortium. (2022). Relationships between global functioning and neuropsychological predictors in subjects at high risk of psychosis or with a recent onset of depression. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, 23(8), 573–581. <https://doi.org/10.1080/15622975.2021.2014955>
61. Bolt, L. K., Amminger, G. P., Farhall, J., McGorry, P. D., Nelson, B., Markulev, C., Yuen, H. P., Schäfer, M. R., Mossaheb, N., Schlögelhofer, M., Smesny, S., Hickie, I. B., Berger, G. E., Chen, E. Y. H., de Haan, L., Nieman, D. H., Nordentoft, M., Riecher-Rössler, A., Verma, S., ... Allott, K. A. (2019). Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: Findings from the NEURAPRO randomized clinical trial. *Schizophrenia Research*, 206, 67–74. <https://doi.org/10.1016/j.schres.2018.12.013>

62. Carrión, R. E., McLaughlin, D., Goldberg, T. E., Auther, A. M., Olsen, R. H., Olvet, D. M., Correll, C. U., & Cornblatt, B. A. (2013). Prediction of Functional Outcome in Individuals at Clinical High Risk for Psychosis. *JAMA Psychiatry*, 70(11), 1133–1142. <https://doi.org/10.1001/jamapsychiatry.2013.1909>
63. Ferraro, L., La Cascia, C., Quattrone, D., Sideli, L., Matranga, D., Capuccio, V., Tripoli, G., Gayer-Anderson, C., Morgan, C., Sami, M. B., Sham, P., De Haan, L., Velthorst, E., Jongsma, H. E., Kirkbride, J. B., Rutten, B. P. F., Richards, A. L., Roldan, L., Arango, C., ... Di Forti, M. (2020). Premorbid Adjustment and IQ in Patients with First-Episode Psychosis: A Multisite Case-Control Study of Their Relationship with Cannabis Use. *Schizophrenia Bulletin*, 46(3), 517–529. <https://doi.org/10.1093/schbul/sbz077>
64. Compton, M. T., Broussard, B., Ramsay, C. E., & Stewart, T. (2011). Pre-illness cannabis use and the early course of nonaffective psychotic disorders: Associations with premorbid functioning, the prodrome, and mode of onset of psychosis. *Schizophrenia Research*, 126(1–3), 71–76. <https://doi.org/10.1016/j.schres.2010.10.005>
65. Zisook, S., Heaton, R., Moranville, J., Kuck, J., Jernigan, T., & Braff, D. (1992). Past substance abuse and clinical course of schizophrenia. *The American Journal of Psychiatry*, 149(4), 552–553. <https://doi.org/10.1176/ajp.149.4.552>
66. Lyngberg, K., Buchy, L., Liu, L., Perkins, D., Woods, S., & Addington, J. (2015). Patterns of premorbid functioning in individuals at clinical high risk of psychosis. *Schizophrenia Research*, 169(1), 209–213. <https://doi.org/10.1016/j.schres.2015.11.004>
67. Lepage, M., Bodnar, M., & Bowie, C. R. (2014). Neurocognition: Clinical and Functional Outcomes in Schizophrenia. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie*, 59(1), 5–12.
68. Ballon, J. S., Kaur, T., Marks, I. I., & Cadenhead, K. S. (2007). Social functioning in young people at risk for schizophrenia. *Psychiatry Research*, 151(1–2), 29–35. <https://doi.org/10.1016/j.psychres.2006.10.012>
69. Tiles-Sar, N., Habtewold, T. D., Liemburg, E. J., van der Meer, L., Bruggeman, R., & Alizadeh, B. Z. (2023). Understanding Lifelong Factors and Prediction Models of Social Functioning After Psychosis Onset Using the Large-Scale GROUP Cohort Study. *Schizophrenia Bulletin*, 49(6), 1447–1459. <https://doi.org/10.1093/schbul/sbad046>
70. Izquierdo, A., Cabello, M., Leal, I., Mellor-Marsá, B., Ayora, M., Bravo-Ortiz, M.-F., Rodriguez-Jimenez, R., Ibáñez, Á., MacDowell, K. S., Malpica, N., Díaz-Marsá, M., Baca-García, E., Fares-Otero, N. E., Melero, H., López-García, P., Díaz-Caneja, C. M., Arango, C., Ayuso-Mateos, J. L., García-Albea, J., ... Albarracín-García, L. (2021). The interplay between functioning problems and symptoms in first episode of psychosis: An approach from network analysis. *Journal of Psychiatric Research*, 136, 265–273. <https://doi.org/10.1016/j.jpsychires.2021.02.024>

71. Addington, J., Piskulic, D., Liu, L., Lockwood, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Bearden, C. E., Mathalon, D. H., & Woods, S. W. (2017). Comorbid diagnoses for youth at clinical high risk of psychosis. *Schizophrenia Research*, 190, 90–95. <https://doi.org/10.1016/j.schres.2017.03.043>
72. Breitborde, N. J. K., Srihari, V. H., & Woods, S. W. (2009). Review of the operational definition for first-episode psychosis. *Early Intervention in Psychiatry*, 3(4), 259–265. <https://doi.org/10.1111/j.1751-7893.2009.00148.x>
73. Sheitman, B. B., Lieberman, J. A., Lee, H., & Strauss, R. (1997). The Evaluation and Treatment of First-episode Psychosis. *Schizophrenia Bulletin*, 23(4), 653–661. <https://doi.org/10.1093/schbul/23.4.653>
74. Altamura, A. C., Buoli, M., Caldiroli, A., Caron, L., Cumerlato Melter, C., Dobreá, C., Cigliobianco, M., & Zanelli Quarantini, F. (2015). Misdiagnosis, duration of untreated illness (DUI) and outcome in bipolar patients with psychotic symptoms: A naturalistic study. *Journal of Affective Disorders*, 182, 70–75. <https://doi.org/10.1016/j.jad.2015.04.024>
75. Santelmann, H., Franklin, J., Bußhoff, J., & Baethge, C. (2016). Diagnostic shift in patients diagnosed with schizoaffective disorder: A systematic review and meta-analysis of rediagnosis studies. *Bipolar Disorders*, 18(3), 233–246. <https://doi.org/10.1111/bdi.12388>
76. Cerqueira, R. O., Ziebold, C., Cavalcante, D., Oliveira, G., Vásquez, J., Undurraga, J., González-Valderrama, A., Nachar, R., Lopez-Jaramillo, C., Noto, C., Crossley, N., & Gadelha, A. (2022). Differences of affective and non-affective psychoses in early intervention services from Latin America. *Journal of Affective Disorders*, 316, 83–90. <https://doi.org/10.1016/j.jad.2022.08.010>
77. Björkenstam, E., Björkenstam, C., Hjern, A., Reutfors, J., & Bodén, R. (2013). A five year diagnostic follow-up of 1,840 patients after a first episode non-schizophrenia and non-affective psychosis. *Schizophrenia Research*, 150(1), 205–210. <https://doi.org/10.1016/j.schres.2013.07.011>
78. Cawksell, P. B., Bolton, K. W., Karmacharya, R., Öngür, D., & Shinn, A. K. (2020). Two-Year Diagnostic Stability in a Real-World Sample of Individuals with Early Psychosis. *Early Intervention in Psychiatry*, 14(6), 751–754. <https://doi.org/10.1111/eip.12930>
79. Kim, J. S., Baek, J. H., Choi, J. S., Lee, D., Kwon, J. S., & Hong, K. S. (2011). Diagnostic stability of first-episode psychosis and predictors of diagnostic shift from non-affective psychosis to bipolar disorder: A retrospective evaluation after recurrence. *Psychiatry Research*, 188(1), 29–33. <https://doi.org/10.1016/j.psychres.2010.09.017>

80. Rodrigues, R., & Anderson, K. K. (2017). The traumatic experience of first-episode psychosis: A systematic review and meta-analysis. *Schizophrenia Research*, 189, 27–36. <https://doi.org/10.1016/j.schres.2017.01.045>
81. Möller, H. J., Jäger, M., Riedel, M., Obermeier, M., Strauss, A., & Bottlender, R. (2011). The Munich 15-year follow-up study (MUFUSSAD) on first-hospitalized patients with schizophrenic or affective disorders: Assessing courses, types and time stability of diagnostic classification. *European Psychiatry: The Journal of the Association of European Psychiatrists*, 26(4), 231–243. <https://doi.org/10.1016/j.eurpsy.2010.04.012>
82. Whitty, P., Clarke, M., McTigue, O., Browne, S., Kamali, M., Larkin, C., & O’Callaghan, E. (2005). Diagnostic stability four years after a first episode of psychosis. *Psychiatric Services (Washington, D.C.)*, 56(9), 1084–1088. <https://doi.org/10.1176/appi.ps.56.9.1084>
83. Stentebjerg-Olesen, M., Pagsberg, A. K., Fink-Jensen, A., Correll, C. U., & Jeppesen, P. (2016). Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. *Journal of Child and Adolescent Psychopharmacology*, 26(5), 410–427. <https://doi.org/10.1089/cap.2015.0097>
84. Ramirez, N., Arranz, B., Salavert, J., Alvarez, E., Corripio, I., Dueñas, R. M., Perez, V., & San, L. (2010). Predictors of schizophrenia in patients with a first episode of psychosis. *Psychiatry Research*, 175(1–2), 11–14. <https://doi.org/10.1016/j.psychres.2009.03.013>
85. Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*, 12(3), 426–445. <https://doi.org/10.1037/0894-4105.12.3.426>
86. Mesholam-Gately, R. I., Giuliano, A. J., Goff, K. P., Faraone, S. V., & Seidman, L. J. (2009). Neurocognition in first-episode schizophrenia: A meta-analytic review. *Neuropsychology*, 23(3), 315–336. <https://doi.org/10.1037/a0014708>
87. Murphy, F. C., & Sahakian, B. J. (2001). Neuropsychology of bipolar disorder. *The British Journal of Psychiatry*, 178(S41), s120–s127. <https://doi.org/10.1192/bjp.178.41.s120>
88. Lewandowski, K. E., Cohen, B. M., Keshavan, M. S., & Öngür, D. (2011). Relationship of neurocognitive deficits to diagnosis and symptoms across affective and non-affective psychoses. *Schizophrenia Research*, 133(1), 212–217. <https://doi.org/10.1016/j.schres.2011.09.004>
89. Torrent, C., Reinares, M., Martínez-Arán, A., Cabrera, B., Amoretti, S., Corripio, I., Contreras, F., Sarró, S., González-Pinto, A., Lobo, A., Cuesta, M.J., Sánchez-Torres, A., Bergé, D., Castro-Fornieles, J., Moreno, C., Bernardo, M., & Vieta, E. (2018). Affective versus non-affective first episode psychoses: A longitudinal study. *Journal of Affective Disorders*, 238, 297–304. <https://doi.org/10.1016/j.jad.2018.06.005>

90. Løberg, E.-M., Helle, S., Nygård, M., Berle, J. Ø., Kroken, R. A., & Johnsen, E. (2014). The Cannabis Pathway to Non-Affective Psychosis may Reflect Less Neurobiological Vulnerability. *Frontiers in Psychiatry*, 5. <https://www.frontiersin.org/article/10.3389/fpsyt.2014.00159>
91. Jepsen, O. H., Erlangsen, A., Nordentoft, M., & Hjorthøj, C. (2023). Cannabis Use Disorder and Subsequent Risk of Psychotic and Nonpsychotic Unipolar Depression and Bipolar Disorder. *JAMA Psychiatry*, 80(8), 803–810. <https://doi.org/10.1001/jamapsychiatry.2023.1256>
92. Del Re, E. C., Yassin, W., Zeng, V., Keedy, S., Alliey-Rodriguez, N., Ivleva, E., Hill, S., Rychagov, N., McDowell, J. E., Bishop, J. R., Mesholam-Gately, R., Merola, G., Lizano, P., Gershon, E., Pearlson, G., Sweeney, J. A., Clementz, B., Tamminga, C., & Keshavan, M. (2023). Characterization of childhood trauma, hippocampal mediation and Cannabis use in a large dataset of psychosis and non-psychosis individuals. *Schizophrenia Research*, 255, 102–109. <https://doi.org/10.1016/j.schres.2023.03.029>
93. Trotta, G., Rodriguez, V., Quattrone, D., Spinazzola, E., Tripoli, G., Gayer-Anderson, C., Freeman, T. P., Jongsma, H. E., Sideli, L., Aas, M., Stilo, S. A., La Cascia, C., Ferraro, L., La Barbera, D., Lasalvia, A., Tosato, S., Tarricone, I., D'Andrea, G., Tortelli, A., ... Di Forti, M. (2023). Cannabis use as a potential mediator between childhood adversity and first-episode psychosis: Results from the EU-GEI case-control study. *Psychological Medicine*, 53(15), 7375–7384. <https://doi.org/10.1017/S0033291723000995>
94. Harley, M., Kelleher, I., Clarke, M., Lynch, F., Arseneault, L., Connor, D., Fitzpatrick, C., & Cannon, M. (2010). Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychological Medicine*, 40(10), 1627–1634. <https://doi.org/10.1017/S0033291709991966>
95. Houston, J. E., Murphy, J., Shevlin, M., & Adamson, G. (2011). Cannabis use and psychosis: Re-visiting the role of childhood trauma. *Psychological Medicine*, 41(11), 2339–2348. <https://doi.org/10.1017/S0033291711000559>
96. Lu, Y., Marshall, C., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Bearden, C. E., Mathalon, D., & Addington, J. (2017). Perceptual abnormalities in clinical high risk youth and the role of trauma, cannabis use and anxiety. *Psychiatry Research*, 258, 462–468. <https://doi.org/10.1016/j.psychres.2017.08.045>
97. Hasan, A., von Keller, R., Friemel, C. M., Hall, W., Schneider, M., Koethe, D., Leweke, F. M., Strube, W., & Hoch, E. (2020). Cannabis use and psychosis: A review of reviews. *European Archives of Psychiatry and Clinical Neuroscience*, 270(4), 403–412. <https://doi.org/10.1007/s00406-019-01068-z>

