2015-06

Adverse childhood experience and asthma onset: a systematic review

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10.1183/16000617.00004114
European Respiratory Review
European Respiratory Society (ERS)

Adverse Childhood Experience & Asthma Onset: A Systematic Review

Running Title: Adverse childhood experience and asthma

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Abstract

Background: Adverse childhood experiences such as abuse and neglect are associated with subsequent immune dysregulation. Some studies show an association between adverse childhood experiences and asthma onset, though significant disparity in results exists in the published literature.

Aims: To review available studies employing a prospective design that investigates associations between adverse childhood experience and asthma.

Methods: A search protocol was developed and studies were drawn from four electronic journal databases. Studies were selected in accordance with pre-set inclusion criteria and relevant data were extracted.

Results: Twelve studies assessing data from a total of 31,524 individuals were identified which investigate the impact of a range of adverse childhood experiences on the likelihood of developing asthma. Evidence suggests that chronic stress exposure and maternal distress in pregnancy operate synergistically with known triggers such as traffic related air pollution to increase asthma risk.

Conclusions: Chronic stress in early life is associated with an increased risk of asthma onset. There is evidence that adverse childhood experience increases the impact of traffic-related air pollution and inconsistent evidence that adverse childhood experience has an independent effect on asthma onset.

Key words: Adverse childhood experiences, asthma, systematic review

Introduction

Physical environmental, genetic and immunological risk factors and the development of rhinovirus infections[1] are well established in asthma aetiology. Additionally, research shows that adverse childhood experience (ACE) are related to immune dysregulation and the subsequent onset and exacerbation of a range of diseases including asthma[2,3,4].

ACE refers to traumatic stressors in the form of physical, emotional or sexual abuse, neglect, negative life events or household dysfunction manifesting as inter-partner violence exposure, household substance abuse, mental illness or incarceration. This list is not exhaustive but each exposure can cause severe and chronic stress with multiple stressors exerting a multiplicative effect on disease morbidity and mortality[5]. Stress is associated with a multiple immune and endocrine changes but there is no evidence of an association between cortisol and asthma onset[6].

Cross-sectional and retrospective research has indicated a link between adverse childhood experience and asthma onset[7,8,9,10]; and there is prospective evidence that ACE is related to the *exacerbation* of asthmatic symptoms and an increase in relevant inflammatory profiles[11,12]. However, no review exists to date that prospectively examines the association between ACE and asthma onset and at present it is unclear whether different types of ACE exert a stronger or weaker influence in this relationship. Furthermore, if this relationship does exist then the conditions under which ACE can lead to asthma onset need to be established; it is not known whether ACE acts independently to increase the odds of asthma onset or if this only occurs when exposure to other established risk factors such as pollution is high.

This systematic review aims to investigate the relationship between ACE and asthma onset in study populations that are asymptomatic at baseline. In order to minimise risk of bias, only prospective cohort studies using reliable methods of measuring ACE and asthma will be included.

Methods

Study selection

Only English language publications were evaluated for the purposes of this review. Four electronic journal databases were used to identify peer-reviewed publications: PsycINFO, Web of Science, Medline and Embase from creation to June 2013. To identify relevant studies, search terms related to asthma, adverse childhood experience and prospective/longitudinal methodology were entered separately into each database (See Appendix A). The search strategy outlined above was informed by the principles set out in the Cochrane Handbook for Systematic Reviews of Interventions[13]. In addition to studies yielded from this search strategy, hand searches of reference lists of relevant articles were completed. Social economic status (SES) was not included as a predictor variable in this review because although it has been linked with increased disease susceptibility in numerous articles, significant disagreement exists regarding the definition and measurement of this concept.

Inclusion criteria

The following inclusion criteria were devised in line with the objectives of this study and were applied to the set of articles yielded in the initial search:

i. Participants do not display any asthma symptoms at baseline. If participants are not recruited at birth or prenatally, thorough examinations are employed to identify participants with any asthmatic symptoms.
ii. Use of an early life stressor as a predictor variable.
iii. Use of appropriate, adequate and non-retrospective method to measure early life stress, occurring before the age of 18 years.
iv. Use of onset of asthma symptoms as an outcome variable.
v. Use of physician asthma diagnosis or valid, reliable and justified alternative to measure onset of asthma symptoms.
vi. Employs a prospective design to assess associations between an early life stressor and the onset of asthma symptoms longitudinally.
vii. Adequate reporting of statistical analyses including effect sizes.

Exclusion of studies and data extraction was conducted independently by two reviewers (DE and AN).

Ethical considerations

Full ethical approval for this study was granted by the University of Bath Psychology Ethics Committee (approval ref 13-101). As this review is concerned with the analysis of published data, ethical considerations regarding direct contact with participants were not applicable.

