

Supplemental Material

Estimating the Joint Association of Adverse Childhood Experiences and Asthma with Subsequent Depressive Symptoms: A Marginal Structural Modeling Approach

Supplemental Method

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Supplemental Method 1. Creation of inverse probability treatment weights (IPTW) for a marginal structural model (MSM).

Inverse probability treatment weights were calculated as the following formula:

$$\frac{\Pr[\text{ACE}]}{\Pr[\text{ACE} | C]} \times \frac{\Pr[\text{Asthma}]}{\Pr[\text{Asthma} | \text{ACE}, C, L]}$$

Where $Pr[.]$ is the probability function. ACE means having one or more ACEs, and Asthma means having a history of asthma. C represents covariates including age, gender, race, ethnicity, and state. L represents exposure-induced mediator-outcome confounders including educational attainment, household income, marital status, employment status, healthcare coverage, social-emotional support, BMI, smoking, and alcohol. Histories of cardiovascular diseases, and diabetes are added as L in the sensitivity analysis.

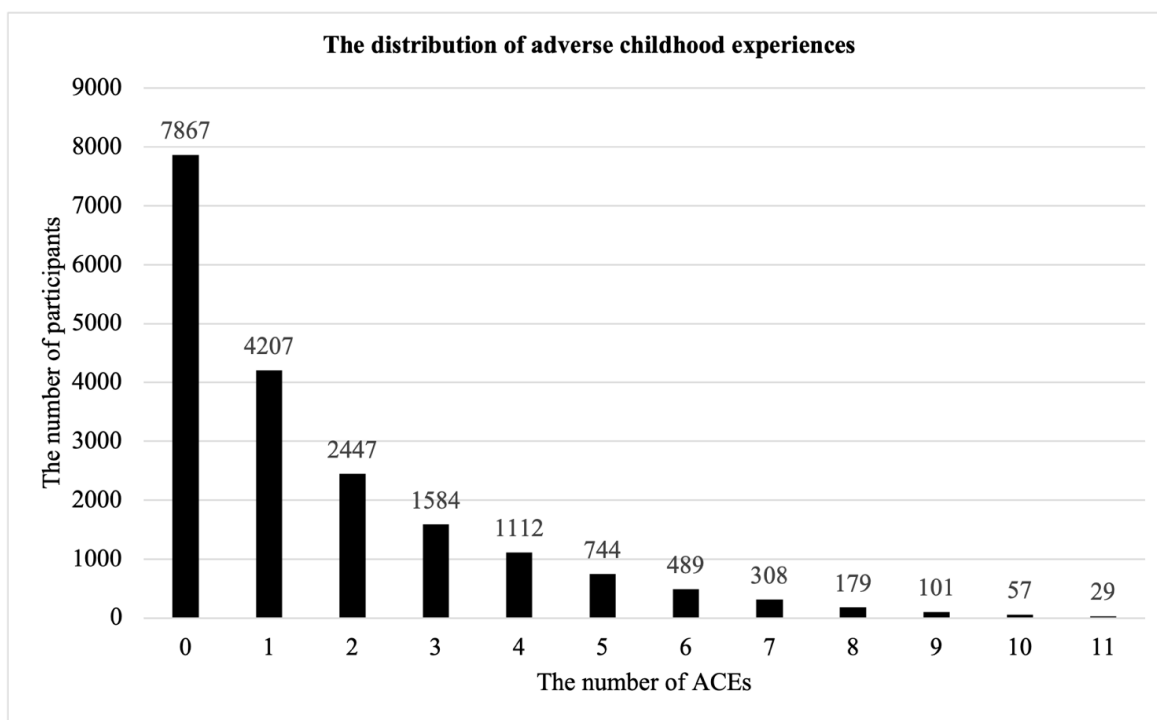
Supplemental Method 2. Calculation of proportion attributable fraction (PAF) of treatment or prevention of asthma among people with adverse childhood experiences (ACEs).

