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Maternal exposure to the holocaust and health complaints in offspring

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Abstract. Although the link between chronic stress and the development of cardiovascular and metabolic diseases of adulthood has been known for some time, there is growing recognition that early environmental influences may result in developmental programming via epigenetic mechanisms, thereby affecting the developmental trajectory of disease progression. Previous studies support the idea that offspring of Holocaust survivors may have been subjected to early developmental programming. We evaluated the relationship between parental exposure to the Holocaust and self-reported health ratings and disorders made by their adult offspring (i.e., second generation Holocaust survivors). A total of 137 subjects were evaluated. Regression analyses demonstrated that maternal but not paternal exposure to the Holocaust was related to poorer subjective impressions of emotional and physical health. This relationship was diminished when the offspring's own level of trait anxiety was considered. Offspring with maternal, but not paternal, Holocaust exposure also reported greater use of psychotropic and other medications, including medications for the treatment of hypertension and lipid disorders. The mechanism linking these health outcomes and maternal exposure deserves further investigation, including the possibility that fetal or early developmental programming is involved.

1. Introduction

Early adverse circumstances that lead to low birth weight are linked to cardiovascular and metabolic diseases in adulthood (e.g. [6,14]). In part, low birth weight is thought to be the result of modifications in offspring neuronal structure and function initiated by these early environmental events, including in utero stressors such as maternal starvation or illness or exposure to maternal stress (for reviews see [2,12,26,30]). Such modifications may be modulated by maternal glucocorticoid activity that is transmitted through the placenta to the fetus, producing persistent alterations of the hypothalamic pituitary adrenal (HPA) axis throughout the offspring's lifespan [15,25,30,33,34,39]. This hypothesis, termed "fetal programming", (also known as developmental programming) has been extended to

include variability in postnatal maternal care (e.g., attachment) that might reflect previous or current environmental challenges.

The latter extension of this theory has been of particular interest in the effort to understand the link between exposure to early life adversity and psychiatric symptoms [7,27,32]. This is in part prompted by the fact that dysregulated glucocorticoid activity is associated with psychiatric disorders such as posttraumatic stress disorder (PTSD). Early adversity is a risk factor for PTSD, suggesting the hypothesis that early environmental exposures produce changes in glucocorticoid programming through epigenetic mechanisms that then contribute to enduring changes in stress responsiveness and an enhanced risk for adult psychopathology [45]. Interestingly, persons with PTSD also show increased rates of cardiovascular and metabolic disease [9,16,17,21,22,29,37].

An extension of the developmental programming hypothesis offers the possibility that mothers exposed to stress prior to or during pregnancy continue to affect their offspring as a result of their own psychopathology.

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For example, having a psychiatric disorder may affect parental attachment behaviors and bonding or parenting style. We have previously reported that Holocaust offspring report the subjective perception of greater emotional abuse and neglect in childhood, relative to non-exposed offspring, particularly when one or both Holocaust exposed parents had PTSD. Holocaust offspring also reported greater maternal and paternal overprotection than comparison subjects. Interestingly, greater maternal, but not paternal overprotection was associated with lower cortisol levels in offspring. Indeed, there are several reports that demonstrate lower levels of cortisol in Holocaust offspring, particularly in offspring with maternal PTSD [41,43,44,46,47]. In Holocaust survivors, lower cortisol levels were associated with changes in glucocorticoid metabolic enzymes that contribute to the development of metabolic syndrome, as well as in increased metabolic syndrome components [42]. Consequently, in the current set of analyses, we set out to evaluate the association between parental exposure to the Holocaust and offspring health, including self-reported health, health behaviors and components of the metabolic syndrome, with a particular interest in comparing maternal to paternal exposure on offspring outcomes.

2. Method

Participants were drawn from a larger sample (e.g. [41]) that was recruited with advertisements requesting Jewish volunteers for research examining effects of the Holocaust on second generation offspring. Participants were chosen for inclusion in the current analyses because they completed a demographic module that incorporated questions about emotional and physical health, including use of medications and health behaviors. The sample used for the current analyses included 137 adults aged 23 to 65 years ($\bar{X} = 47.36$, $s.d. = 8.34$). Seventy-four percent of the sample reported parental exposure to the Holocaust, defined as being interned in a Nazi concentration camp, having witnessed or experienced torture, or having to flee or hide for one's life during World War II. Control participants (i.e., the remainder of the sample) were demographically-matched controls (e.g., Jewish, similar age range and gender distribution). All the participants were born to parents of European or American descent. Chi-squared analyses showed that the subgroup who completed the health behavior interviews did not differ from the parent study sample by gender ($p = 0.39$), maternal expo-

sure ($p = 0.73$), or paternal exposure to the Holocaust ($r = 0.40$). The subsample was older than the total sample ($t = -8.35$, $p < 0.0001$).

