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Association between childhood maltreatment and atopy in the UK: A population based retrospective cohort study

Katrina Nash,[a,b] Sonica Minhas,[c] Nicholas Metheny,[d] Krishna M. Gokhale,[c] Julie Taylor,[e,f] Caroline Bradbury-Jones,[e] Siddhartha Bandyopadhyay,[g] Krishnarajah Nirantharakumar,[c] Joht Singh Chandan,[c,h,*] and Nicola J. Adderley[c,h,**]

[a]Royal Berkshire Hospital, Reading, RG1 5AN, UK
[b]Oxford University Clinical Academic Graduate School, Oxford, OX3 9DU, UK
[c]Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, B152TT, UK
[d]University of Miami School of Nursing and Health Studies, Miami, 33146, USA
[e]School of Nursing, College of Medical and Dental Sciences, University of Birmingham, B152TT, UK
[f]Birmingham Women's and Children's Hospitals NHS Foundation Trust, Birmingham, UK
[g]The Department of Economics, University of Birmingham, B152TT, UK

Summary

Background Childhood maltreatment affects over one in three children worldwide and is associated with a substantial disease burden. This study explores the association between childhood maltreatment and the development of atopic disease.

Methods We did a population-based retrospective matched open cohort study using participating general practices between 1st January 1995 and 30th September 2019. Read codes were utilised to identify patients exposed to childhood maltreatment (either suspected or confirmed) who were matched to up to four unexposed patients by age, sex, general practice, and Townsend deprivation quintile. Cox regression analysis was used to calculate adjusted (age, sex, Townsend deprivation quintile) hazard ratios (aHR) for development of atopy (asthma, atopic dermatitis, or allergic rhino conjunctivitis) during follow up in those without atopy at study entry.

Results 183,897 exposed patients were matched to 621,699 unexposed patients. During the follow up period, 18,555 patients (incidence rate (IR) 28.18 per 1000 person-years) in the exposed group developed atopic disease compared to the 68,368 (IR 23.58 per 1000 person-years) in the unexposed group, translating to an adjusted HR of 1.14 (95% CI 1.12–1.15). Notably, the risk of developing asthma was aHR 1.42 (95% CI 1.37–1.46). Associations were more pronounced in analyses restricted to females and confirmed cases of childhood maltreatment only.

Interpretation Considering the substantial health burden associated with childhood maltreatment, it is important to implement public health policies aimed at enhancing: 1) detection and primary prevention of childhood maltreatment, 2) secondary and tertiary prevention interventions to reduce the burden of ill health associated with exposure to maltreatment and 3) clinical awareness of such associations and subsequent knowledge of management.

Funding None.

Keywords: Childhood maltreatment; Atopy; Asthma; Atopic dermatitis; Rhino-conjunctivitis

Introduction

Childhood maltreatment, defined in the United Kingdom as any form of physical, sexual, or emotional abuse and neglect, is a global public health and human rights issue affecting more than one in three children (<18 years old).[1] The downstream effects of childhood maltreatment account for a substantial global mortality and morbidity burden.[2]

In patients who experience chronic stress, such as childhood maltreatment, there appears to be a shift

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*Corresponding author.
**Corresponding author.
E-mail addresses: j.s.chandan.1@bham.ac.uk (J.S. Chandan), N.J.Adderley@bham.ac.uk (N.J. Adderley).
[h]Joint senior authors.

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Research in context

Evidence before this study

A systematic literature search was carried out on PubMed using the search terms ("child abuse" OR "child maltreatment" OR "childhood maltreatment" OR "adverse childhood experience*") AND ("atopy" OR "atopic disease" OR "atopic condition" OR "asthma" OR "eczema" OR "atopic dermatitis" OR "atopic conjunctivitis" OR "hay-fever" OR "allergic conjunctivitis" OR "allergic rhinitis" OR "IgE allergic reaction" OR "allergy" OR "allergies" OR "allergic" OR "urticaria"). Studies were included if they were published before 20th June 2022 and were in English language. Over 700 epidemiological studies which demonstrated a positive association between asthma and childhood maltreatment were identified, including a 2020 systematic review and meta-analysis assessing the relationship between adverse childhood experiences (ACEs) and chronic lung diseases which showed a positive association between asthma and ACEs. Several other cohort studies have reaffirmed this relationship since. The literature also demonstrates a positive association between ACEs and childhood atopic dermatitis. A significant number of studies have identified physiological changes in both children and adults who have experienced abuse, which may predispose these individuals to atopy. However, to our knowledge, there have been no studies published which assessed the association between allergic rhino-conjunctivitis and childhood maltreatment. Additionally, no studies assessing the association between childhood maltreatment and asthma and/or atopic dermatitis have been conducted in the UK. This is of importance as the definitions of maltreatment, cultural contexts and environmental risk factors varies substantially globally.

