Prenatal famine exposure and mental health in later midlife

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Abstract:

Objectives: Maternal malnutrition during pregnancy may have long-lasting effects on offspring's mental health. We investigate the effect of prenatal exposure to the Dutch famine (mid November 1944 – late April 1945) on mental health in later mid-life.

Methods: Data are from the Netherlands Kinship Panel Study (n=642). We use difference-in-difference analyses to compare mental health in later midlife (measured with the MHI-5 index) across three cohorts ('pre-famine cohort', 'famine cohort', 'post-famine cohort') and across two regions (famine affected cities vs. rest of the country).

Results: In the affected cities, we find poorer mental health for the famine cohort than for the pre-famine and post-famine cohorts. In the non-affected rest of the country, no significant mental health differences between birth cohorts were found. The mental health differences between birth cohorts differ significantly between the affected cities and the rest of the Netherlands.

Conclusion: Our analyses link prenatal famine exposure to poorer mental health in later midlife. This suggests that in utero malnutrition has a long-lasting detrimental effect on mental health.

Introduction

Adversity encountered by mothers during pregnancy, such as stress, substance abuse and malnutrition, may have long-lasting effects on their offspring's mental health (for a review, see Braithwaite, Murphy, & Ramchandani, 2014). Barker (1995) posited in his fetal origins hypothesis that the fetus is "programmed" in utero. In case of mother's malnutrition during pregnancy, biological mechanisms might alter the epigenome of the unborn child, "programming" the fetus in ways that can trigger future disease (cf. Almond & Currie, 2011). Studying the effects of prenatal maternal malnutrition on mental health in midlife and later life is a challenging affair for several reasons: the outcome of interest can only be measured decades after the exposure, maternal malnutrition is highly selective, and setting up an experimental study, in which volunteers are randomly assigned to starve themselves (e.g., Benedict et al., 1919, as cited in Lumey, Stein, & Susser, 2011), is clearly unethical.

Although tragic, famines, such as the Chinese famine of 1959-61, the Swedish and Finnish crop failures of the late 19th and early 20th century and the Dutch famine of 1944-45, are well suited to assess the long-term impact of in utero malnutrition (cf. Lumey et al., 2011). This study focuses on the Dutch famine of 1944-45. The Dutch famine only affected the Western cities of the Netherlands, which were largely cut off from food transports in the last stage of World War II (Barnouw, 1999). In the affected cities, calorie intake per day remained stable until October 1944, but official rations fell below 1,000 kcal in the second half of November 1944 and down to less than 500 kcal per day by April 1945 (Lumey & van Poppel, 2013). After allied forces dropped 11,000 tons of food between 29 April and 8 May 1945, and following the liberation in May 1945, food supply was restored quickly (Barnouw, 1999). The famine entailed an

unanticipated, severe decline in the availability of food in a restricted area and time (cf. Scholte, Van den Berg, & Lindeboom, 2015). These conditions allow conducting a natural experiment to investigate how in utero malnutrition might affect one's health negatively decades later (cf. Lumey & van Poppel, 2013).

The Dutch famine has frequently been used to study effects of prenatal famine exposure on health (for reviews, see Lumey & van Poppel, 2013; Roseboom, Painter, Van Abeelen, Veenendaal, & De Rooij, 2011). The bulk of studies focuses on chronic somatic diseases such as diabetes, coronary disease, and obesity. Fewer focus on mental health outcomes and mainly study major psychiatric disorders, such as affective psychosis (Brown, Susser, Lin, Neugebauer, & Gorman, 1995; Brown, Van Os, Driessens, Hoek, & Susser, 2000), antisocial personality disorder (Neugebauer, Hoek, & Susser, 1999), and schizoid personality disorder (Hoek, Susser, Buck, Lumey, & Al, 1996). Furthermore, there has been work on addiction (Franzek, Sprangers, Janssens, Van Duijn, & Van De Wetering, 2008), cognitive performance (De Groot et al., 2011; De Rooij, Wouters, Yonker, Painter, & Roseboom, 2010) and mental retardation (Z. Stein, Susser, Saenger, & Marolla, 1972).

