Social environmental risk factors for transition to psychosis in an Ultra-High Risk population

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Title: Social environmental risk factors for transition to psychosis in an Ultra-High Risk population

Running title: Social environmental risk factors for transition in UHR

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Abstract

Objective

Despite social environmental factors such as deprivation, urbanicity, migration and adversity being established risk factors for psychotic disorders, there is a paucity of knowledge on the influence of social environmental risk factors in the UHR population. Firstly, we aimed to investigate the association between social deprivation and risk of transition and secondly, we aimed to investigate the association between migration status and the risk of transition.

Method

UHR individuals at the Personal Assessment and Crisis Evaluation (PACE) service in Melbourne were included. Social deprivation as assessed according to postal code area of residence was obtained from census data and Cox regression analysis was used to calculate hazard ratios.

Results

A total of 219 UHR individuals were included and over the median follow-up time of 4.8 years, 32 individuals (14.6%) were known to have transitioned to a psychotic disorder. 8.8% of UHR individuals were first generation migrants and 41.9% were second generation migrants. The level of social deprivation was not associated with the risk of transition (p=0.83). Similarly, first or second generation migrants did not have an increased risk of transition to psychosis (p=0.84).

Conclusions

Despite being established risk factors for psychotic disorders, social deprivation and migrant status have not been found to increase the risk of transition in a UHR population.

Keywords

Psychosis, social deprivation, migrants, ultra-high risk for psychosis

1. Introduction

Over the last two decades, significant progress has been made in prospectively identifying the symptoms and characteristics of the prodromal phase of psychotic disorders (Yung and Nelson, 2011). This has resulted in the ability to identify individuals at higher risk of psychosis compared to the general population, with over one third of these 'clinical high risk' individuals subsequently developing a psychotic disorder within three years (Fusar-Poli et al., 2012). The ultimate purpose in identifying this group is to prevent the first episode of psychosis and a recent meta-analysis has demonstrated provisional success on this front, with the overall effect of diverse interventions, specifically, CBT, omega-3 fatty acids and antipsychotic medications, having a risk reduction of 54% at 12 months with a number needed to treat of 9 (van der Gaag et al., 2013). Further factors that may influence the risk of progression to a psychotic disorder in UHR populations have been identified, specifically low functioning, longer duration of symptoms (Nelson et al 2013) and unusual thought content such as suspiciousness (Thompson et al., 2011;Ruhrmann et al., 2010;Cannon et al., 2008). Cognitive deficits, a core feature of schizophrenia, are more prevalent in UHR individuals compared to healthy controls and are associated with a higher risk of transition to psychotic disorders (Bora et al., 2014). Neuroimaging studies have identified that people who are UHR for psychosis show some brain alterations in comparison to healthy controls, but there is a lack of consistent findings as to which of these alterations is associated with transition to psychosis (Wood et al., 2013). Genetics studies may also contribute to predicting those at

higher risk of psychotic disorders, with certain genetic variations, such as in neuregulin 1, increasing the risk of transition in the UHR population (Bousman et al., 2013). However, while there appears to be a wide range of factors associated with transition to psychotic disorders in the UHR population, the findings of a number of these factors are yet to be replicated.

Despite the established association between psychotic disorders and social environmental risk factors, such as social deprivation, urbanicity, migrant status and social adversity (Kirkbride et al., 2012;Morgan et al., 2008;Kelly et al., 2010), there is a paucity of research in this area in the UHR population. In the Netherlands, Dragt et al found that UHR individuals living in an urban environment or receiving state benefits were more likely to transition to psychosis (Dragt et al., 2011). Furthermore, the study found that ethnicity, birth place, obstetrical complications and employment status were not associated with an increased risk of transition. Velhorst et al identified that UHR individuals from ethnic minorities presented with more negative symptoms and depression (Velthorst et al., 2009). Adversity in early life, specifically the experience of childhood sexual trauma, has been demonstrated to be associated with an increased risk of transition to psychotic disorders in the UHR population (Thompson et al., 2013).

