Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The "polyenviromic risk score": Aggregating environmental risk factors predicts conversion to psychosis in familial high-risk subjects

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ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form 5 October 2016
Accepted 9 October 2016
Available online xxxx

Keywords:
Psychosis
Familial high risk
Schizophrenia
Prediction
Environment

ABSTRACT

Background: Young relatives of individuals with schizophrenia (i.e. youth at familial high-risk, FHR) are at increased risk of developing psychotic disorders, and show higher rates of psychiatric symptoms, cognitive and neurobiological abnormalities than non-relatives. It is not known whether overall exposure to environmental risk factors increases risk of conversion to psychosis in FHR subjects.
Methods: Subjects consisted of a pilot longitudinal sample of 83 young FHR subjects. As a proof of principle, we examined whether an aggregate score of exposure to environmental risk factors, which we term a 'polyenviromic risk score' (PERS), could predict conversion to psychosis. The PERS combines known environmental risk factors including cannabis use, urbanicity, season of birth, paternal age, obstetric and perinatal complications, and various types of childhood adversity, each weighted by its odds ratio for association with psychosis in the literature.
Results: A higher PERS was significantly associated with conversion to psychosis in young, familial high-risk subjects (OR = 1.97, p = 0.009). A model combining the PERS and clinical predictors had a sensitivity of 27% and specificity of 96%.
Conclusion: An aggregate index of environmental risk may help predict conversion to psychosis in FHR subjects.

1. Introduction

Several decades of epidemiological research have demonstrated the association of certain environmental variables with psychosis (van Os et al., 2010). These risk factors include urban birth or upbringing (Krabbendam and van Os, 2005), cannabis use (Kraan et al., 2016), season of birth (Davies et al., 2003), immigrant status (Bourque et al., 2011), paternal age (Torrey et al., 2009), obstetric or perinatal complications (Cannon et al., 2002; Geddes and Lawrie, 1995) and childhood adversity or abuse (Varese et al., 2012), among others.

In parallel with these advances in understanding environmental contributors to schizophrenia, identification of those at high risk of psychosis has become a priority. Several longitudinal studies of individuals at clinical high risk (CHR) or familial high risk (FHR) of schizophrenia have created psychosis prediction models, and a subset have evaluated whether environmental risk factors can enhance prediction of conversion to psychosis (Cannon et al., 2008; Ruhrmann et al., 2010; Shah et al., 2012; Tandon et al., 2012). Relatively few studies have evaluated the ability of environmental risk factors to predict psychosis risk among young subjects at FHR (i.e., first or second degree relatives of people with schizophrenia) (Johnstone et al., 2005; Shah et al., 2013), and these have reported mixed results. The Edinburgh High Risk Study, a longitudinal study of FHR individuals, found that substance abuse, but not obstetric complications or stressful life events, was associated with conversion to psychosis (Johnstone et al., 2005; McIntosh and Lawrie, 2001; Miller et al., 2006), while a study of FHR subjects in Denmark found that an unstable rearing environment predicted conversion to psychosis (Carter et al., 2002). Integrating a range of neuropsychological, clinical, and environmental predictors into a structural equation model, our group has previously reported that cannabis use, obstetric complications, and removal from the parental home were indirectly predictive of conversion to psychosis (Shah et al., 2012). Other studies that assessed environmental risk factors did not retain them in final predictive models. For example, in a study of both CHR and FHR subjects, roughly 25% of whom had first or second degree relatives with psychosis (Ruhrmann et al., 2010), individual environmental risk factors did not significantly enhance prediction of conversion to psychosis and were therefore not included in the final predictive model.

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http://dx.doi.org/10.1016/j.schres.2016.10.014
0920-9964/

However, it remains unknown whether an aggregate score representing loading for multiple environmental risk factors can predict conversion to psychosis in FHR individuals. Such an aggregate score may demonstrate whether cumulative exposure to environmental risk factors increases probability of conversion to psychosis, and could help identify FHR individuals at particularly elevated risk of psychosis. In this pilot longitudinal study of young FHR subjects, we calculated an index of overall loading for environmental risk factors for each subject, which we term the 'polyenviromic risk score' (PERS), analogous to the polygenic risk score used in genetics (Purcell et al., 2009). We evaluated the association of this score with conversion to psychosis over time and compared its predictive ability to a clinical model and to a combined clinical and PERS model. Finally, we present a sample web-based risk prediction application.

2. Methods

2.1. Subjects and clinical assessments

Subjects included 83 first or second degree relatives of people with schizophrenia or schizoaffective disorder, followed longitudinally for an average of 2.9 years. Exclusion criteria at the time of baseline evaluation included recent substance use, mental retardation, major neurological or medical conditions, and a history of psychosis or exposure to antipsychotic medication. Subjects were assessed with the Structured Clinical Assessment for DSM-IV (SCID) (First et al., 2002) or the Schedule for Affective Disorders and Schizophrenia-Child Version (K-SADS) (Ambrosini et al., 1989). This study was approved by the institutional review board of the University of Pittsburgh Medical Center, and was conducted in accordance with the Declaration of Helsinki. Baseline assessments included the Chapman schizotypy scales (Chapman et al., 1978; Eckblad and Chapman, 1983), the Scale of Prodromal Symptoms (Miller et al., 2003), the Wisconsin Card Sorting Test (Heaton et al., 1993), a go/no-go task, performance on the Identical Pairs (digits and shapes) version of the Continuous Performance Test (Cornblatt et al., 1988), a category/letter fluency task (Benton and Hamscher, 1978), and the Penn Emotion Recognition Task (Kohler et al., 2003).