In the current study, we assess the long-term impact of prenatal exposure to the Dutch famine on mental health related quality of life. We identified two studies about the Dutch famine with a similar aim. De Rooij et al. (2011) found an association between prenatal famine exposure and depression in men, but not in women. Stein et al. (2009) found that mothers' exposure to famine prior to conception was associated with poor mental health and higher depression scores of their children in later midlife, but they did not find an effect of mothers' exposure during pregnancy. Given that De Rooij et al. (2011) and Stein et al. (2009) used non-probability samples, it remains somewhat unclear to what extent their results can be generalized (cf. Battaglia, 2008). Their

analyses were restricted to persons born in, respectively, one and three Dutch cities, and to persons born in institutions, whereas the vast majority of children in the Netherlands used to be born at home. Data for the World War II period are not available, but in the early 1950s almost four of every five Dutch births were home births, and home births were the norm when no problems had occurred during pregnancy (Van Daalen, 1988). In the current study, we draw on a representative sample of the non-institutionalized Dutch population and use a difference-in-difference modeling strategy to estimate the effect of prenatal famine exposure on mental health in later midlife.

Data

Sample selection

Data were from the first wave of the Netherlands Kinship Panel Study (NKPS) (Dykstra et al., 2005). The NKPS is a longitudinal dataset set up to shed light on family solidarity in the Netherlands (cf. Dykstra et al., 2006). The NKPS is based on a one-stage simple random sample of addresses of private residences in the Netherlands. Between 2002 and 2004, data from 8,161 non-institutionalized men and women aged 18–80 were collected using computer-assisted personal interviews (CAPI) and supplemented by self-completion questionnaires. The overall response rate was 45 percent.

For the current study, we restricted our sample to respondents born in the Netherlands between 16 November 1942 and 3 February 1948 (n=673). We will explain in further detail later that this range covers the cohort potentially prenatally exposed to the Dutch famine, and the cohorts born up to two years earlier and later. At the time of data collection, these respondents had an average age of 57, which we refer to as 'later

midlife'. List-wise deletion of respondents with missing values on variables of interest resulted in a sample of 642 persons.

Measures

Mental health was measured with the five-item version of the Mental Health Inventory (MHI-5) (Berwick et al., 1991; Weinstein, Berwick, Goldman, Murphy, & Barsky, 1989), which was part of the self-completion questionnaire that all NKPS respondents were asked to complete. The MHI is a mental health screening questionnaire designed to detect affective disorder, depression and anxiety, and has been validated for use in the Dutch population (Hoeymans, Garssen, Westert, & Verhaak, 2004). The MHI-5 has been compared to its longer version (MHI-18), as well as to the 12-item and 30-item versions of the General Health Questionnaire (GHQ), the 28-item Somatic Symptom Inventory (SSI-28) and 5-item, 10-item and 25-item versions of the Hopkins Symptoms Checklist (SCL) (Berwick et al., 1991; Hoeymans et al., 2004; Strand, Dalgard, Tambs, & Rognerud, 2003; Weinstein et al., 1989). These comparisons confirmed that the MHI-5 performed satisfactory in predicting mental health problems. Focusing specifically on the Dutch population, Cuijpers et al. (2009) concluded that the MHI-5 is a good screener for mood disorders in the general population, and an adequate screener for some, but not all, anxiety disorders.

The MHI-5 asks respondents how often in the four weeks prior to the interview they had felt 'particularly tense', 'so down in the dumps that nothing could cheer [them] up', 'calm and peaceful', 'downhearted and miserable', and 'happy'. Respondents indicated the duration of each feeling on a six-point scale ranging from "all of the time" to "none of the time". Positive feelings were reverse coded. Scores on the items were summed and

transformed to range from 0 to 100, with higher scores indicating better mental health. Internal consistency of the scale was high (Cronbach's α=0.87).

Prenatal famine exposure was bound by date and location of birth. Based on date of birth, we define three cohorts, the pre-famine, famine and post-famine cohort. Persons born in the 24 months prior to 16 November 1944 – the approximate start of the famine – were coded as the pre-famine birth cohort. Assuming a uniform gestation period of 40 weeks, persons born between 16 November 1944 and 3 February 1946 (40 weeks after food supply was restored on 29 April 1945), were potentially prenatally exposed to the famine. They were coded as the famine cohort. Persons born in the 24 months following 3 February 1946 were coded as the post-famine birth cohort. We considered Amsterdam, Rotterdam, The Hague, Utrecht, Haarlem and Leiden as the cities affected by famine (cf. Ekamper, van Poppel, Stein, & Lumey, 2014). We used the municipality respondents lived in at age 15 as a proxy measure for place of birth, given that information on the actual place of birth was not collected.

All analyses are adjusted for gender and childhood poverty. Childhood poverty has been linked to poorer mental health in later life (Kamiya, Doyle, Henretta, & Timonen, 2013, 2014). It was measured as respondents' disagreement or strong disagreement with the statement that, at age 15, their families were well off compared to many other families.