The continuum model, which proposes that psychosis exists on a continuum throughout the general population, has gained substantial support, with a prevalence of psychotic like experiences in non-clinical general population samples of approximately 5% (van Os et al., 2009). Interestingly, the social environmental risk factors for psychotic disorders,

such as ethnicity, social disadvantage, urbanity and low socioeconomic status, are also risk factors for psychotic like experiences in the general population (Johns et al., 2002;Morgan et al., 2009;Scott et al., 2006;van Os et al., 2000). It appears that the risk factors for psychosis and schizophrenia mirror some of the risk factors for the prevalence of psychotic-like experiences in the general population. This highlights the importance of establishing at what point in the illness trajectory the social environmental factors influence the disorder. Establishing whether social environmental risk factors are associated with transition to a psychotic disorder in the UHR population could lead to valuable insights into the aetiology of psychotic disorders.

1.1 Aims of the study

In this study, we firstly aimed to determine whether the level of social deprivation at the time of presentation was associated with an increased risk of transition to a psychotic disorder. Secondly, we aimed to investigate whether migration status was associated with an increased risk of transitioning to a psychotic disorder.

2. Material and methods

2.1 Setting

The Personal Assessment and Crisis Evaluation (PACE) service is a specialised clinic for individuals assessed to be at Ultra High Risk (UHR) for psychosis. It is one of the clinics of Orygen Youth Health, a specific youth mental health service for people aged between 15 and 25 years. Orygen Youth Health serves a catchment area of approximately 850,000 people in the inner, mid, north and south Western regions of Melbourne.

2.2 Participants

The PACE clinic accepts young people between the ages of 15 and 25 who fulfill criteria for at least one of the three UHR groups: Attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS) and trait and state risk factors (family history of psychotic disorder or schizotypal personality disorder). The UHR criteria is displayed in table 1. The participants of this study are made up of a sub-group of the PACE 400 study, which is a long term follow-up study of UHR individuals and the inclusion criteria and participants are described by Nelson et al. The PACE400 study sample consisted of all UHR patients who participated in research studies at the PACE clinic between 1993 and 2006. This study included only those subjects between 2000 and 2006 as there was not sufficient information pertaining to the address at the time of presentation in the group prior to 2000.

2.3 Instruments

The Comprehensive Assessment of At-Risk Mental States (CAARMS)(Yung et al 2005) was used to assess the intensity, frequency and duration of psychotic symptoms and determine whether individuals fulfilled criteria for APS, BLIPS or vulnerability group and it was used to determine the outcome measure of transition to psychosis, as it has clear criteria for the presence of a psychotic disorder . In the circumstances that CAARMS data were not available then state public mental health records were used to determine if the individual had transitioned to a psychotic disorder. The level of functioning at the time of presentation was determined using the Global Assessment of Functioning (GAF) which is scored from 0 to 100 with higher scores representing higher levels of functioning.

2.4 Definitions & sources of interview

To compare the level of social deprivation in different postcode areas Socio-Economic Indexes for Areas (SEIFA) were used. These indexes are produced by the Australian Bureau of Statistics and are based on information from the 2001 Census. There are four indexes available, the index of social disadvantage, the index of socio-economic advantage and disadvantage, index of education and occupation and the index of economic resources. For the purpose of this study, as it was a specific measure of deprivation, we used the index of socio-economic disadvantage. SEIFA give an arbitrary numerical value (score) that can then be used to compare and rank the relative socio-economic characteristics of areas. The index of socio-economic disadvantage uses the

variables that indicate relative socio-economic disadvantage and consists of measures of income, education level, employment, occupation, housing and other measures such as receipt of disability benefits. The score is a weighted combination of these variables of disadvantage which have been standardized to a distribution with a mean of 1000 and standard deviation of 100. Thus a score of 1000 indicates an area with all of the variables equal to the national average. Lower scores represent that an area is more disadvantaged compared to an area of a higher score. The areas were initially ordered into deciles on a continuum from most disadvantaged (lowest score) to least disadvantaged (highest score) within the catchment area of the mental health service from which participants were drawn. These deciles were collapsed into quartiles for further analysis for the sake of having reasonable group sizes.