98. Korver, N., Nieman, D. H., Becker, H. E., van de Fliert, J. R., Dingemans, P. H., de Haan, L., Spiering, M., Schmitz, N., & Linszen, D. H. (2010). Symptomatology and neuropsychological functioning in cannabis using subjects at ultra-high risk for developing psychosis and healthy controls. *The Australian and New Zealand Journal of Psychiatry*, 44(3), 230–236. <https://doi.org/10.3109/00048670903487118>
99. Bugra, H., Studerus, E., Rapp, C., Tamagni, C., Aston, J., Borgwardt, S., & Riecher-Rössler, A. (2013). Cannabis use and cognitive functions in at-risk mental state and first episode psychosis. *Psychopharmacology*, 230(2), 299–308. <https://doi.org/10.1007/s00213-013-3157-y>
100. Ferraro, L., Murray, R. M., Di Forti, M., Quattrone, D., Tripoli, G., Sideli, L., La Barbera, D., & La Cascia, C. (2019). IQ differences between patients with first episode psychosis in London and Palermo reflect differences in patterns of cannabis use. *Schizophrenia Research*, 210, 81–88. <https://doi.org/10.1016/j.schres.2019.06.004>
101. Ferraro, L., Quattrone, D., La Barbera, D., La Cascia, C., Morgan, C., Kirkbride, J. B., Cardno, A. G., Sham, P., Tripoli, G., Sideli, L., Seminerio, F., Sartorio, C., Szoke, A., Tarricone, I., Bernardo, M., Rodriguez, V., Stilo, S. A., Gayer-Anderson, C., de Haan, L., ... Murray, R. M. (2023). First-Episode Psychosis Patients Who Deteriorated in the Premorbid Period Do Not Have Higher Polygenic Risk Scores Than Others: A Cluster Analysis of EU-GEI Data. *Schizophrenia Bulletin*, 49(1), 218–227. <https://doi.org/10.1093/schbul/sbac100>
102. Ferraro, L., Russo, M., O'Connor, J., Wiffen, B. D. R., Falcone, M. A., Sideli, L., Gardner-Sood, P., Stilo, S., Trotta, A., Dazzan, P., Mondelli, V., Taylor, H., Friedman, B., Sallis, H., La Cascia, C., La Barbera, D., David, A. S., Reichenberg, A., Murray, R. M., & Di Forti, M. (2013). Cannabis users have higher premorbid IQ than other patients with first onset psychosis. *Schizophrenia Research*, 150(1), 129–135. <https://doi.org/10.1016/j.schres.2013.07.046>
103. Buchy, L., Seidman, L. J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., Stone, W., Tsuang, M. T., Walker, E. F., Woods, S. W., Bearden, C. E., Mathalon, D. H., & Addington, J. (2015). Evaluating the relationship between cannabis use and IQ in youth and young adults at clinical high risk of psychosis. *Psychiatry Research*, 230(3), 878–884. <https://doi.org/10.1016/j.psychres.2015.11.033>
104. Compton, M. T., Broussard, B., Ramsay, C. E., & Stewart, T. (2011). Pre-illness cannabis use and the early course of nonaffective psychotic disorders: Associations with premorbid functioning, the prodrome, and mode of onset of psychosis. *Schizophrenia Research*, 126(1–3), 71–76. <https://doi.org/10.1016/j.schres.2010.10.005>

105. Addington, J., Farris, M., Devoe, D., & Metzack, P. (2020). Progression from being at-risk to psychosis: Next steps. *Npj Schizophrenia*, 6(1), 1–7. <https://doi.org/10.1038/s41537-020-00117-0>
106. Clark, T. G., Bradburn, M. J., Love, S. B., & Altman, D. G. (2003). Survival Analysis Part I: Basic concepts and first analyses. *British Journal of Cancer*, 89(2), 232–238. <https://doi.org/10.1038/sj.bjc.6601118>
107. Weller, B. E., Bowen, N. K., & Faubert, S. J. (2020). Latent Class Analysis: A Guide to Best Practice. *Journal of Black Psychology*, 46(4), 287–311. <https://doi.org/10.1177/0095798420930932>
108. Spurk, D., Hirschi, A., Wang, M., Valero, D., & Kauffeld, S. (2020). Latent profile analysis: A review and “how to” guide of its application within vocational behavior research. *Journal of Vocational Behavior*, 120, 103445. <https://doi.org/10.1016/j.jvb.2020.103445>
109. Bergé, D., Carter, C. S., & Smucny, J. (n.d.). Identification of distinct clinical profiles and trajectories in individuals at high risk of developing psychosis: A latent profile analysis of the north American prodrome longitudinal study consortium-3 dataset. *Early Intervention in Psychiatry*, n/a(n/a). <https://doi.org/10.1111/eip.13514>
110. Healey, K. M., Penn, D. L., Perkins, D., Woods, S. W., Keefe, R. S. E., & Addington, J. (2018). Latent Profile Analysis and Conversion to Psychosis: Characterizing Subgroups to Enhance Risk Prediction. *Schizophrenia Bulletin*, 44(2), 286–296. <https://doi.org/10.1093/schbul/sbx080>
111. Allswede, D. M., Addington, J., Bearden, C. E., Cadenhead, K., Cornblatt, B., Mathalon, D., McGlashan, T., Perkins, D., Seidman, L., Tsuang, M., Walker, E., Woods, S. W., & Cannon, T. D. (2020). Characterizing covariant trajectories of individuals at clinical high-risk for psychosis across symptomatic and functional domains. *The American Journal of Psychiatry*, 177(2), 164–171. <https://doi.org/10.1176/appi.ajp.2019.18111290>
112. Fusar-Poli, P., Micheli, A. D., Signorini, L., Baldwin, H., Pablo, G. S. de, & McGuire, P. (2020). Real-world long-term outcomes in individuals at clinical risk for psychosis: The case for extending duration of care. *eClinicalMedicine*, 28. <https://doi.org/10.1016/j.eclinm.2020.100578>
113. Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., & Nordentoft, M. (2015). Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10year follow-up study in the OPUS cohort. *Schizophrenia Research*, 168(1), 84–91. <https://doi.org/10.1016/j.schres.2015.07.021>

114. Secher, R. G., Hjorthøj, C. R., Austin, S. F., Thorup, A., Jeppesen, P., Mors, O., & Nordentoft, M. (2015). Ten-Year Follow-up of the OPUS Specialized Early Intervention Trial for Patients With a First Episode of Psychosis. *Schizophrenia Bulletin*, 41(3), 617–626. <https://doi.org/10.1093/schbul/sbu155>
115. Morgan, C., Dazzan, P., Lappin, J., Heslin, M., Donoghue, K., Fearon, P., Jones, P. B., Murray, R. M., Doody, G. A., & Reininghaus, U. (n.d.). Rethinking the course of psychotic disorders: Modelling long-term symptom trajectories. *Psychological Medicine*, 52(13), 2641–2650. <https://doi.org/10.1017/S0033291720004705>
116. Gee, D. G., & Cannon, T. D. (2011). Prediction of conversion to psychosis: Review and future directions. *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil: 1999)*, 33 Suppl 2, s129-142. <https://doi.org/10.1590/s1516-44462011000600002>
117. Cornblatt, B. A., Carrión, R. E., Auther, A., McLaughlin, D., Olsen, R. H., John, M., & Correll, C. U. (2015). Psychosis Prevention: A Modified Clinical High Risk Perspective From the Recognition and Prevention (RAP) Program. *The American Journal of Psychiatry*, 172(10), 986–994. <https://doi.org/10.1176/appi.ajp.2015.13121686>
118. Ising, H. K., Kraan, T. C., Rietdijk, J., Dragt, S., Klaassen, R. M. C., Boonstra, N., Nieman, D. H., Willebrands-Mendrik, M., van den Berg, D. P. G., Linszen, D. H., Wunderink, L., Veling, W., Smit, F., & van der Gaag, M. (2016). Four-Year Follow-up of Cognitive Behavioral Therapy in Persons at Ultra-High Risk for Developing Psychosis: The Dutch Early Detection Intervention Evaluation (EDIE-NL) Trial. *Schizophrenia Bulletin*, 42(5), 1243–1252. <https://doi.org/10.1093/schbul/sbw018>
119. Amminger, G. P., Schäfer, M. R., Schlögelhofer, M., Klier, C. M., & McGorry, P. D. (2015). Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nature Communications*, 6, 7934. <https://doi.org/10.1038/ncomms8934>
120. Lin, A., Wood, S. J., Nelson, B., Beavan, A., McGorry, P., & Yung, A. R. (2015). Outcomes of Nontransitioned Cases in a Sample at Ultra-High Risk for Psychosis. *American Journal of Psychiatry*, 172(3), 249–258. <https://doi.org/10.1176/appi.ajp.2014.13030418>
121. Michel, C., Ruhrmann, S., Schimmelmann, B. G., Klosterkötter, J., & Schultze-Lutter, F. (2018). Course of clinical high-risk states for psychosis beyond conversion. *European Archives of Psychiatry and Clinical Neuroscience*, 268(1), 39–48. <https://doi.org/10.1007/s00406-016-0764-8>
122. Addington, J., Farris, M., Stowkowy, J., Santesteban-Echarri, O., Metzack, P., & Kalathil, M. S. (2019). Predictors of Transition to Psychosis in Individuals at Clinical High Risk. *Current Psychiatry Reports*, 21(6), 39. <https://doi.org/10.1007/s11920-019-1027-y>

123. Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2018). Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *Journal of Psychiatric Research*, 99, 22–32. <https://doi.org/10.1016/j.jpsychires.2018.01.010>
124. Santesteban-Echarri, O., Liu, L., Miller, M., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Stone, W. S., Tsuang, M. T., Walker, E. F., Woods, S. W., & Addington, J. (2022). Cannabis use and attenuated positive and negative symptoms in youth at clinical high risk for psychosis. *Schizophrenia Research*, 248, 114–121. <https://doi.org/10.1016/j.schres.2022.08.005>
125. Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: A systematic review. *The Lancet*, 370(9584), 319–328. [https://doi.org/10.1016/S0140-6736\(07\)61162-3](https://doi.org/10.1016/S0140-6736(07)61162-3)
126. Addington, J., Liu, L., Brummitt, K., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Stone, W., Tsuang, M. T., Walker, E. F., Woods, S. W., & Cannon, T. D. (2022). North American Prodrome Longitudinal Study (NAPLS 3): Methods and baseline description. *Schizophrenia Research*, 243, 262–267. <https://doi.org/10.1016/j.schres.2020.04.010>
127. Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M., Walker, E. F., Woods, S. W., & Heinssen, R. (2007). North American Prodrome Longitudinal Study: A Collaborative Multisite Approach to Prodromal Schizophrenia Research. *Schizophrenia Bulletin*, 33(3), 665–672. <https://doi.org/10.1093/schbul/sbl075>
128. Twitchell, G. R., Hertzog, C. A., Klein, J. L., & Schuckit, M. A. (1992). The anatomy of a follow-up. *British Journal of Addiction*, 87(9), 1327–1333. <https://doi.org/10.1111/j.1360-0443.1992.tb02741.x>
129. Addington, J., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Addington, J. A., & Cannon, T. D. (2012). North American Prodrome Longitudinal Study (NAPLS 2): Overview and recruitment. *Schizophrenia Research*, 142(1–3), 77–82. <https://doi.org/10.1016/j.schres.2012.09.012>
130. Monaghesh, E., & Hajizadeh, A. (2020). The role of telehealth during COVID-19 outbreak: A systematic review based on current evidence. *BMC Public Health*, 20, 1193. <https://doi.org/10.1186/s12889-020-09301-4>
131. Moreno, C., Wykes, T., Galderisi, S., Nordentoft, M., Crossley, N., Jones, N., Cannon, M., Correll, C. U., Byrne, L., Carr, S., Chen, E. Y. H., Gorwood, P., Johnson, S., Kärkkäinen, H., Krystal, J. H., Lee, J., Lieberman, J., López-Jaramillo, C., Männikkö, M., ... Arango, C. (2020). How mental health care should change as a consequence of the COVID-19