The proportion attributable fraction (PAF) is calculated as the following formula:

$$\frac{Pr[E = 1] \times (RR - 1)}{Pr[E = 1] \times (RR - 1) + 1}$$

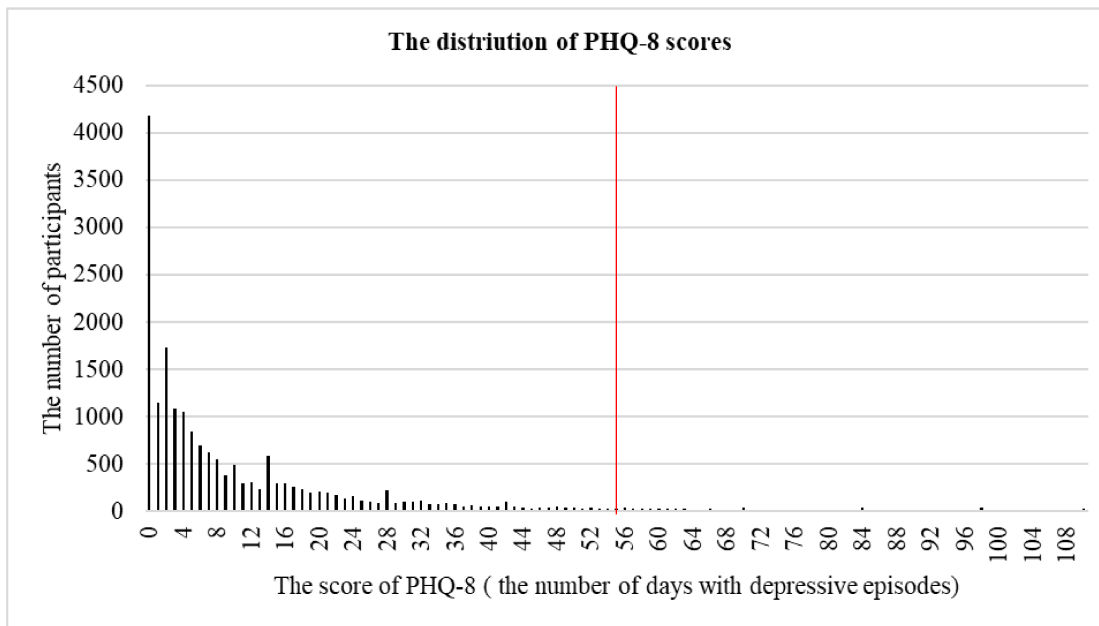
Where $Pr[\cdot]$ is the prevalence function, E means the exposure, and RR means the risk ratio. In our main analysis, participants who experienced ACEs without a diagnosis of asthma showed a higher risk of elevated depressive symptoms (aOR [95% CI] = 3.72 [3.04, 4.71]) and those with both ACEs and diagnosis of asthma also showed a higher risk of elevated depressive symptoms (aOR [95% CI] = 6.21 [5.01, 7.96]), comparing to those who have not experienced either ACEs or diagnosis of asthma. Therefore, participants with both ACEs and diagnosis of asthma showed a higher risk of elevated depressive symptoms, comparing to those who have experienced ACEs but not diagnosis of asthma (aOR [95% CI] = 1.67 [1.44, 1.95]). In addition, prevalence of participants with diagnosis history of asthma among those with ACEs was 2,189 / 12,949. In our study, the prevalence of outcome (1,015 / 21,544) is less than 10%, so it is permissible to approximate the OR as the RR. Thus, the PAF of treatment or prevention of asthma among people with ACEs is:

$$\begin{aligned} & \frac{Pr[E = 1] \times (RR - 1)}{Pr[E = 1] \times (RR - 1) + 1} \\ & \approx \frac{\frac{2,189}{12,949} \times (1.67 - 1)}{\frac{2,189}{12,949} \times (1.67 - 1) + 1} \\ & = 0.101 \dots \\ & \approx 0.10 \end{aligned}$$

Supplemental Figure 1. The distribution of adverse childhood experiences (N = 21,544).

