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Estimating the joint association of adverse childhood experiences and asthma with subsequent depressive symptoms: a marginal structural modelling approach

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ABSTRACT

Background The relationship between adverse childhood experiences (ACEs) and depression risk has been well documented. However, it remains unclear whether stress-related chronic conditions associated with ACEs, such as asthma, increase the long-term mental health burden of ACEs.

Objective To investigate the joint association of ACEs and asthma with subsequent depressive symptoms among US adults.

Methods This study used data from the Behavioural Risk Factor Surveillance System 2010, including 21 544 participants over 18 years old from four states where participants were questioned about ACEs. We used logistic regression models to calculate the adjusted OR (aOR) for elevated depressive symptoms evaluated by Patient Health Questionnaire-8 according to ACEs and asthma, along with marginal structural models (MSM) to consider ACE-related confounders between asthma and depression. We evaluated the additive interaction between ACEs and asthma on depressive symptoms with the relative excess risk due to interaction (RERI).

Findings Of the 21 544 participants (mean age: 56, women: 59.5%), 52.3% reported ≥1 ACEs, 14.9% reported a history of asthma and 4.0% had depressive symptoms. ACEs and asthma were independently associated with elevated depressive symptoms (aORs (95% CI) were 2.85 (2.30 to 3.55) and 2.24 (1.50 to 3.27), respectively). Furthermore, our MSM revealed an additive interaction between ACEs and asthma for depressive symptoms (RERI (95% CI)=+1.63 (0.54 to 2.71)).

Conclusions These findings suggest that asthma amplifies the risk of depressive symptoms associated with ACEs.

Clinical implications Prevention and treatment of asthma, along with establishing preventive environments and services against ACEs, are effective in mitigating the potential burden of ACEs on mental health.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Adverse childhood experiences (ACEs) and asthma are independent risk factors for elevated depressive symptoms among US adults. However, the joint association between ACEs and asthma was not well established.

WHAT THIS STUDY ADDS

⇒ Our marginal structural model revealed that ACEs and asthma were jointly associated with subsequent depressive symptoms on the additive scale, even after adjusting for confounders between asthma and depressive symptoms simultaneously affected by ACEs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings add to the existing body of evidence, underscoring the significance of asthma as a modifying factor in the pathway linking ACEs to mental health outcomes later in life.

⇒ Addressing and managing asthma could play a significant role in mitigating the mental health burden of ACEs in addition to preparing supportive environments and offering services to prevent ACEs themselves.

BACKGROUND

In the USA, around 60% of adults have experienced adverse childhood experiences (ACEs), defined as traumatic events in childhood (0–17 years old) including experiencing physical, sexual or emotional abuse; witnessing violence in the home or having a family member with mental illnesses or suicidal attempt.[1 2] Ample evidence has shown the deleterious effects of ACEs on depression. A previous meta-analysis reported that approximately 40% of cases of depression in North America and more than 25% in Europe were attributed to ACEs.[3] Individuals with ACEs are more likely than those without ACEs to feel loneliness and have diabetes and/or cardiovascular diseases,[4 5] which could lead to depression in later life. To effectively prevent depression and its long-term adverse health outcomes, it is essential to scrutinise the association between ACEs and depression throughout the life course of individuals.[1 4 6]

Accumulating evidence suggests that asthma is on the pathway between ACEs and depression. Asthma is the most common chronic respiratory disease, with its prevalence among US adults estimated to be 8.4% (current prevalence) and 13.9% (lifetime prevalence) in 2020.[7 8] ACEs are considered as a risk factor for asthma, as shown in a

previous meta-analysis including 19 studies from 2002 to 2018; adults who experienced ACEs had 1.32 times higher odds of asthma than those who did not.[9] This study suggested that one of the physiopathological mechanisms underlying the relationship between ACE and chronic diseases such as asthma was responses to chronic psychosocial stresses, including hypothalamic–pituitary–adrenal axis functions.[9] Furthermore, the association between asthma and depression has been reported. A study involving data from 57 countries showed that people with asthma had 2.37 times higher odds of a major depressive episode than those without asthma.[10] This association could be partly explained by inflammatory responses,[11] that leads to depressive symptoms.[12] Of note, asthma generally occurs earlier in life than other consequences of ACEs such as cardiovascular diseases and diabetes.[13] Given the high prevalence, the early onset and the suggested mechanisms of relationships among ACE, asthma and depression, asthma can be an optimal target for clinical and public health interventions to mitigate the burden of ACEs on depression. However, the effect modification of asthma between ACEs and elevated depressive symptoms has not been well elucidated.