- pandemic. *The Lancet. Psychiatry*, 7(9), 813–824. [https://doi.org/10.1016/S2215-0366\(20\)30307-2](https://doi.org/10.1016/S2215-0366(20)30307-2)
132. Jastak, S. (1984). *WRAT-R: Wide range achievement test*. <https://search.library.wisc.edu/catalog/999634037702121>
 133. *Wechsler Abbreviated Scale of Intelligence—Second Edition—PsycNET*. (n.d.). Retrieved January 28, 2023, from <https://psycnet.apa.org/doiLanding?doi=10.1037%2Ft15171-000>
 134. Nuechterlein, K. H., Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., Essock, S., Fenton, W. S., Frese, F. J., Gold, J. M., Goldberg, T., Heaton, R. K., Keefe, R. S. E., Kraemer, H., Mesholam-Gately, R., Seidman, L. J., Stover, E., Weinberger, D. R., Young, A. S., ... Marder, S. R. (2008). The MATRICS Consensus Cognitive Battery, Part 1: Test Selection, Reliability, and Validity. *American Journal of Psychiatry*, 165(2), 203–213. <https://doi.org/10.1176/appi.ajp.2007.07010042>
 135. Keefe, R. S. E., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research*, 68(2–3), 283–297. <https://doi.org/10.1016/j.schres.2003.09.011>
 136. *Hopkins Verbal Learning Test | SpringerLink*. (n.d.). Retrieved July 5, 2024, from https://link.springer.com/referenceworkentry/10.1007/978-0-387-79948-3_1127
 137. Horan, W. P., Braff, D. L., Nuechterlein, K. H., Sugar, C. A., Cadenhead, K. S., Calkins, M. E., Dobie, D. J., Freedman, R., Greenwood, T. A., Gur, R. E., Gur, R. C., Light, G. A., Mintz, J., Olincy, A., Radant, A. D., Schork, N. J., Seidman, L. J., Siever, L. J., Silverman, J. M., ... Green, M. F. (2008). Verbal Working Memory Impairments in Individuals with Schizophrenia and Their First-Degree Relatives: Findings From the Consortium on the Genetics of Schizophrenia. *Schizophrenia Research*, 103(1–3), 218–228. <https://doi.org/10.1016/j.schres.2008.02.014>
 138. Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of Premorbid Adjustment in Chronic Schizophrenia. *Schizophrenia Bulletin*, 8(3), 470–484. <https://doi.org/10.1093/schbul/8.3.470>
 139. Aas, I. M. (2011). Guidelines for rating Global Assessment of Functioning (GAF). *Annals of General Psychiatry*, 10. <https://doi.org/10.1186/1744-859X-10-2>
 140. Carrión, R. E., Auther, A. M., McLaughlin, D., Olsen, R., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Mathalon, D. H., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., & Cornblatt, B. A. (2019). The Global Functioning: Social and Role Scales—Further Validation in a Large Sample of Adolescents and Young Adults at Clinical High Risk for Psychosis. *Schizophrenia Bulletin*, 45(4), 763–772. <https://doi.org/10.1093/schbul/sby126>

141. Cornblatt, B. A., Auther, A. M., Niendam, T., Smith, C. W., Zinberg, J., Bearden, C. E., & Cannon, T. D. (2007). Preliminary Findings for Two New Measures of Social and Role Functioning in the Prodromal Phase of Schizophrenia. *Schizophrenia Bulletin*, 33(3), 688–702. <https://doi.org/10.1093/schbul/sbm029>
142. Bernstein, D. P., Fink, L., Handelsman, L., & Foote, J. (2011). *Childhood Trauma Questionnaire* [Dataset]. <https://doi.org/10.1037/t02080-000>
143. Dohrenwend, B. S., Askenasy, A. R., Krasnoff, L., & Dohrenwend, B. P. (1978). Exemplification of a Method for Scaling Life Events: The PERI Life Events Scale. *Journal of Health and Social Behavior*, 19(2), 205–229. <https://doi.org/10.2307/2136536>
144. Woods, S. W., Walsh, B. C., Saksa, J. R., & McGlashan, T. H. (2010). The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome. *Schizophrenia Research*, 123(2–3), 199–207. <https://doi.org/10.1016/j.schres.2010.08.012>
145. *Statistical Analysis with Missing Data | Wiley Series in Probability and Statistics*. (n.d.). Retrieved October 2, 2023, from <https://onlinelibrary.wiley.com/doi/book/10.1002/9781119013563>
146. Ram, N., & Grimm, K. J. (2009). Growth Mixture Modeling: A Method for Identifying Differences in Longitudinal Change Among Unobserved Groups. *International Journal of Behavioral Development*, 33(6), 565–576. <https://doi.org/10.1177/0165025409343765>
147. Sinha, P., Calfee, C. S., & Delucchi, K. L. (2021). Practitioner’s Guide to Latent Class Analysis: Methodological Considerations and Common Pitfalls. *Critical Care Medicine*, 49(1), e63–e79. <https://doi.org/10.1097/CCM.00000000000004710>
148. Schreiber, J. B. (2022). Chapter 37—Latent class and latent class regression. In S. P. Desselle, V. García-Cárdenas, C. Anderson, P. Aslani, A. M. H. Chen, & T. F. Chen (Eds.), *Contemporary Research Methods in Pharmacy and Health Services* (pp. 541–552). Academic Press. <https://doi.org/10.1016/B978-0-323-91888-6.00044-2>
149. Tein, J.-Y., Coxe, S., & Cham, H. (2013). Statistical Power to Detect the Correct Number of Classes in Latent Profile Analysis. *Structural Equation Modeling : A Multidisciplinary Journal*, 20(4), 640–657. <https://doi.org/10.1080/10705511.2013.824781>
150. Bursac, Z., Gauss, C. H., Williams, D. K., & Hosmer, D. W. (2008). Purposeful selection of variables in logistic regression. *Source Code for Biology and Medicine*, 3(1), 17. <https://doi.org/10.1186/1751-0473-3-17>
151. Aguinis, H. (2004). *Regression Analysis for Categorical Moderators*. Guilford Press.
152. Harris, J. K. (2021). Primer on binary logistic regression. *Family Medicine and Community Health*, 9(Suppl 1), e001290. <https://doi.org/10.1136/fmch-2021-001290>

153. Assessing the Fit of the Model. (2013). In *Applied Logistic Regression* (pp. 153–225). John Wiley & Sons, Ltd. <https://doi.org/10.1002/9781118548387.ch5>
154. Jr, D. W. H., Lemeshow, S., & Sturdivant, R. X. (2013). *Applied Logistic Regression*. John Wiley & Sons.
155. *Multinomial Logistic Regression | R Data Analysis Examples*. (n.d.). Retrieved June 30, 2023, from <https://stats.oarc.ucla.edu/r/dae/multinomial-logistic-regression/>
156. Weller, B. E., Bowen, N. K., & Faubert, S. J. (2020). Latent Class Analysis: A Guide to Best Practice. *Journal of Black Psychology*, 46(4), 287–311. <https://doi.org/10.1177/0095798420930932>
157. Gold, J. M., Millman, Z. B., & Dickinson, D. (n.d.). *Enhancing Prediction of Psychosis Risk With Cognitive Measures*. Retrieved April 26, 2025, from <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2781292>
158. Catalan, A., Salazar de Pablo, G., Aymerich, C., Damiani, S., Sordi, V., Radua, J., Oliver, D., McGuire, P., Giuliano, A. J., Stone, W. S., & Fusar-Poli, P. (2021). Neurocognitive Functioning in Individuals at Clinical High Risk for Psychosis: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, 78(8), 859–867. <https://doi.org/10.1001/jamapsychiatry.2021.1290>
159. Sanders, R. D., Keshavan, M. S., & Goldstein, G. (2003). Clinical Utility of the Neurological Examination in Psychoses. *Psychiatric Annals*, 33(3), 195–200. <https://doi.org/10.3928/0048-5713-20030301-08>
160. Casaletto, K. B., & Heaton, R. K. (2017). Neuropsychological Assessment: Past and Future. *Journal of the International Neuropsychological Society*, 23(9–10), 778–790. <https://doi.org/10.1017/S1355617717001060>
161. Mwesiga, E. K., Akena, D., Koen, N., Senono, R., Obuku, E. A., Gumikiriza, J. L., Robbins, R. N., Nakasujja, N., & Stein, D. J. (2020). A systematic review of research on neuropsychological measures in psychotic disorders from low and middle-income countries: The question of clinical utility. *Schizophrenia Research: Cognition*, 22, 100187. <https://doi.org/10.1016/j.scog.2020.100187>
162. Stübke, M., Schultze-Lutter, F., Kaess, M., Franscini, M., Traber-Walker, N., Walger, P., Schimmelmann, B. G., Vogeley, K., Kambeitz, J., Kindler, J., & Michel, C. (2024). Clinical and neurocognitive profiles of a combined clinical high risk for psychosis and clinical control sample: Latent class analysis. *BJPsych Open*, 10(6), e226. <https://doi.org/10.1192/bjo.2024.815>

163. Guest, R. M., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Mathalon, D. H., Perkins, D. O., Tsuang, M. T., Woods, S. W., Cannon, T. D., Keshavan, M. S., Stone, W. S., & Walker, E. F. (2023). 73 Identification of 24-Month Cognitive Trajectories Among Clinical High Risk for Psychosis (CHR-P) Using Latent Class Mixture Modeling. *Journal of the International Neuropsychological Society*, 29(s1), 857–858. <https://doi.org/10.1017/S1355617723010597>
164. Ryan, A. K. (2010). Gender differences in family formation behavior: The effects of adolescent substance use. *Journal of Studies on Alcohol and Drugs*, 71(6), 938–949. <https://doi.org/10.15288/jsad.2010.71.938>
165. Zhang, T., Xu, L., Wei, Y., Cui, H., Tang, X., Hu, Y., Liu, H., Wang, Z., Chen, T., Yi, Z., Li, C., & Wang, J. (2024). Symptom Dimensions and Cognitive Impairments in Individuals at Clinical High Risk for Psychosis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. <https://doi.org/10.1016/j.bpsc.2024.09.002>
166. Bjornestad, J., Tjora, T., Joa, I., Johannessen, J. O., Sætren, S. S., & ten Velden Hegelstad, W. (2024). Early and later remission from clinical high risk of psychosis. A latent class and predictor analysis. *Schizophrenia Research*, 274, 237–242. <https://doi.org/10.1016/j.schres.2024.09.024>
167. Michel, C., Osman, N., Rinaldi, G., Schimmelmann, B. G., Kindler, J., & Schultze-Lutter, F. (2025). Three-year course of clinical high-risk symptoms for psychosis in the community: A latent class analysis. *Epidemiology and Psychiatric Sciences*, 34, e3. <https://doi.org/10.1017/S2045796024000891>
168. Giannopoulou, I., Georgiades, S., Stefanou, M.-I., Spandidos, D. A., & Rizos, E. (2023). Links between trauma and psychosis (Review). *Experimental and Therapeutic Medicine*, 26(2), 386. <https://doi.org/10.3892/etm.2023.12085>
169. Loewy, R. L., Corey, S., Amirfathi, F., Dabit, S., Fulford, D., Pearson, R., Hua, J. P. Y., Schlosser, D., Stuart, B. K., Mathalon, D. H., & Vinogradov, S. (2019). Childhood trauma and clinical high risk for psychosis. *Schizophrenia Research*, 205, 10–14. <https://doi.org/10.1016/j.schres.2018.05.003>
170. *Diagnostic and Statistical Manual of Mental Disorders*. (n.d.). DSM Library. Retrieved June 22, 2024, from <https://dsm.psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596>
171. Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., Sanislow, C., & Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *The American Journal of Psychiatry*, 167, 748–751. <https://doi.org/10.1176/appi.ajp.2010.09091379>