Notes: The number of missing values is 2,420.

Supplemental Figure 2. The distribution of days with depressive episodes based on PHQ-8 (N = 21,544).



Notes: The participants with over 55 days of depressive episodes were coded as those with elevated depressive symptoms (the red line shows the cut-point.). The number of missing values is 2,185.

Supplemental Table 1. Eleven questions about adverse childhood experiences in BRFSS 2010.

Questions	
1	“Did you live with anyone who was depressed, mentally ill, or suicidal?”
2	“Did you live with anyone who was a problem drinker or alcoholic?”
3	“Did you live with anyone who used illegal street drugs or who abused prescription medications?”
4	“Did you live with anyone who served time or was sentenced to serve time in a prison, jail, or other correctional facility?”
5	“Were your parents separated or divorced?”
6	“How often did your parents or adults in your home ever slap, hit, kick, punch or beat each other up?”
7	“Before age 18, how often did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way? Do not include spanking.”
8	“How often did a parent or adult in your home ever swear at you, insult you, or put you down?”
9	“How often did anyone at least 5 years older than you or an adult, ever touch you sexually?”
10	“How often did anyone at least 5 years older than you or an adult, try to make you touch them sexually?”
11	“How often did anyone at least 5 years older than you or an adult, force you to have sex?”

Notes

Answer choices for question 1 - 4 are “Yes”, “No”, “Don’t know / Not sure”, and “Refused”.

Answer choices for question 5 are “Yes”, “No”, “Parents not married”, “Don’t know / Not sure”, and “Refused”.

Answer choices for question 6 - 11 are “Never”, “Once”, “More than once”, “Don’t know / Not sure”, and “Refused”.

In each of the questions, answers of “Yes”, “once”, and “more than once” were coded as 1. On the other hand, answers of “No” and “Never” were coded as 0. In question 5, the answer to “Parents not married” was coded as 0. Answers of “Don’t know / Not sure” and “Refused” were treated as missing values.

Supplemental Table 2. Eight questions in BRFSS 2010 about mental conditions over the last two weeks on scale of days.

Question
1 “How many days have you had little interest or pleasure in doing things?”
2 “How many days have you felt down, depressed or hopeless?”
3 “How many days have you had trouble falling asleep or staying asleep or sleeping too much?”
4 “How many days have you felt tired or had little energy?”
5 “How many days have you had a poor appetite or eaten too much?”
6 “How many days have you felt bad about yourself or that you were a failure or had let yourself or your family down?”
7 “How many days have you had trouble concentrating on things, such as reading the newspaper or watching the TV?”
8 “How many days have you moved or spoken so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?”

Notes: Each of the eight questions could be answered with a range from 0 to 14 days in the days version PHQ-8.

Thus, the score ranges from 0 to 112 days.

Supplemental Table 3. Associations of (A) adverse childhood experiences (ACEs) and (B) asthma with depressive symptoms additionally adjusting for histories of comorbidities.

Outcome Exposures	Depressive Symptoms	
	Number of events	aOR [95% CI] in Model 3*
A) ACEs once or more than once		
No	150 / 8,595	Ref
Yes	865 / 12,949	2.84 [2.30, 3.54]
B) Past history of asthma		
No	713 / 18,325	Ref
Yes	302 / 3,219	2.22 [1.49, 3.24]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences; BMI = body mass index

* Model 3: adjusted for covariates (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol; histories of diabetes, and cardiovascular diseases)

Supplemental Table 4. Joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms additionally adjusting for histories of comorbidities.