Added value of this study

To our knowledge, this is the first large-scale epidemiological study to assess the association between childhood maltreatment and atopy to include outcomes of asthma, atopic dermatitis and allergic rhino-conjunctivitis both in the UK and globally. Our findings indicate a higher risk of developing all atopic diseases during the study period in those with a recorded exposure to childhood maltreatment in comparison to those with no recorded exposure, with the most evident association seen in asthma diagnosis.

Implications of all the available evidence

The findings of this study impact a large proportion of the population; it is estimated that up to a quarter of children have an experience of atopy and a third of children are affected by childhood maltreatment. These findings add to a significant amount of existing literature which indicates a substantial disease burden associated with childhood maltreatment. Consequently, there is an urgent need to improve public, professional and governmental awareness of this association to implement effective public health preventative measures and clinical interventions to reduce the burden of atopic diseases associated with childhood maltreatment.

towards a proinflammatory state and alterations in white blood cell counts, resulting in a T-helper type 1 (Th1) to a T-helper type 2 (Th2) shift.[3,4] Consequently, patients exhibit a heightened Th2 driven inflammatory response which results in elevated levels of immunoglobulin E (IgE) on exposure to an environmental antigen.[5] It is this immune dysregulation which is thought to predispose patients to atopy, characterised by hypersensitisation to environmental allergens. The most common atopic diseases (asthma, atopic dermatitis (eczema) and allergic rhino-conjunctivitis) are clinical syndromes defined by their individual presentations.[6] These atopic diseases are prevalent in childhood and are estimated to affect one quarter of children.[7]

Recent literature has begun to demonstrate an association between childhood adversity and different atopic diseases. Many studies have explored the relationship specifically with asthma. The most recent meta-analysis assessing the association between adverse childhood experience (ACE) exposure and asthma indicated an odds ratio of 1.32 (95% CI 1.13–1.50)[8] with similar results identified in a 2021 Danish cohort study.[9] A recent cohort study in the United States also found a dose–response relationship between childhood maltreatment and development of atopic dermatitis.[10] However, the majority of these studies have utilised surveys, which lend themselves to recall bias and underreporting of outcomes; a study comparing use of self-reporting data and a child protection agency database for childhood maltreatment found that self-reported data collection significantly underreported the prevalence of childhood maltreatment.[11]

There have yet to be any published large-scale epidemiological studies conducted in the UK which have assessed the association between childhood maltreatment and atopic disease. Currently published cohort studies have had a small sample size and not been generalisable to the UK population. Cross-sectional studies have largely relied on self-reported data, and do not account for reverse causality. Furthermore, the majority of existing studies are limited to the association between childhood maltreatment and asthma,[9,10,12] neglecting exploration of the association between childhood maltreatment and other atopic diseases.

Knowledge of the relationship between childhood maltreatment and atopy will: enable targeted public health policies; further fuel the need for health interventions to mitigate the effects of childhood

maltreatment; and prompt screening among at risk populations. This retrospective open cohort study aims to explore the association between childhood maltreatment and atopy using a large primary care database which is generalisable to the UK population.

Methods

Study design, setting, and population

In this population-based retrospective open cohort study, data were obtained from the IQVIA Medical Research Database (IMRD) UK database. IMRD-UK, previously named 'The Health Improvement Network' (THIN), is a large UK primary care database which is nationally representative of the demographic structure and common comorbidities in the UK population.[13] The study period was defined from 1st January 1995 to the 30th September 2019. Data analysis and reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[14]

IMRD comprises data from primary care general practices using the Vision electronic medical records software system. Symptoms, examinations, and diagnoses in IMRD are recorded using a hierarchical clinical coding system called Read codes.[15] In order to ensure that included practices were accurately recording information in their electronic system and that outcomes were not under-reported, the eligibility date for general practices was defined as the latter of the following two dates: one year after the date that the practice electronic medical records system was installed, and the date the practice attained acceptable mortality recording.[16] In this study we utilised records taken from all participating GP practices, and after applying the exclusion above there were 12 966 394 remaining eligible patients. Data extraction, transformation and loading were facilitated using the 'Data extraction for epidemiological research (DExtER)' tool.[17]

Anonymised data from the data supplier was provided to the University of Birmingham. The use of IMRD is approved by the UK Research Ethics Committee (reference number: 18/LO/0441); in accordance with this approval, the study protocol must be reviewed and approved by an independent Scientific Review Committee (SRC). The protocol has been approved for this project (18THIN034) by the independent SRC. Specifically for the analysis undertaken in this manuscript, an amendment was made to allow for the exploration of atopic disorders as the previous protocol specified cardiometabolic, mental health and central sensitisation outcomes. IMRD incorporates Data from The Health Improvement Network (THIN), A Cegedim Database. Reference made to THIN is intended to be descriptive of the Data asset licensed by IQVIA. This work has used de-identified Data provided by patients as a part of their routine primary care. As the data is de-identified there is no opportunity/ability for the research team to seek independent written consent from those who contribute to the dataset.

