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Original Contribution

Childhood adversity and time to pregnancy in a preconception cohort

Sharonda M. Lovett*[,1], Olivia R. Orta[1], Renée Boynton-Jarrett[2], Amelia K. Wesselink[1], Collette N. Ncube[1], Yael I. Nillni[3,4], Elizabeth E. Hatch[1], Lauren A. Wise[1]

[1]Department of Epidemiology, Boston University School of Public Health, Boston, MA 02118, United States
[2]Division of Health Services Research, Department of Pediatrics, Boston Medical Center, Boston, MA 02118, United States
[3]Department of Psychiatry, Boston University School of Medicine, Boston, MA 02118, United States
[4]National Center for PTSD, Women's Health Sciences Division, VA Boston Healthcare System, Boston, MA 02130, United States

*Corresponding author: Sharonda M. Lovett, Boston University School of Public Health, 715 Albany Street, T421E, Boston, MA 02118 (slovett1@bu.edu)

Abstract

We examined the association between childhood adversity and fecundability (the per-cycle probability of conception), and the extent to which childhood social support modified this association. We used data from 6318 female participants aged 21-45 years in Pregnancy Study Online (PRESTO), a North American prospective preconception cohort study (2013-2022). Participants completed a baseline questionnaire, bimonthly follow-up questionnaires (until pregnancy or a censoring event), and a supplemental questionnaire on experiences across the life course including adverse childhood experiences (ACEs) and social support (using the modified Berkman-Syme Social Network Index [SNI]). We used proportional probabilities regression models to compute fecundability ratios (FRs) and 95% CIs, adjusting for potential confounders and precision variables. Adjusted FRs for ACE scores 1-3 and ≥4 vs 0 were 0.91 (95% CI, 0.85-0.97) and 0.84 (95% CI, 0.77-0.91), respectively. The FRs for ACE scores ≥4 vs 0 were 0.86 (95% CI, 0.78-0.94) among participants reporting high childhood social support (SNI ≥4) and 0.78 (95% CI, 0.56-1.07) among participants reporting low childhood social support (SNI <4). Our findings confirm results from 2 previous studies and indicate that high childhood social support slightly buffered the effects of childhood adversity on fecundability.

Key words: adversity; child abuse; adverse childhood experiences; fertility, time to pregnancy.

Introduction

Adversity during childhood is an established determinant of health, and most US adults have experienced at least 1 form of childhood adversity (eg, abuse, parental separation, living with someone with substance misuse or mental illness).[1] Exposure to childhood adversity (hereafter, referred to as any adversity before age 18 years) is associated with reproductive outcomes (eg, early menarche,[2-5] uterine leiomyomata,[6,7] endometriosis,[8] amenorrhea,[9] sexually transmitted infections[10]) as well as other adult outcomes that may influence fertility, including comorbidities (eg, obesity, diabetes), early initiation of behavioral factors (eg, smoking, heavy alcohol consumption), and mental health conditions.[11-13] Mechanisms through which childhood adversity may impair fertility include persistent activation of the hypothalamic–pituitary–adrenal (HPA) axis or autonomic nervous system (eg, elevations in stress biomarkers such as cortisol and α-amylase)[14-22] and diminished ovarian function[23] via alterations in the hypothalamic–pituitary-ovarian axis (eg, reduced estradiol concentrations).[24] Additional biological pathways, though complex and not fully understood, involve suppressed immune function, inflammatory processes, and epigenetic aging.[25-29]

There is epidemiologic evidence that childhood adversity is associated with reduced fecundability (the probability of conception per menstrual cycle).[9,30] However, to our knowledge, there has been no assessment of this association in a preconception cohort. In a large British study in which data collection began in childhood,[30,31] childhood adversity was associated with reduced fecundability among married or partnered women.[30] That study also found that certain domains of childhood adversity (eg, witnessing abuse, conflict in the home) were associated with increased likelihood of being unable to have children.[30] In a US study, childhood adversity also was associated with reduced fecundability and increased risk of fertility difficulties (eg, receipt of fertility drugs or medical procedures to facilitate pregnancy).[9] Both investigations adjusted for factors that postdate childhood and represent potential mediators (eg, adult factors like body mass index [BMI], education, household income, social class),[9,30] which could introduce bias when estimating the total effect of childhood adversity on fecundability.[32,33] These studies may have also been susceptible to selection bias[9,30] and differential exposure misclassification (recall bias),[9] to which a preconception cohort study is less susceptible.

Using a prospective cohort study of North American pregnancy planners, we investigated the association between childhood adversity and fecundability. We also evaluated the extent to which social support in childhood modified this association, because previous studies recognized childhood social support as a potential buffer of early life stress. Social support has the potential to provide psychological resources that enhance

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problem-solving skills, improve self-efficacy (influencing coping behavior), and regulate activity of the HPA axis.[34-37] We hypothesized childhood adversity would be associated with reduced fecundability, and that high social support in childhood would mitigate the association of childhood adversity with fecundability.

Methods

Study population

Pregnancy Study Online (PRESTO) is an ongoing, internet-based, preconception cohort of couples in the United States and Canada who are trying to conceive.[38] Recruitment began in June 2013, primarily through banner advertisements on social media and health-related websites. Eligible participants self-identified as female, aged 21-45 years, not using contraception or fertility treatments at enrollment, and not pregnant at study entry. Participants completed a baseline questionnaire on sociodemographics (eg, race and ethnicity, education, income, geographic region), lifestyle factors (eg, smoking status, alcohol consumption, multivitamin use), medical conditions (eg, mental health diagnoses), and reproductive history (eg, age at menarche, parity). After enrollment, we mailed 6 home pregnancy tests to participants in the contiguous United States.[39] Beginning in July 2019, we invited former and current PRESTO participants to complete the Life Course Experiences Questionnaire (LCEQ), which included questions about childhood experiences. Thereafter, we sent the LCEQ to all newly enrolled participants 30 days after enrollment. PRESTO was approved by the Institutional Review Board at Boston University Medical Campus, and all participants provided informed consent.

