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Transgenerational effects of genocide exposure on the risk and course of schizophrenia: A population-based study

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ABSTRACT

Background: Hypotheses about the sequel of parental genocide exposures on the offspring's risk and course of schizophrenia remain untested.
Aims: To test hypotheses related to the transgenerational transmission of parental genocide exposure on the risk and course of schizophrenia.
Methods: Data were extracted from the National Population Register on all offspring (N = 51.233; born: 1948–1989) whose parents were born (1922 to 1945) in Nazi- dominated European nations. Both parents either immigrated before (indirect exposure: n = 1627, 3.2%) or after (direct exposure: n = 49.606, 96.8%) the Nazi era. Offspring subgroups were identified from the initial timing of parental exposure (e.g., likely in utero, combined in utero and postnatal, or postnatal). Schizophrenia disorders were ascertained (1950–2014) from the National Psychiatric Case Registry. Cox models were computed to compare the offspring groups with respect to the risk and the adverse course of schizophrenia, adjusting for confounders.
Results: The offspring rates on the risk and course of schizophrenia did not differ by parental affiliation to the direct and indirect exposure groups. Cox models showed that offspring subgroups with maternal Holocaust exposures in utero only (HR = 1.74, 1.13, 2.66) and combined in utero and postnatal (HR = 1.48, 1.05, 2.10); as well as paternal Holocaust exposures combined in utero and postnatal (HR = 1.48, 1.08, 2.05), and early postnatal (aged 1–2; HR = 1.49, 1.10, 2.00) had a significantly ($P < 0.05$) higher psychiatric re-hospitalization rate than the indirect group.
Conclusions: Transgenerational genocide exposure was unrelated to the risk of schizophrenia in the offspring, but was related to a course of deterioration during selected critical periods of early life.

1. Introduction

Systematic, multiple, protracted and intense anti-Semitic persecutions during the Holocaust (Bauer, 1992) generated maximum adversity (Levav, 2015) among European Jews (Sharon et al., 2009). Subsequent studies have shown that compared with European Jews who immigrated to Israel prior to the Holocaust, survivors who immigrated after World War II were at increased risk (Levine et al., 2016a), and more likely to have a worse course of schizophrenia (Levine et al., 2014). With regard to the possible association between parental Holocaust exposure and the incidence and course of schizophrenia disorders among offspring has yet to be specifically ascertained. The convergence of different domains, such as transgenerational theory (Selten and Cantor-Graae, 2007), etiology (Marenco and Weinberger, 2000), clinical observations and research (St Clair et al., 2005; Susser and Stein, 1994; Xu et al., 2009; Yehuda et al., 2015; Yehuda et al., 2014) raise intriguing hypotheses.

Two competing and four nested hypotheses were tested. The two competing hypotheses were that in contrast to a suitable comparison group, the offspring of parents exposed to the Holocaust were (I) at reduced risk and less likely to have an adverse course or, alternatively, (II) at increased risk and more adverse course of schizophrenia. The four nested hypotheses stated that (III) in utero; (IV) early postnatal life (ages 1–2); (V) childhood (over age 2; late postnatal life) and adolescent (age 13 and above) parental genocide exposure in contrast to no such exposure would increase the risk and worsen the course of schizophrenia.

Hypothesis I posits that the resilience of Holocaust survivors was transmitted to their offspring rendering a statistically significant reduction in their risk and for an adverse course of schizophrenia compared to controls. Indeed, epidemiological studies (Levav et al., 1998; Levav et al., 2007a; Schwartz et al., 1994) have shown no statistical difference with respect to the risk of psychiatric disorders among adult offspring born to Holocaust survivors compared to offspring of European parents without direct Holocaust exposure. Competing with Hypothesis I, Hypothesis II would state that vulnerability was transmitted from survivors to offspring thereby elevating the risk and course of schizophrenia. Indeed,

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survivors were reported to be at increased risk (Levine et al., 2016a) and have a poorer course of schizophrenia (Levine et al., 2014). This notion would emerge from social defeat theory (Selten and Cantor-Graae, 2007), as well as from research into epigenetic mechanisms of transgenerational traumatization (Yehuda et al., 2015) and from meta-analysis of clinical studies (Van IJzendoorn et al., 2003).

Four nested hypotheses related to critical periods of parental biopsychosocial-laden genocide exposure were tested with regard to the offspring's risk and adverse course of schizophrenia as a result of epigenetic mechanisms. Hypothesis III proposes that offspring to mothers with in utero exposure are at greater risk and for exacerbation of schizophrenia. This extends the observation that in utero exposure to famine increases the risk (Levine et al., 2016a) and exacerbation of the course (Levine et al., 2014) of schizophrenia. (Painter et al., 2008). Hypothesis IV postulates that early postnatal life (age 1–2) is another critical period. This hypothesis is based on the American Academy of Pediatrics expert opinion document that states that early life biopsychosocial disruptions result from cumulative damage over time or by biological embedding of adversities in critical developmental periods (Shonkoff et al., 2009). Hypothesis V postulates that offspring to parents who were exposed to the Holocaust during the critical period of childhood (over age 2; late postnatal life) are at risk and more likely to have an adverse course of schizophrenia. This hypothesis follows from the neurodevelopmental hypothesis (Weinberger, 1987) that proposes that early (pre- or peri- natal) etiological factors create a static neurodevelopmental deficit that remains relatively constant from childhood. Hypothesis VI proposes that parental exposure during adolescence (age 13 and above) extended to offspring the risk and adverse course of the disorder. This hypothesis extends the late-period neurodevelopmental hypothesis (Feinberg, 1997) that states that pathological brain maturation processes occur during the critical period of adolescence.