OBJECTIVE

To address this knowledge gap, using a nationwide survey of US adults, we investigated the joint association of ACEs and asthma with subsequent depressive symptoms. We employed marginal structural models (MSMs) to account for covariates that are simultaneously intermediate and confounding variables under a certain assumption of time-ordering across covariates (ie, factors that are considered to be affected by ACEs and also be confounders between asthma and depressive symptoms). A deeper understanding of these pathways can provide new insights into potential clinical and policy interventions to attenuate the harmful effects of ACEs on future mental health.

METHODS

Study design and participants

We used data from the Behavioral Risk Factor Surveillance System 2010 (BRFSS 2010), a health-related telephone survey about US residents.[14] From BRFSS 2010, 22 044 participants over 18 years old from four states (Hawaii, Nevada, Vermont and Wisconsin) were asked about ACEs, history of asthma and depressive symptoms. We excluded participants whose age, race and ethnicity were not available, and thus, our analytical data included 21 544 participants in total (figure 1). The prespecified analysis plan is described in online supplemental file 2.

Adverse childhood experiences

In the questionnaire of BRFSS 2010, ACEs were assessed through 11 questions regarding household dysfunction, physical, sexual and emotional abuse (online supplemental table 1). In this study,

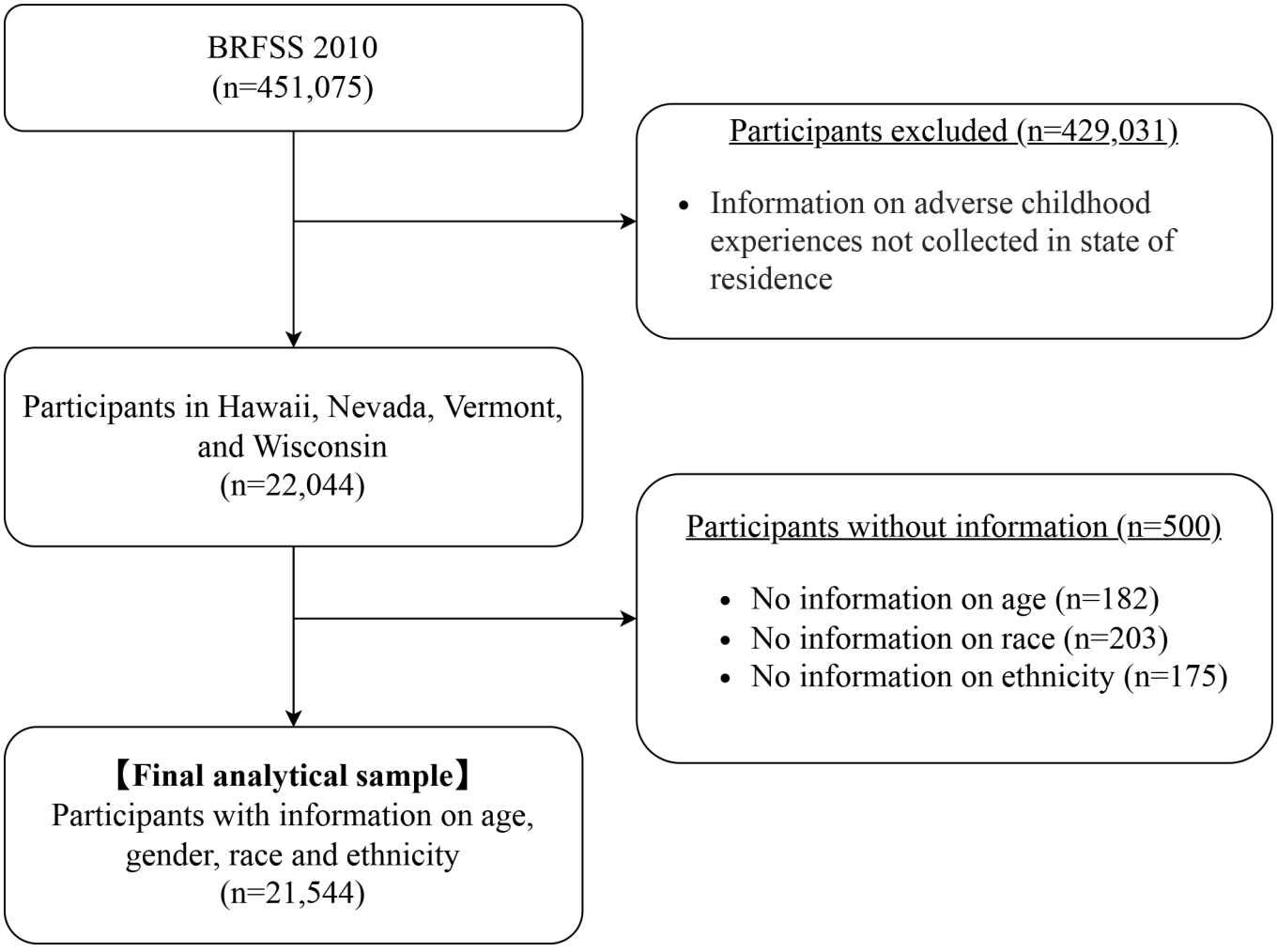

Figure 1 The flow chart of the study sample from BRFSS 2010. BRFSS, Behavioural Risk Factor Surveillance System.

we binarily coded every ACE episode whether participants had experienced the episode or not, which was totalled as ACE score. Then, the ACE score was defined as a binary variable (reported experiencing any ACE at least once vs reported never experiencing any ACEs). Regarding the question on whether the participants' parents were separated or divorced, affirmative responses were considered indicative of ACE, while negative responses, including the response 'parents not married,' were not considered as ACE. For all questions on ACEs, the answers of 'don't know/not sure' and 'refused' were treated as missing values, resulting in 2420 respondents (11.2%) with at least one missing answer.

History of asthma

The BRFSS 2010 asked participants about their history of asthma with the following yes/no question: 'Have you ever been told by a doctor, nurse or other health professional that you had asthma?' We treated the answers of 'don't know/not sure' and 'refused' as missing values, which totalled to 60 (0.3%).

Depressive symptoms