Exposure and outcome definitions

The aim of this study was to explore the risk of developing atopy (composite measure: asthma, atopic dermatitis and allergic rhino-conjunctivitis) in patients with a GP-recorded exposure to childhood maltreatment or maltreatment related concerns in comparison to those with no such exposure recorded.

Codes (appendix p2) relating to childhood maltreatment, maltreatment-related concerns and atopy were selected with the assistance of general health practitioners, public health clinicians, immunologists and supported by the wider literature. Read code selection methodology of both code lists have been described in previously published literature.[18,19] Confirmed childhood maltreatment codes included exposure to physical, sexual, or emotional abuse, neglect or domestic abuse within the household. Read codes for concerns where the child was deemed to be at risk, had social services involvement or was suspected of possible abuse and neglect, were included to identify suspected cases of childhood maltreatment to reduce under-reporting of childhood maltreatment. These Read codes have been adapted from previous research which investigated childhood maltreatment using THIN and were informed by experienced general practitioners.[20]

For each exposed patient (with a documented exposure to childhood maltreatment or maltreatment related concerns), a maximum of four unexposed controls with no documented Read code relating to an exposure were randomly selected from the remaining pool of eligible patients within the datasets. Unexposed patients were individually matched by general practice, age (with variation of up to one year allowed), sex and Townsend deprivation quintile.[21] The Townsend deprivation index is a socio-economic measure of deprivation derived from census data, capturing variables related to employment, home ownership and household crowding.[22,23]

Follow-up period

The index date for those in the exposed group was the date of the first Read code relating to exposure or when they became eligible to enter the study for those with a previous history of exposure (prevalent cases). Therefore, prevalent cases could be adults at cohort entry (index date). However, their episode of maltreatment must have been recorded prior to their 18th birthday. In order to prevent immortal time bias,[24] matched unexposed patients were assigned the same index date as their corresponding exposed patients. The exit date for all patients was defined as the earliest of the following events: patient died, patient left the practice, last data collection from practice, study end date, or if the patient

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was diagnosed with an outcome of interest (atopic disease).

Covariates of age at index date (continuous), sex (male and female), and Townsend deprivation index (quintiles)[21] were used as both model covariates and matching parameters. This technique aimed to reduce any residual confounding after matching. Selection of these variables has taken into account underlying biological mechanisms and published literature documenting risk factors for atopy.[25,26]

In the case of Townsend deprivation index, missing data was treated as a separate missing category and this category included in the final analysis. This approach was deemed to be more suitable than other approaches, such as complete case analysis or multiple imputation methods, due to the large amount of missing data. Use of complete case analysis in this database has been found to reduce the sample size and hence power of studies.[27] Additionally, data may not in all cases be missing at random which is required for multiple imputation methods,[28] as missingness of data in IMRD has been associated with sex, age, deprivation, and presence of chronic disease.[25] It may also be the case the postcode variable indicator is missing for people that frequently move home, have unstable families, or are travellers. However, as a sensitivity analysis for the primary analysis, we have imputed missing Townsend data by performing multiple imputation using chained equations with predictive mean matching. As approximately 20% of the data was missing for this category, we performed 20 imputations.

Smoking status (current smoker, non-current smoker, not available), body mass index (BMI) (underweight <18.5 kg/m^2, normal 18.5–24.9 kg/m^2, overweight 25.0–29.9 kg/m^2, obese >30.0 kg/m^2) and ethnicity (White, Black, South Asian, Mixed, Other)[29] were reported in study entry characteristics but were not included in regression modelling due to substantial missing data. It has previously been noted that recording of ethnicity is poor in primary care databases.[30] Additionally, adjustment for smoking status and BMI was explored, but it was concluded that this approach was not appropriate as these measures are not applicable to young children and missingness of data was found to be highly correlated with age. Although it was detailed in the protocol that an unavailable smoking status would be combined with 'non-smoker' as validated in previous literature,[31] this was not deemed appropriate for the same reason.

Statistical analysis
STATA version 17 was used to conduct all analyses. Normally distributed continuous data has been described using means and standard deviation whereas non-normal data has been presented as median and interquartile range. Categorical data has been presented using proportions. Missing data was treated as a separate missing category, and this category included in the final analysis in line with previously published work.[18]

Crude incidence rates (IR) were calculated within each cohort by dividing the number of outcomes by number of person years. Cox regression analysis was then used to calculate hazard ratios (HR) to compare the hazard of atopy between the exposed and unexposed groups. HR were also adjusted for age at index date, sex, and Townsend deprivation quintile. ORs and HRs are presented with 95% confidence intervals (CI) and statistical significance determined at p < 0.05.