2.2. Longitudinal follow-up

SCIDs were repeated annually in subjects until study completion, drop out from the study, or conversion to psychosis. Conversion to a psychotic disorder was determined during consensus conferences chaired by senior clinicians (MSK and others). These conferences involved review of medical charts and repeat SCID interviews, but did not incorporate research data, such as neuropsychological and clinical symptom scales. While environmental risk factors for psychosis were not explicitly reviewed during the consensus conferences, clinicians may have been exposed to this information either from medical charts or during the earlier research data collection. Repeat SCID interviews were not possible in all participants due to study attrition, which occurred due to subjects moving out of the area, being lost to follow-up or declining further participation in the study (Supplementary Table 1). However, all subjects who converted to psychosis did receive a confirmatory SCID, and there were no instances in which a SCID diagnosis of psychosis was rejected by the consensus conference.

2.3. Selection and binarization of environmental risk factors

An environmental risk factor was defined as an exposure (either physical, chemical, or infectious), a behavior pattern, or life event that could predispose an individual to schizophrenia (Ottman, 1996). We first reviewed our data and made a list of variables potentially meeting this definition of an environmental risk factor. To ensure that we were not missing other potential risk factors available in our data, we also conducted PubMed literature searches of English language meta-analyses and systematic reviews published in the last 5 years using the following search: (schizophrenia or psychosis) and (risk or epidemiology). We reviewed 8 meta-analyses or systematic reviews of environmental risk factors for schizophrenia (Akdeniz et al., 2014; Clarke et al., 2012; Davis et al., 2016; Hamlyn et al., 2013; Laurens et al., 2015; Matheson et al., 2011; Owen et al., 2016; Schmitt et al., 2014). We decided not to include sex or race because these factors may indirectly lead to different environmental exposures, but do not constitute environmental exposures in themselves. Immigrant status was not available in our data.

Second, for each possible risk factor on our list, we searched PubMed to identify meta-analyses, systematic reviews and original research reporting odds ratios for each risk factor's association with psychosis, using the following search structure: (schizophrenia or psychosis) and (risk) and ([name of risk factor]). Manual review of articles was restricted to meta-analyses and systematic reviews when available. If no meta-analyses were available, systematic reviews and original research studies were evaluated. A risk factor was retained if meta-analyses or the majority of original research confirmed an association with psychosis (literature review is presented in Supplementary Table 2). We also examined the previously cited 8 reviews of environmental risk and schizophrenia for references.

Third, once it was decided to include a risk factor in the PERS, an odds ratio representing its association with psychosis or schizophrenia was selected from the literature. All odds ratios were obtained from meta-analyses, and more conservative odds ratios were usually selected when multiple options were available (details in Supplementary Table 2).

Thus, selection of environmental risk factors and odds ratios was based on several criteria: (1) the risk factor met the above definition of an environmental risk factor; (2) data for that risk factor was available in our sample; (3) substantial evidence in the literature supported the association of this risk factor with psychosis, defined as at least one meta-analysis or a consensus among systematic reviews and original research studies; and (4) an odds ratio could be obtained representing association with psychosis in a meta-analysis or original research.

Nine risk factors met these criteria. As will be described next, calculation of the PERS required binarization of each risk factor. Data collection and binarization of risk factors were conducted as follows:

1) Winter or spring birth: Date of birth was obtained at study enrollment. A date of birth between the winter and summer solstices was defined as a winter or spring birth, to match the definition used by the meta-analysis by Davies et al. (2003), which compared winter/spring to summer/fall birth.

2) Urbanicity: Zip codes of primary childhood place of residence were obtained from chart review. Population densities for these zip codes were obtained using year 2000 www.census.gov data. Urban locations were defined as having a population density of at least 1000 people per square mile per the US Census department definition of "urban" (https://www.census.gov/geo/reference/ua/urban-rural-2000.html). There were no meta-analytic odds ratios available by level of urbanicity, so we could not split this variable further by degree of urbanicity.

3) Cannabis use: As cannabis use was a baseline exclusion factor, subjects' medical charts were reviewed for new onset of cannabis use during the course of the study. Because we did not collect data on severity of cannabis use, any level of cannabis use was binarized as being positive for cannabis abuse.

4) Advanced paternal age: This information was obtained by chart review or caregiver interview. Based on a meta-analysis by Torrey et al. (2009), paternal age was binarized at two levels: age ≥35 and <55, and age ≥55.

5) Obstetric and perinatal complications: Two sources of data on obstetric and perinatal complications were available: caregiver report via interview and the Pregnancy History Instrument (PHI) on a subset of individuals (Buka et al., 2000). Information from these two sources was

Please cite this article as: Padmanabhan, J.L., et al., The "polyenviromic risk score": Aggregating environmental risk factors predicts conversion to psychosis in familial high-risk ..., Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.10.014