Statistical approaches to explore clinical heterogeneity in psychosis

Islam, Atiqul

Addendums

Nederlandse Samenvatting (Dutch summary)

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Nederlandse Samenvatting

Mensen met psychotische stoornissen laten grote verschillen zien op het gebied van symptomen (zoals positieve en negatieve symptomen en cognitieve beperkingen) en de presentatie daarvan. Deze heterogeniteit wordt al lang onderkend, maar desondanks vaak genegeerd, zowel in de klinische praktijk als in het onderzoek. Het hoofddoel van dit proefschrift is dan ook het ontrafelen van de heterogeniteit in cognitief functioneren en van de klinische symptomen bij mensen met een psychotische stoornis en hun niet-zieke broers en zusters, gebruikmakend van cross-sectionele en longitudinale gegevens. De nadruk ligt bij dit alles vooral op de statistische benaderingen die zijn gebruikt.

Eén manier om heterogeniteit te onderzoeken bij patiënten met eenzelfde diagnose is door datareductie technieken, zoals klassieke clusteranalyse, en ”group-based trajectory models (GBTM)” toe te passen, om hiermee homogene subtypes te vormen. De studies in dit proefschrift zijn allemaal uitgevoerd binnen het GROUP (Genetic Risk and Outcome of Psychosis) project. Dit is een grote longitudinale multicenter cohort studie in Nederland en België met een uitgebreide eerste meting, gevolgd door nog twee metingen na drie en na zes jaar.

Hoofdstuk 1 geeft een inleiding in de schizofrenie spectrumstoornissen, de klinische heterogeniteit, en de statistische technieken die geschikt zijn om heterogeniteit te kunnen bestuderen. Er is aanzienlijk bewijs voor significante heterogeniteit in cognitief functioneren en klinische symptomen.

In **Hoofdstuk 2** wordt een overzicht gegeven van de meest belovende indices (methodes) om het juiste aantal clusters te berekenen op basis van een hiërarchische clustertechniek, gebruikmakend van de Ward’s agglomeratiemethode. Deze indices zijn toegepast op een achttal cognitieve uitkomstvariabelen bij patiënten met schizofrenie (“case study”) en binnen simulatiedata. Van de 14 onderzochte indices bleken Duda en Hart (DH), Hartigan (H) en Gap/pc de best voorspellende indices. De DH index was het meest consistent, terwijl Gap/pc en WGap/pc in staat bleken te zijn om de aanwezigheid van meerdere clusters aan te tonen.

Hoofdstuk 3 toont cognitieve subtypes van patienten met schizofrenie en hun broers/zussen aan, op basis van een gemiddelde cognitiescore, gebruikmakend van GBTM. Er werden bij patienten vijf subtypes gevonden en bij hun broers en zussen vier subtypes, die stabiel bleken te zijn over de periode van zes jaar. Met het oog op de familiestructuur van de data (patiënten en hun broers en zussen behoren tot dezelfde familie) werd een “clustered multinominal logistic regression” uitgevoerd, met de vraag of subtypes van patiënten de subtypes van hun broers en zussen zouden voorspellen. Dit bleek significant te voorspellen te zijn. Hoe slechter het cognitieve profiel van de patiënt, hoe beter dit voorspelde wat het subtype van de broers en zussen was (OR 10.07, 95% CI 4.15–24.44). Dit bleek ook voor de groep met gematigd cognitief functioneren te gelden (OR 5.7, 95% CI 2.77–11.70). De intraclass correlatie tussen de index-patiënten en hun broers en zussen verklaarde 27% van de totale variatie.

Hoofdstuk 4 beschrijft de toepassing van GBTM bij het bepalen van homogene groepen van patiënten, gebaseerd op het beloop van de negatieve subdomeinen van symptomen, zoals *social amotivation* (SA) en *expressive deficit* (ED). Ook werd hier de vraag gesteld of deze homogene

groepen bijdragen aan meer inzicht in de subdomeinen van negatieve symptomen, en of zij van belang zijn voor het functioneren en kwaliteit van leven. Voor het beantwoorden van deze tweede vraag werd gebruik gemaakt van (generalized) linear mixed models. Er bleek een significante heterogeniteit te bestaan in het beloop van de negatieve symtpomen, suggererend dat negatieve symptomen minder stabiel zijn dan altijd verondersteld werd. Subgroepen binnen de SA- en ED-groep lieten een verschillend beloop zien. Het klinisch belang van de subtypes werd onderstreept door hun verschillende relaties met het beloop en de ernst van de uitkomstmaten (functioneren en kwaliteit van leven).

In **Hoofdstuk 5** gaat het om de toepassing van een " mixture of generalized linear mixed effects models", die gebruikt werd om de ontwikkeling van psychotische belevingen van broers en zussen van patiënten te beschrijven en de relatie met neuro- en sociale cognitie. Slechter verbaal leren voorspelde het optreden van psychotische belevingen en de daarmee gepaard gaande stress drie jaar later. Bovendien bleken Theory of Mind taken (hinting task) geassocieerd te zijn met een afname van psychotische belevingen na drie jaar. In de Hoofdstukken 4 en 5 werd ook de techniek van Multiple Imputation toegepast.