172. Jonas, K. G., Cannon, T. D., Docherty, A. R., Dwyer, D., Gur, R. C., Gur, R. E., Nelson, B., Reininghaus, U., & Kotov, R. (2024). Psychosis superspectrum I: Nosology, etiology, and lifespan development. *Molecular Psychiatry*. <https://doi.org/10.1038/s41380-023-02388-2>
173. Pablo, G. S. de, Besana, F., Arienti, V., Catalan, A., Vaquerizo-Serrano, J., Cabras, A., Pereira, J., Soardo, L., Coronelli, F., Kaur, S., Silva, J. da, Oliver, D., Petros, N., Moreno, C., Gonzalez-Pinto, A., Díaz-Caneja, C. M., Shin, J. I., Politi, P., Solmi, M., ... Fusar-Poli, P. (2021). Longitudinal outcome of attenuated positive symptoms, negative symptoms, functioning and remission in people at clinical high risk for psychosis: A meta-analysis. *eClinicalMedicine*, 36. <https://doi.org/10.1016/j.eclinm.2021.100909>
174. Andreou, C., Eickhoff, S., Heide, M., de Bock, R., Obleser, J., & Borgwardt, S. (2023). Predictors of transition in patients with clinical high risk for psychosis: An umbrella review. *Translational Psychiatry*, 13(1), 1–11. <https://doi.org/10.1038/s41398-023-02586-0>
175. Brandizzi, M., Valmaggia, L., Byrne, M., Jones, C., Iwegbu, N., Badger, S., McGuire, P., & Fusar-Poli, P. (2015). Predictors of functional outcome in individuals at high clinical risk for psychosis at six years follow-up. *Journal of Psychiatric Research*, 65, 115–123. <https://doi.org/10.1016/j.jpsychires.2015.03.005>
176. Rosen, M., Haidl, T. K., Ruhrmann, S., Vogeley, K., & Schultze-Lutter, F. (2020). Sex differences in symptomatology of psychosis-risk patients and in prediction of psychosis. *Archives of Women's Mental Health*, 23(3), 339–349. <https://doi.org/10.1007/s00737-019-01000-3>
177. Cowan, H. R., Mittal, V. A., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., Keshavan, M., Mathalon, D. H., Perkins, D. O., Stone, W., Tsuang, M. T., Woods, S. W., Cannon, T. D., & Walker, E. F. (2025). Longitudinal Trajectories of Premorbid Social and Academic Adjustment in Youth at Clinical High Risk for Psychosis: Implications for Conversion. *Schizophrenia Bulletin*, 51(1), 54–66. <https://doi.org/10.1093/schbul/sbae050>
178. Tognin, S., Catalan, A., Aymerich, C., Richter, A., Kempton, M. J., Modinos, G., Hammoud, R., Gorostiza, I., Vassos, E., van der Gaag, M., de Haan, L., Nelson, B., Riecher-Rössler, A., Bressan, R., Barrantes-Vidal, N., Krebs, M.-O., Nordentoft, M., Ruhrmann, S., Sachs, G., ... McGuire, P. (2025). Association between Adverse Childhood Experiences and long-term outcomes in people at Clinical High-Risk for Psychosis. *Schizophrenia*, 11(1), 1–9. <https://doi.org/10.1038/s41537-025-00562-9>
179. Lin, A., Wood, S. J., Nelson, B., Beavan, A., McGorry, P., & Yung, A. R. (2015). Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. *The American Journal of Psychiatry*, 172(3), 249–258. <https://doi.org/10.1176/appi.ajp.2014.13030418>

180. Penzel, N., Sanfelici, R., Antonucci, L. A., Betz, L. T., Dwyer, D., Ruef, A., Cho, K. I. K., Cumming, P., Pogarell, O., Howes, O., Falkai, P., Upthegrove, R., Borgwardt, S., Brambilla, P., Lencer, R., Meisenzahl, E., Schultze-Lutter, F., Rosen, M., Lichtenstein, T., ... PRONIA Consortium. (2022). Pattern of predictive features of continued cannabis use in patients with recent-onset psychosis and clinical high-risk for psychosis. *Schizophrenia (Heidelberg, Germany)*, 8(1), 19. <https://doi.org/10.1038/s41537-022-00218-y>
181. Di Lisi, A., & Pelizza, L. (2023). *Antipsychotic medication in individuals at Clinical High Risk for Psychosis: What recommendations for clinicians?* <https://doi.org/10.36148/2284-0249-N331>
182. Pelizza, L., Plazzi, E., Leuci, E., Leucci, A. C., Quattrone, E., Azzali, S., Pupo, S., Paulillo, G., Pellegrini, P., & Menchetti, M. (2024). Diagnostic shift in adolescents with first episode psychosis: Findings from the 2-year follow-up of the “Parma Early Psychosis” program. *Social Psychiatry and Psychiatric Epidemiology*. <https://doi.org/10.1007/s00127-024-02721-2>
183. Poletti, M., Pelizza, L., Preti, A., & Raballo, A. (2024). Clinical High-Risk for Psychosis (CHR-P) circa 2024: Synoptic analysis and synthesis of contemporary treatment guidelines. *Asian Journal of Psychiatry*, 100, 104142. <https://doi.org/10.1016/j.ajp.2024.104142>
184. Catalan, A., Salazar de Pablo, G., Aymerich, C., Damiani, S., Sordi, V., Radua, J., Oliver, D., McGuire, P., Giuliano, A. J., Stone, W. S., & Fusar-Poli, P. (2021). Neurocognitive Functioning in Individuals at Clinical High Risk for Psychosis: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, 78(8), 859–867. <https://doi.org/10.1001/jamapsychiatry.2021.1290>
185. Pedruzo, B., Aymerich, C., Pacho, M., Herrero, J., Laborda, M., Bordenave, M., Giuliano, A. J., McCutcheon, R. A., Gutiérrez-Rojas, L., McGuire, P., Stone, W. S., Fusar-Poli, P., González-Torres, M. Á., & Catalan, A. (2023). Longitudinal change in neurocognitive functioning in children and adolescents at clinical high risk for psychosis: A systematic review. *European Child & Adolescent Psychiatry*. <https://doi.org/10.1007/s00787-023-02221-9>
186. Lorenzetti, V., Hoch, E., & Hall, W. (2020). Adolescent cannabis use, cognition, brain health and educational outcomes: A review of the evidence. *European Neuropsychopharmacology*, 36, 169–180. <https://doi.org/10.1016/j.euroneuro.2020.03.012>
187. Pelizza, L., Di Lisi, A., Leuci, E., Quattrone, E., Azzali, S., Pupo, S., Paulillo, G., Pellegrini, P., & Menchetti, M. (2024). Subgroups of Clinical High Risk for Psychosis Based on Baseline Antipsychotic Exposure: Clinical and Outcome Comparisons Across a 2-Year Follow-up Period. *Schizophrenia Bulletin*, 51(2), 432–445. <https://doi.org/10.1093/schbul/sbae029>

188. Raballo, A., Poletti, M., & Preti, A. (2021). Negative Prognostic Effect of Baseline Antipsychotic Exposure in Clinical High Risk for Psychosis (CHR-P): Is Pre-Test Risk Enrichment the Hidden Culprit? *International Journal of Neuropsychopharmacology*, 24(9), 710–720. <https://doi.org/10.1093/ijnp/pyab030>
189. Salazar de Pablo, G., Guinart, D., Armendariz, A., Aymerich, C., Catalan, A., Alameda, L., Rogdaki, M., Martinez Baringo, E., Soler-Vidal, J., Oliver, D., Rubio, J. M., Arango, C., Kane, J. M., Fusar-Poli, P., & Correll, C. U. (2024). Duration of Untreated Psychosis and Outcomes in First-Episode Psychosis: Systematic Review and Meta-analysis of Early Detection and Intervention Strategies. *Schizophrenia Bulletin*, 50(4), 771–783. <https://doi.org/10.1093/schbul/sbae017>
190. Yu, M., Tan, Q., Wang, Y., Xu, Y., Wang, T., Liu, D., Chen, D., Deng, P., Huang, C., Liang, X., Liu, K., & Xiang, B. (2023). Correlation between duration of untreated psychosis and long-term prognosis in chronic schizophrenia. *Frontiers in Psychiatry*, 14. <https://doi.org/10.3389/fpsy.2023.1112657>
191. Kirchner, S.-K., Lauseker, M., Adorjan, K., Anderson-Schmidt, H., Anghelescu, I.-G., Baune, B. T., Budde, M., Dannlowski, U., Dietrich, D. E., Fallgatter, A. J., Falkai, P., Figge, C., Gade, K., Heilbronner, U., Hiendl, L., Juckel, G., Kalman, J. L., Klöhn-Saghatolislam, F., Konrad, C., ... Senner, F. (2022). Medication Adherence in a Cross-Diagnostic Sample of Patients From the Affective-to-Psychotic Spectrum: Results From the PsyCourse Study. *Frontiers in Psychiatry*, 12. <https://doi.org/10.3389/fpsy.2021.713060>
192. Burgess-Barr, S., Nicholas, E., Venus, B., Singh, N., Nethercott, A., Taylor, G., & Jacobsen, P. (2023). International rates of receipt of psychological therapy for psychosis and schizophrenia: Systematic review and meta-analysis. *International Journal of Mental Health Systems*, 17, 8. <https://doi.org/10.1186/s13033-023-00576-9>
193. Bromet, E. J., Kotov, R., Fochtmann, L. J., Carlson, G. A., Tanenberg-Karant, M., Ruggero, C., & Chang, S. (2011). Diagnostic shifts during the decade following first admission for psychosis. *The American Journal of Psychiatry*, 168(11), 1186–1194. <https://doi.org/10.1176/appi.ajp.2011.11010048>
194. Rachid, T., Abarda, A., & Hasbaoui, A. (2024). Latent class analysis: A review and recommendations for future applications in health sciences. *Procedia Computer Science*, 238, 1062–1067. <https://doi.org/10.1016/j.procs.2024.06.135>
195. Lee, J., Jung, K., & Park, J. (2020). Detecting Conditional Dependence Using Flexible Bayesian Latent Class Analysis. *Frontiers in Psychology*, 11, 1987. <https://doi.org/10.3389/fpsyg.2020.01987>

196. Spurk, D., Hirschi, A., Wang, M., Valero, D., & Kauffeld, S. (2020). Latent profile analysis: A review and “how to” guide of its application within vocational behavior research. *Journal of Vocational Behavior*, 120, 103445. <https://doi.org/10.1016/j.jvb.2020.103445>
197. Ranganathan, P., Aggarwal, R., & Pramesh, C. S. (2015). Common pitfalls in statistical analysis: Odds versus risk. *Perspectives in Clinical Research*, 6(4), 222–224. <https://doi.org/10.4103/2229-3485.167092>
198. Viera, A. J. (2008). Odds ratios and risk ratios: What’s the difference and why does it matter? *Southern Medical Journal*, 101(7), 730–734. <https://doi.org/10.1097/SMJ.0b013e31817a7ee4>
199. van Smeden, M., Moons, K. G., de Groot, J. A., Collins, G. S., Altman, D. G., Eijkemans, M. J., & Reitsma, J. B. (2019). Sample size for binary logistic prediction models: Beyond events per variable criteria. *Statistical Methods in Medical Research*, 28(8), 2455–2474. <https://doi.org/10.1177/0962280218784726>
200. Diehl, M., Hay, E. L., & Chui, H. (2012). Personal Risk and Resilience Factors in the Context of Daily Stress. *Annual Review of Gerontology & Geriatrics*, 32(1), 251–274. <https://doi.org/10.1891/0198-8794.32.251>
201. Salazar de Pablo, G., Estradé, A., Cutroni, M., Andlauer, O., & Fusar-Poli, P. (2021). Establishing a clinical service to prevent psychosis: What, how and when? Systematic review. *Translational Psychiatry*, 11, 43. <https://doi.org/10.1038/s41398-020-01165-x>
202. Dixon, L. B., Goldman, H. H., Bennett, M. E., Wang, Y., McNamara, K. A., Mendon, S. J., Goldstein, A. B., Choi, C.-W. J., Lee, R. J., Lieberman, J. A., & Essock, S. M. (2015). Implementing Coordinated Specialty Care for Early Psychosis: The RAISE Connection Program. *Psychiatric Services*, 66(7), 691–698. <https://doi.org/10.1176/appi.ps.201400281>
203. Kennedy, L., Lin, J., Metry, V., Villodas, M., & Cadenhead, K. (2025). Socioenvironmental and Developmental Predictors of Cannabis Initiation and Use in Psychosis: A Systematic Scoping Review. *Current Addiction Reports*, 12(1), 43. <https://doi.org/10.1007/s40429-025-00654-7>
204. Barlati, S., Regina, V., Deste, G., Galluzzo, A., Turrina, C., Valsecchi, P., & Vita, A. (2022). Psychosocial Recovery-Oriented Interventions in Schizophrenia. In B. Carpinello, A. Vita, & C. Menciacci (Eds.), *Recovery and Major Mental Disorders* (pp. 77–98). Springer International Publishing. https://doi.org/10.1007/978-3-030-98301-7_6
205. Fusar-Poli, P., Rocchetti, M., Sardella, A., Avila, A., Brandizzi, M., Caverzasi, E., Politi, P., Ruhrmann, S., & McGuire, P. (2015). Disorder, not just state of risk: Meta-analysis of functioning and quality of life in people at high risk of psychosis. *The British Journal of Psychiatry*, 207(3), 198–206. <https://doi.org/10.1192/bjp.bp.114.157115>

206. Malla, A., & Payne, J. (2005). First-Episode Psychosis: Psychopathology, Quality of Life, and Functional Outcome. *Schizophrenia Bulletin*, 31(3), 650–671.
<https://doi.org/10.1093/schbul/sbi031>
207. Atapattu, M. S., Gonzales, H. M., & Williams, N. (2022). Recovery from Psychosis: An Integrated Model of Interpersonal and Intrapersonal Factors from the Perspective of Psychologists. *Journal of Psychosocial Rehabilitation and Mental Health*, 9(4), 379–393.
<https://doi.org/10.1007/s40737-022-00274-8>

Appendix A. Assumption testing for 2-year follow-up logistic regressions (ggplot2, GGalley)

