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Association of maternal exposure to terror attacks during pregnancy and the risk of schizophrenia in the offspring: A population-based study

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ABSTRACT

This study tested the hypothesis that maternal exposure to terror attacks during pregnancy is associated with the risk of schizophrenia in the offspring. A population-based study was conducted of Israeli children born between 1975 and 1995 and that were registered in the Ministry of Interior and followed up in the Ministry of Health from birth to 2015 for the risk of schizophrenia (N = 201,048). The association between maternal exposure to terror attacks during pregnancy and the risk of schizophrenia in the offspring was quantified with relative risks (RR) and their 95% confidence intervals (CI) fitting Cox regression models unadjusted and adjusted for confounders. Sensitivity analyses were performed to test the robustness of the results. The RR of schizophrenia in offspring of mothers exposed to terror attacks during pregnancy compared to offspring of mothers not exposed during pregnancy were estimated unadjusted (RR = 2.51, 95% CI, 1.33, 4.74) and adjusted (RR = 2.53, 95% CI, 1.63, 3.91). In the sensitivity analyses adjusted RRs were estimated using a sibling-based study design (2.85, 95% CI: 1.31–6.21) and propensity matching (2.45, 95% CI: 1.58–3.81). Maternal exposure to terror attacks during pregnancy was associated with an increased risk of schizophrenia in the offspring, possibly indicating a critical period of neurodevelopment that is sensitive to the stress of terror attacks and affected by epigenetic modifications.

1. Introduction

Maternal exposure to major stressors during pregnancy has been found in some studies to increase the risk of neurodevelopmental, cognitive, and psychiatric disorders in the offspring (Tarabulsy et al., 2014; Van den Bergh et al., 2017). However, the association between maternal exposure to terror attacks during pregnancy and the risk of schizophrenia in the offspring has yet to be examined.

Several epidemiologic studies have examined the association between exposure to fateful stress (i.e. after catastrophic events; Dohrenwend, 2000) and psychopathology. However, relatively few studies have examined maternal exposure to fateful stressors during pregnancy and the risk of schizophrenia in the offspring. For instance, maternal exposure to famine during pregnancy increased the likelihood of schizophrenia in the offspring in the Dutch and Chinese famine studies (Li and Lumey, 2017; Susser and St Clair, 2013). Famine is a fateful stressor but the source is not solely a natural or human-made disaster. Indeed, the Dutch and Chinese famine studies demonstrate and emphasize maternal malnutrition rather than stress during pregnancy as the mechanism for schizophrenia in the offspring (Li and Lumey, 2017; Susser and St Clair, 2013). However, research has reported that maternal exposure to the stress of the five-day invasion and defeat of The Netherlands by Nazi Germany in WWII (1940) significantly increased the risk of schizophrenia in the offspring (van Os and Selten, 1998). Similarly, the combination of exposure during pregnancy and in postnatal life to the maximal adversities (Levav, 1998) of the Holocaust in Europe during WWII (1939–1945) was associated with an increased higher risk of schizophrenia in the offspring (Levine et al., 2016). In contrast, maternal exposure to the Yom-Kippur War (1973–1974) did not show an increase in the risk of schizophrenia in the offspring across the state of Israel (Selten et al., 2003). In addition, intriguing results have been reported regarding the association between maternal exposure to the Six-day War (1967) in Israel during pregnancy and schizophrenia in the offspring. Maternal exposure had a null association with the risk of schizophrenia in the offspring nationally (Selten et al., 2003) but an increased risk was observed among the offspring of residents in Jerusalem exposed in the second and third months of fetal life (Malaspina et al., 2008). A further negative finding was reported showing that prenatal maternal bereavement, a fateful stressor, had a null association with the risk of psychosis in the offspring (Abel et al., 2014). In conclusion, the association between exposure to

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fateful stress during pregnancy and the risk of schizophrenia in the offspring remains unclear.

Across the aforementioned studies, the exposure to fateful stress differs markedly for civilians in the general population. Generally, famine and Holocaust adversities occurred in high proximity to the adverse events with little chance for civilians to escape whereas, mostly, exposure to war was characterized by a more distal proximity (except the Six-day war in Jerusalem; Malaspina et al., 2008). Unlike other forms of fateful stress (notably war), terror attacks in Israel are repeated in time, occur periodically (Mayo and Kluger, 2006) and civilians are often the target (Jaffe et al., 2010; Peleg et al., 2003).

The current study aims to examine the association between maternal exposure to terror attacks during pregnancy and the risk of schizophrenia in the offspring.

2. Experimental/materials and methods

A population-based cohort was established from the merger of four different data sources. First, the source population were offspring born between 1 January 1975 and 31 December 1995 to mothers or fathers of European origin (N = 201,048) in the Israeli Ministry of Interior Registry. Second, terror information was ascertained from the Global Terrorism Database (National Consortium for the Study of Terrorism and Responses to Terrorism, 2013). This included terror attacks that occurred in Israel between 1974 and 1996. Third, the Israeli Psychiatric Case Registry was merged to ascertain schizophrenia (range, 7August 1981 to 1 November 2015). Fourth, The Central Bureau of Statistics (CBS) data were used to ascertain socioeconomic status.