A subgroup analysis with the main cohort disaggregated by sex was undertaken to assess whether findings differed between males and females. Additionally, a sensitivity analysis was undertaken to assess whether results differed between confirmed and suspected maltreatment codes, as a proxy for severity of maltreatment. A second sensitivity analysis using only incident cases (exposure to maltreatment occurred during the study period) and corresponding matched controls was also carried out. In addition, due to the violation of the proportional hazards assumption across certain years as seen in the appendices (appendix p6), we have also reported the results stratified by six yearly calendar periods. To allow for a fair exposure window we set the exit date as the final date (31st December of the last year of the four-year time period) of the patient's category group. Lastly, a sensitivity analysis using Poisson was undertaken as there was evidence of violation of proportional hazards assumption.

Role of the funding source
There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
In the study period, 12 966 394 patients were eligible to enter the study. Of these, 424,517 were identified as having any recorded exposure to childhood maltreatment and were matched to 1 489 991 unexposed patients, in total leading to 1 893 398 in our extracted dataset. 240,620 patients were excluded due to childhood maltreatment being recorded after their 18th birthday when they are no longer defined as a child. Their associated matched unexposed patients were also excluded at this point. This left 183 897 exposed patients who were included in the final cohort, matched to 621 699 unexposed control patients (patient selection flow chart can be seen in Fig. 1). In the primary analysis which included adults, 635,706/805,596 (79%) patients were children (defined as less than 18 years of age) at the index date.
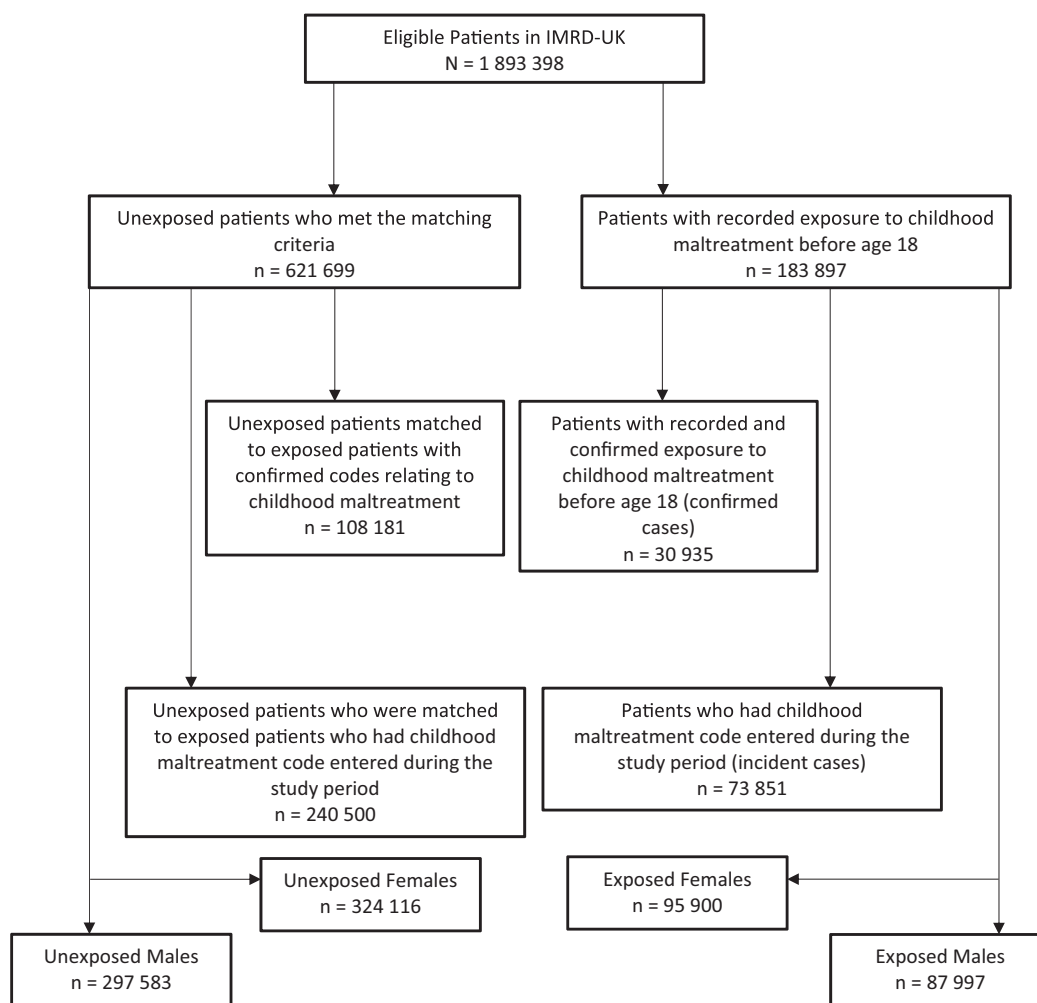
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┌─────────────────────────────────┐
│   Eligible Patients in IMRD-UK   │
│          N = 1 893 398           │
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Fig. 1: Flow chart of patient inclusion and exclusion for analyses.

