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Multiple adverse childhood experiences and asthma onset in adulthood: Role of adulthood risk factors as mediators

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ABSTRACT

Objective: This population-based study of 21,902 Finnish adults examined whether adulthood risk factors for asthma mediate the association between the exposure to multiple adverse childhood experiences (ACEs) assessed retrospectively and the risk of new-onset asthma in adulthood.
Methods: Baseline characteristics, occurrence of ACEs, and risk factors of asthma in adulthood were collected with a postal survey at baseline in 1998. The participants were linked to records on incident asthma from national health registers from 1999 to 2012. Counterfactual mediation analysis was used to examine the effects of multiple ACEs (≥2) on asthma through adulthood risk factors of asthma (mediators).
Results: Of the 21,902 participants without asthma at baseline, 7552 (34%) were exposed to multiple ACEs during childhood. During the follow-up period, 2046 participants were diagnosed with incident asthma. Exposure to multiple ACEs increased the risk of asthma onset by 31% compared with ≤1 ACE. The association between ACEs and asthma onset was partly mediated by the following adulthood risk factors: severe life events (29%), smoking (15%), allergic rhinitis (8%), low education level (6%), and obesity (3%). Specific stressful life events mediating the ACE–asthma association were 'severe financial difficulties' (24%), 'emotional, physical or sexual violence' (15%), 'major increase in marital problems' (8%), 'severe conflicts with supervisor' (7%), and 'divorce or separation' (5%).
Conclusions: Exposure to multiple ACEs increased the risk of asthma in adulthood. Adulthood risk factors of asthma mediated a significant proportion of the effect of ACEs on the risk of asthma onset.

1. Introduction

Asthma is a common chronic airway disease, affecting approximately 270 million people worldwide [1]. It is a major public health problem, imposing a high economic burden [2]. Asthma prevalence has increased during the last decades and continues to increase in most areas of the world [3]. In adults, smoking, obesity, allergic rhinitis, sensitisation or exposure to irritants in the workplace, and stressful life events increase the risk of adult-onset asthma [4].

Adverse childhood experiences (ACEs), a major public health concern influencing the whole life course [5] have been found to accumulate over time across social, health and family-related-dimensions rather than occur independently [6–8] and people who have experienced many adversities in childhood show worse health behaviour and poorer health conditions in adulthood compared with those with only no or few adversities [7,9]. Individuals exposed to psychosocial adversity in childhood may have an increased risk not only for asthma [10–14] but also for the risk factors of asthma, such as smoking, obesity [9], and stressful life events [15] in adulthood. This implies that multiple ACEs may set an individual on a risk pathway leading to future exposures. Moreover, adulthood risk factors may link ACEs and adult-onset asthma, representing a pathway model [16].

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However, it is not known to what extent the association between multiple ACE and asthma is mediated by adulthood risk factors.

In the present study, we extended prior research on the association of multiple ACEs on the risk of adult asthma onset utilising national health registers. We first tested whether multiple ACEs were associated with an increased risk of asthma determined during a 14-year follow-up. Next, we used mediation analysis [17] to determine to what extent the association between multiple ACEs and risk of asthma was mediated by adulthood risk factors.

2. Materials and methods

2.1. Study population

The Health and Social Support Study (HeSSup) is a prospective observational follow-up study on the psychosocial health of the Finnish working-age population. The HeSSup Study population consisted of a random sample delivered by the Finnish Population Register Centre, stratified according to gender to four age groups: 20–24, 30–34, 40–44 and 50–54 in 1998 [18]. At baseline, a total of 25,901 respondents (response rate = 40%) returned the questionnaire and written consent to link the data to national health registers was received from 24,057 (93%) of the respondents. The cohort has been followed by surveys in 2003 and 2012 and from several national health registers. The compatibility of the HeSSup sample with the Finnish general population was tested using official statistics and the conclusion was that the differences in physical health between participants and the general population were small [18,19].

For this study, we included participants, who had responded to the baseline survey and had given consent to the register follow-up. We excluded participants who died ($n = 6$) or had asthma ($n = 1778$) before the start of the follow-up (January 1999) and who had missing information on ACEs ($n = 371$). Thus, the final sample consisted of 21,902 participants (12,850 women and 9052 men). The participants were followed up from 1 January 1999 to 31 December 2012 from national health registers to detect incident cases of asthma (Fig. 1). The HeSSup study was approved by the joint ethics committee of the University of Turku and the Turku University Central Hospital.