Outcome		Depressive Symptoms	
ACEs once or more than once	History of asthma	Number of events	aOR [95%CI] in Model 3 ^{*,†}
No	No	110 / 7,565	Ref
Yes	No	603 / 10,760	3.75 [3.06, 4.75]
No	Yes	40 / 1,030	1.78 [1.15, 2.57]
Yes	Yes	262 / 2,189	6.23 [4.98, 7.92]
OR for the interaction term (multiplicative scale)			0.93 [0.61, 1.50]
RERI (additive scale) [‡]			+1.70 [0.65, 2.76]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

BMI = body mass index; RERI = relative excess risk due to interaction.

* The following covariates were adjusted (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol; histories of diabetes, and cardiovascular diseases)

† The number of iterations performed for bootstrapping to calculate 95% CI was 500.

‡ additive interaction was estimated by RERI

$$(OR_{ACEs(\geq 1)_Asthma(yes)} - OR_{ACEs(\geq 1)_Asthma(no)} - OR_{ACEs(0)_Asthma(yes)} + 1; \text{ null value} = 0)$$

Supplemental Table 5. Associations of (A) adverse childhood experiences (ACEs) and (B) asthma with depressive symptoms in the complete-case analysis (N = 15,874).

Outcome Exposures	Depressive Symptoms	
	Number of events	aOR [95% CI] in Model 2*
A) ACEs once or more than once		
No	101 / 6,358	Ref
Yes	584 / 9,516	2.79 [2.16, 3.66]
B) Past history of asthma		
No	471 / 13,523	Ref
Yes	214 / 2,351	2.30 [1.41, 3.63]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

BMI = body mass index

* Model 2: adjusted for covariates (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol)

Supplemental Table 6. Joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms in the complete-case analysis (N = 15,874).

Outcome		Depressive Symptoms	
ACEs once or more than once	History of asthma	Number of events	aOR [95%CI] in Model 2 ^{*,†}
No	No	74 / 5,597	Ref
Yes	No	397 / 7,926	3.66 [2.78, 4.80]
No	Yes	27 / 761	1.76 [1.05, 2.76]
Yes	Yes	187 / 1,590	6.60 [4.98, 9.08]
OR for the interaction term (multiplicative scale)			1.04 [0.62, 1.85]
RERI (additive scale) [‡]			+2.19 [0.86, 3.78]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

BMI = body mass index; RERI = relative excess risk due to interaction.

* The following covariates were adjusted (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol)

† The number of iterations performed for bootstrapping to calculate 95% CI was 500.

‡ additive interaction was estimated by RERI ($OR_{ACEs(\geq 1)_{Asthma(yes)}} - OR_{ACEs(\geq 1)_{Asthma(no)}} - OR_{ACEs(0)_{Asthma(yes)}} + 1$; null value = 0)

Supplemental Table 7. Joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms using a continuous ACEs score.

Outcome	Depressive Symptoms
Exposures	aOR [95%CI] in Model 2 ^{*,†}
continuous ACE score	1.38 [1.34, 1.42]
History of Asthma	1.62 [1.26, 2.08]
aOR for the interaction term (multiplicative scale)	1.00 [0.95, 1.06]
RERI (additive scale) [‡]	+0.23 [0.15, 0.34]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

RERI = relative excess risk due to interaction.

* The following covariates were adjusted (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol)

† The number of iterations performed for bootstrapping to calculate 95% CI was 500.

‡ additive interaction was estimated by RERI ($OR_{ACEs_Asthma(yes)} - OR_{ACEs_Asthma(no)} - OR_{ACEs_Asthma(yes)} + 1$; null value = 0)

Supplemental Table 8. Joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms using a categorical ACEs score.