Results

The search terms produced 1,070 articles which were assessed against the inclusion criteria on the basis of their titles and abstracts, resulting in the exclusion of 1,021 articles. Table 1 provides an overview of the reasons for exclusion of these articles at the first stage. Forty-nine articles were retained for closer inspection and full text versions were retrieved. This resulted in the exclusion of thirty-nine articles. Table 2 provides an overview of reasons for exclusion at the second stage. Two of the retained articles addressed more than one research question[14,15] and as such each research question was regarded as a separate study in the analysis. In all, 12 studies in 10 articles were included in the review. Fig. 1 provides a flow chart depicting the exclusion process.

Table 1. Reasons for exclusion of articles at stage 1 on the basis of titles and abstracts

Reason for exclusion at stage 1	Total (%)
Focus on medical or physical environmental factors	302 (28)
Focus on conditions subsequent to development of asthma	163 (15)
Focus on adverse experience occurring in adult life	94 (9)
Does not follow prospective/longitudinal design	80 (7)
Focus on treatment interventions	192 (18)
Focus on adherence	57 (5)
Focus on diseases or conditions other than asthma	85 (8)
Focus on impact of health behaviours on asthma symptoms	48 (4)
Articles retained for further review	49 (5)
Total	1070 (100)

Table 2. Reasons for exclusion at stage 2 on the basis of full text articles

Reason for exclusion at stage 2	Total (%)
Adverse experience inadequately measured (e.g. retrospectively)	12 (24)
Does not follow a prospective/longitudinal design	9 (18)
Report on the same cohort (e.g. at an earlier follow-up stage)	6 (12)
Asthma status inadequately measured (e.g. only uses stress biomarkers)	5 (10)
Participants are not asymptomatic at baseline	7 (14)
Articles retained for systematic review	10 (20)
Total	49 (100)

Insert Figure 1 here

Study characteristics

The electronic supplement associated with this article details the key contents of the studies included for review. There was a large disparity in sample size within the studies retained for review, ranging from 145 to 13,907. The studies investigated the association of a broad range of adverse childhood experiences with asthma onset and as such employed a broad variety of measurement tools. Eleven of the 12 studies used prenatal recruitment and one study recruited asymptomatic children aged five to nine years. The results of these studies are organised into categories and considered separately below. Studies are referred to by their first author and year as in the electronic supplement for ease of reference.

Parental mental health difficulties and asthma onset

Four studies examined the relationship between mental health difficulties amongst parents and the onset of asthma symptoms in their children. Calam (2005)[16] found no significant effect of self-reported depression or anxiety (using the HAD) and the general health questionnaire (GHQ). This study employed a relatively small sample size (*n* = 411) and measurements were taken at a single time point when the child was three years of age. This study found a highly significant effect of behavioural difficulties preceding the onset of parent-reported wheeze (OR 8.95). Kozyrskyj (2007)[17] used medical records to investigate the link between maternal depression and/or anxiety diagnosis and physician diagnosis of asthma. At seven year follow-up, the authors report a mildly significant effect (OR 1.25) with subsequent analyses revealing a dose-response relationship between intensity and severity of mental health difficulties and likelihood of asthma diagnosis. Whilst this study is based on a large sample size (*n*=13,907), analysis was not adjusted for maternal health behaviours such as smoking. Both Guxens (2013)[18] and Cookson (2009)[19] investigated the impact of maternal mental health difficulties in pregnancy, employing large sample sizes (*n*=4,848 and *n*=5,810 respectively). Guxens (2013)[18] assessed maternal distress in pregnancy using the self-reported brief symptom inventory (BSI) reporting an increased risk of parent reported wheeze at six year follow-up (OR 1.6). Similarly, Cookson (2009)[19] found an increased risk of physician diagnosed asthma at seven and a half year follow-up associated with higher anxiety measured on the Crown-Crisp Experiential Index (OR 1.64). Guxens (2013)[18] proposes an intrauterine programming effect of prenatal stress exposure to explain this increased vulnerability and found no significant effect of paternal distress during the partner's pregnancy.

Parenting difficulties and asthma onset

Four studies examined the relationship between parenting difficulties and the onset of asthma symptoms in children. Three of these studies[15,20,21] relied on parental self-reporting via the perceived stress scale (PSS) and the parenting stress index (PSI). One study[22] employed a clinician-administered interview to assess parenting risk which considered a range of variables including emotional availability, behavioural regulation strategies, commitment to child care and psychiatric history. Three of the four studies used physician diagnosis of asthma at follow up as the outcome variable

whereas Wright (2001)[21] assessed asthma status via parental reporting of wheeze. Sample sizes varied between 145[20] and 2,497 [20] with follow up intervals ranging from fourteen months[21] up to eight years[22]. One study measured serum IgE levels in combination with physician diagnosis of asthma, finding a highly significant correlation[22].

