Schizophrenia and Urban Living; a study on half a million people from three countries.

Submission ID 3003672

Submission Type Oral/Poster Presentation

Topic Schizophrenia

Status Submitted

Submitter Lucia Colodro Conde

Affiliation QIMR Berghofer Medical Research Institute

SUBMISSION DETAILS

Adolescent Research No

Presentation Type Poster and Oral

Background Schizophrenia is more prevalent in urban than in rural areas. This association has been observed in different countries and remains significant after controlling for possible confounders (OR [95% CI] = 1.72 [1.53, 1.92] according to meta-analysis). A large body of research has been generated on this topic after the classic study from Faris and Dunham in 1931. The stress of urban living has been proposed as a risk (and causal) factor for the disease.
We have investigated an alternative (but not incompatible) explanation: that people with higher genetic risk for schizophrenia tend to live in more urbanized areas due to selective migration in either past or current generations.

Methods We used data of genotyped adults individuals from four independent non clinical cohorts. Analyses performed in the discovery cohort (QIMR, Australia, N=15,544) were replicated in participants from the UKB (United Kingdom, N = 456,426), the NTR (The Netherlands, N = 16,434) and QSKIN (Australia, N = 15,726).
We calculated polygenic risk scores (PRS) of schizophrenia for our participants, using the summary statistics of the GWAS on schizophrenia published in 2014 by the Psychiatric Genomics Consortium. We fit linear mixed models with population density of the area of residence as the outcome and the PRS as a predictor, controlling for demographic variables and ancestry principal components. Using multi-instrument Mendelian Randomisation (MR) we tested the hypothesis that having a higher propensity to schizophrenia causes a person to live in a denser and less remote area. Although with reduced statistical power, we also tested the reverse causation hypothesis that population density induces the onset of schizophrenia.

Results Our polygenic risk score analysis showed that PRS for schizophrenia predicted population density in our discovery and replication cohorts, so a higher genetic risk for the disease was associated with a denser area of residence. This association remained significant after controlling for socio-economic status (SES) of the area of residence. We also tested whether PRS for

schizophrenia predicted SES of the area of residence. Results were only significant in the UKB, so a higher genetic risk would be associated with living in more deprived neighbourhoods.
Our MR results suggested that schizophrenia could be a causal factor for living in denser areas. These results were only significant in the UKB, our largest cohort. Results are suggestive of a reverse positive causal relationship between population density and schizophrenia, with an effect size five times higher than the effect observed for schizophrenia causing living in more populated areas (0.20 vs. 0.04).

Discussion Our study investigates the association between genetic risk for schizophrenia and characteristics of where people live with the aim of increasing our knowledge of why this disease is more prevalent in cities. We used data on where people live collected as part of four studies, from three countries (Australia, UK, Netherlands) for a total number of 504,130 participants.
Our results show that the distribution of the genetic risk for the disorder is not uniform and concentrates in more populated, providing empirical evidence that the increased schizophrenia prevalence in urbanized areas is not only due to the environmental stressors of the city but also on the genetic risk for the disease. Altogether, our results support the selective migration hypothesis.

Co-Authors

* Presenting Author

First Name	Last Name	Affiliation	E-mail
Lucia *	Colodro Conde *	QIMR Berghofer Medical Research Institute	lucia.colodroconde@qimrberghofer.edu.au
Baptiste	Couvy-Duchesne	University of Queensland	baptiste.couvyduchesne@gmail.com
John	Whitfield	QIMR Berghofer Medical Research Institute	John.Whitfield@qimrberghofer.edu.au
Fabian	Streit	CIMH Mannheim	fabian.streit@zi-mannheim.de
Loic	Yengo	University of Queensland	l.yengodimbou@uq.edu.au
Maciej	Trzaskowski	Institute for Molecular Bioscience, University of Queensland	m.trzaskowski@uq.edu.au
Eveline	de Zeeuw	Vrije Universiteit Amsterdam	el.de.zeeuw@vu.nl
Michel	Nivard	VU University	m.g.nivard@vu.nl
David	Whiteman	QIMR Berghofer Medical Research Institute	David.Whiteman@qimrberghofer.edu.au
Dorret	Boomsma	VU Univ	di.boomsma@vu.nl

Jian	Yang	University of Queensland	jian.yang@imb.uq.edu.au
Marcella	Rietschel	Central Institute of Mental Health	marcella.rietschel@zi-mannheim.de
John	McGrath	QLD Brain Institute	j.mcgrath@uq.edu.au
Sarah E.	Medland	QIMR Berghofer Medical Research Institute	sarah.medland@qimrberghofer.edu.au
Nick	Martin	Queensland Institute of Medical Research	nick.martin@qimr.edu.au

Statement 1 I Agree.

Statement 2 I Agree.

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Statement 4 I Agree.

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Statement 6 I Agree.

Signature Lucia Colodro Conde