Patients in the exposed cohort were followed up for 2.23 years (IQR 0.88–5.09) in comparison to 3.49 years (IQR 1.51–6.84) in the unexposed cohort. As the groups were matched, the mean age at cohort entry and sex distribution were similar between the groups. Exposure to childhood maltreatment in the exposed group occurred at a mean age of 6.05 years (SD 5.24). Where data were recorded, the average BMI appeared similar between the two groups, though patients in the exposed group were more likely to be a current smoker (20,696 [11.25%] vs 38,276 [6.16%]). Further details outlining the study entry characteristics are described in Table 1.

During the study period, 18,555 patients (incidence rate (IR) 28.18 per 1000 person-years) in the exposed group developed atopic disease compared to the 68,368 (IR 23.58 per 1000 person-years) in the unexposed group. Following adjustment for covariates, this translated into an increased aHR of 1.14 (95% CI 1.12–1.15); asthma (aHR 1.42, 95% CI 1.37–1.46); atopic eczema

(aHR 1.09, 95% CI 1.07–1.12); allergic rhino-conjunctivitis (aHR 1.07, 95% CI 1.04–1.11). Further details can be found in Table 2 and Fig. 2.

When examining the findings disaggregated by sex (appendix p7-9), we noted females were older than males at both cohort entry (mean 11.88 [10.23] vs 10.41 [SD 9.67]) and the age at which childhood maltreatment occurred (6.46 [5.43] vs 5.60 [4.99]). At study entry, both males and females had a higher likelihood of having an asthma diagnosis and lower likelihood of having a diagnosis of allergic rhino-conjunctivitis or atopic dermatitis in the exposed group compared to the unexposed group. During the study period, although both had an increased risk of developing atopic disease, males (aHR 1.08, 95% CI 1.05–1.10) had a slightly lower risk than females (aHR 1.19, 95% CI 1.16–1.22). This was reflected for all sub-types of atopic disease.

In the first sensitivity analysis, 30,935 patients in the exposed group had confirmed codes relating to

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	Exposed	Unexposed
Number of patients	183,897	621,699
Median (IQR) follow-up period (person years)	2.23 (0.88–5.09)	3.49 (1.51–6.84)
Mean (SD) age at cohort entry (years)	11.18 (9.99)	11.05 (9.95)
Mean (SD) age at which maltreatment occurred (years)	6.05 (5.24)	n/a
Sex, n (%)		
Male	87,997 (47.85)	297,583 (47.87)
Female	95,900 (52.15)	324,116 (52.13)
Body mass index, n (%)		
Underweight (<18.5 kg/m^2)	2554 (1.39)	6693 (1.08)
Normal (18.5–24.9 kg/m^2)	13,016 (7.08)	47,900 (7.70)
Overweight (25.0–29.9 kg/m^2)	4927 (2.68)	20,066 (3.23)
Obese (>30.0 kg/m^2)	3582 (1.95)	13,151 (2.12)
Not available	159,818 (86.91)	533,889 (85.88)
Smoking status, n (%)		
Current smoker	20,696 (11.25)	38,276 (6.16)
Non-current smoker	23,215 (12.62)	115,226 (18.53)
Not available	139,897 (76.12)	468,197 (75.31)
Townsend index, n (%)		
(Least deprived) 1	15,166 (8.25)	52,690 (8.48)
2	18,136 (9.86)	61,031 (9.82)
3	29,966 (16.29)	99,781 (16.05)
4	41,195 (22.40)	134,878 (21.70)
5	42,506 (23.11)	134,407 (21.70)
Not available	36,928 (20.08)	138,407 (22.26)
Ethnicity, n (%)		
White	90,286 (49.10)	251,624 (40.47)
Black	4247 (2.31)	15,158 (2.44)
South Asian	2716 (1.48)	17,603 (2.83)
Mixed	3502 (1.90)	7548 (1.21)
Other	2046 (1.11)	12,142 (1.95)
Missing	81,100 (44.10)	317,624 (51.09)

Abbreviations: IQR, interquartile range; SD, standard deviation.