2.2. Assessment of multiple ACEs

The occurrence of ACEs was assessed retrospectively by self-report at baseline in 1998 using a six-item scale [20,21]. The participants reported whether they had experienced any of the six adversities in their childhood: divorce/separation of the parents, long-term financial difficulties in the family, serious conflicts in the family, frequent fear of a family member, serious or chronic illness of a family member, and alcohol problem of a family member (response categories for each item: no; yes; or cannot say) (Appendix A; A1). A priori, although there was no written statistical analysis plan, the decision was made to focus on multiple ACEs, as examination of multiple ACEs enables a better assessment of the extent of childhood adversity and its relation with adult health than does examination of single ACEs [7,9]. Thus we calculated the number of the adversities the participants had been exposed to and placed the cut-off to divide those with multiple adversities (two or more) from those with no or one adversity.

2.3. Case definition for asthma

We used the unified personal identification code system (national social security number) covering all Finnish citizens to link and obtain records from three administrative and comprehensive Finnish national health registers to identify individuals with asthma. Cases were identified based on the clinical diagnosis from the Drug Reimbursement Register or on more detailed information about purchases of prescribed medication from the Drug Prescription Register held by the Social Insurance Institution (SII) [22] or the Hospital Discharge Register held by the National Institute for Health and Welfare [23]. A participant was classified as having incident asthma when the case was verified for the first time from any of the three data sources between 1 January 1999 and 31 December 2012.

The Drug Reimbursement Register of Finland [22] contains

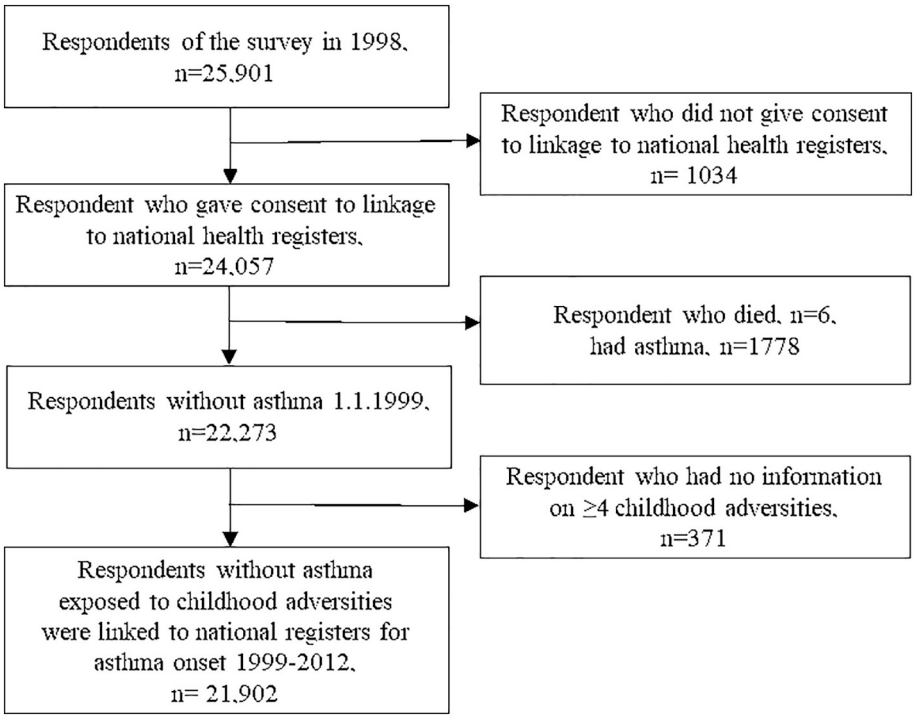

Fig. 1. Selection of study participants without asthma exposed to ACEs linked to asthma onset 1999–2012 from the Health and Social Support Study in Finland, 1998–2012. The onset of asthma was identified based on national health registers.

information on persons entitled to special reimbursement for certain chronic diseases, such as asthma. Patients who apply for special reimbursement must attach a detailed medical certificate prepared by the treating physician, who also provides data to confirm the diagnosis. The application is then reviewed by an authorised physician in the SII to determine whether the uniformly defined criteria for the disease are met. From this register, participants were defined as asthma cases if they were for the first time recorded in the Central Drug Register as eligible for asthma treatment during the follow-up.