De heterogeniteit van somatische aandoeningen en klachten van patiënten, hun broers en zussen, en gezonde controle personen wordt beschreven in **Hoofdstuk 6**. Het effect van de familiaire gevoeligheid voor psychosen, naast het effect van geslacht en leeftijd, werd onderzocht met generalized linear mixed effects modelling. Familiaire kwetsbaarheid bleek een significante predictor van multimorbiditeit te zijn.

Hoofdstuk 7 bestudeert de risicofactoren voor de duur van onbehandelde psychose (DOP) met behulp van ordinale logistische regressie, samen met het "Cox-proportional hazard" regressiemodel. DOP geeft de tijd weer tussen het ontstaan van de psychotische klachten en het begin van de behandeling. Uit beide analyses bleken migratiestatus, leeftijd van ontstaan van de klachten en geslacht significant samen te hangen met de DOP. Mannelijke, eerste generatie migranten met een jonge leeftijd van ontstaan van de klachten, bleken het hoogste risico te hebben op een lange DOP.

Tenslotte worden in **Hoofdstuk 8** de belangrijkste bevindingen en de gebruikte statistische benaderingen samengevat en bediscussieerd. Ook wordt het wetenschappelijk belang van de bevindingen besproken, samen met de nieuwe methodologische overwegingen en aanbevelingen voor toekomstig onderzoek.

Samenvattend, voor cross-sectionele data blijkt hiërarchisch clustering volgens de Duda en Hart index de beste benadering te zijn om het aantal clusters te bepalen. Echter, een model-based clustering benadering zou de voorkeur hebben om deze clusters te bevestigen. In longitudinale studies GBTM met finite-mixture modelling voldoet het beste als benadering om omschreven trajectories in beeld te brengen.

Gebruikmakend van deze benaderingswijzen, laat dit proefschrift duidelijk de validiteit van de cognitieve subtypes zien voor patiënten en broers en zussen, die stabiel zijn over de tijd. Daarmee worden ook nieuwe klinische inzichten verschaft. Ook draagt dit proefschrift bij aan onze kennis van negatieve symptomen en de subdomeinen SA en ED, door te laten zien dat deze subtypes persistent zijn en samen hangen met klinische uitkomsten.

De toepassing van een mixture of generalized linear mixed effects modelling bij een “zero-inflated” continue uitkomstmaat van psychotische belevingen bij broers en zussen van patiënten, liet het effect zien van deze parameters op neuro- en sociaal cognitief functioneren. Tegelijkertijd leverde dit belangrijke inzichten op over de klinische ontwikkeling van psychotische symptomen over drie jaar.

Psychotische belevingen en symptomen vormen wellicht een continuüm reikend van de algemene bevolking tot aan mensen met een schizofrenie spectrumstoornis. De bevindingen van dit proefschrift laten echter zien dat voor patienten en hun broers en zussen heterogeniteit bestaat op het gebied van cognitie en negatieve symptomen, en dat betekenisvolle subtypes gevonden kunnen worden. Deze subtypes kunnen tot nieuwe wegen leiden, met meer inzicht en een betere behandeling van mensen met een psychotische stoornis.

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Co-authors

André Aleman: Department of Neuroscience, University Medical Center Groningen, University of Groningen, The Netherlands

Annemarie P. M. Stiekema: School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands

Behrooz Z. Alizadeh: Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands

Bouke Sterk: Department of Psychiatry, Academic Medical Centre, University of Amsterdam, the Netherlands

Edith J. Liemburg: University Center for Psychiatry, Rob Giel Research Center, University of Groningen, University Medical Center Groningen, The Netherlands

Edwin R. van den Heuvel: Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, The Netherlands

Frank D. van Es: University Center for Psychiatry, Rob Giel Research Center, University of Groningen, University Medical Center Groningen, The Netherlands

Gerdina H.M. Pijnenborg: Department of Clinical Psychology, University of Groningen, The Netherlands

Harold Snieder: Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands

Jaap van Weeghel: Parnassia Group, Dijk en Duin Mental Health Center, Castricum, Department of TRANZO, Tilburg School of Social and Behavioral Sciences, Tilburg University, The Netherlands

Lisette van der Meer: University Center for Psychiatry, Rob Giel Research Center, University of Groningen, University Medical Center Groningen, The Netherlands

Mark van der Gaag: Department of Clinical Psychology, VU University and EMGO Institute of health and Care Research, Amsterdam, The Netherlands

M. Feroz Hayat Khan: Consultant, WHO, Bangladesh, and University Center for Psychiatry, Rob Giel Research Center, University of Groningen, University Medical Center Groningen, The Netherlands

Piotr J. Quee: University Psychiatric Centre (UPC), KU Leuven, campus Kortenberg, Leuven, Belgium