Forty two percent of the sample was male and the majority of the sample (64%) was married/partnered. The sample averaged 16.85 (± 2.75) years of education, although five people did not report their level of education. Exclusion criteria included lifetime history of psychosis, bipolar disorder, alcohol or substance dependence, organic mental disorder (including stroke) or dementia; use of oral corticosteroids were excluded. All subjects provided written informed consent and the protocol was approved by the Institutional Review Boards at Mount Sinai School of Medicine and the James J Peters VAMC.

2.1. Measures

Emotional and physical health ratings. Participants rated their emotional and physical health on a 5-point scale (e.g., poor, fair, good, very good, excellent). Two people did not report physical health ratings.

Childhood Trauma Exposure (CTQ) [8]. The CTQ is a 28 item self-report scale that measures retrospective reports of childhood emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Five people did not complete the CTQ.

Civilian Mississippi PTSD Scale (C-Mississippi). The C-Mississippi is an adaptation of the Mississippi PTSD Scale that was created to evaluate combat-related PTSD symptoms [24]. In the C-Mississippi, eleven items that referred specifically to past military service were reworded to refer to the past in more general terms. Respondents are asked to respond to 39 items that reflect DSM-III-R PTSD criteria on a 5-point Likert scale. One person did not complete the C-Mississippi.

Spielberger State-Trait Anxiety Inventory (STAI) [36]. The trait scale of the STAI is a 20 item scale that measure a person's tendency to perceive stressful situations as threatening or dangerous. Items are scored on a 1 to 4 scale (almost never, sometimes, often, and almost always for the trait scale). Ten people did not complete the STAI.

Metabolic syndrome risk factors. Non-insulin dependent diabetes, hypertension, and dyslipidemia were inferred on the basis of research chart review (by LMB), which included a medical history containing current medical diagnoses, current use of medications and a follow up interview with a study physician. Body mass index (BMI) was computed from height and weight measurements taken at the time of study participation.

BMI was unavailable for two people. A count variable was created for each participant to represent number of metabolic syndrome components, including the presence of non-insulin dependent diabetes, hypertension, dyslipidemia and/or obesity ($BMI \geq 25$).

2.2. Statistical analyses

Because we were interested in effects of maternal versus paternal exposure to the Holocaust on self reported health, two dichotomous variables were created to denote maternal and paternal exposure (1 = yes, 0 = no). The association between maternal exposure and demographic and clinical characteristics was evaluated first with t-tests and chi-squared analyses, where appropriate. Next, a series of linear regression analyses was conducted on the quantitative measures (e.g., BMI, health ratings) entering the two parental exposure variables into the model. Age and participant gender were entered first into the model as covariates. Separate follow-up analyses were conducted to evaluate whether associations between parental exposure and the health ratings were attenuated by offspring symptomatology or childhood trauma exposure.

3. Results

As shown in Table 1, offspring with maternal exposure to the Holocaust were more likely to be men, were older, and had fewer children relative to offspring whose mothers were not exposed to the Holocaust. The majority of the group (88%) also reported paternal exposure to the Holocaust. The groups did not differ with respect to education or marital status.

Regarding health outcomes, maternal exposure was associated with being a nonsmoker, but greater use of psychotropic and other medications, including those used for the treatment of hypertension and dyslipidemia. Maternal exposure was also associated with having 2 or more metabolic syndrome conditions (e.g., hypertension, dyslipidemia, Type 2 diabetes, and overweight) but the two groups did not differ by body mass index. Birth year ranged from 1940 (i.e., some offspring were born after parents had safely fled camp or were evacuated to safety) to 1980 and reflected the years since exposure to the Holocaust (e.g., 0 to 40 years). Note that the parents of the person born in 1940 had left Birth year was lower in offspring reporting maternal exposure to the Holocaust relative to controls, $t(135) = 4.45, p < 0.0001$, but was not related to pa-

ternal exposure ($p = 0.08$). Table 2 shows that childhood trauma exposure and current trauma symptoms did not differ between the two groups, but people with maternal exposure to the Holocaust reported higher levels of trait anxiety ($p = 0.009$).