Moreover, we used prescription data to assess the initiation of the medical treatment for asthma. In Finland, the SII provides basic reimbursement for all filled outpatient prescriptions that are recorded in the Drug Prescription Register according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) Classification [22,24]. The date of purchase is also recorded [22]. We identified all participants with two or more prescriptions for drugs for obstructive airway diseases (ATC code R03) in any year during the follow-up by using the day of the first purchase as an indicator of asthma onset.

Finally, we obtained data from the Hospital Discharge Register, which includes records on all inpatient hospital admissions [23]. This register comprises countrywide information on virtually all hospitalisations and specialised outpatient care [23]. All participants discharged from hospitals with the main diagnosis ICD-10 J45 (asthma) within the follow-up were also defined as asthma cases.

Of all 2046 incident cases of asthma detected from any of the three registers, 2043 (99.8%) had purchases of prescribed medication for asthma and 533 (26%) had a clinical diagnosis of asthma in hospitalisation or special reimbursement records. Of the latter cases, 530 (99%) had also purchases of prescribed medication for asthma.

All individuals who were identified as having asthma in any of these registers before follow-up (1 January 1999) were excluded from the analysis, as well as those who reported a lifetime diagnosis of asthma in the baseline survey.

2.4. Adulthood risk factors of asthma

The following adulthood risk factors for asthma were considered as possible mediators between the association of multiple ACEs and adult asthma: smoking, obesity, reported allergic rhinitis, stressful life events, and low socioeconomic status (low education level and manual work) a proxy for hazardous exposures in the workplace. These factors were measured by a survey at baseline in 1998. The participants reported their current and past smoking habits, which was used to identify current smokers from never and ex-smokers. Reports of height and weight were used to calculate body mass index (BMI; which was used to categorise study participants into obese (BMI $\geq$ 30 kg/m2) and non-obese (BMI $<$ 30 kg/m^2). The participants were asked whether a doctor had previously told them that they have or have had allergic rhinitis (yes/no). They reported their level of education, dichotomised into 'low' (basic or vocational) and 'high' (college or university) level, and the type of work they did. 'Manual work' was characterised by work involving mainly (1) standing, walking, lifting, and carrying or (2) heavy physical activity and 'non-manual work' by work involving mainly (3) sitting or (4) light work including standing and walking.

Adulthood life events were measured based on a list of 19 types of life events. For each event, there were four response alternatives (never, within the previous 6 months, within the previous 5 years, and $>$ 5 years ago). For this study, we considered the seven most burdensome specific events occurring within the previous 6 months or 5 years: the death of own child or spouse; exposure to emotional, physical, or sexual violence; severe illness of a family member; a major increase in marital problems; divorce or separation; severe conflicts with a supervisor; and severe financial difficulties [25] (Appendix A; A3 and Table A2). These life events were analysed separately and as an overall exposure to multiple life events ($\leq$1 life event: 'no' and $\geq$ 2 life events: 'yes'). 'Severe conflicts with a supervisor' was considered only for those employed.

2.5. Statistical analyses

We examined the associations between multiple ACEs and asthma onset using Cox proportional hazard models adjusted for age and sex. Participants without asthma at baseline were followed up to the first of recorded occurrence of asthma, death, or end of follow-up (31 December 2012), whichever occurred first. The assumption of proportional hazards was not violated when assessed with supremum test, which supported validity of cox model. Empirical survival functions of asthma onset were presented for 0, 1, 2, 3, and 4–6 ACEs.

The sex difference in the association of multiple ACEs to asthma onset was assessed with the interaction term "sex* exposure to multiple ACEs". Because no significant interaction was found (p = 0.70), we analysed men and women together in the main analyses.

We used counterfactual mediation analysis to examine the effects of multiple ACE (exposure) on asthma through each adulthood risk factor of asthma (mediator), controlling for sex and age (confounders). The mediation analysis was performed using a SAS macro [17].

Counterfactual mediation analysis extends from the traditional mediation analysis by allowing for the interaction between the exposure and mediator. The causal effects were estimated on a hazard ratio (HR) scale and divided into natural direct effects (NDEs), natural indirect effects (NIEs), and total effects (TEs). "Natural" refers for natural variation in the level of the mediator between subjects [26]. NDE provides HR for the association between multiple ACEs and asthma onset in a scenario where the level of exposure to the mediator is similar among individuals exposed and non-exposed to ACE. NIE refers to the excess risk of asthma onset among those exposed to multiple ACEs that is due to their exposure to asthma risk factors in adulthood. In TE, both natural direct and indirect effects are considered to estimate the HR for the association between multiple ACEs and asthma onset. The SAS macro produced also the proportion (%) of the TE that the mediator in question explains. The mediation analysis was adjusted for age and sex.