This study aims to test the aforementioned six hypotheses by contrasting the offspring of Holocaust survivors with the offspring of parents from an ethnically identical group with indirect genocide trauma exposure via their family or social group (Pat-Horenczyk et al., 2013). For this study, we used a national population dataset, and adjusted for confounders, i.e., parental age at childbirth (Lopez-Castroman et al., 2010; Malaspina et al., 2001) and parental diagnoses of schizophrenia (Sorensen et al., 2014); and offspring birth year, gender (Aleman et al., 2003) and SES (Dohrenwend et al., 1992).

2. Methods

The Institutional Review Board at the University of Haifa approved merging the study data sources. Study data were extracted from the Ministry of the Interior, to identify the study populations; the Central Bureau of Statistics, for socioeconomic status information; and the Ministry of Health, to ascertain the cases with schizophrenia disorder. Common unique identification numbers were encrypted before the data were received to ensure participant anonymity and confidentiality.

2.1. Nation-wide population register of the Ministry of the Interior

Ninety percent of Holocaust survivors who immigrated to Israel were born after 1920 (Eitinger, 1972). Hence, the source population comprised of offspring born to European parents both of whom: (I) were born in Holocaust-exposed European countries from 1922 to 1945; and (II) immigrated to Israel by 1966 before or after the era of Nazi domination in each European nation. These criteria had been used to examine the association between Holocaust exposure and the risk of schizophrenia and suicide (Levine et al., 2016a; Levine et al., 2016b). All offspring were born from 1948 to 1989 inclusive, to adequately follow-up for schizophrenia disorder to 2014 when follow-up ended. At the end of follow-up, the oldest cohort had 66 years of follow-up while the youngest cohort had an age of 25, thus exceeding the average age of onset of 22 (Levine et al., 2011). Data were at the individual-level and included encrypted identification numbers; birth, immigration and death years; and current residence.

2.2. Central Bureau of Statistics (CBS) registry

Residential status area (a neighborhood measure of socioeconomic status) was identified for each individual with this measure. This measure is derived from household census data that are based on number of electrical appliances per person and per capita income (Statistics, 1995). Residential status was obtained by joining each individual address from the Population Register of the Ministry of Interior with the CBS census track and neighborhood ranking.

2.3. Ascertainment of schizophrenia

2.3.1. The National Psychiatric Case Registry (NPCR)

Psychiatric care in Israel is freely available by law to all *de-jure* residents (Levav and Grinshpoon, 2004). Hospitalization was the prevailing treatment policy for persons with psychotic disorders during a majority of the study years. Since 2001 onward, however, the national healthcare policy has slightly reduced in-patient psychiatric hospitalization rates (22). The NCPR started in the 1950's and consists of all nation-wide out- and in-patient admissions to mental hospitals or psychiatric units of general hospitals. Research has found that the NPCR captures almost all people with schizophrenia (Weiser et al., 2012), especially for the Israel-born, which is the case for most offspring. By mandate, all inpatient and day care psychiatric settings submit information on all admissions and discharges to the Ministry of Health. A special unit verifies reporting compliance, updating diagnostic coding schemes and information consistency. The registry information is comprised of admission and discharge dates, and the respective ICD-10 diagnoses by a certified psychiatrist.

2.3.2. NPCR diagnoses

To ascertain schizophrenia, the last registry discharge or admission if currently hospitalized of schizophrenia was used. Validation research has shown that the last diagnosis of schizophrenia in the NPCR registry has acceptable sensitivity and specificity when assessed against research diagnosis (Weiser et al., 2005), and is longitudinally reliable (Rabinowitz et al., 1994). This approach was adopted in prior studies (Davidson et al., 1999; Levav et al., 2007b; Levine et al., 2016a; Levine et al., 2014; Weiser et al., 2000).

2.4. Statistical analysis

2.4.1. Exposure groups and subgroups

The offspring population was disaggregated into groups and subgroups based on parental definitions of exposure by nation and period (Levine et al., 2016a; Levine et al., 2016b). Across all analyses, the reference group comprised of offspring to both parents that were born in European nations where the Holocaust occurred, and had immigrated to pre-State Israel before the persecution of the Jews begun or markedly increased. This group was not directly exposed to the Holocaust, but likely had family and social ties to people who were exposed to it, "indirect exposure group" (Pat-Horenczyk et al., 2013).

The "direct exposure group" comprised of all offspring in the study population whose both parents immigrated after the end of World War II (1945). Like prior research (Levine et al., 2016a; Levine et al., 2016b; Levine et al., 2014), national differences were accounted for by the beginning of maximal adversity periods (Bauer, 1992) (e.g., Germany, 1933).

The direct exposure group was disaggregated into subgroups according to the initial developmental period of the parental exposure: (a) "Likely in utero only" subgroup, if they were born at the last year of the war (e.g., 1945); (b) combined "Likely in utero and postnatal"

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