Data-driven subphenotypic dissection of the clinical heterogeneity of schizophrenia spectrum disorders

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CHAPTER 8

Nederlandse samenvatting

List of Research Institute SHARE thesis

Acknowledgments

About the author

Nederlandse samenvatting

Eén van de belangrijkste uitdagingen voor de traditionele classificatie van psychische stoornissen, waaronder schizofrenie-spectrumstoornissen is wel de heterogeniteit (én de homogeniteit) van het fenotype binnen en tussen stoornissen. De heterogeniteit kan deels verklaard worden door het ontbreken van objectieve diagnostische criteria, maar ook door de hoge comorbiditeit met andere psychiatrische en somatische aandoeningen. Het doel van mijn proefschrift was om de fenotypische heterogeniteit van schizofrenie-spectrumstoornissen te ontleden met behulp van data-gestuurde statistische benaderingen. Het onderzoek werd uitgevoerd binnen het Genetic Risk and Outcome Project (GROUP), een naturalistische, longitudinale cohort studie in de Nederlandse bevolking. GROUP maakt het mogelijk om patiënten met een schizofrenie-spectrumstoornis (N=1.119) te vergelijken met hun nog niet-getroffen broers en zussen die genetische en omgevingsrisicofactoren delen met patiënten (N=1.059), en met de controlepersonen die een basisrisico hebben (N=586). Dit proefschrift onderzocht de rol van socio-demografische, klinische, cardiometabole risicofactoren, en van de genetische risicofactoren, zoals de polygene risicoscore van schizofrenie (PRS_{SCZ}), en diabetes type 2 (PRS_{T2D}) op het beloop van de stoornis. In **Hoofdstuk 2** tot en met **5** werd aangetoond dat positieve, negatieve en cognitieve symptomen zeer heterogeen zijn; er werden tot zes subtypen met variabele trajecten door de tijd onderscheiden. Daarnaast waren verschillende socio-demografische en klinische factoren geassocieerd met het beloop van deze symptomen. We vonden beperkt bewijs dat genetische risico het symptoomverloop beïnvloedt. **Hoofdstuk 6** toonde aan dat metabole ontregeling, gemeten als geglyceerde hemoglobine (HbA1c), geassocieerd was met hogere leeftijd waarop schizofrenie zich openbaart.

Hoofdstuk 2 beschrijft een systematisch review van 34 cross-sectionele en 19 longitudinale, data-gedreven studies die clusters en trajecten van positieve, negatieve en cognitieve symptomen onderzochten in patiënten, broers en zussen en gezonde controles. Ik toonde aan dat cross-sectionele studies tussen de twee en de vijf clusters rapporteerden, en longitudinale studies twee tot zes trajecten. Van de 58 onderzochte factoren, waren socio-demografische kenmerken, zoals mannelijk geslacht, hogere leeftijd, lager opleidingsniveau, en een niet-Kaukasische etniciteit geassocieerd met symptomatische clusters en trajecten. Daarnaast waren klinische factoren belangrijke voorspellers van clusters en/of trajecten,

waaronder hoge leeftijd van ziekteopenbaring, ernstige positieve en negatieve symptomen, beperkte cognitieve functie, comorbide stoornissen, aanwezigheid van depressieve symptomen, laag pre-morbide functioneren, laag globaal functioneren en een slechte kwaliteit van leven. De review liet ook een aantal methodologische beperkingen zien in eerdere cluster- en traject gebaseerde studies, waaronder gebrek aan modelvalidatie, gebruik van verschillende instrumenten om vergelijkbare symptoomdimensies te meten, gebrek aan een fit-to-purpose studieopzet, onvoldoende data-analyse, en het ontbreken van richtlijnen voor het publiceren van data gedreven studies. De heterogeniteit in het klinisch verloop van de symptomen en de bijbehorende factoren was overtuigend, ondanks de methodologische beperkingen in de verschillende studies. Het definiëren van subgroepen binnen symptomen en het identificeren van hun voorspellers kan helpen om patiënten met zekerheid toe te wijzen aan één homogene groep, teneinde klinische en functionele uitkomstem en de respons op interventies beter te voorspellen. Samenvattend, kan deze kennis bijdragen aan de ontwikkeling van een model voor het voorspellen van ziekterisico's of behandeluitkomsten, en uiteindelijk aan de implementatie van gepersonaliseerde zorg.