Outcome assessment

We assessed time to pregnancy (TTP) prospectively, using data from baseline and follow-up questionnaires. At baseline, participants reported the first day of their last menstrual period (LMP), their usual menstrual cycle length (if having regular menstrual cycles), and the number of menstrual cycles they had been attempting pregnancy. Regarding the validity of self-reported LMP information, approximately 97.7% of PRESTO participants reported their LMP on the baseline questionnaire within 1 day of LMP recorded using FertilityFriend.com, a menstrual charting application.[38] On follow-up questionnaires, participants reported their most recent LMP date, whether they conceived since the prior questionnaire (~8 weeks between questionnaires), and method of pregnancy confirmation. We accepted confirmation of pregnancy via a self-reported, positive home pregnancy test, blood or urine test from a doctor's office, or ultrasound. Among participants who reported irregular cycles (ie, not being able to "predict about when [their] next period would start"), we estimated cycle length using baseline LMP date and LMP dates reported during follow-up. We calculated TTP based on the total cycles at risk, as follows: (cycles of attempt at study entry) + [(LMP date from most recent follow-up questionnaire − date of baseline questionnaire completion)/usual cycle length] + 1.

Exposure assessment

We ascertained childhood adversity using the adapted Adverse Childhood Experiences (ACE) module from the Behavioral Risk Factor Surveillance System (Table S1).[40] Participants were asked to recall any exposure before age 18 years to adversities across 8 domains: household mental illness, household substance abuse, household incarceration, parental separation or divorce, parental intimate partner violence (IPV), physical abuse, emotional abuse, and sexual abuse. We further examined experiences of physical and sexual abuse across the life course using modified questions from the Brief Trauma Questionnaire (BTQ; Table S2), in which frequency (ie, "once," "a few times," "more than a few times") and timing (ie, child [age ≤11 years], teen [12-17 years], adult [≥18 years]) of the experience also were reported.[41,42] Notably, the BTQ was designed to assess exposure to traumatic events classified as criterion A (life threat or serious injury) in alignment with the *Diagnostic and Statistical Manual of Mental Disorders*.[41,42] We defined childhood physical abuse as the report of being physically attacked by anyone (eg, pushed, shoved, kicked, hit with something that could hurt) at least once before age 18 years. We defined childhood sexual abuse as the report of ever being made or pressured into having some type of unwanted sexual contact (involving their private parts or someone else's private parts) at least once before age 18 years.

Modifier assessment

We ascertained social support as a child or teen (ie, <18 years) and in adulthood (≥18 years) using 8 questions adapted from the Berkman-Syme Social Network Index (SNI)[43] (Table S3). The SNI assesses the type and closeness of contacts, including sociability (number and frequency of close friends or relatives). We summed up the total number of "yes" responses to each of the 8 types of support before age 18 years and defined childhood social support as high (SNI ≥4) or low (SNI <4) (range of scores, 0-8). Our cutpoint aligns with those "socially integrated" on the SNI with increasing social connectedness (eg, high intimate contacts, membership in community groups) vs fewer social connections ("socially isolated").[43]

Mediator assessment

On the baseline questionnaire, we collected detailed information on potential mediators, including current BMI (calculated as weight [kg] divided by height squared [m^2]; computed from self-reported weight in pounds and height in feet and inches); current intake of alcohol; current smoking status; current intercourse frequency ("in the past month"); current perceived stress ("in the past month") using the 10-item version of the Perceived Stress Scale (score range: 0-40, with a score ≥25 indicating greater perceived stress)[44]; and current depressive symptoms ("during the past 2 weeks") from the 12-item Major Depression Inventory (score range: 0-50, with a score ≥30 classified as severe depression symptomatology according to the *International Statistical Classification of Diseases, 10th Revision*).[45,46] Clinical diagnoses of depression (ie, "Have you ever been diagnosed with depression?") or anxiety (i.e., "Have you ever been diagnosed with anxiety/panic disorder?") before study entry, as well as history of gynecologic conditions (eg, uterine leiomyomata ["myomas, leiomyomas, smooth muscle tumors of uterus"], endometriosis ["when uterine lining appears outside of uterus"], polycystic ovary syndrome) were also ascertained at baseline. Using data collected through the LCEQ, we defined probable diagnosis of post-traumatic stress disorder (PTSD) as a score ≥3 for items from the Primary Care PTSD (PC-PTSD-5 instrument; Table S4)[42,47] and adult trauma as any report of trauma after age 18 years based on adapted items to the BTQ (Table S2).[42]

Exclusions

From June 2013 through October 2022, 16 736 eligible participants completed a baseline questionnaire and were followed using bimonthly follow-up questionnaires until reported pregnancy or 12 months. We excluded 167 participants whose baseline

Table 1. Baseline characteristics of 6318 PRESTO participants stratified by childhood adversity, June 2013-October 2022