Information pertaining to migration status was obtained from interviews with participants. Individuals who moved to Australia after birth were defined as 'first generation migrants'. Individuals who were born in Australia and had one or both parents who were born outside of Australia were defined as 'second generation migrants'. Non-migrants were defined as individuals who and whose parents were all born in Australia. The population characteristics of the state of Victoria were obtained from the 2001 census data and population reports (Australian Bureau of Statistics, 2001).

2.5 Statistical analysis

The main outcome measure was transition to psychosis and this was analyzed using survival analysis. In particular, Cox regression analysis was used to examine the significance of predictor variables and hazard ratios were calculated. The two main predictor variables, social deprivation and migration status, were initially examined individually using Cox regression and a further Cox regression analysis was performed controlling for factors known to be associated with transition. The following factors were controlled for in the analysis because they have been demonstrated to be related to transition to psychosis: Functioning (Cannon et al., 2008), BLIPS UHR criteria and baseline year (in categories of 2000 to 2003 and 2004 to 2006) (Nelson et al 2013) and duration of symptoms prior to entry (Nelson et al 2013). The PACE400 cohort consists both of individuals who received treatment-as-usual and individuals who participated in intervention studies. In order to allow for the possible influence of different treatments, Nelson et al conducted their analysis of the cohort twice: once for the treatment-as-usual participants and once for the entire cohort. The results were essentially the same in both groups, so therefore this analysis was not repeated in the current study.

3. Results

3.1 Participants

In the study period, there were 219 individuals at UHR of psychosis who participated in research studies in the PACE clinic and of these, 42.5% (N=93) were male and the mean age at the time of presentation was 18.8 years (S.D. 3.0). The demographic and clinical

characteristics of participants are displayed in Table 2. A total of 67.6% (N=148) had follow-up interviews and 10.5% (N=23) were followed up by phone interviews and 0.9% (N=2) by written correspondence and 0.5% (N=1) had died. The median time to follow up from baseline was 4.77 years (I.Q.R 3.89 – 5.70 years).

The mean level of functioning by GAF score at the time of presentation was 56.1 (S.D. 8.7) and at follow-up it was 66.5 (S.D. 14.6). A total of thirty-two individuals (14.6%) in the cohort are known to have transitioned to a full threshold psychotic disorder. Information on the area of residence at the time of presentation was available for 91.3% (N=200) of participants.

3.2 Social deprivation and transitions to psychotic disorders

The level of social deprivation according to area of residence of UHR individuals at the time of presentation was not found to be significantly associated with transition to a psychotic disorder and these findings were consistent for both deciles (p=0.83) and quartiles (p=0.69) of deprivation. The Cox regression analyses are displayed in Table 3.

3.3 Migrant status and transition to psychotic disorders

Information pertaining to the country of birth of the individual or their parents was available for 67.6% (N=148) of the total UHR cohort. A total of 8.8% (N=13) of individuals were classified as ‘First generation migrants’ as they were not born in Australia. 41.9% (N=62) were classified as “Second generation migrants’ because either

one or both of their parents were born in countries other than Australia. 49.3% (N=73) of individuals were born in Australia and both of their parents were born in Australia.

Migrant status, either first or second generation, was not found to be significantly associated with transition to a psychotic disorder (p=0.84). The results of the Cox regression analysis are displayed in Table 4.

3.4 Social deprivation, migration and established associated factors with transition

Cox regression analysis was used to test the association between transition to psychosis and social deprivation and migration status controlled for established factors associated with the risk of transition. The results of the Cox regression analysis are presented in Table 5. When controlling for potential confounders, social deprivation and migrant status were not found to be associated with transition to psychosis.

4. Discussion

4.1 Summary of findings

The main findings of this study are the level of social deprivation according to the area of residence and migration status did not appear to influence the risk of transition in a UHR cohort.

4.2 Comparison with previous literature

4.2.1 Social deprivation

As far back as 1939, it was identified by Faris and Dunham in Chicago that there were higher rates of schizophrenia in the more socially disadvantaged areas (Faris and Dunham, 1939). The finding of a higher incidence of psychotic disorders in areas of higher levels of social deprivation has been replicated in the UK (Kirkbride et al., 2012) and Canada (Anderson et al., 2012). However, these studies have examined the social environment at the time of presentation of a first episode of psychosis and therefore they cannot distinguish whether individuals drifted into these areas of higher social deprivation following the onset of the psychotic disorder or whether living in the area of higher social deprivation precedes the onset of psychosis and could possibly be involved in the aetiology of the disorder. A study by Werner et al (2007) conducted in Israel did find that higher levels of social deprivation in the area of residence at the time of birth was a risk factor for developing psychosis (Werner et al., 2007), however these findings have yet to be replicated. While the current study indicates that social deprivation is not a risk factor for transition in UHR patients, it has not differentiated whether residing in a more socially deprived area may be a cause or a consequence of psychotic disorder. An epidemiological cohort of UHR individuals with comprehensive information on all areas of residence since birth and a long period of follow-up could address this important research question.

4.2.2 Migration status & risk of psychosis

Literature from Europe and America has demonstrated that being a migrant is associated with an increased risk of a psychotic disorder. In 1932, Ødegaard identified a higher incidence of schizophrenia in Norwegian immigrants in the United States (Odegaard, 1932). This finding has since been replicated in different migrant populations in Europe, with a meta-analysis by Cantor-Graae and Selten (2005) finding a mean weighted relative risk for developing schizophrenia among first-generation migrants of 2.7 (95% C.I. 2.3 – 3.2) and for second-generation migrants a relative risk of 4.5 (95% C.I. 1.5 – 13.1) (Cantor-Graae and Selten, 2005). In the United Kingdom, the East London First Episode Psychosis study found an increased risk of psychotic disorders for all of the ethnic groups compared with white British individuals (Coid et al., 2008). Similarly, in Sweden, migrants had a significantly increased risk for schizophrenia-spectrum disorders compared to the native population (Zolkowska et al., 2001), as did the Surinamese immigrants to the Netherlands (Selten et al., 2001) .

However, while there has been limited research on the association between psychosis and migration in Australia, it appears that the relationship is not consistent with that of Europe and America. In a case-control study, McGrath et al (2001) found that first and second generation migrants in Australia had a reduced risk of a psychotic disorder compared to those born in Australia (McGrath et al., 2001). Similarly, Nielssen et al (2013) examined the psychiatric admission rate for psychotic disorders in New South Wales (Australia) over a ten year period and found no difference in the admission rates between migrants and the Australian born population (Nielssen et al., 2013).

Furthermore, the results of our study replicate the findings of Dragt et al that ethnicity is not associated with an increased risk of transition to a psychotic disorder (Dragt et al. 2011). It is important to highlight that this study examined the risk of transition to psychosis in individuals identified as being at UHR risk for psychosis and it does not establish whether there is a higher risk of psychosis in the migrant population in Australia. There have been a number of environmental risk factors proposed to explain the increased risk of psychosis in migrants, including Vitamin D deficiency (McGrath et al., 2010), the ethnic density in the neighbourhood of residence (Bosqui et al., 2013) and the social defeat theory (Selten et al. 2013). If it could be established if there is a different "dose" of these possible environmental factors in Australia and whether the incidence of psychotic disorders in migrants is associated with this 'dose', then valuable insights into the aetiology of psychotic disorders could be gained.