1. Linearity of continuous predictor variables to response variable

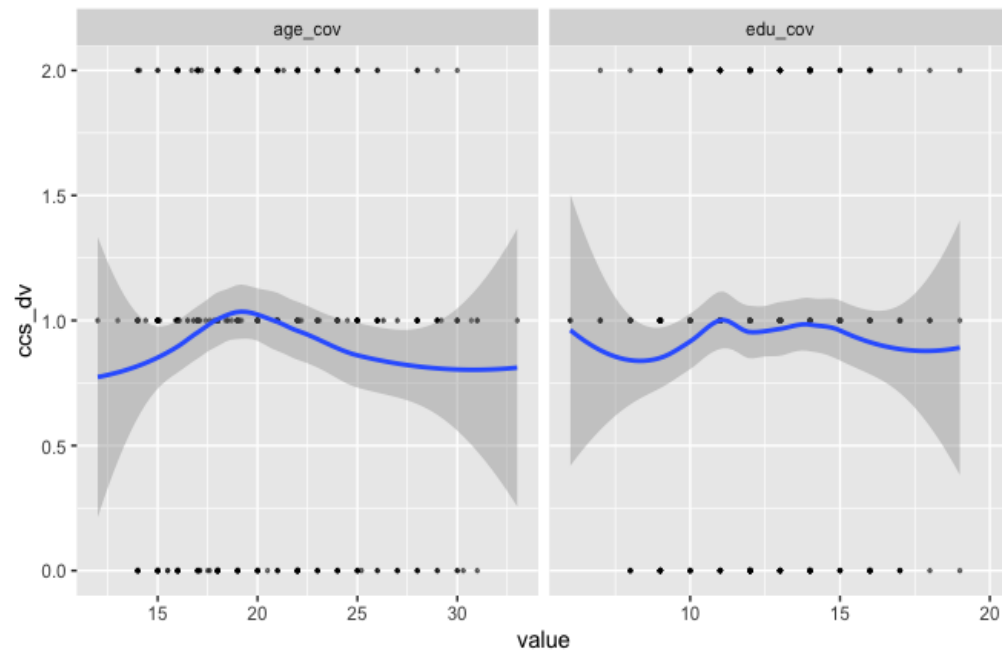


Figure 12: Assumption Testing for Appendices A-C, linearity

2. Multicollinearity

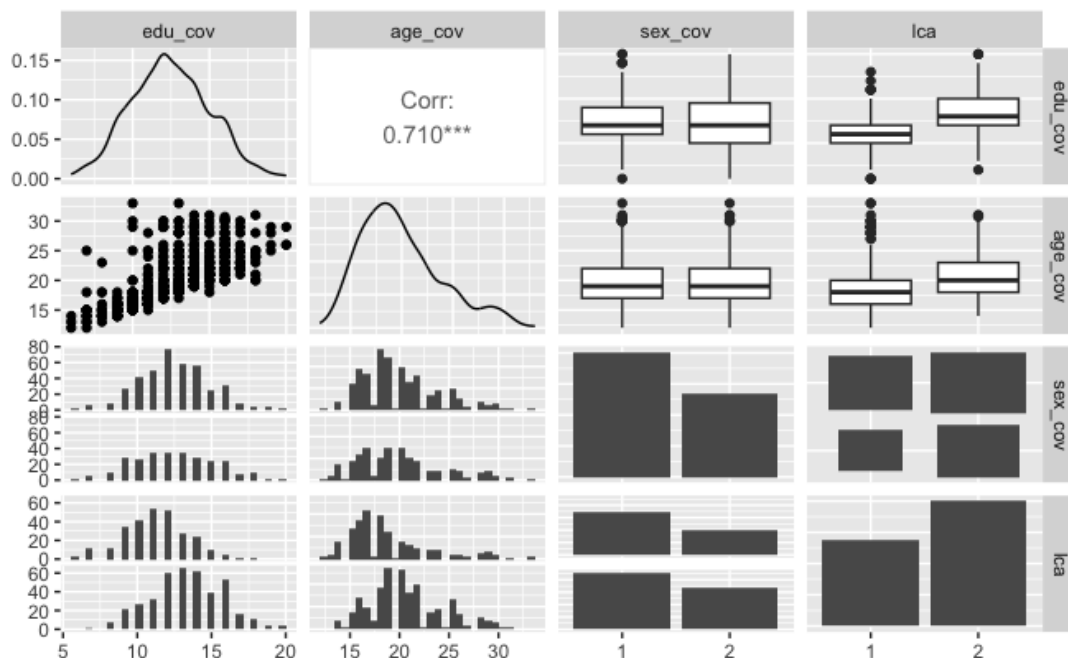


Figure 13: Assumption Testing for Appendices A-C, multicollinearity

3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	lca
2.36	2.07	1.01	1.21

1. Linearity of continuous predictor variables to response variable

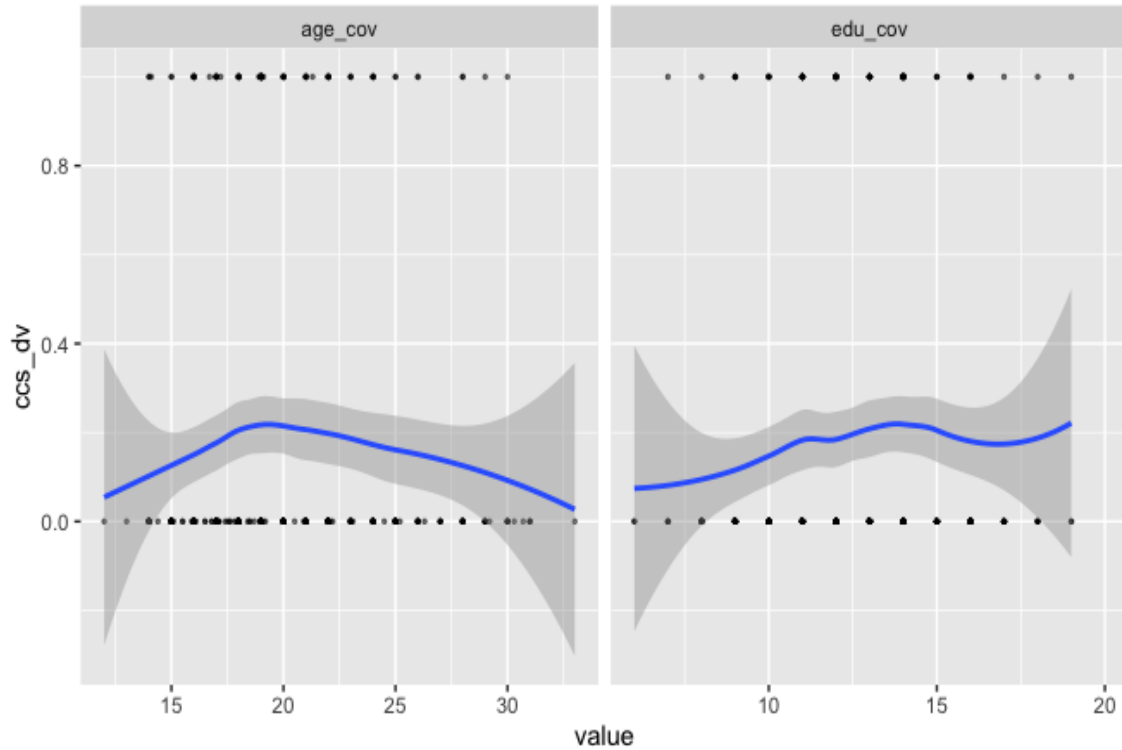


Figure 14: Appendix A CCS (2-Level) Outcome- LCA with GCI, linearity

2. Multicollinearity; demonstrated above

3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	lca
2.76	2.40	1.01	1.24

1. Linearity of continuous predictor variables to response variable

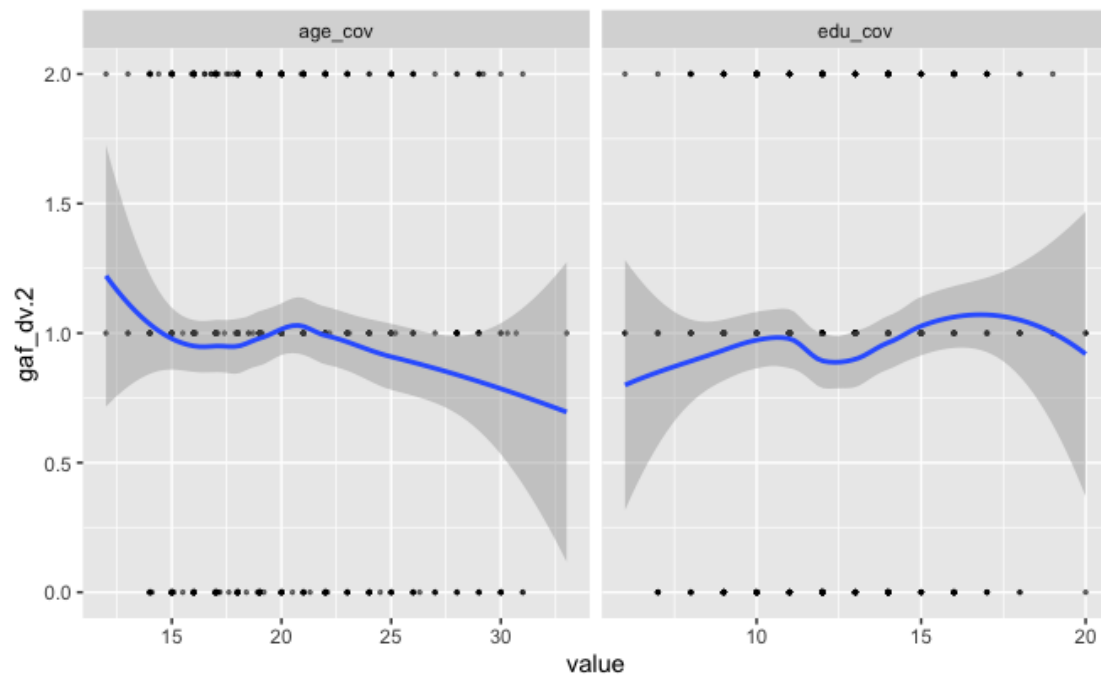


Figure 15: Appendix A GAF (3-level) Outcome- LCA with GCI, linearity

2. Multicollinearity; demonstrated above

3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	lca
2.35	2.07	1.01	1.21

1. Linearity of continuous predictor variables to response variable

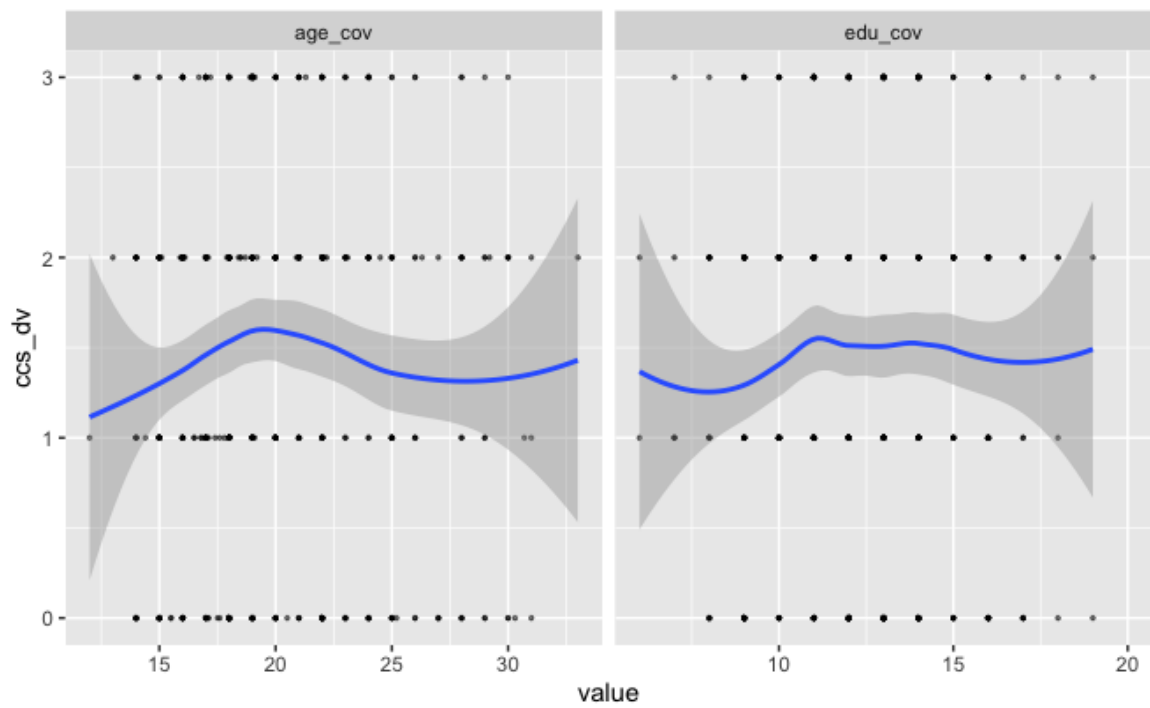


Figure 16: Appendix A CCS (3-Level) Outcome- LCA without GCI, linearity

2. Multicollinearity

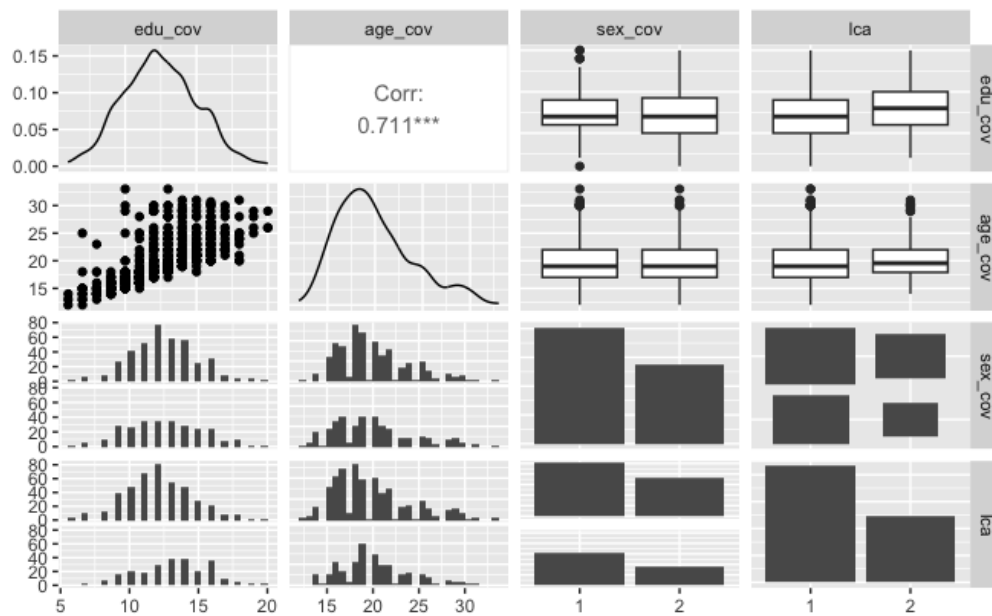


Figure 17: Appendix A CCS (3-Level) Outcome- LCA without GCI, multicollinearity