Outcome		Depressive Symptoms	
The number of ACEs	History of asthma	Number of events	aOR [95%CI] ^{*, †}
0	No	110 / 7,565	Ref
1	No	108 / 4,106	1.74 [1.32, 2.28]
2	No	94 / 2,415	2.59 [1.95, 3.38]
3	No	96 / 1,504	4.46 [3.31, 5.94]
≥4	No	305 / 2,735	8.12 [6.59, 10.46]
0	Yes	40 / 1,030	1.98 [1.29, 2.91]
1	Yes	28 / 634	2.47 [1.52, 3.80]
2	Yes	35 / 420	4.47 [2.78, 6.50]
3	Yes	29 / 335	5.40 [3.15, 8.14]
≥4	Yes	170 / 800	13.9 [10.9, 18.3]
aOR for the interaction term (multiplicative scale when ACE = 1)			0.71 [0.37, 1.39]
aOR for the interaction term (multiplicative scale when ACE = 2)			0.85 [0.47, 1.43]
aOR for the interaction term (multiplicative scale when ACE = 3)			0.60 [0.31, 1.12]
aOR for the interaction term (multiplicative scale when ACE ≥4)			0.87 [0.54, 1.39]
RERI (additive scale when ACE = 1) [‡]			-0.24 [-1.60, 1.14]
RERI (additive scale when ACE = 2) [‡]			+0.81 [-0.98, 2.58]
RERI (additive scale when ACE = 3) [‡]			-0.01 [-2.71, 2.53]
RERI (additive scale when ACE ≥4) [‡]			+4.75 [2.02, 7.90]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

RERI = relative excess risk due to interaction.

* The following covariates were adjusted (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol)

[†]The number of iterations performed for bootstrapping to calculate 95% CI was 500.

[‡]additive interaction was estimated by RERI ($OR_{ACEs(\geq 1)_Asthma(yes)} - OR_{ACEs(\geq 1)_Asthma(no)} - OR_{ACEs(0)_Asthma(yes)} + 1$; null value = 0)

Supplemental Table 9. Joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms using the diagnosis history of depression as the outcome.

Outcome	Diagnosis history of depression		
	History of asthma	Number of events	aOR [95%CI] ^{*, †}
ACEs once or more than once			
No	No	620 / 7,565	Ref
Yes	No	2,342 / 10,760	2.92 [2.65, 3.19]
No	Yes	160 / 1,030	1.68 [1.34, 2.05]
Yes	Yes	766 / 2,189	4.59 [4.02, 5.23]
aOR for the interaction term (multiplicative scale)			0.94 [0.75, 1.18]
RERI (additive scale) [‡]			+1.00 [0.46, 1.55]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

RERI = relative excess risk due to interaction.

* The following covariates were adjusted (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol)

†The number of iterations performed for bootstrapping to calculate 95% CI was 500.

‡additive interaction was estimated by RERI ($OR_{ACEs(\geq 1)_{Asthma(yes)}} - OR_{ACEs(\geq 1)_{Asthma(no)}} - OR_{ACEs(0)_{Asthma(yes)}} + 1$; null value = 0)

Supplemental Table 10. Joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms using a continuous PHQ-8 score (days version) as the outcome.

Outcome		Days with depressive symptoms (PHQ-8)
ACEs once or more than once	History of asthma	aOR [95%CI] ^{*, †}
No	No	Ref
Yes	No	6.80 [6.36, 7.28]
No	Yes	2.16 [1.23, 3.14]
Yes	Yes	11.67 [10.73, 12.56]
aOR for the interaction term (multiplicative scale)		2.70 [1.24, 4.25]
RERI (additive scale) [‡]		+3.70 [2.24, 5.25]

aOR = adjusted odds ratio; CI = confidence interval; ACEs = adverse childhood experiences;

RERI = relative excess risk due to interaction.

* The following covariates were adjusted (age; gender; race; ethnicity; state; educational attainment; household income; marital status; employment status; healthcare coverage; social-emotional support; BMI; smoking; alcohol)

†The number of iterations performed for bootstrapping to calculate 95% CI was 500.

‡additive interaction was estimated by RERI ($OR_{ACEs(\geq 1)_Asthma(yes)} - OR_{ACEs(\geq 1)_Asthma(no)} - OR_{ACEs(0)_Asthma(yes)} + 1$; null value = 0)