BRFSS 2010 asked about depressive symptoms using the days version of the Patient Health Questionnaire 8 (PHQ-8), which consists of eight questions about respondents' mental conditions over the last 2 weeks (online supplemental table 2). We used PHQ-8 scores as the outcome to mitigate reverse causality from depressive symptoms to asthma, assuming that any new history of asthma did not occur within 2 weeks before the survey. The days version of scoring the PHQ-8 ranges from 0 to 112 days (each of the eight questions could be answered with a range from 0 to 14 days). A previous study indicated that the optimal cut-point of the days version of PHQ-8 to identify individuals with a major depressive episode was 55 days with high sensitivity and specificity, 0.91 (95% CI 0.90 to 0.93) and 0.99 (95% CI 0.99 to 0.99) respectively, as compared with the 'gold standard' Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) derived PHQ-8 algorithm. Additionally, the prevalence of major depressive episodes, as estimated by the day-version of PHQ-8, is closely aligned with the prevalence estimates derived from DSM-identified PHQ major depressive episodes.[15] Therefore, we defined participants with a total score of over 55 days from the PHQ-8 as those with elevated depressive symptoms. The number of missing values for this binary variable was 2185 (10.1%).

Other covariates

Demographic characteristics included age, gender (men, women), race (white, black or African American; Asian and others), ethnicity (Hispanic or Latino; or not), state (Hawaii, Nevada, Vermont and Wisconsin), educational attainment (less than high school, graduated high school, attended college or technical school, or graduated from college or technical school), annual household income (less than US$25 000; between US$25 000 and US$75 000 or more than US$75 000), marital status (not married, married, divorced, widowed or separated or unmarried couple), employment status (not working, working or unable to work), healthcare coverage and social-emotional support (rarely or never or more than sometimes). As for employment status, we integrated five answers ('out of work for more than 1 year,' 'out of work for less than 1 year,' 'a homemaker,' 'a student' and 'retired') into one category of 'not working.' Physical and behavioural characteristics included body mass index (BMI), smoking (never, former smoker, now smokes some days or now smokes every day) and alcohol consumption (at least once a day or not). BMI was calculated in kg/m^2 from self-reported height and weight. History of illnesses included self-reported diabetes and cardiovascular diseases. A history of diabetes was further categorised as diabetes versus pre-diabetes or borderline diabetes.