3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	lca
2.17	2.11	1.00	1.07

1. Linearity of continuous predictor variables to response variable

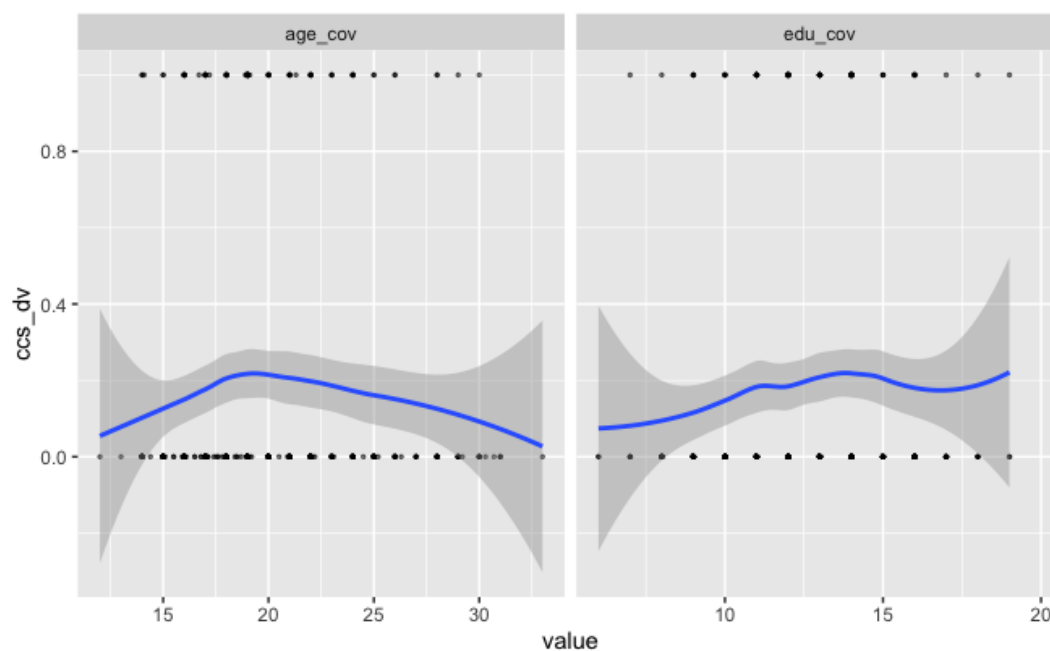


Figure 18: Appendix A CCS (2-Level) Outcome- LCA without GCI, linearity

2. Multicollinearity; described above

3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	lca
2.76	2.41	1.01	1.25

1. Linearity of continuous predictor variables to response variable

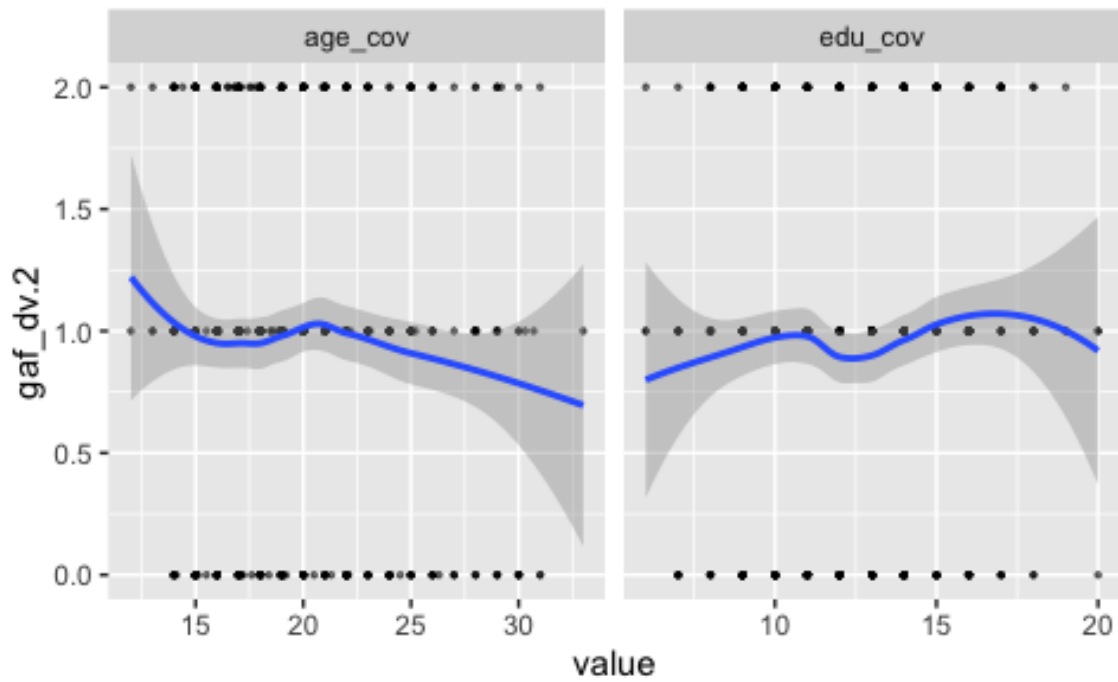


Figure 19: Appendix A CCS (3-Level) Outcome- LCA without GCI, linearity

2. Multicollinearity; demonstrated above

3. Variation Inflation Factor

edu_cov	age_cov	sex_cov	lca
2.34	1.08	1.01	1.21

Appendix B. Assumption testing for 5–20-year long-term follow-up (LTF) logistic regressions (ggplot2, GGalley)

1. Linearity of continuous predictor variables to response variable

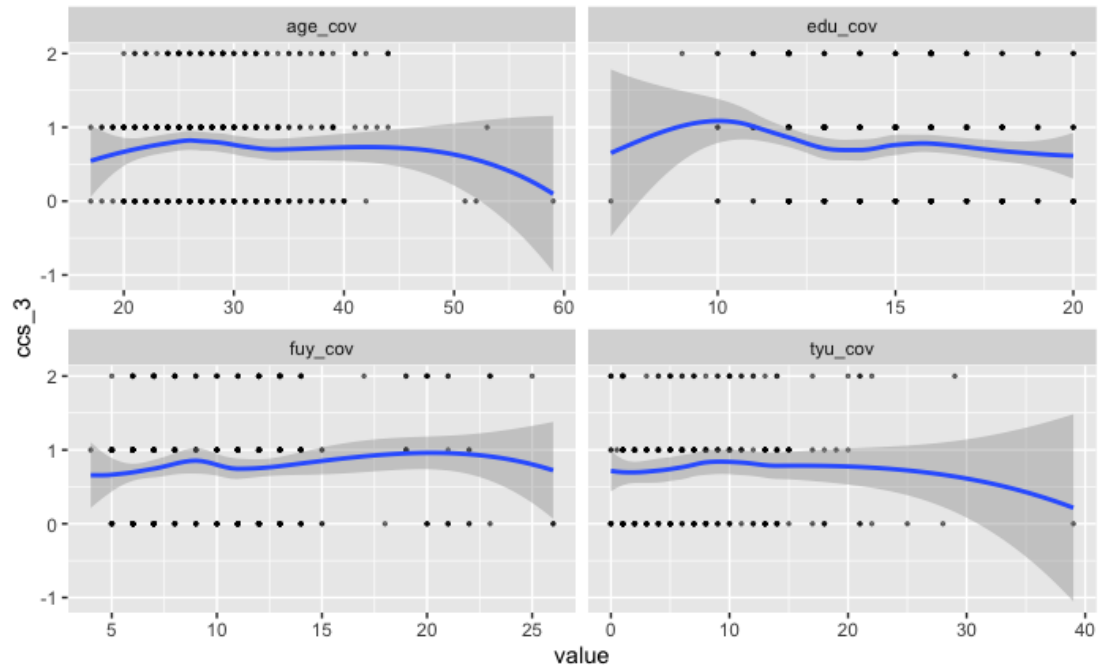


Figure 20: Appendix B CCS (3-Level) Outcome- LCA with GCI, linearity

1. Multicollinearity

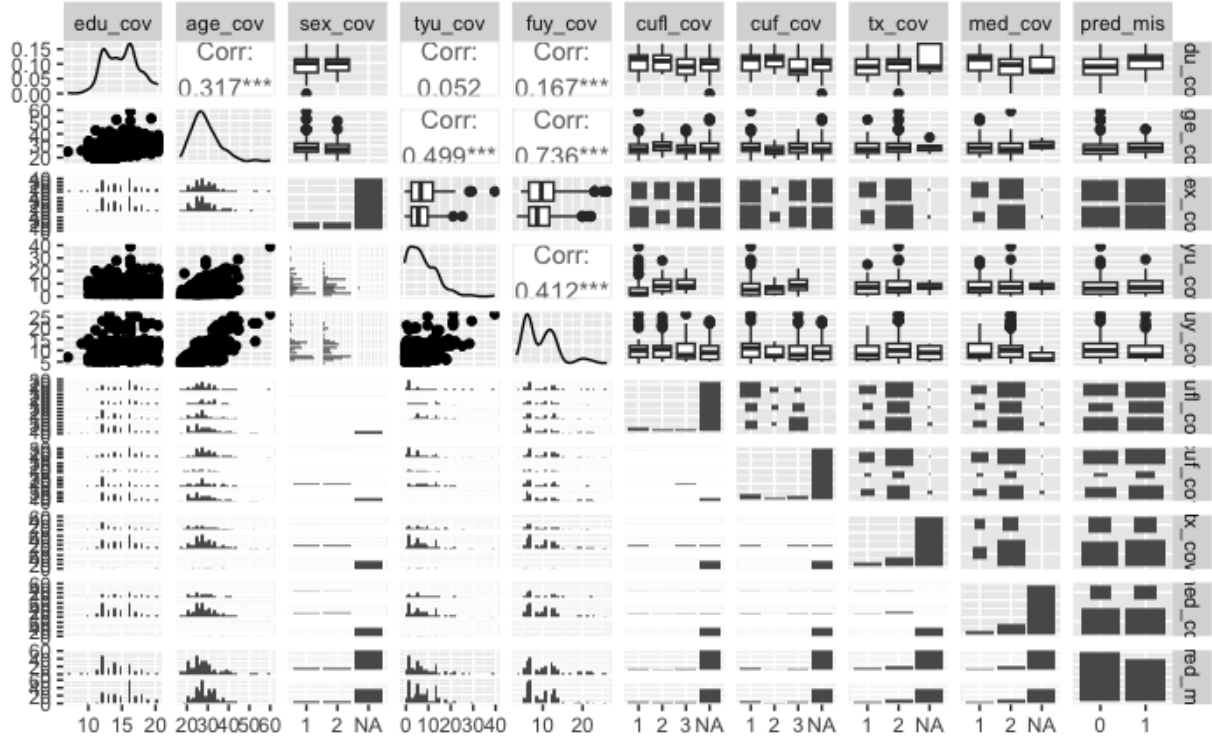


Figure 21: Appendix B CCS (3-Level) Outcome- LCA with GCI, multicollinearity

2. Variance Inflation Factors

edu_co	age_co	sex_co	pred_mi	tyu_co	fuy_co	cufl_co	cuf_co	tx_co	med_co
v	v	v	s	v	v	v	v	v	v
1.44	3.17	1.05	1.20	1.68	2.59	1.70	1.53	1.12	1.12