<Table 1 here>

Methods

We used ordinary least squares regression to analyze mental health in later midlife using a difference-in-difference approach (Lechner, 2011). In our study, we assessed whether differences between cohorts varied by region. More specifically, this implies comparing mental health of members of the famine cohort born in the affected cities to

mental health of pre-famine and post-famine cohort members born in the affected cities, as well as to mental health of members of all three cohorts born in the non-affected part of the Netherlands. The strength of our analytical strategy is that omitted variable bias can only be caused by unobserved characteristics associated with the combination of (a) being a member of the birth cohort of interest and (b) being born in the affected cities.

Weighting was applied to reduce potential bias due to selective non-response. We used the supplied weights to make the NKPS sample representative for the non-institutionalized adult population of the Netherlands in 2003 with regard to sex, age, household type, region and level of urbanization (Dykstra et al., 2005).

Results

Descriptive statistics of our sample are presented in Table 1. Overall, mental health was somewhat poorer among respondents from affected cities than among their counterparts from the rest of the country. A weights adjusted Wald-test indicated that this difference was not statistically significant, however ($F(1,\ 641) = 0.69$, $p = .41$).

<Table 2 here>

The results of our analyses are presented in Table 2. The main effects of the birth cohorts indicate that in the affected cities mental health was significantly better for the pre-famine and post-famine cohorts compared to the famine cohort. These differences are also displayed in the left panel of Figure 1. This figure also shows that there were no substantial differences between birth cohorts in non-affected part of the Netherlands. The interaction terms in Table 2 indicate that the mental health differences between birth cohorts differed significantly between the affected cities and the rest of the Netherlands. Consistent with our expectations, our difference-in-difference model thus

links prenatal famine exposure to poorer mental health in later midlife. The model further shows that women had poorer mental health in later midlife than men. No effect of childhood poverty was found.

<Figure 1 here>

Discussion

The Dutch famine of 1944-1945 has been considered a "human laboratory" (Lumey & van Poppel, 2013), because it satisfies the conditions for a natural experiment to study the long-term effects of maternal malnutrition on offspring's health. In this study, we investigated how prenatal famine exposure was associated with mental health in later midlife. Using a difference-in-difference approach and drawing on nationally representative data, we established a link between prenatal famine exposure and poorer mental health in later midlife.

We identified two earlier studies on the impact of prenatal famine exposure on mental health in later midlife in the Netherlands (De Rooij et al., 2011; A. D. Stein et al., 2009). As described earlier, these studies relied on non-probability samples limiting the generalizability of their results. Their large sample sizes, however, allowed them to analyze men and women separately and differentiate between famine exposure by gestation period. Our study, in contrast, benefitted from nationally representative data, but the small sample size made it unfeasible to estimate models stratified by gender or by gestation period. This is unfortunate, because the findings of De Rooij et al. (2011) suggest that prenatal famine exposure was particularly detrimental for men's mental health. It should be noted, however, that Huang et al. (2013) found that the adverse mental health effects of prenatal exposure to the Chinese famine of 1959-61 were

stronger for women than for men. Future research is needed to learn more about the gendered impact of prenatal famine exposure on mental health.

The use of respondents' municipality of residence at age 15 as a proxy measure for birth location constituted another limitation of our study. However, we expect measurement error of our indicator to be limited, because respondents had reached age 15 before substantial migration out of the large cities in the West of the Netherlands occurred (1965-1980, see Van Huis, Nicolaas, & Croes, 1999). Finally, it should be considered that prenatal famine exposure might imply more than just in utero malnutrition. Limited, unpredictable food supply might also induce stress for expecting women. Just like maternal malnutrition, stress during pregnancy might have long-term detrimental effects for offspring's mental health (Braithwaite et al., 2014).

It is well established that adversity in childhood can have a detrimental impact on mental health that may last until later midlife and old age (Burns, Loh, Byles, & Kendig, 2017; Kamiya et al., 2013). Our findings corroborate the idea that adversity experienced prenatally – particularly in utero malnutrition – can also have long-lasting effects on mental health (cf. Braithwaite et al., 2014). It is worth noting that the Dutch famine presented extreme conditions. The dramatic and unexpected drop in calorie intake experienced by the population of the famine affected Dutch cities in the last months of 1944 and first months of 1945 were of a different magnitude than the reduction in calorie intake that can be noted among substantial groups of expecting women coping with, for instance, severe morning sickness (Lee, Lee, & Lim, 2004). More research is needed to learn whether there are also long-lasting detrimental effects on offspring's mental health of such reductions of calorie intake.