Statistical analyses

After describing the distribution of sociodemographic characteristics and other covariates, we employed multivariable logistic regression models to calculate the adjusted OR (aOR) of depressive symptoms according to ACEs and asthma, respectively. We selected a priori potential confounders that may affect depressive symptoms and might also be associated with ACEs or asthma (figure 2).[3 5 16] In model 1, we included age, gender, race, ethnicity, state, educational attainment, household income, marital status, employment status, healthcare coverage

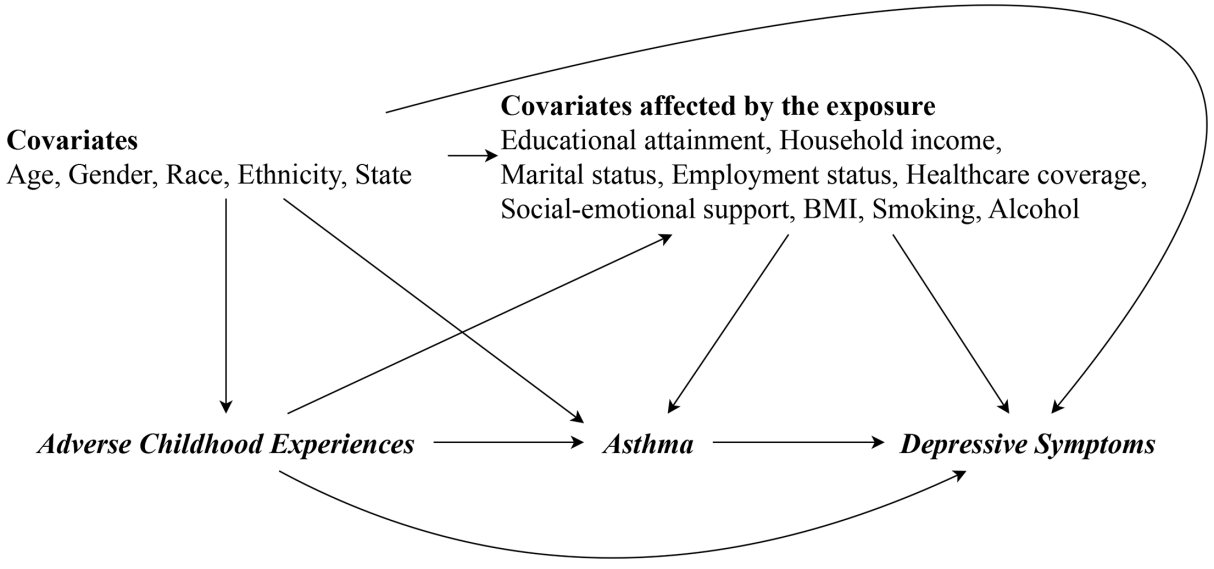

Figure 2 Directed acyclic graph illustrating proposed causal structure from adverse childhood experiences, through asthma, to depressive symptoms. BMI, body mass index.

and social-emotional support. In model 2 (our main model), we additionally included BMI, smoking and alcohol consumption. Among the analytical data sample, 15 560 participants (72.2%) had complete data. To mitigate bias from missing values (the maximum missingness for any one variable was 11.2% of annual household income), missing variables were imputed by chained random forests with an assumption of missing at random.

Because educational attainment, household income, marital status, employment status, healthcare coverage, social-emotional support, BMI, smoking and alcohol consumption could be affected by ACEs (ie, they are affected by ACEs and are simultaneously confounders between asthma and depressive symptoms), we further applied MSMs with inverse probability of treatment weights (IPTW) to investigate the association between ACEs and depressive symptoms, accounting for the intermediary role of asthma (online supplemental method 1).[17 18] We estimated the multiplicative interaction by adding the interaction term between ACEs and asthma to the main regression model, and also calculated the additive interaction using the relative excess risk due to interaction (RERI).[19] Robust 95% CIs were estimated by repeating analyses on 500 bootstrapped samples.