Table 1: **Study entry characteristics of those exposed and unexposed to childhood maltreatment.**

childhood maltreatment who were matched to 108,181 unexposed patients. The age at entry to the cohort was higher (mean age 17.58 [SD 12.76]) than in the main cohort. The findings remained in line with the primary analysis, with exposed patients having a higher risk of atopic disease (aHR 1.31, 95% CI 1.26–1.37). Further details can be found on appendix p12-13. In the second sensitivity analysis, 73,851 exposed patients had a childhood maltreatment code recorded during the study period, forming the cohort of incident cases who were matched to 240,500 unexposed patients (appendix p10-11). In this cohort, there was a younger mean age (5.92 years, SD 5.22) at study entry. In this subgroup analysis, the direction of the effect sizes remained similar to the main analysis, with an aHR of 1.04 (95% CI 1.01–1.06). In the third sensitivity analysis, use of Poisson regression (appendix p14) showed similar findings to use of Cox proportional hazards analysis despite evidence of proportional hazards violation. However, the effect size although remained positive throughout did reduce over time (appendix p15). Lastly, the multiple imputation approach to deal with missing Townsend data remained robust with the missing category approach we initially undertook (Table 2).

Discussion

To our knowledge, this is the first large-scale epidemiological study evaluating the relationship between childhood maltreatment and the development of atopy in a UK retrospective cohort derived from medical records. Our study found that exposure to childhood maltreatment was associated with an increased risk of developing atopic disease with the risk of being diagnosed with asthma almost doubling in patients with childhood maltreatment exposure. When disaggregated by sex, we also found a greater incidence rate of atopic disease in female patients exposed to childhood maltreatment in comparison to males.

	All atopic disease		Asthma		Atopic dermatitis		Allergic rhino-conjunctivitis	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Number of outcomes	18,555	68,368	4808	14,511	10,766	40,680	5338	21,532
Person years (years)	658,349	2 899 857	718,230	3178210	694,214	3048713	715,609	3138255
Incidence rate (per 1000 person years)	28.18	23.58	6.69	4.57	15.51	13.34	7.46	6.86
Hazard ratio (95% confidence intervals)[a]	1.13 (1.11–1.15)		1.41 (1.37–1.46)		1.08 (1.06–1.10)		1.07 (1.04–1.10)	
p-value	<0.001		<0.001		<0.001		<0.001	
Adjusted hazard ratio (95% confidence intervals)[b]	1.14 (1.12–1.15)		1.42 (1.37–1.46)		1.09 (1.07–1.12)		1.07 (1.04–1.11)	
p-value	<0.001		<0.001		<0.001		<0.001	
Adjusted hazard ratio (95% confidence intervals)[c]	1.13 (1.11–1.15)		1.41 (1.37–1.46)		1.08 (1.06–1.10)		1.07 (1.04–1.10)	
p-value	<0.001		<0.001		<0.001		<0.001	

[a]Unadjusted hazard ratio.[b]Adjusted hazard ratio (Townsend missing data dealt with using a missing category approach): adjusted for age, sex and Townsend deprivation quintile at study entry.[c]Adjusted hazard ratio (Townsend missing data dealt with using a multiple imputation approach): adjusted for age, sex and Townsend deprivation quintile at study entry.

Table 2: **The risk of developing atopic disease in those exposed and unexposed to childhood maltreatment.**

Our findings correlate with existing studies which show a positive association between atopy and childhood maltreatment. The majority of studies have evaluated the relationship between childhood maltreatment and asthma, with the most recent meta-analysis finding a similar pooled odds ratio of 1.32 (95% CI 1.13–1.50).[8] However, this is not directly comparable as our study has been conducted in a UK setting and we have used a different method to define the exposure. McKenzie et al. also found a positive association between childhood maltreatment and atopic dermatitis.[10] Although point estimates in this previously published study were slightly higher than in our main analyses, these estimates are not directly comparable as this study calculated odds ratios, rather than hazard ratios. Nonetheless, the results showed a stronger association with increasing severity of childhood maltreatment, which supports our subgroup analyses of a stronger association seen in officially confirmed cases (which are likely to be more severe than suspected cases). Furthermore, evidence indicates that childhood maltreatment may lead to more detrimental health consequences in females than males, which was also seen in our subgroup analyses by sex.[32]