In Hoofdstuk 3 worden sub-fenotypering, polygene risicoscores en data-gedreven methodes gecombineerd om voor het eerst het zesjarige klinische beloop van positieve en negatieve symptomen te onderzoeken en om onderliggende genetische en niet-genetische factoren te identificeren bij patiënten, gezonde broers en zussen en gezonde controles. Deze studie rapporteerde drie trajecten van positieve en negatieve symptomen bij patiënten en controles, en vier trajecten bij broers en zussen, die omschreven konden worden als stabiele, afnemende, toenemende en terugvallende longitudinale patronen. Deze studie toonde ook aan dat er een verband bestaat tussen PRS_{SCZ} en trajecten van positieve en negatieve symptomen, hoewel dit verband verdween na correctie voor co-variaten. Een laag pre-morbide functioneren, een slechte kwaliteit van leven en ernstige positieve en negatieve symptomen aan het begin van de studie, waren de sterkste voorspellers. Bovendien bleken geringe positieve en negatieve symptomen gerelateerd te zijn aan een normaal tot bovengemiddeld cognitief functioneren. Kortom, heb ik aangetoond dat zowel positieve als negatieve symptomen even heterogeen zijn een vergelijkbaar verloop in de tijd hebben en dat zowel omgevings als genetische factoren van belang zijn.

In **Hoofdstuk 4** onderzocht ik de heterogeniteit en stabiliteit van algemene cognitie bij patiënten en gezonde broers en zussen. Om het effect van familiaal genetisch en omgevingsrisico te onderzoeken, poogde deze studie de cognitieve subtypes van gezonde broers en zussen te voorspellen aan de hand van de subtypes van hun zieke verwanten. Ik identificeerde vijf (in patiënten) en vier (in gezond verwanten) stabiele cognitieve trajecten, variërend van sterk verminderde tot hoge cognitieve prestaties. Het cognitieve traject van de patiënten voorspelde het cognitieve traject van hun gezonde broers en zussen. Bovendien verschilden patiënten en broers en zussen met cognitieve stoornissen significant van diegenen zonder cognitieve stoornissen op het gebied van baseline IQ, educatieniveau, premorbide functioneren, en positieve en negatieve symptomen. De cognitieve stoornissen van de broers en zussen waren stabiel, en over het geheel iets minder ernstig dan bij de patienten. Dit maakt deze cognitieve trajecten tot een geschikt endofenotype voor schizofrenie, vooral voor genetische studies.

Hoofdstuk 5 onderzocht de relatie tussen PRS_{SCZ} en cognitieve stoornissen bij patiënten, gezonde broers en zussen, gezonde controles, en alle deelnemers samen. Vijf cognitieve subtypes met variabele trajecten werden geïdentificeerd bij patiënten, vier bij broers en zussen en controles, en zes bij alle deelnemers samen. Opmerkelijk genoeg voorspelde PRS_{SCZ} significant ernstige cognitieve dysfunctie binnen de gecombineerde sample. Deze bevindingen onderschrijven het heterogene karakter van de cognitieve stoornissen en tonen aan dat PRS_{SCZ} vooral ook cognitieve stoornissen voorspelt. Deze resultaten versterken het bewijs gevonden in het **Hoofdstuk 4 en** ondersteunen de hypothese dat cognitie een geschikt endofenotype voor schizofrenie is.