3.1. Regression analyses

Body Mass Index. Paternal exposure tended to be associated with higher body mass index ($t = 1.66, p = 0.10$) after controlling for age and gender but maternal exposure was not related to body mass index ($t = -0.78, p = 0.44$).

Emotional health rating. Offspring whose mothers were exposed to the Holocaust reported poorer emotional health ($t = -2.75, p = 0.007$), after controlling for gender, age and paternal exposure, ($F(4,136) = 2.43, p = 0.05$). The addition of childhood trauma exposure to the model did not attenuate the relationship between maternal exposure and emotional health ratings ($t = -2.81, p = 0.006$) and was itself related to poorer emotional health ($t = -4.72, p < 0.0001$). In contrast, trait anxiety was associated with poorer emotional health ($t = -10.92, p < 0.0001$) and accounted for the relationship between maternal exposure and emotional health ratings ($p = 0.35$).

Physical health rating. Physical health ratings were also lower among offspring with maternal exposure ($t = -2.05, p = 0.04$) after controlling for gender, age and paternal exposure although the model was not significant ($F(4,134) = 1.11, p = 0.35$). In parallel with results presented above, childhood trauma exposure was associated with poorer physical health ratings ($t = -2.72, p = 0.008$), but the association between maternal exposure and physical health persisted ($t = -1.95, p = 0.05$). Trait anxiety was associated with poorer physical health ($t = -4.09, p < 0.0001$) and diminished the relationship between physical health ratings and maternal exposure ($p = 0.24$).

Given that offspring levels of trait anxiety were strongly associated with emotional and physical health ratings, the relationship between trait anxiety and parental exposure was evaluated in a regression model. Results indicated that maternal exposure was related to higher trait anxiety in offspring when controlling for age, and gender ($t = 2.97, p = 0.004$). In contrast, paternal exposure was not associated with trait anxiety ($p = 0.15$). Of note, age itself was unrelated to offspring anxiety and health ratings, ($r(126)_{ageandtraitanxiety} = 0.018$; $r(136)_{ageandemotionalhealthrating} = -0.12$; $r(136)_{ageandemotionalhealthrating} = -0.03$).

Table 1
Demographic and health characteristics by maternal exposure

	Maternal exposure		p
	NO	YES	
	n = 55	n = 82	
Gender # and (%) male	32 (58%)	25 (31%)	0.001
Age	43.65 (9.522)	49.84 (6.39)	< 0.0001
Father exposed (%)	20 (36%)	72 (88%)	< 0.0001
Years of Education	17.18 (2.41)	16.63 (2.95)	0.27
Marital Status (% married)	31 (57%)	56 (68%)	0.39
Number of children	1.4 (1.67)	2.18 (1.73)	0.009
Alcohol Use (never drank)	12 (22%)	26 (33%)	0.15
Current Smoker	10 (18%)	5 (6.2%)	0.03
Body Mass Index	25.95 (3.90)	25.90 (5.07)	0.82
Psychotropic Medication Use	3 (5.7%)	18 (23%)	0.01
Other Medication Use	20 (38%)	42 (57%)	0.03
# with ≥ 2 metabolic syndrome	1 (2%)	12 (15%)	0.03

Table 2
Demographic and health characteristics by maternal exposure

	Maternal exposure		p
	NO	YES	
	n = 55	n = 82	
Childhood Trauma Questionnaire (CTQ)	39.26 (13.34)	39.56 (14.49)	0.91
CTQ emotional abuse	8.68 (4.81)	9.54 (5.16)	0.33
CTQ physical abuse	6.64 (3.10)	6.59 (2.81)	0.93
CTQ sexual abuse	6.53 (4.30)	6.05 (2.87)	0.45
CTQ emotional neglect	10.74 (5.42)	11.00 (5.10)	0.78
CTQ physical neglect	6.68 (3.40)	6.81 (3.33)	0.83
Civilian Mississippi Scale	69.94 (18.41)	75.95 (19.09)	0.07
Spielberger Trait Anxiety	15.98 (10.32)	21.41 (12.05)	0.009

4. Discussion

Results indicated that maternal but not paternal exposure to the Holocaust was associated with poorer subjective impressions of emotional and physical health in offspring. The relationship between maternal exposure and health ratings was not accounted for by the offspring's reports of perceived trauma exposure in childhood or current symptoms of PTSD, but the association was attenuated by the offspring's level of trait anxiety. Adult offspring who reported maternal exposure were also more likely to report that they were taking psychotropic and other medications, including medications for hypertension and dyslipidemia.