Richard Bruggeman: University Center for Psychiatry, Rob Giel Research Center, University of Groningen, University Medical Center Groningen, The Netherlands

Robert A. Schoevers: University Center for Psychiatry, University of Groningen, University Medical Center Groningen, The Netherlands

Sanne Y. Apeldoorn: University Center for Psychiatry, University of Groningen, University Medical Center Groningen, The Netherlands

Stefanie M. de Vries: Department of Clinical and Developmental Neuropsychology, University of Groningen, The Netherlands

Stynke Castelein: University Center for Psychiatry, Rob Giel Research Center, University of Groningen, University Medical Center Groningen, Lentis Psychiatric Institute, The Netherlands

S. Gülöksüz: Department of Psychiatry and Psychology, Maastricht University Medical Center, School for Mental Health and Neuroscience, Maastricht, The Netherlands

Tesfa D. Habtewold: Department of Epidemiology, University Medical Center Groningen, University of Groningen, The Netherlands

Y. van der Steen: Department of Psychiatry and Psychology, Maastricht University Medical Center, School for Mental Health and Neuroscience, Maastricht, The Netherlands

Genetic Risk and Outcome of Psychosis (GROUP) investigators: Behrooz Z. Alizadeh[a], Agna A. Bartels-Velthuis[a], Nico J. van Beveren[b,c,d], Richard Bruggeman[a], Wiepke Cahn[e], Lieuwe de Haan[f], Philippe Delespaul[g], Carin J. Meijer[f], Inez Myin-Germeys[h], Rene S. Kahn[e], Frederike Schirmbeck[f], Claudia J.P. Simons[g,j], Neeltje E. van Haren[e], Jim van Os[g,j], Ruud van Winkel[g,h]

[a]University of Groningen, University Medical Center Groningen, University Center for Psychiatry, Groningen, The Netherlands
[b]Antes Center for Mental Health Care, Rotterdam, The Netherlands
[c]Erasmus MC, Department of Psychiatry, Rotterdam, The Netherlands
[d]Erasmus MC, Department of Neuroscience, Rotterdam, The Netherlands
[e]University Medical Center Utrecht, Department of Psychiatry, Brain Centre Rudolf Magnus, Utrecht, The Netherlands
[f]Academic Medical Center, University of Amsterdam, Department of Psychiatry, Amsterdam, The Netherlands
[g]Maastricht University Medical Center, Department of Psychiatry and Psychology, School for Mental Health and Neuroscience, Maastricht, The Netherlands
[h]KU Leuven, Department of Neuroscience, Research Group Psychiatry, Center for Contextual Psychiatry, Leuven, Belgium
[i]GGzE, Institute for Mental Health Care Eindhoven and De Kempen, Eindhoven, The Netherlands
[j]King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London, United Kingdom

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সবাইকে অনেক ধন্যবাদ।

ABOUT THE AUTHOR

Md. Atiqul Islam was born on January 01, 1981 in Pabna, Bangladesh, where he obtained secondary and higher secondary school certificates accredited by Santhia Pilot High School and Govt. Edward College. Next, he studied both Bachelor of Science (B.Sc.) and Master of Science (M.Sc.) programs in Statistics at the Department of Statistics, Shahjalal University of Science and Technology (SUST), Sylhet, Bangladesh from August 1999 to November 2006. He secured first position in both programs and awarded in recognition of the highest talent and greatest achievement among all graduates of the Department of Statistics at the Bachelor's and the Master's level examinations. After graduating as a statistician, he was appointed as a young academic lecturer at the same department. Later in 2009, he received VLIR-UOS awards scholarships from Flemish Government to pursue Master in Biostatistics at the Center for Statistics (CenStat), Hasselt University, Belgium. This has led to his master thesis in Biostatistics, entitled "*Herd-level risk factors associated with bovine brucellosis sero-positivity and abortion in Banglades*h". He applied joint mixed effects modeling to identify the factors that associated with bovine brucellosis sero-positivity and abortion. In 2011, he obtained his second Master in Biostatistics from CenStat.

It was November 2011, Atiqul was interviewed and granted for a PhD position jointly supported by the Department of Psychiatry and Department of Epidemiology, University Medical Center Groningen (UMCG), University of Groningen, the Netherlands. During his PhD trajectory, he explored the heterogeneity in cognitive functioning and clinical symptoms in people with psychotic disorders and their unaffected siblings using cross-sectional and longitudinal data under Genetic Risk and Outcome of Psychosis (GROUP) project. Throughout this period, he was also involved in teaching and supervising Medical and Clinical and Psychosocial Epidemiology students. He is also appointed as a researcher in data handling, statistical and genetic analysis of GROUP-project till date.

Since September 2016, Atiqul is working as a post-doctoral researcher in Biostatistics at the Department of PharmacoTheraphy, -Epidemiology & Economics, University of Groningen. He also holds the position as an Assistant Professor at the Department of Statistics, Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh.