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Original Contribution

Early-Life Adversity Due to Bereavement and Inflammatory Diseases in the Next Generation: A Population Study in Transgenerational Stress Exposure

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Emerging evidence suggests that trauma experienced in childhood has negative transgenerational implications for offspring mental and physical health. We aimed to investigate whether early-life adversity experienced as bereavement is associated with chronic inflammatory health in offspring. The study population included 3 generations of Swedish families with a base population of 453,516 children (generation 3) born in 2001–2012. Exposure was defined as the middle generation's (generation 2) experiencing bereavement in childhood due to the death of a parent (generation 1). Outcomes in generation 3 included 2 diagnoses of inflammatory diseases, including asthma, allergic diseases, eczema, and autoimmune diseases. Survival analysis was used to identify causal pathways, including investigation of mediation by generation 2 mood disorders and socioeconomic status (SES). We found that early-life bereavement experienced by women was associated with early-onset offspring asthma (hazard ratio = 1.15, 95% confidence interval: 1.08, 1.23); mediation analysis revealed that 28%–33% of the association may be mediated by SES and 9%–20% by mood disorders. Early-life bereavement experienced by men was associated with autoimmune diseases in offspring (hazard ratio = 1.31, 95% confidence interval: 1.06, 1.62), with no evidence of mediation. In conclusion, adversity experienced early in life may contribute to an increased risk of inflammatory diseases which is partly mediated by mood disorders and SES.

adverse childhood experiences; allergy; asthma; bereavement; inflammatory disease; transgenerational stress

Abbreviations: CI, confidence interval; G, generation; HPA, hypothalamic-pituitary-adrenal; HR, hazard ratio; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, Tenth Revision*; LISA, Longitudinal Integration Database for Health Insurance and Labor Market Studies; SES, socioeconomic status; Th, T-helper.

Childhood inflammatory disease such as atopic disease (asthma, eczema, allergy) and autoimmune diseases continue to be highly pervasive worldwide despite much research into prevention. Fetal origins research suggests that programming of chronic inflammatory diseases may begin early in life (1, 2). In particular, maternal stress during pregnancy is associated with a greater risk of asthma, eczema, and diabetes in offspring (3–6). Further, there is some preliminary evidence to suggest that adversity or trauma experienced in the preconception period may be associated with offspring asthma (7–9). We are unaware of human studies that have evaluated other inflammatory diseases apart from asthma. More research using large populations is needed.

There is growing interest in the possibility of transgenerational associations, particularly the impact of different types of environmental exposures, such as adversity or smoking, on the birth and health outcomes of subsequent generations (10, 11). Transgenerational epidemiology has the potential to improve our understanding of disease mechanisms, particularly regarding gene-environment interplay and early developmental programming: How early is early? Regarding early adversity, the majority of transgenerational research has been based on animals rather than humans, finding that offspring have increased psychopathology, metabolic changes, and altered physiological responses to stress, including evidence of epigenetic changes (10, 12). The few transgenerational stress research studies on humans have

shown that the offspring of parents who suffer childhood trauma often experience negative birth outcomes and poor psychological health (9, 13–15). However, it is unclear whether transgenerational outcomes of early adverse exposure are transferred maternally, paternally, or through both parents (16–20). Possible pathways for the transgenerational transfer of stress could be inherited epigenetic changes in male and/or female gametes (16–20) or physiological changes that modify the in utero environment and the growing fetus, such as increased stimulation of placental corticosteroid hormone (21).

One type of early-life adversity is bereavement due to loss of a parent during childhood (22). Persons experiencing bereavement have been shown to suffer long-term health consequences, such as ongoing physical and mental health problems and changes in bioregulation (22, 23). In addition, loss of a parent early in life has been shown to have compounding consequences, such as lowered family income, lack of support from the surviving parent (who may be suffering as a result of bereavement), taking on more fiscal and home responsibilities, and adjusting to changes such as relocation (22, 24). Therefore, because of the length of time between exposure (the parent's childhood) and outcome (the offspring's childhood), it is plausible that some of these consequences of bereavement may exist on the causal pathway between early bereavement and offspring outcomes, particularly lower socioeconomic status (SES) and mood disorders. By studying these "mediators," we aimed to highlight possible mechanisms of any transgenerational associations. This study builds on the 2011 analysis of Swedish families by Fang et al. (25), which showed that experiencing bereavement just prior to or during pregnancy was associated with increased risk of offspring asthma, by extending the period of bereavement earlier to childhood and increasing the number of disease outcomes of interest.

Our objective in this study was to investigate whether bereavement in early life increases the risk of chronic inflammatory diseases in offspring and whether there is a difference in bereavement experienced by women or men. Further, we aimed to explore whether associations could be explained in part by mediation through SES or mental health.

METHODS

Study population

A nationwide Swedish cohort was established using the Swedish personal identity number, which enables unambiguous linkage between the national health and sociodemographic registers maintained by the Swedish National Board of Health and Welfare and Statistics Sweden. We identified all children in the Swedish Medical Birth Register who had been born in Sweden from January 2001 to December 2012 (ages ≤12.9 years; median duration of follow-up, 4.4 years), hereafter called generation 3 (G3). Their biological parents (generation 2 (G2)), born in 1973–1997, were then identified from the Medical Birth Register (mothers) and the Multi-Generation Register (fathers). Similarly, 4 grandparents for each child (generation 1 (G1)) were identified from the Medical Birth Register (mothers of G2) and the Multi-Generation Register (fathers of G2). Although it was a requirement that G3 and G2 were all born in Sweden in order to capture the exposure, the requirement for G1 (grandparents) was only that they had a Swedish personal identity number at the time of G2 birth.

Exposure

Bereavement experienced by G2 during early life was defined as the death of a parent (G1) in the first 18 years of life due to any cause. Deaths of G1 were identified from the Cause of Death Register. In addition, we separated the exposure into parental death experienced in childhood (age ≤12 years) or adolescence (ages 13–18 years).

Outcomes

Chronic inflammatory diseases in children (G3) were defined in 2 different ways. The first was to use 2 diagnoses for atopic and autoimmune diseases in the National Patient Register, which records information on outpatient specialist care and inpatient hospital diagnoses. Two diagnoses rather than a single diagnosis were used to ensure a definitive diagnosis and to avoid misclassification. Diseases were grouped into 3 categories: asthma (*International Classification of Diseases, Tenth Revision* (ICD-10) code J45 or J46); atopic diseases—eczema/atopic dermatitis, allergic rhinitis, and allergic urticaria (ICD-10 codes L20, L30.9, J30, J31.0, and L500); and autoimmune diseases—insulin-dependent diabetes mellitus, autoimmune thyroid disease, juvenile arthritis, vasculitis, systemic lupus erythematosus, juvenile dermatopolymyositis, celiac disease, Crohn disease, and ulcerative colitis (ICD-10 codes E03.9/E05, M08, M30/M31.3/31.4/31.7, M32, M33, K90, K50, and K51). The first date of diagnosis was considered to be the date of the incident case for analysis. Secondly, we included medication data from the Swedish Prescribed Drug Register in order to identify atopic diseases that are more likely to be managed by primary health-care providers—that is, asthma, allergic rhinitis, and atopic eczema. In Sweden, although diagnoses made and managed in primary care are not available through national registers, all dispensed prescribed medications have been recorded in the Swedish Prescribed Drug Register since July 2005. The case identification using records of medication prescriptions and/or diagnosis was based on validated and previously used algorithms (26, 27). Additional information on the algorithms is provided in the Web Appendix (available at https://doi.org/10.1093/aje/kwab236).

Covariates

From the Medical Birth Register, we were able to retrieve data on the birth weight and gestational age of G3 and on whether their mothers (G2) had smoked during pregnancy, as well as maternal height and weight at the first antenatal appointment (for calculation of body mass index (weight (kg)/height $(m)^2$)). We further obtained data on birth years and SES (defined as level of completed education (grade

9 or less, grades 10–12, or ≥2 years of tertiary education)) for both parents (G2) at the time of the birth of G3, retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA). The SES of G1 was determined as the combined income of G1 couples at the time of G2's birth, retrieved from the Income and Taxation Register for births occurring in 1973–1989 and from the LISA for births occurring in 1990–1997. We adjusted incomes for inflation on the basis of the Swedish consumer price index (in place since 1973) and then log-transformed the results because of skewed distributions. The asthma status of G2 was defined as at least 1 diagnosis of asthma (ICD-10 code J45/J46 or *International Classification of Diseases, Ninth Revision* (ICD-9) code 493) in the National Patient Register between the ages of 15 years and the birth of G3. For G2 women, asthma status also included a positive response regarding having asthma at the first prenatal-care visit. A diagnosis of mood disorder in G2 was defined as at least 1 diagnosis of depression, bipolar depression, anxiety, or a stress-related disorder in the National Patient Register between age 15 years and the birth of the child (ICD-10 codes F30–F45; ICD-9 codes 296, 300, and 311; and *International Classification of Diseases, Eighth Revision*, codes 296, 300, and 311).

Statistical analysis

We used Cox proportional hazards regression to perform survival analysis with attained age as the underlying time scale to generate hazards ratios (HRs) and 95% confidence intervals (CIs). The end of follow-up was defined as the first known of the following events: incident disease, emigration from Sweden, death, or the end of the study period (December 31, 2013). We censored individuals who did not have the incident disease by the end of follow-up. HRs were generated separately for mothers and fathers (G2). Subject-matter–informed directed acyclic graphs were used to assess covariates as potential confounders (Web Figure 1) (28). Based on the directed acyclic graph, adjusted models included the SES of G1 and the birth year of G2. A sandwich estimator was used to account for correlation caused by clustering of observations within families. In some models, the proportional hazards assumption appeared to be violated. Closer inspection of the smoothed hazards graph revealed noticeably nonproportional hazards; therefore, we split the time scale at age 3 years for these models (Web Figure 2). We conducted stratified analyses splitting the ages of bereavement into childhood (age ≤12 years) and adolescence (ages 13–18 years). We added interaction terms to models to test for effect modification by sex.

Mediation analysis. Mediation analysis was only performed for associations in the primary analyses that had a *P* value below 0.05. Using the directed acyclic graph, we identified G2 asthma, G2 education (SES), and G2 mood disorders as potential mediators (Web Figure 1). Because we were interested in the separate associations of G2 education and G2 mood disorders with the causal pathway, we performed separate mediation analyses for each of these variables. Since maternal or paternal (G2) and offspring (G3) asthma share causes that we could not control for (i.e., familial genes and environment), conditioning on G2 asthma—or any of its effects, such as G3 birth outcomes (for maternal asthma)—in a mediation analysis could introduce collider stratification bias between exposure (G2) (i.e., bereavement) and outcome (G3) (e.g., asthma). Therefore, we were unable to test mediation through G2 asthma. Direct and indirect effects were calculated using the regression-based approach of Valeri and VanderWeele (29), with the SAS macro provided by the authors. We further checked for interaction between exposure and mediators using the same macro. To explore the sensitivity of the estimates for one mediator regarding influences by the other potential mediator, we also ran the analyses adjusting for the other mediator.

Proportion mediated was calculated as the indirect effect divided by the total effect. It represents the proportion of the total effect that is attributed to the mediating pathway.

Sensitivity analysis. We conducted 2 sensitivity analyses. First, for the adjusted estimates in the main analysis that were statistically significant, we calculated E-values and their lower estimates according to the method of VanderWeele and Ding (30). E-values provide a measure of robustness of the estimate to unmeasured confounding. The E-value and its lower limit indicate the strength an unmeasured confounder or combination of unmeasured confounders would need to have with both the exposure and the outcome to explain away the observed association. Second, to assess whether asthma in children (G3) under age 3 years associated with G2 bereavement was more transitory in nature (due to the challenge of diagnosing asthma at this age and the high prevalence of infectious wheezing illnesses) as compared with asthma in children (G3) whose mothers (G2) did not experience bereavement, we assessed the relative proportions of children who continued to have asthma at age 5 years (measured as an asthma diagnosis or medication use in the fifth year of life).

Statistical analyses were conducted using SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina) and STATA, version 15 (StataCorp LLC, College Station, Texas). The study protocol was approved by the regional ethics review board in Stockholm, Sweden.

RESULTS

In total, G3 included 453,516 children who had both parents (G2) born in Sweden and all 4 grandparents (G1) with Swedish personal identity numbers (36.8% of all children born in Sweden during 2001–2012). G2 included 547,721 parents of G3 (n = 273,585 mothers, n = 274,136 fathers). G1 included 970,606 grandparents of G3 (n = 241,792 maternal grandmothers, n = 242,273 maternal grandfathers, n = 243,180 paternal grandmothers, n = 243,361 paternal grandfathers). The average age of grandmothers (G1) who died was 40.2 (standard deviation, 7.6) years (range, 17–62), and the average age of grandfathers (G1) who died was 43.4 (standard deviation, 9.9) years (range, 16–86). The number of G2 women who experienced bereavement in the first 18 years of life was 17,440, and the equivalent number of G2 men was 17,210. This translates to 33,871 (7.5%)

Table 1. Incidence of Inflammatory Disease Among Swedish Children Born in 2001–2012 (Generation 3)

Inflammatory Disease	Incidence[a]		
	Total	Age at Onset, years	
		<3	≥3
2-diagnosis definition			
Any inflammatory or autoimmune disease	20.4	31.4	8.6
Asthma	14.4	23.0	5.5
Atopic diseases	6.7	9.5	3.9
Autoimmune diseases	1.4	1.4	1.5
Diagnosis and/or medication use definition			
Asthma	21.1	29.5	12.0
Atopic eczema	19.9	30.2	8.9
Allergic rhinitis	19.1	20.3	17.7

[a] No. of cases per 1,000 person-years.

G3 with at least 1 parent (G2) who had suffered childhood bereavement (exposure). The incidence of any inflammatory disease in G3 was 20.4 per 1,000 person-years; see Table 1 for all incidence rates.

Characteristics of the children (G3) and their parents (G2) by exposure (parental bereavement in G2 childhood) are shown in Table 2. The main observable differences are that G2 women who experienced bereavement were more likely to smoke during pregnancy and to be obese than those who had not suffered bereavement; and both G2 men and women who experienced bereavement were less likely to have more than 2 years of tertiary education and more likely to have diagnosed mood disorders (Table 2).

For G2 women who experienced bereavement in childhood, the increased incidence of their children's (G3) developing asthma before age 3 years was between 6% (diagnosis and medication definition: adjusted HR = 1.06, 95% CI: 1.00, 1.13) and 15% (2-diagnosis definition: adjusted HR = 1.15, 95% CI: 1.08, 1.23), while no difference was noted for the risk of developing asthma at or after the age of 3 years (Table 3). Other G3 outcomes did not appear to be associated with early bereavement experienced by G2 women, with HRs close to 1 (Table 3). Analyses stratified by age produced results similar to the main results and did not show that age at bereavement had a different impact on risk of disease (Web Table 1), except for bereavement at ages 13–18 years, which showed an association with offspring atopic disease onset at or after age 3 years (adjusted HR = 1.23, 95% CI: 1.01, 1.49). This result was not supported by further analysis for atopic diseases—eczema and allergic rhinitis (Web Table 1). Early bereavement experienced by G2 males was associated with an increased risk of offspring's (G3) developing autoimmune diseases, particularly with onset over age 3 years (adjusted HR = 1.31, 95% CI: 1.06, 1.62) but not with any other outcomes (Table 4). Analyses stratified by bereavement period (childhood or adolescence) showed results similar to those for all ages combined (Web Table 2). Interaction terms indicated there were no differences in outcomes by sex.

Mediation analysis

Mediation analysis was conducted only for those outcomes that had a positive association with G2 bereavement. For the association between parental bereavement exposure in childhood for G2 women and offspring (G3) asthma, the individually estimated proportions mediated were 9%–20% for maternal mood disorders (G2) and 28%–33% for maternal educational attainment (G2) (Table 5). There was no observed mediation by paternal mood disorders (G2) or paternal educational attainment (G2) in the association between parental bereavement exposure in childhood for G1 men and offspring (G3) autoimmune diseases. There was no evidence of interaction between the mediators and the exposure, nor did the estimates change when each (other) potential mediator was added as a covariate to the models.

Sensitivity analysis

E-value and lower-limit calculations for the estimates of positive associations with bereavement experienced by G2 women were 1.57 and 1.37 for asthma defined by 2 diagnoses and 1.34 and 1.00 for asthma defined by diagnosis and/or medication use; and for the bereavement experienced by G2 men, they were 1.95 and 1.34, respectively, for autoimmune disease association. In children under age 3 years with asthma, 35% continued to have asthma at age 5 years regardless of whether their mother had experienced childhood bereavement (both asthma definitions).

DISCUSSION

The main findings of this study are that bereavement experienced by women in early life is associated with a modest

Table 2. Characteristics of Children (Generation 3) and Parents (Generation 2) According to Parental Bereavement Exposure in Childhood (Generation 2) in a Swedish Birth Cohort, 2001–2012

Characteristic	Parental Bereavement Exposure			
	Nonexposed[a] (*n* = 419,646)		Exposed[b] (*n* = 33,871)	
	No.	%	No.	%
G3 sex				
Male	215,693	51.4	17,574	51.9
Female	203,950	48.6	16,297	48.1
Missing data	3		0	
G3 birth weight, g				
≤2,999	57,285	13.7	4,877	14.4
3,000–3,499	129,364	30.9	10,489	31.1
3,500–3,999	149,923	35.8	11,862	35.0
4,000–4,499	66,237	15.8	5,254	15.5
≥4,500	16,146	3.9	1,330	3.9
Missing data	691	0.2	59	0.2
G3 gestational age, days				
≤244	10,034	2.4	826	2.4
245–265	35,855	8.5	2,933	8.7
266–287	283,630	67.6	23,029	68.0
≥288	89,988	21.4	7,068	20.9
Missing data	139	< 01	15	< 01
G3 maternal smoking during pregnancy				
None	371,003	88.4	28,232	83.4
≤9 cigarettes/day	24,182	5.8	3,213	9.5
>9 cigarettes/day	6,191	1.5	983	2.9
Missing data	18,270	4.4	1,443	4.3
G2 birth year				
Women				
1973–1976	112,578	26.9	8,817	26.0
1977–1980	146,253	34.9	11,298	33.4
1981–1984	98,575	23.5	8,068	23.8
1985–1988	48,261	11.5	4,329	12.8
1989–1992	12,776	3.0	1,254	3.7
1993–1996	900	0.2	105	0.3
Missing data	3		0	
Men				
1973–1976	174,366	41.6	13,928	41.2
1977–1980	138,481	33.0	10,973	32.4
1981–1984	72,669	17.3	5,893	17.4
1985–1988	27,988	6.7	2,461	7.3
1989–1992	5,812	1.4	559	1.7
1993–1996	324	0.1	47	0.1
Missing data	6		0	

Table continues

Table 2. Continued

Characteristic	Parental Bereavement Exposure			
	Nonexposed[a] (*n* = 419,646)		Exposed[b] (*n* = 33,871)	
	No.	%	No.	%
Age of G2 women at G3 child's birth, years				
≤18	5,077	1.2	646	1.9
19–22	41,672	9.9	4,371	12.9
23–26	104,179	24.8	9,001	26.6
27–30	150,542	35.9	11,212	33.1
31–34	96,125	22.9	6,908	20.40
≥35	22,051	5.3	1,733	5.1
Missing data	2		0	
Body mass index[c] of G2 women				
≥30 (obesity)	43,038	11.2	4,136	13.4
Missing data	34,522	8.2	2,916	8.6
Highest G2 education attained				
Women				
Grade 9 or less	38,094	9.1	4,981	9.5
Grades 10–12	183,426	43.7	16,289	48.1
≥2 years of tertiary education	196,765	46.9	12,342	36.4
Missing data	1,371	0.3	259	0.8
Men				
Grade 9 or less	43,094	10.3	5,384	15.9
Grades 10–12	227,939	54.3	19,305	57.0
≥2 years of tertiary education	147,133	35.1	9,004	26.6
Missing data	1,480	0.4	178	0.5
Combined G1 income[d], log(mean SEK)				
G2 women's parents	10.50 (0.41)		10.46 (0.50)	
G2 men's parents	10.47 (0.47)		10.42 (0.57)	
Missing data	0		0	
G2 mood disorder				
Women	29,222	7.0	3,096	9.1
Men	13,769	3.3	1,627	4.8
Missing data	0		0	
G2 asthma[e]				
Women	47,740	11.4	4,015	11.9
Men	6,632	1.6	585	1.7
Missing data	0		0	

Abbreviations: G, generation; SEK, Swedish kroner.
[a] No parental bereavement in G2 childhood.
[b] Parental bereavement in G2 childhood.
[c] Weight (kg)/height $(m)^2$.
[d] Values are expressed as mean (standard deviation).
[e] Asthma based on hospital visits for asthma in both G2 women and men and, additionally for women, a positive report of ever having asthma at the first midwife visit.

risk of offspring early-onset asthma and that bereavement experienced by men in childhood is associated with a risk of offspring autoimmune diseases. The observed associations with asthma may be attributed in part to the negative associations of early bereavement with SES and development of mood disorders in women.

Table 3. Association Between Women's (Generation 2) Experiencing Bereavement in Childhood and Inflammatory Disease Outcomes in Offspring (Generation 3) in a Swedish Birth Cohort, 2001–2012

G3 Outcome and Age at Onset, years	Bereavement Exposure in G2 Women			
	Unadjusted HR	95% CI	Adjusted[a] HR	95% CI
2-diagnosis definition				
Asthma				
≤3	1.15	1.08, 1.23	1.15	1.08, 1.23
≥3	0.97	0.85, 1.10	0.96	0.84, 1.10
Atopic diseases				
≤3	0.95	0.86, 1.05	0.94	0.85, 1.04
≥3	1.11	0.97, 1.28	1.12	0.97, 1.29
Autoimmune diseases				
≤3	1.09	0.85, 1.39	1.09	0.85, 1.39
≥3	0.99	0.79, 1.26	1.0	0.79, 1.27
Diagnosis and/or medication use definition				
Asthma				
≤3	1.07	1.01, 1.13	1.06	1.00, 1.13
≥3	0.94	0.84, 1.04	0.94	0.85, 1.03
Atopic eczema				
≤3	0.94	0.89, 1.00	0.94	0.89, 1.00
≥3	1.02	0.92, 1.12	1.02	0.93, 1.13
Allergic rhinitis				
≤3	1.00	0.94, 1.07	1.01	0.94, 1.08
≥3	0.96	0.89, 1.03	0.97	0.90, 1.04

Abbreviations: CI, confidence interval; G, generation; HR, hazard ratio.
[a] Adjusted for G1 socioeconomic status and G2 birth year.

To our knowledge, this population-based cohort analysis of 453,516 children is the largest study to date to have investigated the transgenerational association of early trauma with offspring asthma, and it is the first that we are aware of to have investigated other chronic inflammatory and autoimmune disease outcomes. In other transgenerational asthma-related studies, Le-Scherban et al. (9) followed 350 parent-child dyads and found that adverse events in the parent's childhood were associated with worse overall health and more asthma diagnoses in offspring. Similarly, Tomfohr-Madsen et al. (8) found that 2-year-old offspring were more likely to develop asthma and allergy if their mothers had suffered child abuse. Our study confirms the findings of these earlier studies.

The association between early bereavement experienced by women and early-onset asthma in their offspring may operate through a mother-specific mechanism, such as epigenetic changes in the ovum or programmed changes to the in utero environment. There is a body of animal and human research that describes how stress during pregnancy alters the hypothalamus-pituitary-adrenal (HPA) axis of the mother, which in turn may alter the in utero environment, affecting the immune system development of the fetus (31, 32). Furthermore, emerging transgenerational research suggests that stress in early maternal life may lead to alteration of the HPA axis in offspring, reducing cortisol production, which in turn modulates the immune response to become proinflammatory and T-helper 2 cell (Th2) in nature, leading to asthma and allergy (19, 21, 33). Other transgenerational stress research points to stress-induced epigenetic changes that may occur in gametes early in life, which are then inherited by the offspring, resulting in altered immunity over multiple generations (12, 18).

This is the first study we know of that has investigated early-life trauma experienced by fathers and its association with child asthma and inflammatory diseases. The associations between childhood bereavement in men and offspring autoimmune diseases in the current study and the lack of mediation via mood disorders and SES suggests that epigenetic changes to the germline may be occurring early in life. This supports findings from animal studies in which animals have been separated from parents at birth to induce depression and anxiety; such studies have found a number of epigenetic changes increasing offspring disease risk and stress axis sensitivity, such as DNA methylation, populations of small noncoding RNAs, and posttranslational histone modifications (17, 18).

One implication of the current research is that asthma programming may begin before conception and may be linked to mother-specific factors, including SES and mood

Table 4. Association Between Men's (Generation 2) Experiencing Bereavement in Childhood and Inflammatory Disease Outcomes in Offspring (Generation 3) in a Swedish Birth Cohort, 2001–2012

G3 Outcome and Age at Onset, years	Bereavement Exposure in G2 Men			
	Unadjusted HR	95% CI	Adjusted[a] HR	95% CI
2-diagnosis definition				
Asthma				
≤3	1.05	0.99, 1.12	1.06	0.98, 1.10
≥3	0.93	0.81, 1.06	0.94	0.82, 1.08
Atopic diseases				
≤3	1.04	0.94, 1.14	1.04	0.93, 1.15
≥3	0.88	0.75, 1.03	0.88	0.76, 1.04
Autoimmune diseases				
≤3	1.25	0.99, 1.57	1.25	0.99, 1.57
≥3	1.30	1.05, 1.60	1.31	1.06, 1.62
Diagnosis and/or medication use definition				
Asthma				
≤3	1.05	0.99, 1.12	1.05	0.99, 1.12
≥3	0.92	0.84, 1.01	0.92	0.84, 1.01
Atopic eczema				
≤3	0.98	0.93, 1.04	0.99	0.93, 1.05
≥3	1.01	0.92, 1.12	1.03	0.93, 1.14
Allergic rhinitis				
≤3	1.03	0.97, 1.10	1.03	0.97, 1.10
≥3	0.94	0.87, 1.02	0.95	0.88, 1.02

Abbreviations: CI, confidence interval; G, generation; HR, hazard ratio.
[a] Adjusted for G1 socioeconomic status and G2 birth year.

disorders throughout life. Similar to Tomfohr-Madsen et al. (8), we found evidence for mediation through maternal mood disorders, although we focused on diagnoses between exposure and birth rather than postnatal diagnoses. Although the proportion mediated through mood disorders was moderate, in the region of 9%–20%, this variable was based on hospital and specialist diagnoses, which may mean that the mediatory role is underrepresented, since primary-care diagnoses and therefore potentially milder cases are not captured. One explanation for a causal contribution of maternal mood disorders could be that experiencing early trauma leads to later psychopathology such as depression and anxiety (34) during pregnancy, which in turn is known to be associated with childhood asthma (5, 6). Possible mechanisms include dysregulation of the HPA axis due to stress exposure in utero leading to asthma and wheezing (35) and epigenetic changes in signaling required for lung maturation (36). Another possible explanation is the role of a common genetic factor for both asthma and depression (37).

We also found that maternal education mediated up to one-third of the observed association (28%–33%). Lower SES is known to be associated with increased psychosocial stress, due to less access to health care and social support and less financial and social capital, which in turn is associated with increased asthma in both adults and their offspring (38, 39). It is also possible that lower SES or mood disorders could increase the likelihood of smoking in pregnancy, high body mass index, or adverse birth outcomes such as low birth weight, all of which are known risk factors for asthma (as shown by the causal pathways in the directed acyclic graph) (40). This finding highlights the possible overlap between intergenerational health and poverty perpetuated by transmission of "toxic stress" between generations (24).

Regarding the larger odds ratio seen for the 2-diagnosis asthma definition as compared with the medication/diagnosis definition, this was probably due to the medication/diagnosis patients only requiring 1 hospital diagnosis or at least 2 medications—thereby capturing a larger group with milder disease, as seen with the incidence rate, which was higher than that for patients with 2 diagnoses (21.1 cases per 1,000 person-years vs. 14.4 cases per 1,000 person-years). However, some caution must be taken in interpreting our definition of early-onset asthma. Asthma is challenging to diagnose below 5 years of age because of the high number of upper respiratory tract infections in this age group and the difficulty of using spirometry on young children. Therefore, "asthma" at this age can often be a mixture of early transient wheezing due to infection and true asthma cases (41). One

Table 5. Mediation of Associations Between Parental (Generation 2) Bereavement Exposure in Childhood and Offspring (Generation 3) Inflammatory Disease by Generation 2 Mood Disorders and Education Status in a Swedish Birth Cohort, 2001–2012

G3 Outcome	Mood Disorders			Educational Attainment		
	HR[a]	95% CI	% Mediation	HR[a]	95% CI	% Mediation
Bereavement Exposure in G2 Women and Mediators						
Asthma onset at age <3 years[b]			8.7			27.7
Direct effect	1.14	1.07, 1.21		1.10	1.04, 1.17	
Indirect effect	1.01	1.01, 1.01		1.04	1.03, 1.04	
Asthma onset at age <3 years[c]			20.4			33.0
Direct effect	1.05	0.99, 1.11		1.04	0.98, 1.09	
Indirect effect	1.01	1.01, 1.01		1.018	1.01, 1.02	
Bereavement Exposure in G2 Men and Mediators						
Autoimmune diseases at age ≥3 years[b]			0			0
Direct effect	1.31	1.06, 1.61		1.33	1.08, 1.63	
Indirect effect	1.00	0.99, 1.00		0.99	0.98, 1.00	

Abbreviations: CI, confidence interval; G, generation; HR, hazard ratio.
[a] Adjusted for socioeconomic status G1 and G2 birth year.
[b] Two-diagnosis definition.
[c] Diagnosis and/or medication use definition.

possible explanation of the findings is that the observed transgenerational association is actually associated with a T-helper 1 cell (Th1) immune response with early transient infectious wheezing such as bronchiolitis misdiagnosed as asthma, rather than an inflammatory Th2 pathway. However, in defense of our definition, the sensitivity analysis showed that offspring early-onset asthma associated with maternal childhood bereavement was no more likely to be transient in nature than early-onset asthma in offspring whose mothers had not experienced early bereavement.

Another of the limitations in this study is the "noise" that could be affecting associations, especially over such a long period of time, such as confounders that we were unable to measure. We primarily tried to reduce this by using early-life experience of bereavement as the trauma exposure, which is less influenced by socioeconomic confounding structures than other types of early trauma, such as parental imprisonment, parental substance abuse, or neglect. We also used a sensitivity analysis (E-value) to assess the robustness of our findings to potential unmeasured confounding (30), showing that an unknown confounder has to have an influence on each bereavement experienced by G2 women and G3 asthma of at least HR = 1.57 (2-diagnoses asthma) or HR = 1.34 (diagnosis/medication asthma) to explain the association. Similarly, for bereavement experienced by G2 men, unmeasured confounding would need to reach an association of HR = 1.95 to negate the findings. We cannot be sure that there is not an unmeasured confounder (or combined group) that could have this association, but given the minimal changes that occurred with the well-recognized confounders we did adjust for, it is difficult to conceive of another unmeasured confounder that could generate these levels of association. Finally, although parental death is one of the most stressful events that can happen in a child's life due to loss of a critical attachment relationship, we had no way of verifying for each individual in G2 that the bereavement caused trauma; therefore, the results may have been skewed toward the null. However, bereavement research suggests that loss of a parent during childhood leads to long-term psychological, sociological, and health consequences, supporting the use of bereavement as a type of trauma exposure (22, 23, 42). We were unable to measure other types of early trauma, such as child abuse and neglect, since these are not recorded in population-based registers. Further research is needed to investigate other types of trauma (43) and whether the associations are influenced by the manner of death in G1 or possible mediation by adverse childhood experiences occurring in G3 (44).

In conclusion, we have shown that maternal transgenerational trauma experienced as early bereavement may be associated with a modest risk of early-onset asthma in their offspring, mediated in part by maternal mood disorders and SES. Similarly, we have shown that paternal transgenerational trauma experienced as early bereavement may be associated with a modest risk of autoimmune diseases in offspring. More research is needed to understand the mechanisms by which parental stress in early life is passed to offspring and how they differ for men and women.

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