There are a number of potential pathways from parental trauma exposure to offspring illness. For example, the association may be mediated by learned (or inherited) behaviors that represent risk factors for the development of cardiovascular diseases, including tobacco use. This explanation is not supported by the current findings as offspring with maternal exposure to the Holocaust were less likely to use tobacco, but it must be acknowledged that this explanation cannot be ruled out in the current sample because a full as-

essment of behavioral risk factors was not conducted. With respect to non-environmental contributions, it is likely that the attributes measured here are heritable and can be associated with inherited molecular genetic variants. However, the results reported here are more consistent with a parent-of-origin pattern of inheritance than with classical Mendelian inheritance [28,40].

A second explanation is that mothers influence their offspring's subjective evaluation of their own health. The explanation is supported by the results showing the trait anxiety attenuated the association between maternal exposure and health ratings. Trait anxiety is considered to be a major component of the construct of Neuroticism or negative affectivity, which is linked to major illness. Although research on the association between Neuroticism and illness has been criticized as reflecting a tendency to over report somatic complaints [11,38], recent reviews support a prospective link between Neuroticism and cardiovascular disease endpoints. Although we cannot rule out the possibility that offspring with maternal exposure are more likely to complain about their health, the lack of a relationship between age and anxiety or age and health ratings supports the idea that anxiety symptoms are not

simply the manifestation of age-related physical health conditions.

Another potential mechanism for the association between trait anxiety and health complaints/conditions that should be considered is that people with higher levels of anxiety are simply more aware of their health status because they are help-seeking. That is, because all of the health complaints/conditions that were examined in the current study were self-reported, the people who did not report such diagnoses are not necessarily illness-free. These individuals may be unaware of undetected hypertension or dyslipidemia because they do not attend regular medical appointments and have never received a diagnosis. Future research incorporating objective indicators of illness risk (e.g., measurements of blood pressure and lipids) in conjunction with symptom reports would rule out this alternative explanation.

Finally, as noted above, the fetal programming hypothesis has been developed to explain how in utero exposure or even postnatal exposure to stress or deprivation can influence offspring health and psychiatric outcomes. This explanation would be most strongly supported by evidence that GC metabolites are lower among offspring whose mothers were exposed to the Holocaust, relative to offspring with paternal exposure and/or no parental exposure to the Holocaust. The absence of such metabolic markers (or alternative markers of HPA axis functioning) is a limitation of the current study, but the results offer proof of principle that environmental exposures or behaviors in one generation are associated with health outcomes in the next generation. In support of this view are two recent reports showing an association between early parental care and adult risk factors for cardiovascular disease [1,10].

Interpretation of the findings in the current study is limited by several aspects of the study design. For example, the results may not be generalizable to other populations as the sample was relatively healthy (i.e., many medical conditions were exclusionary for participation in the study) and well educated. The sample was also relatively young and so may not yet show signs of metabolic syndrome factors. In addition, because the study was not designed to evaluate metabolic disorders, the assessment of hypertension, lipid disorders and other conditions was made by self-report rather than by direct measurement of blood pressure and serum cholesterol. The measures used for behavioral risk factors were necessarily brief and not comprehensive.

In sum, we observed an association between maternal exposure to the Holocaust and offspring health that was mediated by offspring anxiety. Although, the asso-

ciation of trait anxiety with health ratings is well known and may reflect some degree of construct overlap, neuroticism is increasingly recognized as a prospective contributor of longevity and quality of life [23]. Understanding the origins of this relationship should lead to better strategies for improving health and preventing the chronic illnesses of adulthood. The use of objective and standardized indicators of health collected during a clinical evaluation (e.g., lipid levels, blood pressure) and the incorporation of metabolic, epigenetic and other markers are necessary next steps in the evaluation of maternal trauma exposure and offspring health.

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