Our analyses showed a more apparent positive relationship between asthma than other atopic diagnoses. It has previously been described that presenting behaviour may differ in those exposed to childhood maltreatment, particularly in children who are neglected.[33] On the other hand, there may be a proportion of cases which are misdiagnosed, as evidence indicates that atopic dermatitis is frequently misdiagnosed as the physical manifestations of childhood maltreatment.[34] These factors may explain the lower risk of atopic dermatitis and allergic rhino-conjunctivitis seen in our analyses. Conversely, it could be the case that a different underlying mechanism may be at play. Although all diseases we have explored are atopic in nature, the lungs are unique in their relationship with the nervous system. Exposure to stress, such as childhood maltreatment, activates the sympathetic nervous system and suppresses the parasympathetic nervous system, resulting in alterations in vagal tone which regulates bronchial contractility.[35] Miller et al. previously demonstrated that emotional responsivity and increased vagal reactivity were associated with increased airway reactivity and decreased pulmonary function in children with asthma.[36] Emin et al. also demonstrated a dose response relationship between autonomic nervous system dysfunction and asthma severity.[37] Thus, increased vagal reactivity may be a significant contributing factor explaining the increased risk of asthma development in children who experience maltreatment. Additionally, exposure to environmental factors such as tobacco smoking, indoor air pollution, and common allergens like household mould, is strongly associated in the literature with an asthma diagnosis and outcomes in children.[38,39] Child neglect is a common form of child maltreatment, defined as failure to meet the physical and/or psychological needs of a child.[40] A common marker of child neglect is failure to provide adequate shelter and a safe home environment.[40,41] Poor housing conditions are often synonymous with levels of indoor household allergens, mould and dust,[42] known contributors to asthma. Therefore, it is possible that children exposed to child neglect as opposed to other forms of child maltreatment are at greater risk of developing atopy. Additionally, these living conditions can lead to chronic exposure of neglect further enhancing the young person's risk of developing atopy. However, limitations exist in clinical coding as it is difficult to specify the type and chronicity of child maltreatment which the child experienced, meaning in our study it was not possible to explore the relationships between different types of abuse and the development of atopic disease.
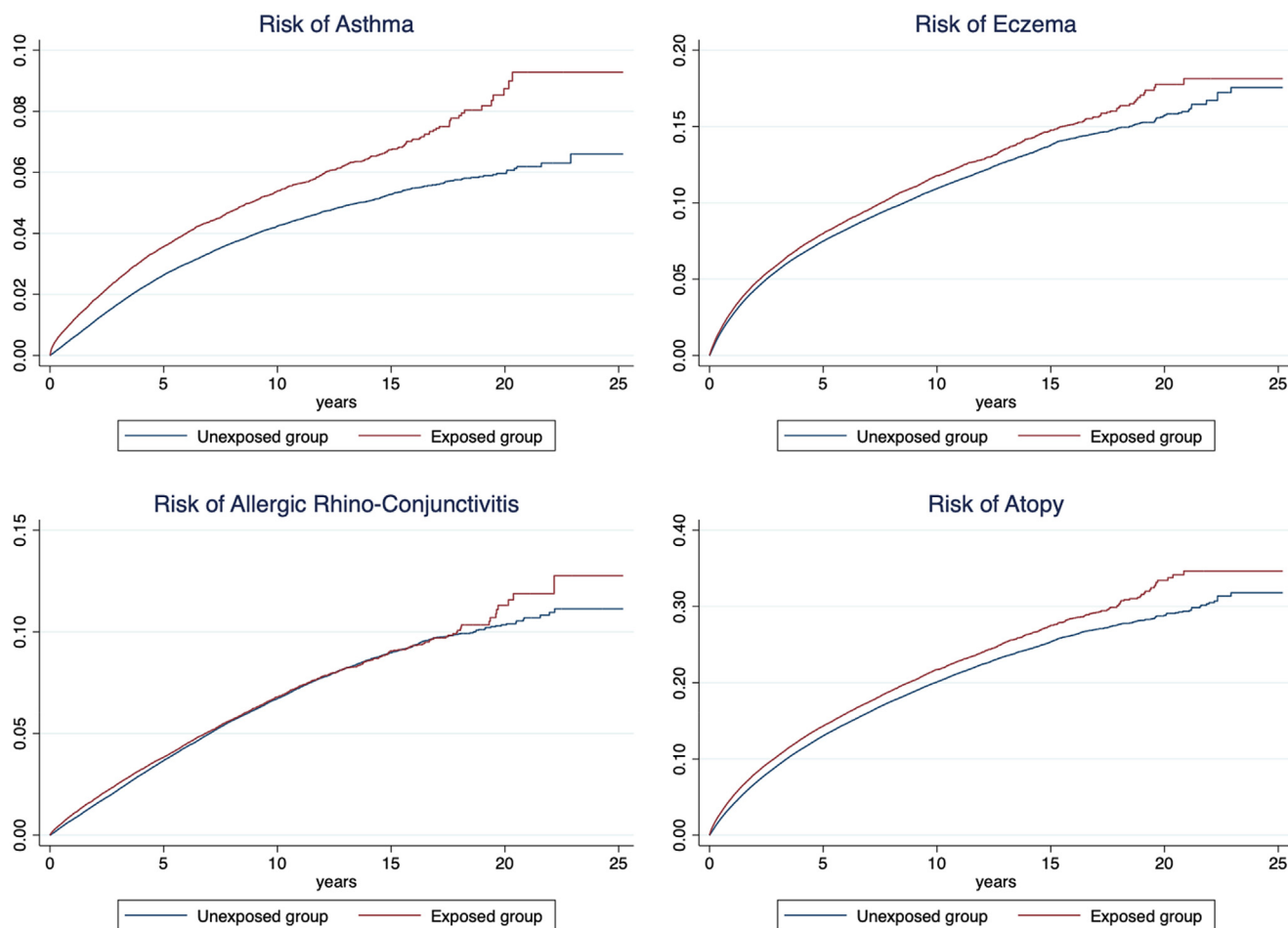
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Fig. 2: Kaplan–Meier curves describing the risk of developing atopic disease in those exposed and unexposed to childhood maltreatment.