1. Linearity of continuous predictor variables to response variable

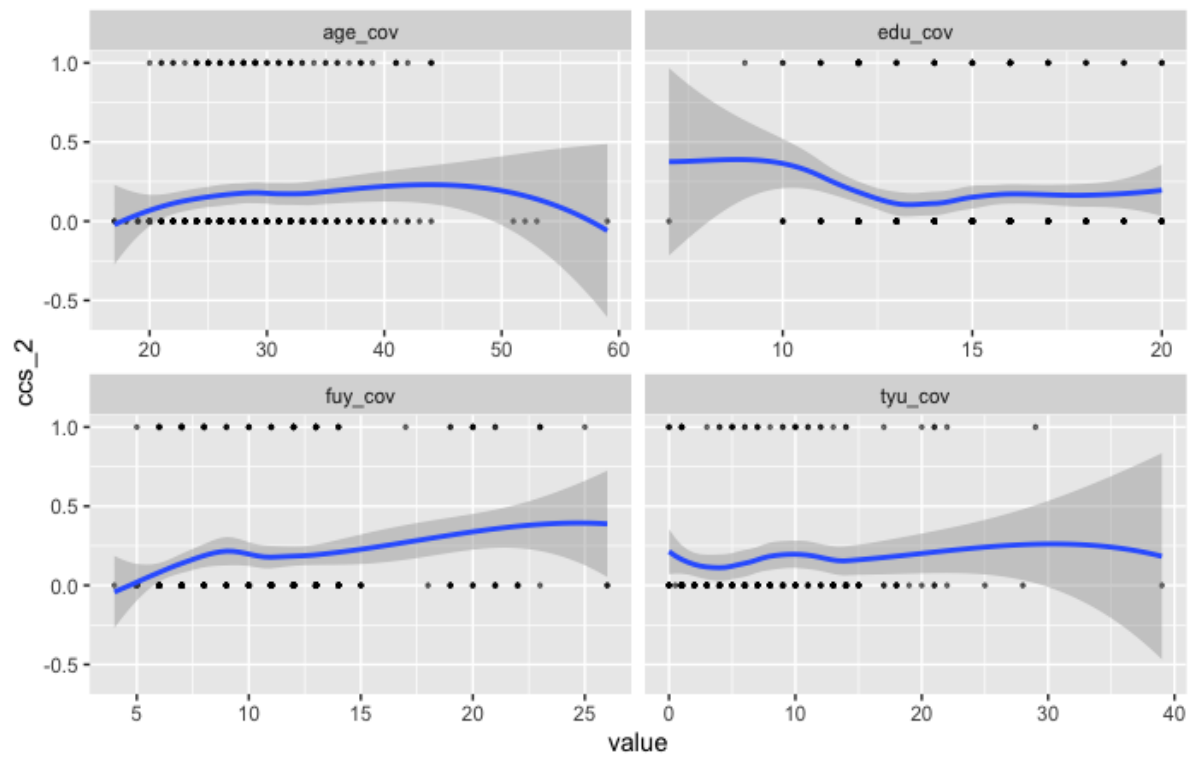


Figure 22:Appendix B CCS (2-Level) Outcome- LCA with GCI, linearity

2. Multicollinearity; demonstrated above
3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	pred_mis	tyu_cov	fuy_cov	cuf_l_cov	cuf_cov	tx_cov	med_cov
1.44	3.40	1.11	1.19	1.78	2.83	1.79	1.63	1.14	1.06

1. Linearity of continuous predictor variables to response variable

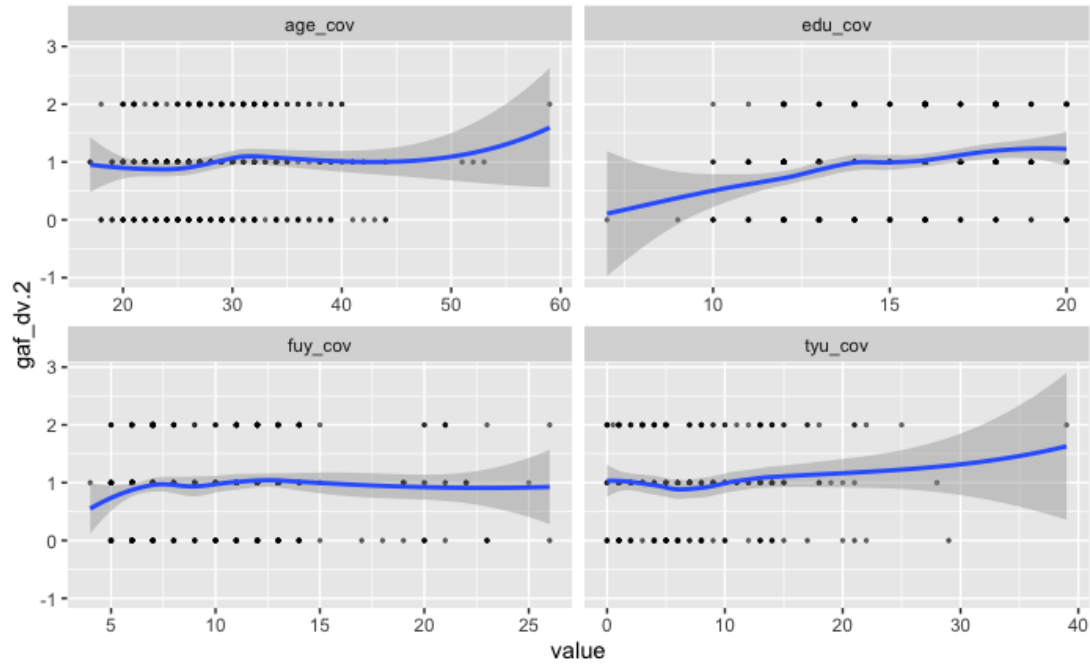


Figure 23: Appendix B GAF (3-Level) Outcome -LCA With GCI, linearity

2. Multicollinearity; demonstrated above
3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	pred_mis	tyu_cov	fuy_cov	cuf1_cov	cuf_cov	tx_cov	med_cov
1.44	3.40	1.11	1.19	1.78	2.83	1.79	1.63	1.14	1.06

1. Linearity of continuous predictor variables to response variable

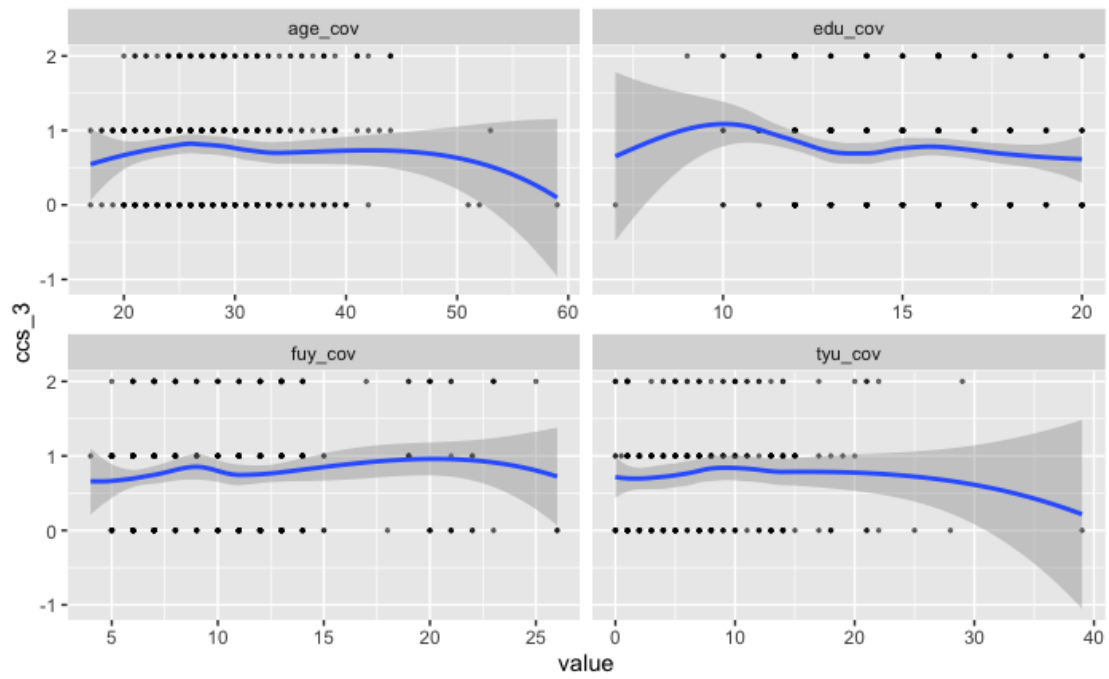


Figure 24: Appendix B CCS (3-Level) Outcome- LCA without GCI, linearity

2. Multicollinearity, demonstrated above

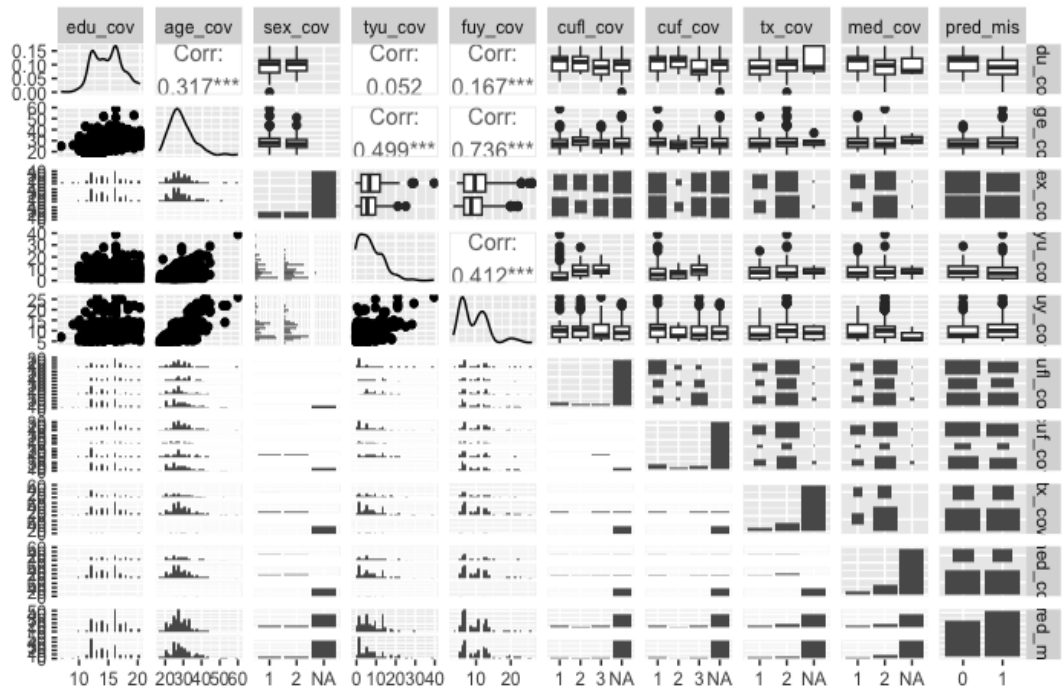


Figure 25: Appendix B CCS (3-Level) Outcome- LCA without GCI, multicollinearity

3. Variance Inflation Factors

edu_cov	age_cov	sex_cov	pred_mis	tyu_cov	fuy_cov	cuf_l_cov	cuf_cov	tx_cov	med_cov
1.44	3.07	1.10	1.10	1.38	2.38	1.70	1.53	1.16	1.20

1. Linearity of continuous predictor variables to response variable

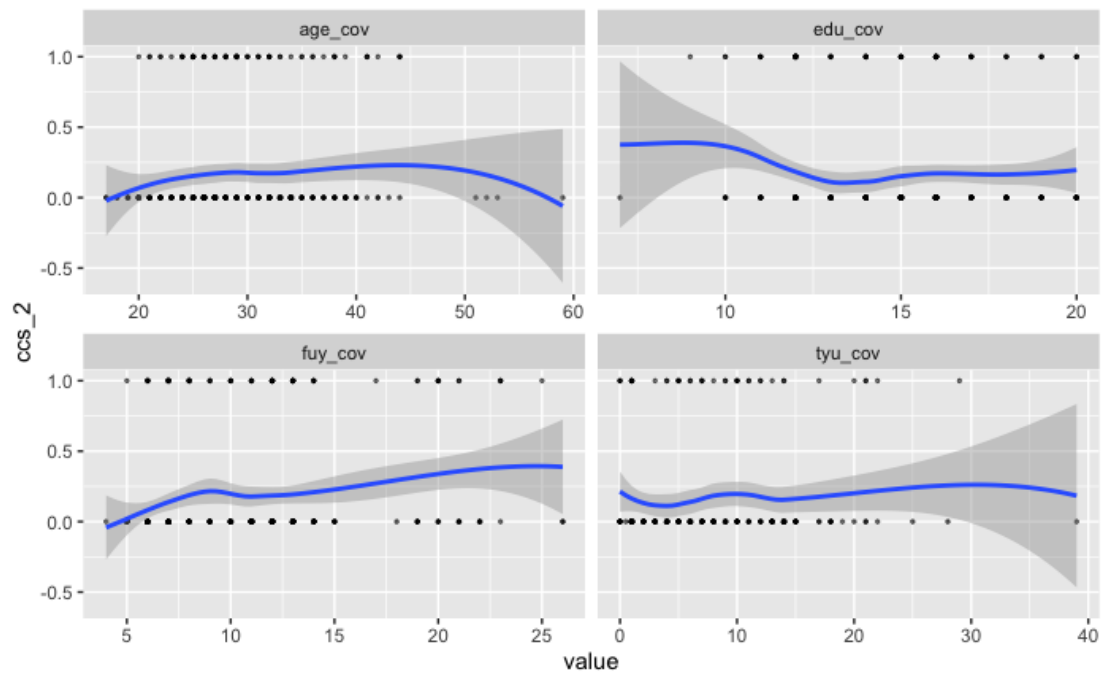


Figure 26: Appendix B CCS (2-Level) Outcome- LCA without GCI, linearity

2. Multicollinearity; demonstrated above
3. Variance Inflation Factors

edu_co	age_co	sex_co	pred_mi	tyu_co	fuy_co	cufi_co	cuf_co	tx_co	med_co
v	v	v	s	v	v	v	v	v	v
1.42	3.28	1.10	1.09	1.81	2.68	1.80	1.62	1.14	1.06