Additional analyses

We conducted the following five sensitivity analyses. First, we reconducted the main analysis additionally adjusting for histories of diabetes and cardiovascular diseases, as mediator-outcome confounders affected by ACEs in model 3. Second, we conducted the complete case analysis using data from participants without any missing variables (n=15 560). Third, to assess the dose–response relationship, we reanalysed the data using ACEs (1) as continuous exposure or (2) as a categorical exposure (ie, the number of ACEs=0, 1, 2, 3 and ≥4). Fourth, we reanalysed the data redefining the outcome as (1) the diagnosis history of depression or (2) days with depressive symptoms evaluated by PHQ-8. Lastly, we calculated a proportion attributable fraction (PAF) of asthma among people with ACEs in the analysis with the main analysis (online supplemental method 2).[20] All statistical analyses were conducted using R V.4.2.0.

FINDINGS

Among 21 544 participants, 11 257 (52.3%) had at least one ACE and 3219 (14.9%) had a history of asthma. The mean (SD) age of participants was 56 (16), and the proportion of women was 59.5%. Participants with at least one ACE were more likely to be unmarried, unable to work and current smokers compared with those without ACEs (table 1). The distribution of ACEs is shown in online supplemental figure 1.

Overall, 856 (4.0%) had elevated depressive symptoms (online supplemental figure 2). In the multivariable logistic regression models, both ACEs and asthma were associated with elevated depressive symptoms after adjusting for all covariates in model 2 (ACEs, aOR (95% CI)=2.85 (2.30 to 3.55); asthma, aOR (95% CI)=2.24 (1.50 to 3.27); table 2).

When we applied IPTW to adjust for mediator-outcome confounders affected by the exposure, we found that participants who experienced ACEs without a diagnosis of asthma showed a higher risk of elevated depressive symptoms compared with those who have not experienced either ACEs or diagnosis of asthma (aOR (95% CI)=3.72 (3.04 to 4.71)). Participants with asthma who did not experience ACEs also showed a higher risk of elevated depressive symptoms (aOR (95% CI)=1.86 (1.23 to 2.71)). When participants had both ACEs and asthma, aOR (95% CI) was 6.21 (5.01 to 7.96). RERI (95% CI) was +1.63

Table 1 Characteristics of participants according to the number of adverse childhood experiences (N=21 544)

Characteristic	Overall	ACEs*	
	N=21 544	0, N=7867	≥1, N=11 257
Age, mean (SD)	56 (16)	60 (16)	54 (16)
Gender, N (%)			
Men	8720 (40.5)	3225 (41.0)	4514 (40.1)
Women	12 824 (59.5)	4642 (59.0)	6743 (59.9)
Race, N(%)			
White	16 477 (76.5)	5814 (73.9)	8878 (78.9)
Black or African American	709 (3.3)	169 (2.1)	380 (3.4)
Asian	2750 (12.8)	1435 (18.2)	1060 (9.4)
Others	1608 (7.5)	449 (5.7)	939 (8.3)
Ethnicity (Hispanic or Latino), N (%)	840 (3.9)	228 (2.9)	475 (4.2)
State, N(%)			
Hawaii	6422 (29.8)	2620 (33.3)	3206 (28.5)
Nevada	3803 (17.7)	1121 (14.2)	2165 (19.2)
Vermont	6622 (30.7)	2487 (31.6)	3547 (31.5)
Wisconsin	4697 (21.8)	1639 (20.8)	2339 (20.8)
Educational attainment, N (%)			
Not graduate high school	1314 (6.1)	392 (5.0)	679 (6.0)
Graduated high school	6444 (29.9)	2311 (29.4)	3296 (29.3)
Attended college or technical school	5965 (27.7)	2024 (25.7)	3269 (29.0)
Graduated from college or technical school	7775 (36.1)	3135 (39.9)	4002 (35.6)
Missing	46 (0.2)	5 (0.1)	11 (0.1)
Marital status, N (%)			
Not married	2819 (13.1)	848 (10.8)	1628 (14.5)
Married	11 967 (55.5)	4670 (59.4)	6092 (54.1)
Divorce, widow or separate	6114 (28.4)	2210 (28.1)	3133 (27.8)
Unmarried couple	561 (2.6)	123 (1.6)	377 (3.3)
Missing	83 (0.4)	16 (0.2)	27 (0.2)
Employment status, N (%)			
Not working	9023 (41.9)	3790 (48.2)	4168 (37.0)
Working	11 317 (52.5)	3832 (48.7)	6348 (56.4)
Unable to work	1113 (5.2)	225 (2.9)	721 (6.4)
Missing	91 (0.4)	20 (0.3)	20 (0.2)
Annual household income, N (%)			
<US$25 000	4935 (22.9)	1587 (20.2)	2677 (23.8)
US$25 000–US$75 000	8900 (41.3)	3243 (41.2)	4795 (42.6)
>US$75 000	5293 (24.6)	2091 (26.6)	2821 (25.1)
Missing	2416 (11.2)	946 (12.0)	964 (8.6)
Have healthcare coverage, N (%)	19 858 (92.2)	7472 (95.0)	10 252 (91.1)
Missing	46 (0.2)	13 (0.2)	18 (0.2)
Social-emotional support, N (%)			
Rarely or never	1858 (8.6)	713 (9.1)	909 (8.1)
Sometimes, usually, or always	18 712 (86.9)	7067 (89.8)	10 267 (91.2)