Bethesda (2010)[15] found no significant association between self-reported PSI at one month after the child's birth and asthma onset in any stage of childhood, concluding that parental stress does not exert an effect on asthma onset. Shankardass (2009)[20] separated their analyses into children who are exposed to either high or low levels of traffic-related air pollution (TRAP), derived by geo-coding addresses according to traffic density and locally measured CO^2 levels. Parental stress (derived via self-reporting of perceived stress scale or PSS) was categorised into four quartiles and the authors use the lowest quartile as a reference category in their analysis. They conclude that amongst those exposed to high TRAP, only those children whose parents report high levels of stress are at increased risk of developing physician diagnosed asthma (HR 1.51). Children in the high stress, low TRAP group are not at an increased risk of asthma diagnosis leading the authors to suggest that chronic exposure to parental stress may lead to an immunological vulnerability and increased inflammatory responding in children. Wright (2001)[21] also employed the PSS as a proxy for parental stress in their investigation of a genetically predisposed community birth cohort. In adjusted analysis, they reported a significant effect size (RR 1.4), though this was amongst a considerably smaller sample than Shankardass (2009)[20]. In this study, PSS was dichotomised simply as yes/no and parent-reported wheeze was employed as the outcome variable. Klinnert (2001)[22] employed more objective measurement strategies with regards to parenting difficulties compared to other studies in this category; parenting risk (PRS) was assessed by clinician interview. Klinnert (2001)[22] reports that PRS is significantly associated with physician diagnosed asthma onset at six to eight year follow-up (OR 2.07), with associated asthma biomarkers (serum IgE) supporting the association. This study did however have the smallest sample size in this category (n=145).

Exposure to violence and asthma onset

Two studies investigated the impact of violence exposure on the development of asthma symptoms and one study investigated the combined effects of violence exposure and poor housing conditions. Clougherty (2007)[23] measured children's exposure to violence (ETV) in questionnaires completed by parents or by the child if they were over eight years old. This measure was primarily concerned with neighbourhood violence exposure and domestic violence was included as a control variable in analysis. The study also investigated exposure to traffic-related air pollution (TRAP) and susceptibility to asthma onset. The authors reported an increased likelihood of physician diagnosis of asthma at three year follow-up for children who experienced high TRAP and high ETV (OR 1.63), though experiencing high ETV alone did not significantly increase asthma risk. This investigation employed a relatively small sample size (*n*=413) and focussed on low SES neighbourhoods in one US city. Suglia (2010)[14] employed a comparatively large sample (*n*=2,013) and investigated maternal reports of inter-partner violence (IPV). Measures were taken at 12 and 36 months, with analysis revealing that chronic IPV exposure (occurring at both time points) was significantly associated with increased risk of physician diagnosed asthma at three year follow-up. Single time point IPV exposure was not significantly related to increased asthma risk. In further analysis, housing disarray (assessed by interviewer at 12 months after birth) was found to be significantly associated with physician diagnosed asthma (OR 1.5). A combination of high IPV exposure and housing disarray resulted in a multiplicative effect (OR 4.6) leading the authors to suggest that asthma risk factors multiply rather than accumulate.

Ethnic minority status and asthma onset

One study reported effect sizes for ethnic minority status as a risk factor for physician diagnosed asthma. Bethesda (2010)[15] reported a significantly increased asthma onset risk (OR 2.77) for non-Caucasians in a population birth cohort (*n*=984). This finding was bracketed by broad confidence intervals (95% CIs 1.39-5.49) and did not provide data concerning specific ethnic groups. This finding was independent of social economic status and other common asthma risk factors, suggesting that

stresses associated with ethnic minority status may contribute to increased disease susceptibility.

Discussion

Main Findings

In all, twelve studies contained in ten articles concerning the relationship between adverse childhood experience and asthma onset amongst a total of 31,524 individuals were evaluated in this systematic review. Four studies investigated parental mental health difficulties, four studies investigated parenting difficulties, two studies investigated exposure to violence, one study investigated ethnic minority status and one study investigated housing conditions. Within these studies, a wide range of measurement instruments were employed using different methodologies including self-report, medical records and interviews. Ten of the twelve studies reported statistically significant effects of early life stress on asthma onset with ORs ranging from borderline significance to exceeding double the baseline measure. Two studies produced significant effects only under certain conditions. Shankardass (2009)[20] found that a combination of high PSS and high TRAP was necessary to produce an increased risk of disease susceptibility. Similarly, Clougherty (2007)[22] found that ETV is not independently associated with asthma onset risk but that ETV is associated with a greater susceptibility to TRAP reactivity. These findings suggest that ACE may not be sufficient to increase asthma risk in the absence of environmental exposures, indicating a diathesis-stress explanation for the ACE-asthma link.