Hoofdstuk 6 beschrijft de associatie tussen PRS_{SCZ} en HbA1c bij patiënten met een niet-effectieve psychose. Ik vond geen bewijs voor een verband tussen een hoog HbA1c-niveau en een verhoogde PRS_{SCZ}, wat aangeeft dat het genetische risico op schizofrenie geen invloed lijkt te hebben op het risico op metabole stoornissen. Daarbij was een oudere leeftijd van eerste psychose geassocieerd met een hoog HbA1c-niveau. Deze bevindingen suggereren dat aandoeningen als hyperglykemie ten minste gedeeltelijk onafhankelijk zijn van de genetische aanleg voor SCZ. Hyperglykemie toont wel een verband met PRS_{T2D}, hogere leeftijd van aanvang van de ziekte, het mannelijk geslacht, een verhoogde body mass index en een hoge diastolische bloeddruk.

Tot slot, het bleek uit dit proefschrift dat schizofrenie onderverdeeld kan worden in twee tot zes subgroepen met verschillende symptoomernst, gekenmerkt door stabiele, toenemende, afnemende en terugvallende trajecten in de loop van de tijd. Deze subgroepen onderscheiden zich door verschillende socio-demografische, genetische, metabole en klinische factoren. Het gebruik van cognitieve endofenotypes om subgroepen van patiënten met schizofrenie-spectrum stoornissen te identificeren kan van betekenis zijn voor de gepersonaliseerde psychiatrie.

Data-gedreven methoden kunnen helpen schizofrenie-spectrumstoornissen te ontrafelen, door alle symptoomdomeinen van zowel gezonde als aangedane personen samen te voegen.

De geïdentificeerde subgroepen kunnen ondersteunen bij behandelkeuze, om zo de doeltreffendheid van de behandeling te verbeteren en om de kosten te minimaliseren en onnodige bijwerkingen van antipsychotica, zoals cardiometabole dysfunctie, te voorkomen. Bovendien kunnen deze bevindingen van dienst zijn bij het ontwerpen van toekomstige onderzoeken of de retrospectieve her-analyse van eerdere onderzoeken en kunnen ze clinici helpen bij het beter begrijpen van de heterogeniteit van schizofrenie. Bovendien kunnen -zolang er geen objectieve diagnostische criteria voor schizofrenie bestaan- de bevindingen in dit proefschrift bijdragen aan een nauwkeurige voorspelling en diagnostisering van schizofrenie.

Tot slot, zal mijn proefschrift hopelijk een wake-up call zijn voor het ontwikkelen van DSM-6 door het karakteriseren van aandoeningen, niet per categorie, maar op basis van een verzameling van symptomen langs het continuüm, rekening houdend met het verloop van de ziekte.

Research Institute SHARE theses

These theses are recently published within the **Research Institute SHARE** (Science in Healthy Ageing and healthcaRE) of the University Medical Center Groningen / University of Groningen. Further information regarding the institute and its research can be obtained from our internet site: http://www.share.umcg.nl/

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About the author

Biography

Tesfa Dejenie Habtewold was born on January 29, 1987 in Yewello, Ethiopia. In 2009, he graduated and obtained his Bachelor of Science (B.Sc.) degree in Nursing from Hawassa University, Ethiopia. In 2013, he obtained his Master of Science (M.Sc.) degree in Adult Health Nursing from Addis Ababa University, Ethiopia. He did his master thesis entitled "Identifying factors affecting depressive symptoms in patients diagnosed with type 2 diabetes" at Black Lion Hospital, Addis Ababa, Ethiopia. Since 2013, he has worked as a lecturer at the Debre Berhan University, Ethiopia. In 2015, he is also registered as Chief Adult Health Nurse practitioner by the Amhara National Regional State Health Bureau. In the same year, he started with the M.Sc. in Clinical and Psychosocial Epidemiology at the University of Groningen, Groningen, the Netherlands and obtained his degree in 2017. He did his master thesis entitled "Polygenic risk score for schizophrenia and glycemic level (HbA1c) in patients with non-affective psychosis" under the supervision of Dr. B. Z. Alizadeh and Prof. R. Bruggeman at University Medical Center Groningen (UMCG), the Netherlands.