1. Linearity of continuous predictor variables to response variable

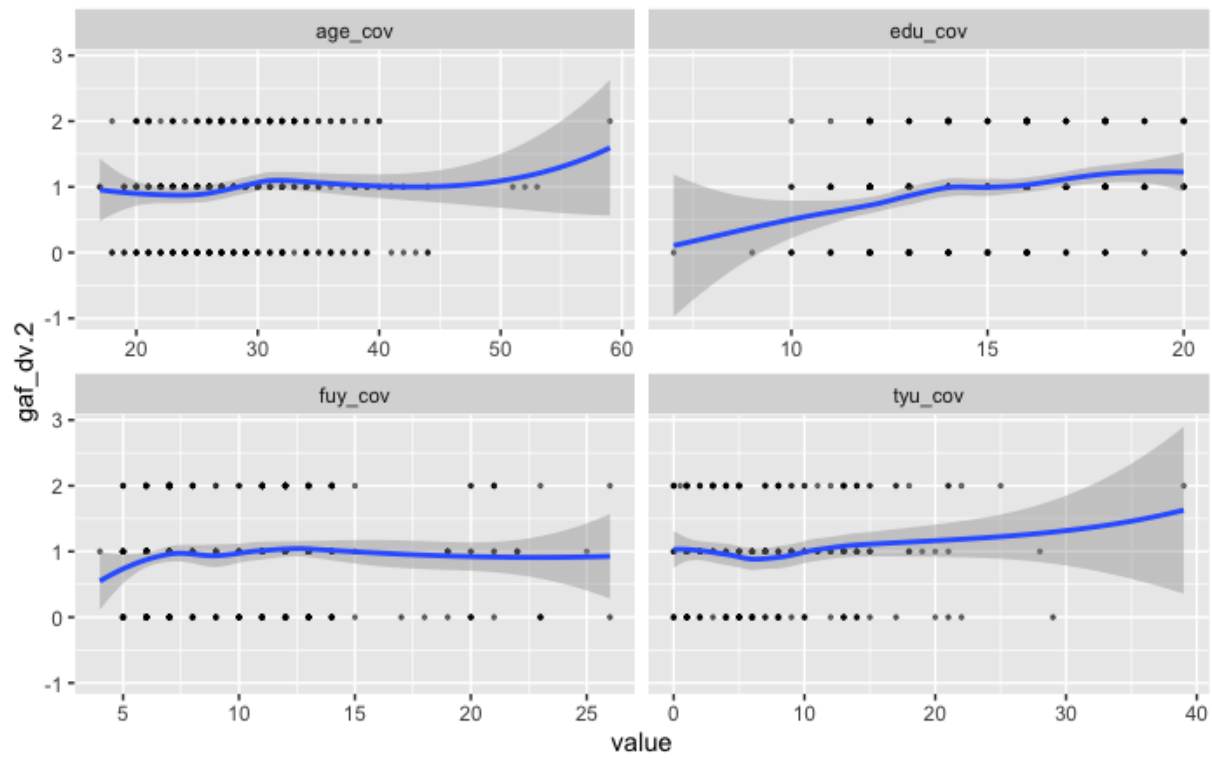


Figure 27: Appendix B GAF (3-Level) Outcome- LCA without GCI, linearity

2. Multicollinearity; demonstrated above

3. Variance Inflation Factors

edu_co	age_co	sex_co	pred_mi	tyu_co	fuy_co	cufi_co	cuf_co	tx_co	med_co
v	v	v	s	v	v	v	v	v	v
1.44	3.12	1.08	1.08	1.87	2.43	1.82	1.55	1.13	1.07

Appendix C. Assumption testing for 5-20 year follow-up (LTF) psychosis diagnosis (affective vs. non-affective) logistic regressions (ggplot2, GGalley)

1. Linearity of continuous predictor variables to response variable

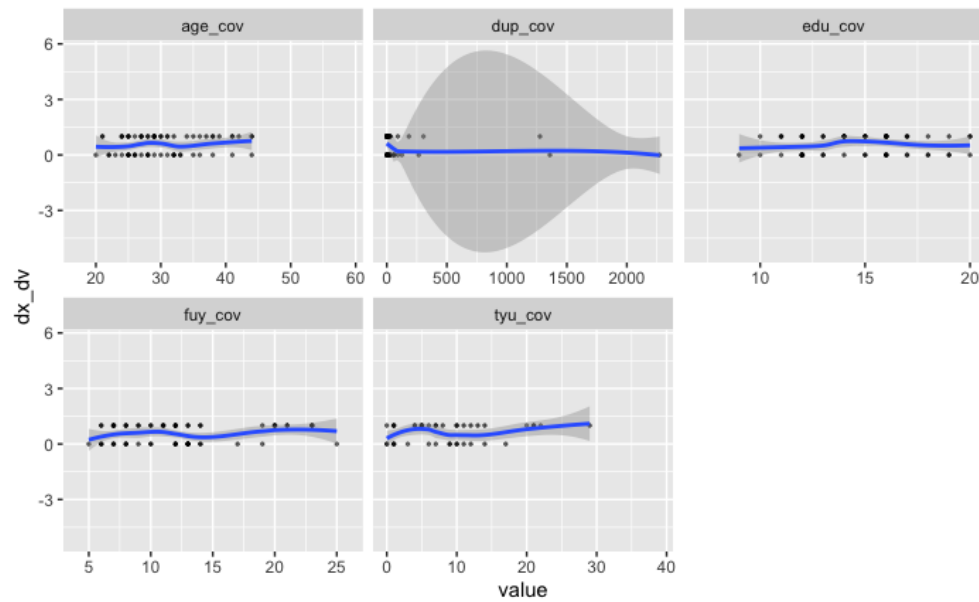


Figure 28: Appendix C Binary Diagnosis Outcome-LCA with GCI, linearity

2. Multicollinearity

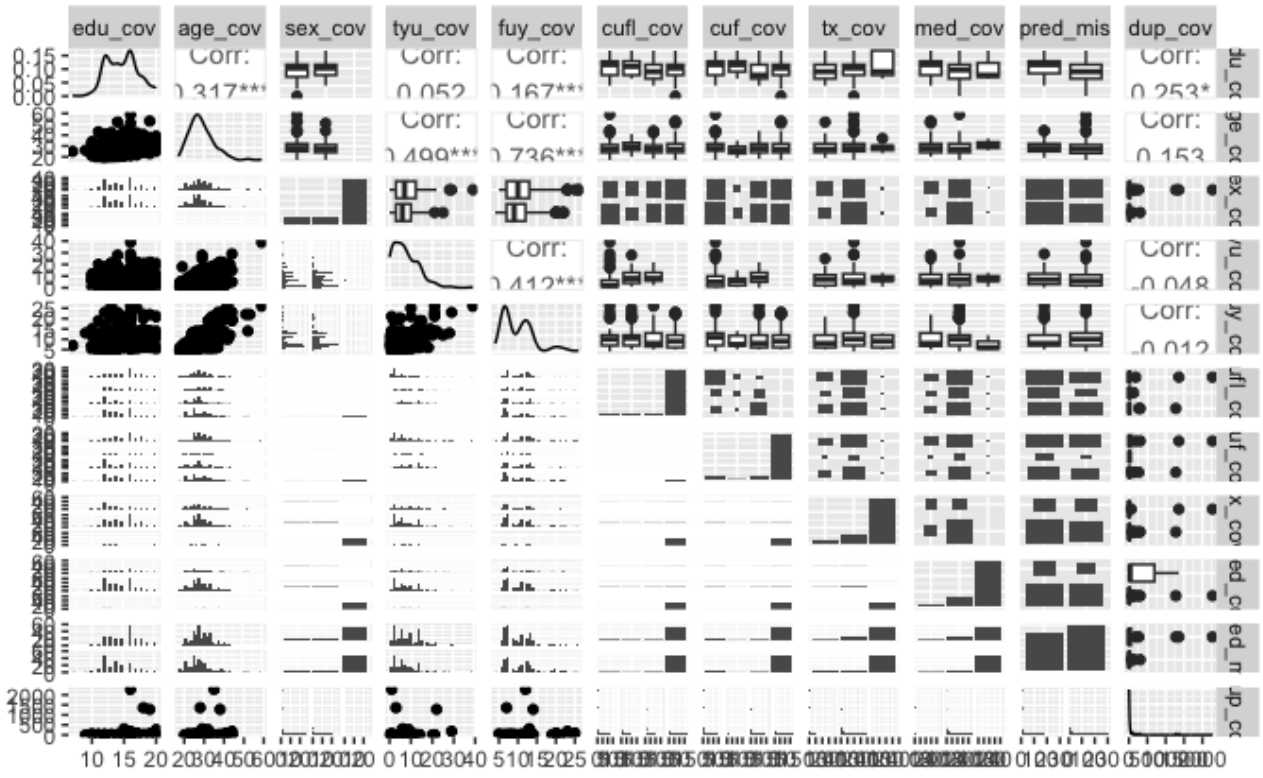


Figure 29: Appendix C Binary Diagnosis Outcome-LCA with GCI, multicollinearity

3. Variance Inflation Factors

edu_co v	age_co v	sex_co v	pred_mi s	tyu_co v	fuy_co v	cufl_co v	cuf_co v	tx_co v	med_co v	dup_co v
2.43	3.33	2.62	2.24	3.93	3.66	3.82	2.04	2.36	1.0	1.30

1. Linearity of continuous predictor variables to response variable; demonstrated above
2. Multicollinearity

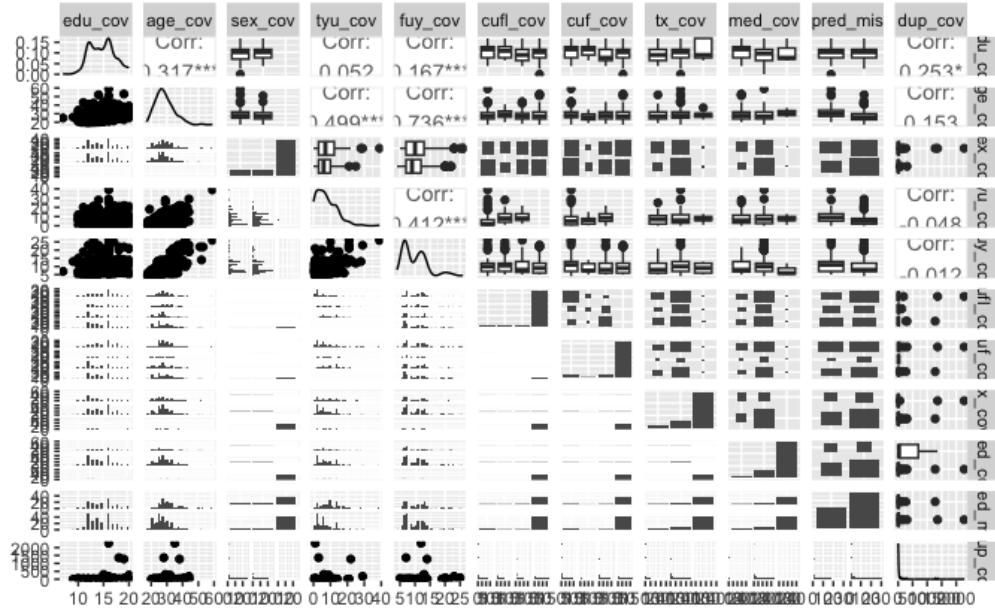


Figure 30: Appendix C Binary Diagnosis Outcome-LCA with GCI, multicollinearity

3. Variance Inflation Factors

edu_co v	age_co v	sex_co v	pred_m is	tyu_co v	fuy_co v	cufl_co v	cuf_co v	tx_co v	med_co v	dup_co v
2.07	3.29	1.89	1.59	3.84	2.46	3.17	2.35	1.95	1	1.23