4.2.3 Other factors associated with transition to psychosis

Another interesting finding of this study is that factors that have been demonstrated to be associated with an increased risk of transition, specifically lower functioning and longer duration of symptoms prior to presentation (Cannon et al 2008, Nelson et al 2013), were not associated with an increased risk of transition in this cohort. However, this fits the trend in the UHR research, in that the majority of predictor variables have failed to be replicated in subsequent research. There may be a number of explanations why these variables were found to be not associated with transition. First, this cohort was recruited from 2000 to 2006, a period in which the time between the symptom onset and referral to

PACE clinic halved compared to 1995 to 1996, thereby reducing the duration of symptoms substantially (Nelson et al., 2013;Wiltink et al., 2013). Furthermore, the proportion of transitions in this cohort was 14.6%, which is reflective of the trend of declining transition rates (Yung et al., 2007;Nelson et al., 2013) and this reduces the power to detect factors associated with transition to psychotic disorders.

4.3 Other possible explanations for findings

There are a number of possible explanations for our findings that must be considered. Firstly, this is not an epidemiological cohort, rather it is an amalgamation of UHR cohorts that participated in research studies at a specialized UHR clinic. Previous research has indicated that individuals from the lower social classes, those with lower educational attainment and ethnic minorities (non-white races) are less likely to participate in research studies (Patel et al., 2003). Therefore, it is possible that individuals from more socially deprived areas or migrants were less likely to participate in research and this could have introduced a selection bias. Furthermore, migrants could have been less likely to consent to studies or some may have been excluded as fluent English was an inclusion criteria for all studies.

It has been established that migrant populations who subsequently develop a psychotic disorder have a longer duration of untreated psychosis than the native population (Nerhus et al., 2013) and this could be a result of migrants being unfamiliar with the local health-care system in the new country or a greater stigma associated with psychotic disorders.

Therefore, it is possible that migrants are more likely to present to the mental health services long after the psychotic disorder has developed, as opposed to presenting in the prodrome. Interestingly, the level of social deprivation at the neighbourhood level does not appear to influence the duration of untreated psychosis (Kirkbride et al., 2010).

Furthermore, to expand our knowledge on the association between migration and psychosis, we should move beyond characterising migrants into simple groups such as first and second generation migrants. Individuals migrate for a variety of reasons, some who may have still afforded a good lifestyle in their country of birth decide to avail of better opportunities in a different country and others who are seeking asylum and are forced to leave their country of birth. While some studies have differentiated whether migrants come from developing or developed countries, ultimately combining these two quite distinct groups into the one variable of 'migrants' is clearly a limitation to the research that has been conducted to date, including ours.

4.5 Strengths and limitations

The strengths of this study are that we had a large cohort of individuals at ultra-high risk of psychosis with a long period of follow-up. The results of this study must be considered within the limitations of the study. First, as mentioned, this is not an epidemiological cohort, which would be the preferred methodology when examining the influence of any environmental factor on the risk of psychosis or transition to psychosis. Second, there

may be a selection bias, as the level of deprivation in the area of residence or migrant status may be associated with being in research. Third, there were missing data pertaining to migrant status for a number of participants and there were also missing data for a number of individuals at follow-up. Finally, the study may have lacked sufficient power to detect a difference, while the study had a comparably large sample size, the transition rates were low, reducing the statistical power.

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Table 1: Criteria for Ultra High-Risk (UHR) Criteria

Group	**Criteria**
1. Attenuated positive psychotic symptoms (APS)	Presence of one or more of the following: positive symptoms including unusual or non-bizarre ideas such as paranoia, perceptual abnormalities or disorganized speech and thought at a frequency, intensity and duration below the threshold for a psychotic disorder. Symptoms must be present within the past year and have a duration of greater than one week and less than five years.
2. Brief limited intermittent psychotic symptoms (BLIPS)	Presence of transient, frank psychotic symptoms that resolved spontaneously, without antipsychotic medication, within one week. Symptoms must have occurred within the past year.
3. Trait and state	Presence of a family history of psychosis in a first degree relative or

risk factors	schizotypal personality disorder and.
In addition to the above criteria, to be classified as UHR individuals, there must be a decline in functioning represented by a 30% drop that is maintained for at least a month but is less than five years. Decline in functioning must have occurred within the past year	