We performed a sensitivity analysis to examine whether the association between multiple ACEs and asthma onset depended on the cut-off point used to define multiple ACEs by using as an alternative definition exposure to 3–6 ACEs vs. 0–2 ACEs. We also replicated the main analyses in men and women separately to investigate the potential differences in the adulthood risk factors mediating the effect of the ACEs on the risk of asthma. Finally, we examined the extent to which the internal correlation of adulthood risk factors (potential mediators) affected our results. In these analyses, we used counterfactual mediation analysis to examine the effects of multiple ACE (exposure) on asthma through the adulthood risk factor (mediator), controlling for sex, age and all other adulthood risk factors (potential confounders for the mediator-outcome association) [17].

All analyses were performed using the SAS Enterprise Guide 6.1 M1HF5 (6.100.0.4180) statistical software (SAS Institute, Cary, NC, USA).

3. Results

Of the ***21,902 participants at baseline,*** 59% were women. Table 1 presents the participant characteristics and the association between ACEs as per the baseline characteristics. In all, 7552 (34%) ***participants*** had been exposed to multiple ACEs. (Appendix A; Table A1.) Women, older participants, participants with a low education level, current smokers, those with allergic rhinitis, obese participants, and those who had a higher score on stressful adult life events reported multiple ACEs more often than others.

During a mean (SD) follow-up of 13.2 (2.6) years, 2046 participants were diagnosed with asthma. Exposure to multiple ACEs was associated with 1.31-fold (95% confidence interval [CI] 1.20–1.43) greater risk of asthma than exposure to $\leq$1 ACE. This relationship remained significant even after adjusting for age and sex (hazard ratio [HR] 1.26 [95% CI 1.16–1.38]). Empirical survival functions of asthma onset from 1999 to

Table 1
Baseline characteristics by adverse childhood experiences. Health and Social Support Study in Finland, 1998–2012.

		Number of adverse childhood experiences		
	N (%)	0–1 N (%)	2–6 N (%)	P Value[a]
Total	21,902	14,350 (66)	7552 (34)	
Sex				<0.001
Women	12,850 (59)	8108 (63)	4742 (37)	
Men	9052 (41)	6242 (69)	2810 (31)	
Age group (years)				<0.001
20–24	6011 (27)	4174 (69)	1837 (31)	
30–34	5192 (24)	3306 (64)	1886 (36)	
40–44	5249 (24)	3325 (63)	1924 (37)	
50–54	5450 (25)	3545 (65)	1905 (35)	
Level of education				<0.001
Low	11,865 (55)	7482 (63)	4383(37)	
High	9822 (45)	6714 (68)	3108 (32)	
Occupational status				<0.001
Manual work	7471 (44)	4777 (64)	2694 (36)	
Non-manual work	9343 (56)	6345 (68)	2998 (32)	
Smoking				<0.001
Current smoker	5494 (27)	3180 (58)	2314 (42)	
Non-current smoker	14,639 (73)	9919 (68)	4720 (32)	
Allergic rhinitis				<0.007
Yes	5437 (25)	3484 (64)	1953 (36)	
No	16,328 (75)	10,791 (66)	5537 (34)	
Obesity (BMI ≥ 30)[b]				<0.001
Yes	2003 (9)	1201 (60)	802 (40)	
No	19,782 (91)	13,078 (66)	6704 (34)	
Multiple life events				<0.001
Yes (2–8)	4915 (23)	2522 (51)	2393 (49)	
No (0–1)	16,327 (77)	11,362 (70)	4965 (30)	
Asthma onset				<0.001
Yes	2046 (9)	1221 (60)	825 (40)	
No	19,856 (91)	13,129 (66)	6727 (34)	

Abbreviations: BMI, body mass index.
[a] *P* value for difference between the exposure groups (Pearson's chi-squared test).
[b] BMI was calculated as weight (kg) / height (m^2).

2012 for the five categories of ACEs shows that the excess asthma risk in participants who reported multiple ACEs was apparent across the entire follow-up period (Appendix B; Fig. B1).