In September 2017, he started with his Ph.D. project under the supervision of Dr. B. Z. Alizadeh, Prof. R. Bruggeman, Prof. M. Boezen, and Dr. E. Liemburg at the department of Epidemiology and University Center Psychiatry at the UMCG. His research project was part of the Genetic Risk and Outcome of Psychosis (GROUP) national cohort study in the Netherlands. The project focus on data-driven, subphenotyping and polygenic risk score analyses in patients with schizophrenia spectrum disorders, their unaffected siblings and healthy controls. His research focus is on epidemiological and statistical modeling of schizophrenia spectrum disorders, major depressive disorders and bipolar disorders. He has been co-authored in more than 30 papers. He also finished Senior Scientific Epidemiological Researcher (Epidemiologist B) training by the Netherlands Epidemiological Society

(VvE). Additionally, he was a teaching assistant in Epidemiology and Applied Statistics course and co-supervised two research master degree theses. Moreover, he works for two years as SHARE Ph.D. council member. During his Ph.D. study, he got married to Kenean Tesfaye and have a handsome son (Noah Tesfa).

After three years, in September 2020, his thesis was submitted to the reading committee and it will be defended on the 1st of February 2021. Since September 2020, he is working as a postdoc at the department of Quantitative Economics, Maastricht University, Maastricht, the Netherlands. The project, coordinated by Dr. Nalan Bastürk, Prof. F. Peeters and Dr. S. van Bronswijk, investigates treatment effectiveness and dropout in patients with major depressive disorder.

Master thesis co-supervisor

1. Prospective prediction of social inclusion in patients with schizophrenia-spectrum disorder. A follow-up Study in Dutch population.
2. Housing Trajectories in Schizophrenia and the influence of cognitive profiles, quality of life and social functioning.

Publications of the PhD thesis

1. **Habtewold TD**, Rodijk LH, Liemburg EJ, Sidorenkov G, Boezen HM, Bruggeman R, Alizadeh BZ. A systematic review and narrative synthesis of data-driven studies in schizophrenia symptoms and cognitive deficits. **Translational psychiatry**. 2020; 10:224. (Chapter 2)
2. Heterogeneity of clinical trajectories, disease liability and underlying factors in schizophrenia spectrum disorders: data-driven phenotypic analyses. (**Accepted in Molecular Psychiatry**) (Chapter 3)
3. Islam MA, **Habtewold TD**, van Es FD, Quee PJ, van den Heuvel ER, Alizadeh BZ, Bruggeman R, GROUP Investigators, BartelsVelthuis AA, van Beveren NJ, Cahn W. Long term cognitive trajectories and heterogeneity in patients with schizophrenia and their unaffected siblings. **Acta Psychiatrica Scandinavica.** 2018; 138:591-604. (Chapter 4)
4. **Habtewold TD**, Liemburg EJ, Islam MA, de Zwarte SM, Boezen HM, GROUP Investigators, Bruggeman R, Alizadeh BZ. Association of schizophrenia polygenic risk score with data-driven cognitive subtypes: a six-year longitudinal study in patients, siblings and controls. **Schizophrenia Research**. 2020; 223: 135-147. (Chapter 5)
5. **Habtewold TD**, Islam MA, Liemburg EJ, GROUP Investigators, Bruggeman R, Alizadeh BZ. Polygenic risk score for schizophrenia was not associated with

glycemic level (HbA1c) in patients with non-affective psychosis: Genetic Risk and Outcome of Psychosis (GROUP) cohort study. **Journal of Psychosomatic Research.** 2020; 132:109968. (Chapter 6)

Book chapter publication

1. Stevanovic D, **Habtewold TD**, Niksić A, Avicena M, Mehta G, Popović L, Erić AP, Ristic S, Ćurković KD, Bježančević M, Stanković M, Pavlović TA, Knez R. **Anxiety and depressive disorders in diabetes.** In. Sadikot's International Textbook of Diabetes. Jaypee Brothers, Medical Publishers Pvt. Limited; 2019, Page 823-828.

Other publications

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