The Institutional Review Board at the University of Haifa granted ethical permission to perform the study with a waiver of informed consent because the data were received by the researchers unidentified.

2.1. Data sources

2.1.1. Ministry of Interior Registry

This Registry provided information on parents and their children. It includes information on family relations, sex, date of birth, date of death, and place of residence.

2.1.2. Psychiatric Case Registry

By law, psychiatric care in Israel is available to all *de jure* residents (Levav et al., 2004). The Israeli National Psychiatric Case Registry comprises of all hospitalizations in psychiatric hospitals, psychiatric units of general hospitals and psychiatric day care centers (Levav et al., 2007). Psychiatric settings are legally mandated to submit information regarding all hospitalizations to a special department in the Ministry of Health. The registry documents admission and discharge dates and ICD-10 diagnoses by a board-certified psychiatrist. Validation studies have shown that the last registry diagnosis of schizophrenia has acceptable sensitivity and specificity compared to research diagnosis (Weiser et al., 2005), and acceptable reliability, as indicated by the stability of diagnoses over time (Rabinowitz et al., 1994). For these reasons, we defined persons diagnosed with schizophrenia as those with a final diagnosis of schizophrenia disorder, as in earlier studies (Levine et al., 2011).

2.1.3. Central Bureau of Statistics (CBS) Registry

This Registry facilitated the identification of each person's residential status area (i.e., a neighborhood measure of socioeconomic status). This measure is derived from household census data that are material-based (e.g., number of electrical appliances) *per person* and income *per capital* (Central Bureau of Statistics, 1995).

2.1.4. Global Terrorism Database

The Global Terrorism Database was established in 1970 by the University of Maryland's National Consortium for the Study of Terrorism and Response to Terrorism Center in the US (National Consortium for the Study of Terrorism and Responses to Terrorism, 2013). This is a comprehensive terror attack database and has been widely used in research (Borooah, 2009; LaFree et al., 2010; Wang et al., 2008; Webb and Cutten, 2009). This information source supplied information on the dates of the terrorist attacks.

2.2. Exposure

Maternal exposure to terror attacks during pregnancy was classified as exposed if a terror attack occurred in the interval from 270 days before the birth date to the birth date of the offspring. This interval has been used in prior research to identify exposure during pregnancy (Levine et al., 2018). For each child, this was computed as the difference between the birth date in the Ministry of the Interior Registry and the date of the terror attack in the Global Terrorism Database.

2.3. Covariates

The covariates were: birth year cohort (Suvisaari et al., 1999), sex (Aleman et al., 2003), socioeconomic status (Werner et al., 2007), parental history of schizophrenia by childbirth (Mortensen et al., 1999), and parental age at childbirth (Malaspina et al., 2001). All these variables have been associated with the risk of schizophrenia. Birth year was classified as 1975–1985 and 1986–1995. Parental age at childbirth was calculated from the difference between the parental and offspring dates of birth. Paternal and maternal ages were categorized as below and above 30. A maternal and paternal diagnosis of schizophrenia by childbirth was identified in the psychiatric case registry and classified as present or absent. Socio-economic status (SES) was estimated from the residential status area by linking each individual address from the Ministry of the Interior with the Central Bureau of Statistics census track and neighborhood ranking and classified as low, high and undefined (for small-sized residential areas). We used SES as a covariate because low SES has been found to increase the risk of schizophrenia in the Jerusalem Perinatal Study (Werner et al., 2007).

2.4. Statistical analysis

Relative risks (RR) of schizophrenia in the offspring and the associated two-sided 95% confidence intervals (CI) were estimated by the hazard ratios from Cox regression models. The Cox regression models were fitted using age from childbirth as the underlying time scale. Each model was fitted unadjusted and adjusted for the aforementioned covariates. To account for the potential within-maternal correlations due to multiple births from the same mother, we used robust standard errors in the computation of RR and CI (Barlow, 1994). Each child was followed-up from birth until the last registry diagnosis of schizophrenia, death, or end of follow-up in 2015, whichever came first. The RRs and 95% CI of schizophrenia among the offspring in the group with maternal exposure during pregnancy were compared to the reference group of offspring to mothers not exposed during the pregnancy.

2.5. Sensitivity analysis

We subjected the results to three sensitivity analysis to test the robustness of the main results. First, we statistically tested if the adjusted primary model significantly deviated from the Cox model proportional hazards assumption (Grambsch and Therneau, 1994). The proportional hazards assumption states that survival curves for two strata (determined by the predictor values) should have hazard functions that are proportional over time (i.e. constant relative hazard).

Second, the primary model was reanalyzed using a sibling-based study design (Frisell et al., 2012). The association between the main study variables and the risk of schizophrenia in the offspring was examined among matched sets of outcome discordant siblings from the

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