To examine possible mediators of the association between ACEs and incident asthma in adulthood, we performed a mediation analysis (Table 2). The following mediators were identified: severe life events (HR [95% CI]) for NIE (1.07 [1.04–1.09]), smoking (1.03 [1.02–1.05]), allergic rhinitis (1.02 [1.00–1.03]), low education level (1.01 [1.00–1.02]), and obesity (1.01 [1.00–1.01]). The proportion of the total effect of ACEs mediated by the mediators was 29% for life events, 15% for smoking, 8% for allergic rhinitis, 6% for low education level, and 3% for obesity.

Of the specific stressful life events, 'severe financial difficulties' mediated 24%, 'emotional, physical or sexual violence' 15%, 'major increase in marital problems' 8%, 'severe conflicts with supervisor' 7%, and 'divorce or separation' 5% of the total effect of ACEs on asthma (Appendix B; Fig. B2 and Table B1).

Sensitivity analysis changing exposure cut-off from two adversities for multiple ACEs to at least three adversities also resulted in practically the same findings regarding the mediators (Appendix B; Table B2). Sensitivity analysis investigating the ACEs - mediator - asthma associations in women and men separately showed no major differences in the NIEs between the sexes (Appendix B, Table B3). A further sensitivity analysis taking into account *the correlation of adulthood risk factors (potential mediators)* replicated the finding from the main analysis (Appendix B, Table B4).

4. Discussion

We found that exposure to multiple ACEs increased the risk of asthma in adulthood and that adulthood risk factors mediated a significant proportion of the effect of ACEs on asthma. The increased risk of asthma onset among individuals with multiple ACEs compared with those with ≤1 ACE was partially attributed to an increased likelihood of having risk factors of asthma in adulthood, such as smoking, prevalent allergic rhinitis, low education level, obesity, and stressful life events. The most important mediators were severe financial difficulties; exposure to emotional, physical, or sexual violence; and marital problems. However, the effect of ACEs was only partially explained by the adulthood risk profile examined in this study.

Our results are consistent with studies investigating the association between ACEs and asthma onset. Both specific individual ACEs, such as physical and sexual abuse, and multiple ACEs are associated with an increased risk of asthma [9,10,12,13]. In our previous study following the same cohort for 7 years, those who reported ≥3 ACEs had a 1.6-fold greater risk of asthma than those without ACEs [11]. In this follow-up of 14 years, the corresponding risk was 1.3-fold. The attenuation of hazard after adjustment for risk factors of asthma in these studies, it suggests that adulthood risk factors may partially link asthma onset with ACEs. However, no study has examined the associations between multiple ACEs, risk factors for asthma in adulthood, and subsequent risk of asthma in a single analytic setting and applying counterfactual mediation analyses [16] to examine the higher risk of asthma onset among individuals exposed to multiple ACEs mediated by their exposure to asthma risk factors in adulthood. Our study suggests that approximately

Table 2
Direct and indirect (through adulthood risk factors) effect of multiple adverse childhood experiences on new-onset asthma in adulthood. Health and Social Support Study in Finland, 1998–2012.

Asthma risk factor in adulthood (mediator)	Natural direct effect			Natural indirect effect through mediator			Total effect			Percentage mediated
	HR	95% CI		HR	95% CI		HR	95% CI		
Basic model	1.26	1.16	1.38							
Severe life events	1.19	1.09	1.31	1.07	1.04	1.09	1.27	1.16	1.39	29
Current smoking	1.24	1.13	1.36	1.03	1.02	1.05	1.28	1.17	1.40	15
Allergic rhinitis	1.24	1.13	1.35	1.02	1.00	1.03	1.25	1.15	1.37	8
Low education	1.26	1.15	1.37	1.01	1.00	1.02	1.27	1.16	1.39	6
Obesity	1.25	1.15	1.37	1.01	1.00	1.01	1.26	1.15	1.38	3
Manual work	1.23	1.11	1.36	1.00	0.99	1.01	1.23	1.11	1.37	0.5

Data are presented as hazard ratios (HR) with 95% confidence intervals (CI).
Basic model is adjusted for sex and age. Mediator adjusted models include sex, age and the mediator. Natural direct effect refers to the hazard ratio for the association between multiple ACEs and incident asthma in a scenario that asthma risk factors (life events, smoking, allergic rhinitis, low education, obesity) among participants with multiple ACEs were at the level similar to that among those with no multiple ACEs. Natural indirect effect refers to the excess risk of asthma among the participants with multiple ACEs that is due to their higher exposure to asthma risk factors in adulthood. In the total effect, both natural direct and indirect effects are taken into account to estimate of the association between multiple ACEs and incident asthma.

one-third of the high risk of asthma could be related to the development of a worse risk profile in adulthood, including smoking, obesity, and stressful life events.