Characteristic[a]	ACE score			Childhood physical or sexual abuse			
	0 (*n* = 1452)	1-3 (*n* = 3266)	≥4 (*n* = 1600)	Neither (*n* = 3882)	Physical only (*n* = 639)	Sexual only (*n* = 1087)	Both (*n* = 710)
Age, mean, years	30.7	30.6	30.0	30.7	30.3	30.2	29.8
Current body mass index,[b] mean	25.6	26.8	28.9	26.6	27.7	27.3	28.9
Current alcohol consumption, mean drinks/week	3.1	2.9	3.0	3.0	2.8	3.0	2.9
Non-Hispanic White, %	90.9	87.2	81.7	88.6	83.5	84.6	82.0
Non-Hispanic Black, %	0.7	1.6	2.8	1.3	1.8	2.2	2.5
Hispanic/Latina, %	3.5	5.7	7.5	4.8	6.6	7.2	7.4
Non-Hispanic other[c], %	4.9	5.5	8.0	5.3	8.2	6.0	8.1
Married, %	93.4	91.8	83.9	91.9	90.9	88.5	82.4
Parental education: less than Bachelor's degree, %	23.2	34.2	50.9	30.9	42.7	39.7	50.9
Less than Bachelor's degree, %	9.0	14.3	27.9	12.4	18.3	19.7	31.9
Household income <$50 000, %	8.3	10.7	19.1	9.8	11.8	14.3	21.7
Current unemployment, %	9.0	11.2	15.1	10.3	13.9	11.6	17.7
Current smoker, %	2.2	3.7	8.8	3.4	3.9	6.1	10.3
Current intercourse frequency (<1 time/week), %	21.4	22.7	26.0	22.1	26.2	24.2	24.9
Age at menarche <12 years, %	19.6	23.0	28.0	21.3	25.5	25.6	30.6
Parous, %	28.5	30.6	37.5	29.9	28.4	34.3	42.9
Prenatal vitamin or multivitamin use, %	85.9	83.9	82.3	85.0	82.8	82.7	81.5
Last method of contraception: oral contraceptive pills, %	32.3	30.1	29.1	30.9	29.2	31.9	25.9
High perceived stress (PSS score: ≥25), %	4.0	7.9	11.8	6.1	8.4	10.4	14.0
Severe depressive symptoms (MDI score: ≥30), %	0.4	2.6	6.7	1.9	3.4	3.5	8.8
Probable diagnosis of PTSD, %	9.8	21.3	43.5	13.8	35.6	35.1	53.9
Diagnosed with depression, %	15.5	26.6	39.2	22.9	29.0	32.1	43.5
Diagnosed with anxiety, %	18.1	26.6	38.6	23.3	32.2	31.0	42.9
History of uterine leiomyomata, %	2.1	2.2	2.0	2.1	2.0	2.1	2.0
History of endometriosis, %	2.1	2.4	3.6	2.2	3.6	2.6	4.2
History of polycystic ovary syndrome, %	5.2	6.9	9.9	6.1	9.2	8.6	9.8
High childhood social support, %	95.5	90.1	74.8	92.1	79.1	87.0	70.0
High adult social support, %	99.3	97.8	94.2	98.4	96.1	97.1	92.6

Abbreviations: ACE, Adverse Childhood Experiences; MDI, Major Depression Inventory; PRESTO, Pregnancy Study Online; PSS, Perceived Stress Scale; PTSD, post-traumatic stress disorder.
[a]All characteristics (except age) are standardized to the age distribution of the cohort at baseline.
[b]Calculated as weight (kg) divided by the square of height (m^2).
[c]Includes participants who self-identified as Asian or Pacific Islander, American Indian or Alaskan Native, mixed race, or another race.

date of LMP was >6 months before study entry and 86 participants with missing or implausible LMP data. To minimize selection bias, we further excluded participants with >6 cycles of attempt time at enrollment (*n* = 3253). As of October 2022, 6318 of the 13 230 remaining participants completed the LCEQ, 49.9% retrospectively with respect to the outcome (defined as >60 days after enrollment) and 50.1% prospectively with respect to the outcome (defined as within 60 days of enrollment, allowing participants 30 days to complete the LCEQ).

Statistical analysis

Participants contributed observed menstrual cycles at risk from baseline until reported pregnancy (regardless of the outcome of pregnancy), fertility treatment initiation, loss to follow-up, cessation of pregnancy attempt, or 12 menstrual cycles of follow-up, whichever came first. Participants who did not conceive within 12 cycles of attempted conception were censored at 12 cycles, the time after which couples typically seek fertility treatment.[48] We used life-table methods to calculate the percentage of participants who conceived during follow-up (12 cycles), accounting for censoring events.[49] We then fit proportional probabilities regression models[50] to estimate fecundability ratios (FRs) and 95% CIs that were weighted by the inverse probability of LCEQ completion. An FR <1 indicates a longer TTP (reduced fecundability) comparing exposed and unexposed participants, signifying that the exposure is associated with lower chances of conception in any given menstrual cycle. The proportional probabilities regression model differs from discrete proportional hazards models because it includes cycle-specific indicator variables for each menstrual cycle at risk to account for the expected baseline decline in cohort fecundability with increasing pregnancy attempt time. Moreover, the Andersen-Gill data structure (ie, 1 observation per menstrual cycle at risk, excluding earlier unobserved cycles)[51] accounts for variation in pregnancy attempts at study entry (range, 0-6 cycles) and reduces left truncation bias.[52,53]

Given that the LCEQ in PRESTO is optional and baseline characteristics may influence whether participants complete the supplemental questionnaire, we applied inverse probability weights to the FRs to account for potential selection bias due to differential completion.[54,55] Briefly, participants who were less likely to complete the LCEQ tended to have lower levels of education (<16 years of education: 32.0% vs 17.6%) and household income <$50 000 (22.0% vs 13.3%) (Table S5). We fit pooled logistic regression models predicting the probability of LCEQ completion using factors hypothesized to influence participation (eg, socioeconomic disadvantage, mental health disorders; Table S6). We then computed predicted probabilities and stabilized weights such that participants with a lower probability of completing the LCEQ based on measured characteristics received larger weights.

We characterized exposure to ACEs before age 18 years after summing "yes" vs "no" responses across domains (range of incidents, 0-8) similar to other studies.[12,13,56] We modeled ACEs

Table 2. Associations between childhood adversity and fecundability in PRESTO, June 2013-October 2022

Exposure	Overall (*n* = 6318)			
	No. of pregnancies	No. of cycles	Crude FR (95% CI)[a]	Adjusted FR (95% CI)[a,b]
		ACE Module		
Cumulative score				
0	1065	5839	1.00 (Referent)	1.00 (Referent)
1-3	2247	13 839	0.89 (0.83-0.95)	0.91 (0.85-0.97)
≥4	1005	6951	0.79 (0.73-0.86)	0.84 (0.77-0.91)
Per 1-unit increase in ACE score			0.96 (0.95-0.97)	0.97 (0.95-0.98)
Substantive domain[c]				
Household mental illness	1948	12 282	0.86 (0.80-0.92)	0.89 (0.82-0.96)
Household substance abuse	1357	8730	0.84 (0.78-0.90)	0.87 (0.80-0.94)
Household incarceration	313	2164	0.78 (0.69-0.87)	0.81 (0.70-0.94)
Parental separation or divorce	1292	8655	0.81 (0.75-0.87)	0.86 (0.79-0.93)
Parental IPV	637	4366	0.79 (0.72-0.87)	0.86 (0.77-0.96)
Physical abuse	878	6214	0.78 (0.72-0.84)	0.82 (0.74-0.90)
Emotional abuse	2053	13 500	0.84 (0.78-0.90)	0.87 (0.81-0.94)
Sexual abuse	750	5276	0.78 (0.72-0.85)	0.82 (0.75-0.91)
		Brief Trauma Questionnaire		
No abuse	2738	16 109	1.00 (Referent)	1.00 (Referent)
Physical abuse only	404	2762	0.85 (0.77-0.94)	0.88 (0.80-0.97)
Sexual abuse only	719	4712	0.89 (0.82-0.96)	0.92 (0.85-0.99)
Physical and sexual abuse	456	3046	0.90 (0.83-0.99)	0.94 (0.86-1.03)

Abbreviations: ACE, Adverse Childhood Experiences; FR, fecundability ratio; IPV, intimate partner violence; PRESTO, Pregnancy Study Online.
[a]Applies inverse probability weights to adjust for differential completion of the supplemental Life Course Experiences Questionnaire.
[b]Adjusted for age, race and ethnicity, childhood economic resources, highest level of parental education, prenatal vitamin or multivitamin use, and last method of contraception.
[c]Exposure referent: no adverse childhood experiences.

categorically (0, 1-3, ≥4) and continuously (per 1-unit increase) based on the cumulative score. Next, we generated restricted cubic splines[57,58] of associations between ACE score as a continuous variable and fecundability to examine the potential for a nonlinear association. To evaluate potential for buffering effects of social support before age 18 years, we stratified the data by high vs low social support (SNI ≥4 vs <4). We then modeled child and teen physical and sexual abuse as categories defined by frequency (once, a few times, more than a few times), timing of first exposure (child [≤ 11 years] vs teen [12-17 years]), and chronicity (child only, teen only, child and teen), with no physical or sexual abuse before age 18 years as the common referent for all analyses of abuse.

Selection of potential confounders and precision variables was determined a priori based on a review of the literature and hypothesized pathways using a causal diagram, excluding potential mediators (Figure S1).[33,59] Here, we conceptualized precision variables to be baseline characteristics in adulthood (ie, current age, prenatal vitamin or multivitamin use, last method of contraception) that are strong predictors for the outcome (fecundability). Final models were adjusted for current age (continuous), self-reported race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic/Latina, Non-Hispanic other [defined as Asian or Pacific Islander, American Indian or Alaskan Native, mixed race, or some other race]), childhood economic resources (ie, limited income for food or housing, loan for medical expenses, public assistance or welfare) (yes vs no), highest level of parental education (≤12, 13-15, 16, ≥17 years), prenatal vitamin or multivitamin use (yes vs no), and last method of contraception (oral contraceptives, other hormonal contraceptives, barrier methods, withdrawal, rhythm, and/or other methods). We view race as a socially and politically constructed variable that shapes many aspects of the lived experience.

We used fully conditional specification methods to impute missing data for exposure, covariate, and outcome information, assuming data were missing at random conditional on observed data.[60-62] Specifically, we used logistic regression to impute dichotomous and ordinal variables, the discriminant function to impute nominal variables, and linear regression to impute continuous variables.[60] None of the continuous variables used in the imputation required transformations to deal with non-normality. We then generated 20 imputed data sets across which we pooled effect estimates and SEs.[63] To ensure validity and quality of the imputation, we examined trace plots for continuous variables and compared the frequency distribution of noncontinuous variables before and after imputation.[64] For participants who did not complete any follow-up questionnaires (2.1%), we assigned 1 cycle of follow-up and multiply imputed their pregnancy status (yes vs no) at the cycle. Missingness for analytic variables ranged from <0.1% (age) to 24.6% (probable diagnosis of PTSD was added to the first version of the LCEQ in July 2019 and was only ascertained among participants reporting ≥1 stressful life events via the BTQ at least once across the life course [skip pattern]). Responses of "don't know" and "prefer not to answer" ranged from <0.1% (parental separation or divorce) to 6.4% (household mental illness) and were coded as missing before imputation.

We performed several sensitivity analyses to assess the potential for selection bias, including stratification by retrospective vs prospective completion of the LCEQ and pregnancy attempt time at enrollment (<3 cycles vs 3-6 cycles). If findings differed across strata, we assumed that results from prospective completion of the LCEQ and <3 cycles of attempt time were more valid. In exploratory analyses, we also investigated potential mediation by possible causal intermediates (eg, current smoking status, current intercourse frequency, probable diagnosis of PTSD, adult trauma) to improve understanding of the childhood adversity–TTP relationship. We used mediation analysis,[65] with exposure-mediator interaction (ie, product terms), to estimate natural indirect effects (NIE) of the mediator on the natural direct effects (NDE) of childhood adversity and fecundability. We computed the proportion

Table 3. Associations between childhood adversity and fecundability in PRESTO stratified by social support before age 18 years (June 2013-October 2022)

Exposure	High childhood social support (n = 5525)[a]			Low childhood social support (n = 793)[a]		
	No. of pregnancies	No. of cycles	Adjusted FR (95% CI)[b,c]	No. of pregnancies	No. of cycles	Adjusted FR (95% CI)[b,c]
			ACE Module			
Cumulative score						
0	1020	5576	1.00 (Referent)	45	263	1.00 (Referent)
1-3	2046	12 339	0.92 (0.86-0.99)	201	1500	0.83 (0.62-1.13)
≥4	766	5152	0.86 (0.78-0.94)	239	1799	0.78 (0.56-1.07)
Per 1-unit increase in ACE score			0.97 (0.95-0.99)			0.98 (0.94-1.02)
Substantive domain[d]						
Household mental illness	1636	10 012	0.91 (0.84-0.98)	312	2270	0.77 (0.57-1.05)
Household substance abuse	1131	7059	0.89 (0.82-0.97)	226	1 671	0.76 (0.55-1.05)
Household incarceration	243	1621	0.86 (0.74-1.02)	70	543	0.67 (0.40-1.11)
Parental separation or divorce	1084	7079	0.88 (0.81-0.96)	208	1576	0.76 (0.71-0.82)
Parental IPV	484	3193	0.89 (0.79-1.00)	153	1173	0.81 (0.56-1.17)
Physical abuse	658	4509	0.84 (0.76-0.93)	220	1705	0.75 (0.54-1.05)
Emotional abuse	1691	10 812	0.89 (0.83-0.97)	362	2688	0.80 (0.59-1.09)
Sexual abuse	593	4180	0.81 (0.73-0.90)	157	1096	0.90 (0.63-1.28)
			Brief Trauma Questionnaire			
No abuse	2556	14 695	1.00 (Referent)	182	1414	1.00 (Referent)
Physical abuse only	329	2108	0.91 (0.82-1.02)	75	654	0.89 (0.69-1.15)
Sexual abuse only	625	4089	0.89 (0.82-0.97)	94	623	1.18 (0.94-1.48)
Physical and sexual abuse	322	2175	0.90 (0.81-1.00)	134	871	1.22 (0.99-1.51)

Abbreviations: ACE, Adverse Childhood Experiences; FR, fecundability ratio; IPV, intimate partner violence; PRESTO, Pregnancy Study Online.
[a]Defined via an adapted Berkman-Syme Social Network Index (score: ≥4 [high] vs <4 [low]).
[b]Applies inverse probability weights to adjust for differential completion of the supplemental Life Course Experiences Questionnaire.
[c]Adjusted for age, race and ethnicity, childhood economic resources, highest level of parental education, prenatal vitamin or multivitamin use, and last method of contraception.
[d]Exposure referent: no adverse childhood experiences.

mediated as follows: $(FR_{NDE} \times [FR_{NIE} - 1])/(FR_{NDE} \times FR_{NIE} - 1)$. All analyses were performed using SAS, version 9.4.[66]

Results

During 12 menstrual cycles of follow-up, 6318 female participants contributed 4317 pregnancies (cumulative conception percentage after accounting for censoring, 78.4%). At baseline, the mean age of participants was 30.5 years and 86.7% identified as non-Hispanic White. Furthermore, >25% of participants reported a mental health diagnosis (depression: 27.4%, anxiety: 27.8%). The prevalence of childhood adversity domains ranged from 8.1% (household incarceration) to 49.3% (emotional abuse), with 77.0% of participants reporting at least 1 form of childhood adversity (Table S7). Participants with an ACE score ≥4 were more likely to identify as nonmarried, have higher BMI, have lower household

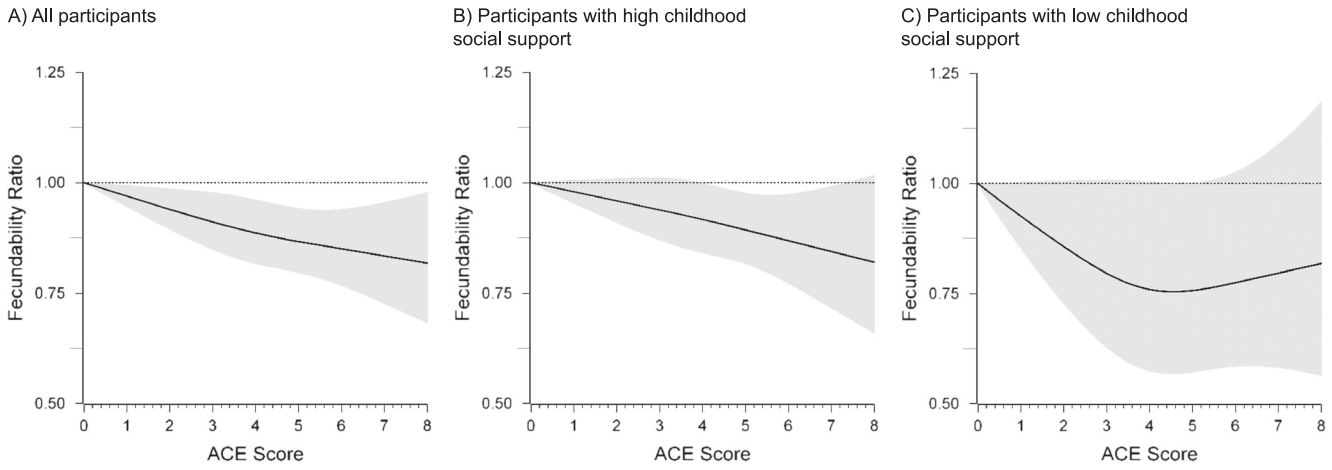

Figure 1. Restricted cubic splines of Adverse Childhood Experiences (ACE) score and fecundability in PRESTO, June 2013-October 2022. Graphs are plots of restricted cubic splines, where observations are trimmed at the 99th percentile and 3 knots are located at the 50th, 75th, and 95th percentiles. The reference level is the minimum value of the exposure (ACE score = 0). The black solid line indicates the fecundability ratio (FR) and the shaded gray area is the 95% CI, adjusted for age, race and ethnicity, childhood economic resources, highest level of parental education, prenatal vitamin or multivitamin use, and last method of contraception. Childhood social support is defined via an adapted Berkman-Syme Social Network Index (score: ≥4 [high] vs <4 [low]). PRESTO, Pregnancy Study Online.

Table 4. Associations of abuse before age 18 years (frequency, timing of first exposure, and chronicity) with fecundability in PRESTO, June 2013-October 2022

Exposure	No. of participants	No. of pregnancies	No. of cycles	Crude FR (95% CI)[a]	Adjusted FR (95% CI)[a,b]
No physical or sexual abuse before age 18 years	3882	2738	16 109	1.00 (Referent)	1.00 (Referent)
		Frequency[c]			
Physical abuse					
Once	238	154	1011	0.91 (0.78-1.05)	0.93 (0.80-1.08)
A few times	654	432	2824	0.92 (0.84-1.01)	0.94 (0.85-1.03)
More than a few times	457	274	1973	0.82 (0.73-0.91)	0.86 (0.77-0.97)
Sexual abuse					
Once	614	405	2626	0.95 (0.86-1.04)	0.97 (0.89-1.07)
A few times	806	538	3436	0.90 (0.83-0.98)	0.92 (0.85-1.01)
More than a few times	377	232	1696	0.81 (0.72-0.92)	0.84 (0.74-0.95)
		Timing of First Exposure[c]			
Physical abuse					
Child	824	525	3498	0.89 (0.82-0.97)	0.93 (0.85-1.01)
Teen	525	335	2310	0.87 (0.78-0.96)	0.89 (0.80-0.99)
Sexual abuse					
Child	631	408	2715	0.89 (0.81-0.98)	0.94 (0.86-1.04)
Teen	1166	767	5043	0.90 (0.83-0.96)	0.91 (0.84-0.98)
		Chronicity[c]			
Physical abuse					
Child only	281	180	1114	0.97 (0.85-1.11)	1.00 (0.88-1.15)
Teen only	525	335	2310	0.87 (0.78-0.96)	0.89 (0.80-0.99)
Child and teen	543	345	2384	0.85 (0.77-0.94)	0.88 (0.79-0.98)
Sexual abuse					
Child only	373	244	1553	0.92 (0.82-1.03)	0.97 (0.86-1.10)
Teen only	1166	767	5043	0.90 (0.83-0.96)	0.91 (0.84-0.98)
Child and teen	258	164	1162	0.86 (0.75-0.98)	0.91 (0.80-1.05)

Abbreviations: FR, fecundability ratio; PRESTO, Pregnancy Study Online.
[a]Applies inverse probability weights to adjust for differential completion of the supplemental Life Course Experiences Questionnaire.
[b]Adjusted for age, race and ethnicity, childhood economic resources, highest level of parental education, prenatal vitamin or multivitamin use, and last method of contraception.
[c]Exposure referent: no physical or sexual abuse according to responses to modified Brief Trauma Questionnaire.

income, be current smokers, and report probable diagnosis of PTSD compared with participants reporting no ACEs (Table 1). We observed a similar distribution of baseline characteristics, on average, for participants reporting both physical and sexual abuse before age 18 years.

Adjusted FRs for ACE scores 1-3 and ≥4 vs 0 were 0.91 (95% CI, 0.85-0.97) and 0.84 (95% CI, 0.77-0.91), respectively (Table 2). We observed slight differences in fecundability across domains of childhood adversity (range of FRs, 0.81-0.89). However, the strongest association was with household incarceration (FR = 0.81; 95% CI, 0.70-0.94). The FRs for ACE scores ≥4 vs 0 were 0.86 (95% CI, 0.78-0.94) among participants reporting high childhood social support (SNI ≥4) and 0.78 (95% CI, 0.56-1.07) among participants reporting low childhood social support (SNI <4; Table 3). Analyses of restricted spline curves were generally consistent with the categorical results, indicating decreases in fecundability with higher ACE scores and slightly attenuated associations among those with high childhood social support (Figure 1).

We observed generally stronger associations among participants reporting more frequent incidents of abuse (Table 4). The FRs of physical abuse for "once," "a few times," and "more than a few times" vs never having experienced physical or sexual abuse before age 18 years were 0.93 (95% CI, 0.80-1.08), 0.94 (95% CI, 0.85-1.03), and 0.86 (95% CI, 0.77-0.97), respectively. The FRs for sexual abuse comparing "once," "a few times," and "more than a few times" vs no physical or sexual abuse before age 18 years were 0.97 (95% CI, 0.89-1.07), 0.92 (95% CI, 0.85-1.01), and 0.84 (95% CI, 0.74-0.95). Results based on timing of first exposure to physical or sexual abuse did not reveal any appreciable differences (Table 4). Fecundability among those first exposed as a child (physical abuse: FR = 0.93, 95% CI, 0.85-1.01; sexual abuse: FR = 0.94, 95% CI, 0.86-1.04) were similar to those first exposed as a teen (physical abuse: FR = 0.89, 95% CI, 0.80-0.99; sexual abuse: 0.91, 95% CI, 0.84-0.98). The FRs were strongest for participants reporting abuse both as a child and as a teen or as a teen only (Table 4). For example, fecundability was lowest among those reporting abuse during both life stages (physical abuse: FR = 0.88, 95% CI, 0.79-0.98; sexual abuse: FR = 0.91, 95% CI, 0.80-1.05).

In sensitivity analyses by completion of the LCEQ retrospectively versus prospectively, we observed similar results across strata, although both physical and sexual abuse, and some domains of childhood adversity (eg, household substance abuse, household incarceration, parental separation or divorce, parental IPV) were slightly stronger among those with prospectively collected LCEQ data (Table S8). Associations across strata of pregnancy attempt time at enrollment were also generally similar, but some domains of childhood adversity were stronger for participants reporting shorter attempt times at enrollment (<3 cycles; Table S9).

In mediation analyses considering exposure-mediator interaction (Table 5), probable diagnosis of PTSD mediated the largest proportion of the association between ACE score ≥4 vs 0 and fecundability (26.2%), followed by mental health diagnosis (anxiety: 20.1%, depression: 15.8%) and adult trauma (12.6%). Proportions mediated by behavioral factors (eg, lower current intercourse frequency, current smoking) were small (≤4.7%), whereas

Table 5. Natural direct and indirect effects of ACE score (≥4 vs 0)[a] and fecundability in PRESTO, June 2013-October 2022

Mediator	Product term	Natural indirect effect		Natural direct effect		Proportion mediated, %[d]
		Adjusted FR (95% CI)[b,c]		Adjusted FR (95% CI)[b,c]		
Less than Bachelor's degree (yes vs no)	Yes	0.99	(0.97-1.00)	0.84	(0.77-0.93)	6.9
Household income <$50 000 (yes vs no)	Yes	0.99	(0.98-1.00)	0.84	(0.77-0.92)	5.6
Current body mass index (≥30 vs <30 kg/m^2)	Yes	1.06	(1.04-1.09)	0.83	(0.72-0.95)	
Current alcohol consumption (≥7 vs <7 drinks/week)	Yes	1.00	(1.00-1.00)	0.84	(0.69-1.02)	
Current smoker (yes vs no)	Yes	0.99	(0.98-1.00)	0.84	(0.76-0.92)	4.7
Current intercourse frequency (<1 vs ≥1 times/week)	Yes	1.00	(0.99-1.00)	0.84	(0.76-0.92)	1.6
High perceived stress (PSS score: ≥25 vs < 25)	Yes	1.01	(1.00-1.02)	0.74	(0.54-1.02)	
Severe depressive symptoms (MDI score: ≥30 vs < 30)	Yes	1.02	(1.00-1.03)	0.51	(0.20-1.27)	
Probable diagnosis of PTSD (yes vs no)	Yes	0.95	(0.92-0.98)	0.87	(0.79-0.97)	26.2
Diagnosed with depression (yes vs no)	Yes	0.97	(0.94-0.99)	0.86	(0.78-0.94)	15.8
Diagnosed with anxiety (yes vs no)	Yes	0.96	(0.94-0.98)	0.86	(0.78-0.95)	20.1
History of uterine leiomyomata (yes vs no)	Yes	1.00	(1.00-1.00)	0.83	(0.76-0.91)	
History of endometriosis (yes vs no)	Yes	1.00	(0.99-1.01)	0.83	(0.76-0.92)	0.3
History of polycystic ovary syndrome (yes vs no)	Yes	0.98	(0.97-0.99)	0.85	(0.77-0.93)	8.9
Adult trauma (yes vs no)	Yes	0.97	(0.94-1.01)	0.85	(0.77-0.94)	12.6

Abbreviations: ACE, Adverse Childhood Experiences; FR, fecundability ratio; MDI, Major Depression Inventory; PRESTO, Pregnancy Study Online; PSS, Perceived Stress Scale; PTSD, post-traumatic stress disorder.
[a]Participants with an ACE score 1-3 are excluded.
[b]Adjusted for age, race and ethnicity, childhood economic resources, highest level of parental education, prenatal vitamin or multivitamin use, and last method of contraception.
[c]All FRs are unweighted (ie, inverse probability weights are not applied).
[d]Proportion mediated is not reported when the natural indirect and natural direct effects are in opposite directions.

selected indicators of socioeconomic disadvantage were slightly larger (<16 years of education, 6.9%; household income <$50 000, 5.6%). Mediation results without interaction were comparable (data not shown).

Discussion

To our knowledge, this is the first study to assess childhood adversity and fecundability using prospectively collected TTP data. In this preconception cohort of North American pregnancy planners, female participants with higher ACE scores had reduced fecundability, and associations of fecundability were relatively similar across domains of childhood adversity. High childhood social support appeared to buffer the effect of childhood adversity on TTP, but the differences in effect were small. Chronicity to physical or sexual abuse as a teen only showed slightly stronger associations with TTP than exposure as a child only, and neither life stage emerged as a more sensitive period of first exposure with respect to timing of abuse.

Our results are consistent with those of 2 prior studies that observed inverse associations between childhood adversity and fertility.[9,30] In the British National Child Development Study, married or partnered women reporting ≥4 vs 0 childhood social hardships had an FR of 0.87 (95% CI, 0.78-0.97) after minimal adjustment.[30] However, these results were attenuated after additional adjustment for adult social class and education (FR = 0.99; 95% CI, 0.88-1.10). In another study of reproductive-aged women (18-45 years) residing in southeastern Louisiana, the adjusted FRs were 0.72 (95% CI, 0.52-0.99) and 0.81 (95% CI, 0.60-1.08) for ACE scores ≥4 and 1-3 vs 0, respectively (including adjustment of smoking, education, and income).[9]

Potential mechanisms for the inverse association observed between childhood adversity and fecundability, in addition to the mechanisms analytically explored in our mediation analysis, include chronic activation of the HPA axis (which can lead to amenorrhea[9] and dysregulation of ovarian hormones that are critical for reproduction[67,68]). Childhood adversity may also increase the risk of mental health disorders (eg, probable diagnosis of PTSD, depression, anxiety)[69-73] and reproductive outcomes (eg, polycystic ovary syndrome[74]). In our study, not all hypothesized factors (eg, current perceived stress, uterine leiomyomata,[6,7] endometriosis[8]) showed evidence of meaningful mediation, despite being linked to reduced fertility in prior literature.[75-80] Collectively, these findings suggest that the mechanism(s) by which childhood adversity affects fertility may differ depending on the study population examined.

Our findings should be interpreted in light of several limitations. Individuals with higher levels of childhood adversity may have been less likely to complete the LCEQ. Participants reporting childhood adversity are also less likely to plan their pregnancies[81,82] (an eligibility criterion for this study) and are more likely to identify with a racial or ethnic group that has historically been marginalized[83-86] (which constitutes only 18.5% of the PRESTO cohort). Thus, the study may have limited generalizability. However, we implemented inverse probability weights to compensate for underrepresentation of selected participants in our cohort. Results comparing weighted and unweighted FRs (data not shown) were similar, suggesting selection bias may only play a minimal role in this analysis.

Another key limitation in our study is selection bias, because participants with longer pregnancy attempt times had greater opportunity to complete the LCEQ.[87] However, further exploration of this possibility indicated little evidence of selection bias. Although self-reported measures of childhood adversity have high validity (ie, few false-positive reports) in several populations,[88-90] there is potential for recall bias among participants who retrospectively completed the LCEQ. Nevertheless, findings were similar comparing those who completed the LCEQ retrospectively vs prospectively.

Our measures of childhood adversity do not capture variation in duration, severity, perpetrator, or co-occurrence of multiple adversities (which is likely prevalent),[91] and frequency, timing, and chronicity of only some adversities were explored (physical and/or sexual abuse only) using the BTQ vs ACE module. Thus, we

cannot speak to the evaluation of sensitive periods (child vs teen) across all domains of childhood adversity.[92] Cumulative ACE score is not a clinical indicator and should only be viewed as 1 operationalization of childhood adversity.[91,93,94] For example, we did not evaluate "expanded ACEs," which include community-level experiences (eg, neighborhood crime, environmental stressors like natural disasters) and experiences less often explored (eg, bullying, homelessness, discrimination), to more comprehensively assess childhood adversity on fecundability across multiple levels.[95]

Limited data on other determinants in early life (eg, household income, household composition or family dynamics, food insecurity) may have contributed to residual or unmeasured confounding. We also did not assess mediation by biomarkers of preconception stress (eg, cortisol, α-amylase, dehydroepiandrosterone) or other hypothesized mediators debated in literature (eg, neighborhood environment).[18,96] Finally, continuous variables used in our mediation analysis were subject to measurement error following categorization.[97]

Study strengths include prospective collection of TTP data and enrollment of participants during preconception soon after discontinuing contraception, allowing an investigation of couples across the full fertility spectrum.[87,98] We also ascertained adversity in early life across multiple domains (eg, household substance abuse, household incarceration, parental IPV), including frequency and timing of certain adversities. Our study builds upon previous studies and implements a causal mediation analysis to elucidate selected paths of potential mediators.

Conclusion

This study indicates that childhood adversity is associated with reduced fecundability, especially among those with low childhood social support. Our results highlight the importance of continued efforts to prevent childhood adversity and their long-lasting health effects.

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Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

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Conflict of interest

L.A.W. has received in-kind donations from Kindara.com and Swiss Precision Technologies, and also serves as a consultant for AbbVie Inc. and the Gates Foundation. The other authors declare no competing interests.

Disclaimer

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of this article.

Data availability

Individual-level data related to this article cannot be shared publicly because PRESTO participants did not provide informed consent to share their information with external entities.

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