Continued

Table 1 Continued

Characteristic	Overall	ACEs*	
	N=21 544	0, N=7867	≥1, N=11 257
Missing	974 (4.5)	87 (1.1)	81 (0.7)
History of asthma, N (%)	3219 (14.9)	943 (12.0)	1883 (16.7)
Missing	60 (0.3)	25 (0.3)	26 (0.2)
History of diabetes, N (%)			
No	18 843 (87.5)	6856 (87.1)	9902 (88.0)
Pre-diabetes or borderline diabetes	416 (1.9)	143 (1.8)	223 (2.0)
Diabetes	2265 (10.5)	861 (10.9)	1124 (10.0)
Missing	20 (0.1)	7 (0.1)	8 (0.1)
History of cardiovascular diseases, N (%)	2114 (9.8)	783 (10.0)	1033 (9.2)
Missing	326 (1.5)	107 (1.4)	148 (1.3)
History of depression, N (%)	3497 (16.2)	636 (8.1)	2559 (22.7)
Missing	1144 (5.3)	14 (0.2)	23 (0.2)
Smoking, N (%)			
Now smokes every day	2376 (11.0)	566 (7.2)	1498 (13.3)
Now smokes some days	865 (4.0)	214 (2.7)	540 (4.8)
Former smoker	7215 (33.5)	2463 (31.3)	3951 (35.1)
Never smoked	11 018 (51.1)	4599 (58.5)	5236 (46.5)
Missing	70 (0.3)	25 (0.3)	32 (0.3)
BMI, mean (SD)	27.1 (5.8)	26.5 (5.2)	27.6 (6.1)
Missing, N (%)	700 (3.2)	215 (2.7)	271 (2.4)
Alcohol, N (%)	11 695 (54.3)	4183 (53.2)	6448 (57.3)
Missing	372 (1.7)	77 (1.0)	58 (0.5)

*The sum of the sample sizes for the ACEs categories in this table (before random forest imputation) is not equal to the overall sample size (n=21 544) because of the missing values in the data of ACEs.
ACEs, adverse childhood experiences; BMI, body mass index.

Table 2 Associations of (A) adverse childhood experiences (ACEs) and (B) asthma with depressive symptoms

Outcome	Depressive symptoms		
Exposures	No of events	aOR (95% CI) in model 1*	aOR (95% CI) in model 2†
(A) ACEs once or more than once			
No	150/8595	Ref	Ref
Yes	865/12 949	3.13 (2.54 to 3.90)	2.85 (2.30 to 3.55)
(B) History of asthma			
No	713/18 325	Ref	Ref
Yes	302/3219	2.38 (1.60 to 3.45)	2.24 (1.50 to 3.27)

*Model 1: the following covariates were adjusted (age, gender, race, ethnicity, state, educational attainment, household income, marital status, employment status, healthcare coverage, social-emotional support).
†Model 2: 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).
aOR, adjusted OR; BMI, body mass index.