These findings are of importance for informing global policy and practice. The issue posed here affects a large proportion of the population; atopy is estimated to affect one quarter of children[7] and childhood maltreatment is estimated to affect over a third of children.[1] Thus, our findings indicate that there may be a considerable burden of atopic disease associated with childhood maltreatment, which may be preventable or currently not detected. In order to address this issue, it is vital to improve our public health approach to both prevent and detect childhood maltreatment in the first instance, and to prevent development of atopic disease in those who have been exposed to childhood maltreatment. Evidence indicates that measures such as improving social support, building resilience in children and implementation of a trauma-informed healthcare approach may prevent the negative downstream consequences of childhood maltreatment.[43,44] Although this study demonstrates a clear association between childhood maltreatment and atopy, further research is required to validate these findings using other datasets

and outside of high-income settings, explore factors and biological mechanisms which mediate this relationship, and evaluate interventions intended to reduce the burden of atopy and childhood maltreatment.

Although the reported prevalence of childhood maltreatment is thought to be 1 in 3 children,[1] recording has been demonstrated in GP practices to be substantially lower, as reported by a UK-based epidemiological study using this database.[20] In recent years, new coding strategies have been explored and successfully introduced across general practices, which reduces the likelihood of under-reporting. Under-estimation of the exposed population creates a misclassification bias which may have resulted in an underestimation of the effect size. Conversely, it is highly likely that GPs will diagnose and suspect a higher proportion of the severe cases of childhood maltreatment in comparison to mild cases. Our subgroup analyses also indicated a stronger association in confirmed cases in comparison to the main cohort, indicating a potential dose response relationship between severity of abuse and atopic disease.

Therefore, our estimate may not be representative of the association between atopy and less severe cases of childhood maltreatment. Equally, GPs may have not utilised Read codes consistently or completely to record the outcomes of interest. However, as some atopic diseases feature in the Quality and Outcomes Framework,[45] it is anticipated recording of these conditions is likely to be of high quality. Additionally, although median follow up time period was relatively short, atopic conditions tend to present in childhood.[6]

This study is unable to indicate causative mechanisms as data for multiple factors, such as genetic phenotypic, is unavailable. Due to substantial amounts of missing data, our analyses were unable to adjust for BMI, ethnicity, and smoking. Furthermore, potential confounders which are not well recorded in IMRD cannot be included in analysis, such as family history of atopy, parental psychiatric history, education status, parental marital status, breastfeeding, maternal smoking during pregnancy, air pollution, and early life sensitization to aeroallergens.[26] Additionally, the age at which exposed patients experienced childhood maltreatment cannot be accounted for due to heterogeneity in GP reporting. A younger age at exposure may have a greater impact on immune dysregulation, as the critical window for sensitisation is thought to be between zero and eight years old.[4] Our analysis is also unable to account for undiagnosed or unsuspected cases of childhood maltreatment.

In conclusion, our study has shown patients who have experienced childhood maltreatment have a higher risk of developing atopic diseases, with the strongest association seen between exposure and subsequent development of asthma, especially in females. Implementation of public health measures, guidance for health professionals and clinical interventions are vital to mitigate the effects of childhood maltreatment and thus contribute to the prevention of atopic diseases.

Contributors
Conceptualisation (NA, JSC), data curation and verification of underlying data (KMG, KN), data analysis and access to data (KN, SM, NA, JSC), methodology (NA, JSC, KN), writing - original draft (KN, SM), writing - review & editing (all authors; KN, SM, NM, KMG, JT, CB-J, SB, KN, JSC, NA). All authors approved the final version.

Data sharing statement
Upon publication, the analysis code will be available upon request from the corresponding author (JSC). In order to obtain access to the raw data which were used for all the analyses, approval must be sought from the data provider (IQVIA) and independent SRC who approved the ethics for this project who will be able to share the IMRD dataset. It is likely that this process will incur a cost bespoke to the Institution requesting the data. This can be done with support of the corresponding author (JSC).

Declaration of interests
All authors declare no competing interests.

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