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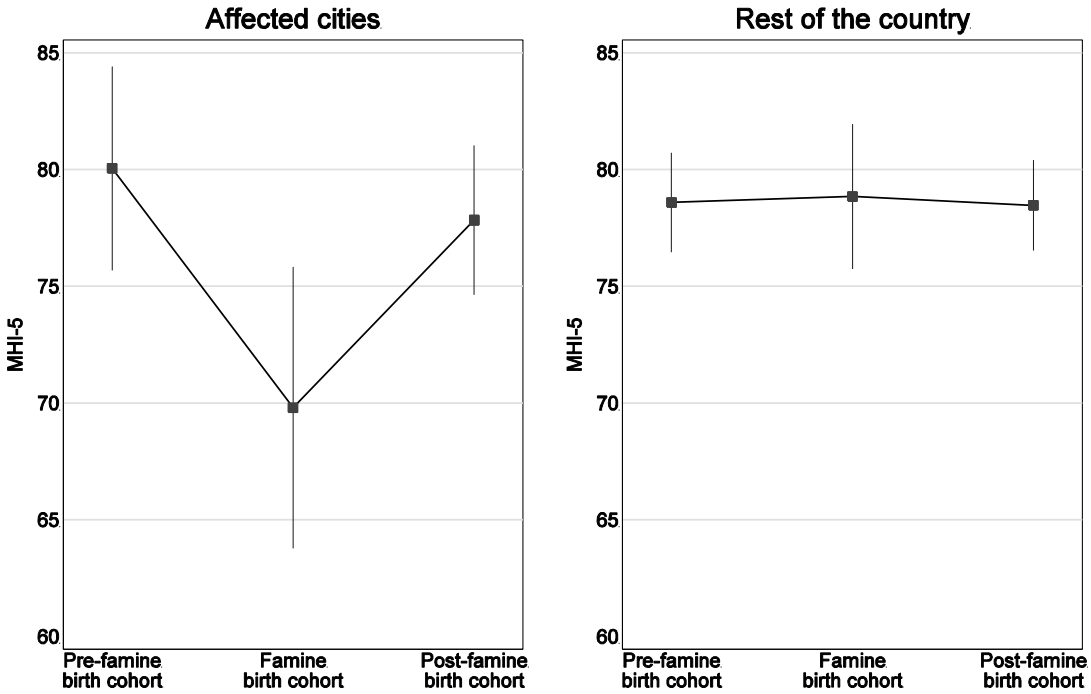

Figure 1. Predicted mental health MHI-5 scores

Notes: Predicted scores with 95% confidence intervals by birth cohort and location of birth. Predicted scores were calculated with childhood poverty and gender set at overall sample mean (see Table 1).

Table 1. Descriptive statistics; Mean score and percentages.

VARIABLES	All	Affected cities			Rest of the country		
		Pre-famine cohort	Famine cohort	Post-famine cohort	Pre-famine cohort	Famine cohort	Post-famine cohort
Mean MHI-5	78.3	80.1	69.9	78.0	78.4	79.6	78.3
(Standard deviation)	(14.9)	(12.6)	(16.4)	(17.9)	(14.2)	(14.7)	(14.6)
Childhood poverty	46.0%	61.4%	44.0%	55.9%	44.6%	44.9%	41.2%
Woman	46.4%	47.0%	45.9%	41.5%	47.0%	38.3%	50.8%
Number of observations	642	41	23	83	187	89	219

Notes: Data are from Netherlands Kinship Panel Study (2002-2004); Data are weighted

Table 2. Full results of linear regression analyses of mental health (MHI-5).

VARIABLES	Coef.	(95% CI)
Birth cohort:		
Pre-famine cohort	10.45**	(3.08; 17.82)
Famine cohort (reference)	0	
Post-famine cohort	8.01*	(1.30; 14.73)
Non-affected part of the Netherlands	9.30**	(2.67; 15.94)
Non-affected part of the Netherlands X pre-famine cohort	-11.14**	(-19.40; -2.88)
Non-affected part of the Netherlands X post-famine cohort	-8.68*	(-16.31; -1.05)
Childhood poverty	-1.00	(-3.31; 1.30)
Woman	-5.41***	(-7.71; -3.11)
Constant	72.79***	(66.70; 78.88)
Observations	642	
R^2	0.05	

Notes: Data are from Netherlands Kinship Panel Study (2002-2004); Data are weighted;, * p < 0.05, ** p < 0.01, *** p < 0.001