Table 3 The joint association of adverse childhood experiences (ACEs) and asthma on depressive symptoms using marginal structural models to adjust for confounders

Outcome		Depressive symptoms	
ACEs once or more than once	History of asthma	No of events	aOR (95% CI)*,†
No	No	110/7565	Ref
Yes	No	603/10 760	3.72 (3.04 to 4.71)
No	Yes	40/1030	1.86 (1.23 to 2.71)
Yes	Yes	262/2189	6.21 (5.01 to 7.96)
aOR for the interaction term (multiplicative scale)			0.89 (0.59 to 1.44)
RERI (additive scale)‡			+1.63 (0.54 to 2.71)

*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).
aOR, adjusted OR; BMI, body mass index; RERI, relative excess risk due to interaction.

(0.54 to 2.71) indicating the presence of an additive interaction, although we did not find evidence of a multiplicative interaction (aOR=0.89 (95% CI 0.59 to 1.44)) (table 3).

Additional analyses

These results were consistent with our sensitivity analyses when we additionally adjusted for histories of diabetes, and cardiovascular diseases in model 3 (online supplemental tables 3 and 4) and when we reconducted complete case analysis without multiple imputation (online supplemental tables 4 and 5). When we used ACEs as (1) continuous variable and (2) five categorical variables, we also found the additive interaction between ACEs and asthma (online supplemental table 7 and 8), particularly for ACE≥4 (online supplemental table 8). We also found the consistent results when redefining the outcome as (1) the diagnosis history of depression or (2) days with depressive symptoms evaluated by PHQ-8 (online supplemental table 9 and 10). The PAF (95% CI) of asthma among people with ACEs was about 10% (7% to 14%).

DISCUSSION

Using a subset of a nationwide survey of US adults, this study showed that ACEs and asthma were independently associated with subsequent depressive symptoms in adulthood. In addition, we found that ACEs and asthma were jointly associated with subsequent depressive symptoms on the additive scale, after adjusting for confounders between asthma and subsequent depressive symptoms affected by ACEs within the counterfactual framework. These findings provide additional evidence on the effect modification of asthma in the association between ACEs and later-life mental health.

Our results suggest that prevention and treatment for asthma, along with establishing preventive environments and services against ACEs, are imperative to alleviate the harmful effects of ACEs on depression. The interaction between ACEs and asthma on the multiplicative scale had a wide CI, which was likely due to the limited statistical power resulting from the small number of participants with both ACEs and asthma.[21] Nonetheless, our

findings of the additive interaction of ACEs and asthma on subsequent depressive symptoms have important public health implications regarding how to combat ACE-related health issues.[19] In addition, the PAF of asthma among people with ACEs was about 10%, which indicates that prevention and treatment of asthma in people with ACEs could result in a decrease of elevated depressive symptoms by about 10%. Given that the significance of addressing social determinants, including childhood adversity, as a component to be incorporated in asthma prevention and management is emphasised, aiming to achieve better outcomes in asthma management,[22] our findings support such previous studies' suggestions and indicate that we can simultaneously reduce the mental burden associated with ACEs by preventing asthma.

There are potential psychosocial mechanisms that link ACEs and asthma to subsequent depressive symptoms. A previous study suggests that lower socioeconomic status (SES) mediates the association between ACEs and depression.[16] Asthma might lead to lower SES because it can increase absences from school and work,[23] which may impose additional stressful social experiences, such as interpersonal conflicts and poor work/school performance. Other studies suggest that individuals who experienced ACEs are vulnerable to stressful events[24] due to difficulties in cognitive emotional regulation and psychological inflexibility.[25 26] Given that SES has been widely recognised as a key driver of ACEs, asthma and depressive symptoms, it is plausible that ACEs and asthma, each contributing to lower SES and psychological vulnerability in response to stressful events, interactively influences mental health.