Table 2: Demographic and clinical characteristics of UHR individuals

Gender	%	N	Mean ±SD
Male	42.5	93	
Female	57.5	126	
Mean Age at baseline			18.8 ± 3.0
Place of birth [a]			
Australia	91.3	136	
New Zealand	1.3	2	
Europe	3.4	5	
Asia	3.4	5	
North America	0	0	
Central & South America	0	0	
Africa	0.6	1	
Migrant status [a]			
First generation migrants	8.8	13	
Second generation migrants	41.9	62	
Non-migrant	49.3	73	
UHR Group [b]			
Attenuated psychotic symptoms	84.9	186	
BLIPS	6.8	15	
Vulnerability	22.8	50	
Social deprivation of area of residence [c]			
Quartile 1 (Most deprived)	31.5	63	
Quartile 2	35.5	71	
Quartile 3	15.5	31	
Quartile 4 (Least deprived)	17.5	35	
Clinical Characteristics			
Global Functioning – mean GAF at baseline			56.1 ± 8.7
Mean duration of symptoms at presentation (days)			373 ± 434

[a]Information available for 68% (N=149) [b] It is possible for participants to fulfil more than one of the UHR criteria, [c]Information available for 91.3% (N=200)

Table 3: Cox Regression model for association between transition and deciles of social deprivation

	B	**S.E.**	**df**	**P**	**Hazard ratio**	**95% Confidence interval**	
						Lower	**Higher**
Social deprivation - deciles			9	0.83			
1st decile (most deprived)	-0.81	0.77	1	0.29	0.45	0.10	2.00
2nd decile	-1.16	0.91	1	0.23	0.33	0.06	1.98
3rd decile	-0.76	0.71	1	0.28	0.47	0.12	1.87
4th decile	-0.49	0.76	1	0.52	0.61	0.14	2.74
5th decile	-0.41	0.77	1	0.60	0.67	0.15	2.98
6th decile	-1.66	1.16	1	0.15	0.19	0.02	1.84
7th decile	0.20	0.82	1	0.81	1.22	0.25	6.06
8th decile	-0.45	0.91	1	0.62	0.64	0.11	3.80
9th decile	-0.44	0.82	1	0.59	0.64	0.13	3.19
Social deprivation - quartiles			3	0.69			
Quartile 1 (Most deprived)	-0.55	0.49	1	0.26	0.58	0.22	1.51
Quartile 2	-0.42	0.47	1	0.37	0.66	0.27	1.64
Quartile 3	-0.53	0.61	1	0.39	0.59	0.18	1.96

The 10th decile (least deprived) was used as the reference for deciles and the 4th quartile (least deprived was used as reference for quartiles

Table 4: Cox Regression model for association between transition and migrant status

	B	S.E.	df	P	Hazard ratio	95% Confidence interval	
						Lower	Higher
Migrant status			2	0.84			
First generation migrant	0.05	0.78	1	0.95	1.05	0.23	4.80
Second generation migrant	0.25	0.44	1	0.46	1.29	0.55	3.04

Table 5: Cox Regression model for association between transition and each individual variable at baseline after adjusting for variables known to be associated with transition

	B	S.E.	df	P	Hazard ratio	95% Confidence interval	
						Lower	Higher
Migrant status			2	0.65			
First generation migrant	-0.12	0.83	1	0.89	0.89	0.18	4.50
Second generation migrant	0.43	0.51	1	0.40	1.53	0.56	4.17
Social deprivation			3	0.30			
Quartile 1 (Most deprived)	-0.86	0.65	1	0.19	0.42	0.12	1.51
Quartile 2	-0.80	0.64	1	0.21	0.45	0.13	1.58
Quartile 3	-1.77	1.09	1	0.10	0.17	0.02	1.43
GAF at baseline	-0.03	0.02	1	0.20	0.97	0.92	1.02
Baseline year	0.10	0.56	1	0.86	1.10	0.37	3.32
BLIPS	-0.84	0.66	1	0.20	0.43	0.12	1.56
Duration of symptoms	0.01	0.00	1	0.16	1.00	1.00	1.01