Our findings are consistent with the life course model providing a framework for understanding the link between ACEs and later adult health [16]. Individuals exposed to ACEs are more vulnerable to disease through both differences in physiological development and health-damaging behaviours [9,27,28]. How ACEs can influence adult asthma can be explained by several potential mechanisms. ACEs might programme autonomic, endocrine, and immunological systems, probably predisposing to asthma later in life [27]. Environmental exposure can cause epigenetic changes, thereby contributing to asthma onset. Prenatal exposure to nicotine in e-cigarettes has been associated with epigenetic alterations, which disrupt normal foetal lung development and contribute to the multigenerational transmission of asthma [29]. In addition, prenatal exposure to tobacco products (i.e. maternal smoking, environmental tobacco smoke, and e-cigarette vapour) may have harmful effects on neonatal and later adult respiratory outcomes [30]. ACEs act as prolonged or serious psychological stress and heighten the magnitude of inflammatory responses to various environmental triggers (e. g. parental smoking or environmental smoking) and imbalance in autonomic, neuroendocrine, and immune systems may alter both allergic and nonallergic airway inflammation and hyperreactivity up to adulthood [31]. For example, financial adversity during childhood is associated with poor lung function partly through poor housing and other socially disadvantaged and associated environmental exposures and behaviours [32]. ACEs have been associated with life-course obesity [33], and both mechanical factors and altered inflammatory and immune responses related to the obese state can contribute to asthma pathogenesis [34]. Furthermore, ACEs tend to cluster and are linked together [16]. Considerable evidence links multiple ACEs with people's health and behaviour throughout the life course [9,27,35–37].

In our study, no sex differences were noted in the association between ACEs and asthma. However, girls are more affected by postnatal stress and cumulative stress than boys in relation to asthma risk in childhood [38,39]. The lack of sex difference in the association between ACEs and asthma in our study is likely because of health-related selection. Although sex differences in new-onset asthma risk among those with ACEs may prevail over several decades, they are likely to be diluted in our cohort as most vulnerable to developing asthma following ACEs were likely prevalent cases at baseline and, thus, excluded from our sample. In addition, we did not observe major sex differences in the NIEs when examining the ACEs–mediator–asthma onset associations in women and men separately.

The strengths of this study are its large sample size and a study design that allowed the determination of the temporal order between exposure to ACEs, occurrence of risk factors, and asthma onset. Moreover, practically all respondents (96%) consented to the linkage of data from national health registers, allowing for a reliable measurement of incident asthma and few losses to follow-up. In Finland, the validity of the national registers has been found to be high [40], reasonably accurate, and highly reliable for epidemiological study [41].

This study has some limitations. First retrospective assessment of ACEs is subject to reporting and recall biases. Although not a serious liability [42], this may have under- or overestimated the observed associations [43]. The use of retrospective measures also allows differential misclassification error, i.e., selective recall of ACEs by individuals who are depressed during adulthood [44]; however, there is some evidence that the self-reported measure of ACE has good reliability [45]. Second, we examined six ACEs, but many other important types could not be examined, such as sexual and physical abuse [9]. However, such adversities might partially be reflected in the fear of a family member, which was surveyed in our study. Third, the use of counterfactual mediation analysis did not allow the estimation of multiple mediators in the same model. However, controlling for other adulthood risk factors as potential confounders for the mediator–outcome association replicated the findings from the main analysis. This suggests that the relative contributions of the mediators to asthma found were not biased due to their correlation. Finally, the response rate at baseline (40%) was relatively low, albeit similar to many other population-based studies during last decades [46,47]. This potentially could introduce bias and influence the estimates [48]. However, no major health-related selection was detected in a non-response analysis [18].

5. Conclusions

Exposure to multiple ACEs increased the risk of asthma in adulthood. Up two one-third of this association was mediated by adulthood risk factors such as smoking, prevalent allergic rhinitis, low education level, obesity, and stressful life events, especially severe financial difficulties, exposure to violence, and marital problems. ACEs should be recognised as factors affecting people's health and behaviour throughout the life course and increasing their risk of developing subsequent asthma.

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Declaration of Competing Interest

The authors have no competing interest to declare

Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2021.110388.

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