In addition to psychosocial mechanisms, inflammation is one of the factors contributing to a biological mechanism. Previous studies reported that C reactive protein, a major inflammation biomarker, partially mediated the relationship between ACEs and depressive symptoms.[12] Such mediation could be facilitated due to the elevated expression of proinflammatory genes associated with childhood trauma.[27] Furthermore, a UK-based cohort study on children demonstrated that interleukin 6 (IL-6), another inflammatory marker, acted as a partial mediator in the association between childhood exposure to adverse life events and depressive symptoms at the beginning of adolescence.[28] Additionally, there is ample evidence indicating that asthma is associated with depression through immune-inflammatory pathways. For instance, a meta-analysis reported that allergy-related inflammatory factors, including IL-6, were elevated in individuals with depression.[11] Another study suggested that chronic airway inflammation mediated the pathway from asthma to depression through its impact on the central nervous system, particularly serotonin and corticotropin-releasing hormone signalling pathways.[29] Therefore, ACEs and asthma are likely to interactively increase inflammation levels, which in turn results in elevated depressive symptoms.

Several limitations should be acknowledged in this study. First, our findings might be impacted by recall bias and misclassification of the exposure. Participants of BRFSS 2010 retrospectively answered questionnaires about ACEs, and thus the information about ACEs might be affected by the mental health status of participants at the time of survey and by the types of ACEs they experienced. Particularly, people with depressive symptoms are more likely to have false recall of negative events than those without depressive symptoms.[30] Second, although we applied MSMs to adjust for mediator-outcome confounders affected by the exposure, we cannot rule out the possibility of the impact of unmeasured confounders between exposure and mediator or outcome (eg, parental SES) nor those between mediator and outcome (eg, air pollution and genome). Third, the temporal relationship between ACEs, asthma and depressive symptoms could not be fully established because we used the observational data. Participants may have developed asthma first and subsequently experienced ACEs due to the increased risk of childhood adversity associated with chronic physical illnesses such as asthma.[31] In such scenario, our estimates might suffer from bias away from the null. However, given that our primary interest is interaction between ACEs and asthma rather than mediation, we do not believe the unclear temporality between ACEs and asthma significantly change our results. In addition, although we used PHQ-8 to evaluate depressive symptoms as an outcome measure to mitigate the potential for reverse causality, we were unable to determine when the symptoms of depression began. Therefore, it is possible that some individuals experienced depressive symptoms before being diagnosed with asthma. Lastly, our findings may have limited transportability for clinical practice and policy decision-making in the overall USA or other countries because BRFSS was limited in the states and survey years with questions on ACEs. Future studies are needed to validate our findings with longitudinal cohorts and intergenerational information among the general population.

In conclusion, ACEs and asthma were independently and jointly associated with depressive symptoms among US adults. Our study addresses the knowledge gap of existing literature by using MSMs to account for asthma and depressive symptom risk factors that are also affected by ACEs, and by calculating RERI to assess the interaction between ACEs and asthma on the additive scale. Furthermore, by calculating PAF of asthma among people with ACEs, it is suggested that asthma prevention among people with ACEs could decrease the cases of elevated depressive symptoms by about 10%. These indicate that asthma prevention and management taking into account social determinants can simultaneously reduce the mental burden associated with ACEs.

CLINICAL IMPLICATIONS

Direct interventions in ACEs are desirable to prevent depression in later life as indicated by ample evidence linking ACEs and depression. While complete detection and prevention of ACEs is difficult, identifying factors with potential interventions that can then reduce the mental health burden of ACEs is critical to advance the health of those with ACEs. In addition to providing environments and services that protect against ACEs, prevention and treatment of stress-related conditions, such as asthma, may be effective in mitigating the harmful effects of ACEs on mental health.

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Contributors Concept and design: YT and KI. Acquisition, analysis or interpretation of data: YT, KS, RL, MI, NK and KI. Drafting of the manuscript: YT and KI. Critical revision of the manuscript for important intellectual content: KS, RL, MI, NK and KI. Statistical analysis: YT and KI. Guarantor: KI

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Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and this study was approved from institutional board review at Kyoto University (R3044).This is a secondary analysis of publicly available anonymous data.

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Data availability statement Data are available in a public, open access repository. Data are available at https://www.cdc.gov/brfss/annual_data/annual_2010.htm.

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