Interpretation of findings in relation to previously published work

Considered collectively, the results of this review indicate that exposure to traumatic stress in childhood significantly increases the risk of subsequent asthma onset. This contrasts with the conclusions of a review by Tibosch *et al* (2011)[11] who investigated parental psychological characteristics in relation to both asthma onset and exacerbation, finding no conclusive evidence of an elevated asthma onset risk. This contrast may be attributable to the broader range of adverse childhood events included in this review. Furthermore, evidence has emerged of an interaction or

'synergistic'[23] effect between ACE and physical environmental risk factors; when combined with environmental exposures, experiencing ACE has the potential to elevate sensitivity and pro-inflammatory responding, resulting in a significantly increased risk of developing asthma. This may be explained by the process of biological embedding of stress[4] or allostatic load theory[24] or body programming[25], a proposal that is supported by the observation that immune biomarkers are elevated in line with parental stress and that such elevated levels are strongly correlated with asthma diagnosis[22]. Studies concerned with prenatal stress exposure produced markedly similar results, warranting further investigation into the relationship between maternal distress and subsequent disease susceptibility. Such 'perinatal programming' effects are reviewed by Wright (2005)[26] who reports that maternal exposure to chronic stress can stimulate placental secretion of CRH, subsequently activating the HPA axis in the developing foetus and potentially resulting in dysregulation or decreased glucocorticoid sensitisation. This has been empirically linked with atopic disorders including asthma, eczema and food allergies[26].

Strengths and Limitations of this study

The majority of studies were conducted in the UK, USA and Canada and subsequently the extent to which results can be generalised to the global population are limited. The potential influence of publication bias cannot be discounted and it is possible that an historical tendency to publish significant results may have skewed findings. Studies of statistical association do not provide unequivocal evidence of causality. ACE is associated with a variety of societal factors, including socioeconomic status and such factors (e.g., smoking) may have a causal role in asthma. Only two studies (Guxens 2013[18] and Shankardass 2009[20]) have adjusted their results to the main well-known asthma risk factors. Finally, neither doctor diagnosed nor self-diagnosed asthma provides an entirely accurate assessment of asthma prevalence in a population.

Implications for future research, policy and practice

This review has identified two key areas of concern; firstly that exposure to chronic stress in early life is associated with increased sensitivity to environmental asthma triggers and secondly that maternal distress during pregnancy is associated with

increased risk of asthma onset. Increasing evidence supporting the role of perinatal stress programming in asthma susceptibility suggests that an improvement in holistic ante-natal support for expectant mothers would help to reduce population rates of asthma prevalence. Prioritisation of mothers with asthma or a family history of asthma/atopy would potentially have a significant effect. In addition to these principle findings, there is some evidence that exposure to multiple stressors can have a multiplicative effect on the risk of asthma onset; statistical analyses indicate that concurrent multiple stress exposure increases asthma risk to a greater extent than that expected by adding together the ORs for each separate stressor. This exponential effect warrants a focus on the identification of infants experiencing multiple stressors for health professionals working closely with families.

Conclusion

The results of this systematic review indicate that exposure to perinatal or early-life stress significantly increases the risk of asthma onset alongside elevating levels of asthma-relevant biomarkers. There is emerging evidence of a synergistic effect in which high stress combines with environmental exposures resulting in asthma onset. Exposure to multiple and chronic stressors presents a particular risk for receiving an asthma diagnosis and action should be taken from the stage of conception to identify and address dysfunctional family environments.

Acknowledgements

The authors would like to thank Julie Turner-Cobb at the University of Bath

Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article

Author Contributorship

Mr Dan Exley: Main author of manuscript and principle reviewer

Dr Alyson Norman: Support with writing and second reviewer, assistance with technical aspects of systematic reviewing

Professor Michael Hyland: Expertise in asthma research, extensive support with manuscript writing

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Appendix A: Search terms

(“asthma*”) AND (“stress*” OR “distress” OR “abuse*” OR “internali$ing” OR “threat*” OR “violen*” OR “allosta*” OR “bully*” OR “psychosocial” OR “divorce*” OR “bereave*” OR “parent*” OR “life event*” OR “distress” OR “cortisol” OR “trauma” OR “PACE” OR “PRS” OR “PSS” OR “maltreat*” OR “depress*” OR “anx*”) AND (“prospective*” OR “longitudinal*”).