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Changes in the relationship between asthma and associated risk factors over fifty years

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RUNNING TITLE: Risk factors for asthma over fifty years

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Supplementary table 1. A summary and explanation of variables included in the models A, B and C of the analysis.

Supplementary table 2. Odds ratios [95% confidence interval] for a child having wheeze in last 3 years, over given time periods, following adjustment for changing prevalences of asthma and covariates.

Supplementary figure 1. A line chart showing the population attributable risk for life time asthma in the context of eczema, parental asthma and parental smoking.

ABSTRACT PAGE

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Abstract

Background: Childhood asthma is a common condition whose prevalence is changing. We hypothesised that the relationship between asthma and associated risk factors has changed over a 50-year period.

Methods: An ecological study design was used. Children aged 8–13 attending schools in Aberdeen city were surveyed on seven occasions between 1964 and 2014. The following were determined: history of asthma, history of eczema, parental smoking, parental asthma, sex and socioeconomic status. Analysis was by a structural change model with two knots. The outcome reported was the change in odds ratio between asthma and a given risk factor during a given period.

Results: There were 23,241 questionnaires distributed and 17,439 returned (75%). The odds ratio (OR) for a child with asthma to have eczema increased between 1989 and 1999 by 1.031 [95% CI 1.028, 1.035] and by 1.042 between 2004 and 2014 [1.038, 1.047].The OR for a child with asthma to have a parent who smoked rose by 1.032 [1.028, 1.036] between 1989 and 1999 and by 1.043 [1.038, 1.047] between 2004 and2014), and to have a parent with asthma (1.027 [1.022, 1.031] for 1994-99 and 1.042 [1.037, 1.048] for 2004-2014). The OR for a child with asthma being male and being from the most deprived communities also rose between 1989-1999 and 2004-2014.

Conclusions: The relationship between asthma prevalence and particular risk factors changed over the 50 year period of study and this might reflect changes in children's environment and/or susceptibility.

Key words: Asthma; Atopy; Child Health; Environmental epidemiology; Smoking

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Introduction

Asthma is the most prevalent chronic childhood medical condition globally[1] and places a significant burden on family life, society and healthcare systems.[2] Childhood asthma prevalence rose markedly in many countries during the second half of the twentieth century[3] and falling prevalence has been observed in some countries during the first decade of the twenty-first century.[4-6] However, asthma prevalence differs geographically[7] and it continues to rise in more locations globally than it falls.[8]

Asthma is a complex condition, which has been associated with a range of risk factors in cross-sectional and longitudinal studies.[9] The mechanisms for the rise, and possible fall, in childhood asthma prevalence within populations remain uncertain, and argues against paradigms such as the hygiene hypothesis.[10] Shifts in environmental exposures and

susceptibility are plausible explanations. Asthma prevalence is highest in Western countries and a change to a "Westernised" lifestyle has been associated with increased risk for wheeze in young children[11] and but not asthma in school-aged children[12] suggesting that early exposure is important. The underlying mechanisms that alter an individual's susceptibility to asthma in the context of their environment are unknown, but epigenetic factors might partly explain how, for example, second-hand smoke (SHS) exposure is associated with increased risk for childhood asthma.[9,13]

In order to gain insight into changing susceptibility to asthma, we adopted a novel approach of analysing relationships between asthma and associated risk factors in repeated cross-sectional surveys of a defined population of school children over a 50 year period. Ecological analysis of repeated cross-sectional surveys of such a defined population over a long timespan are useful to provide insight into population-level changes in associations between asthma and known risk factors. The Aberdeen Schools Asthma Survey (ASAS) first took place in 1964 and has subsequently been repeated on six occasions making this among the longest-running surveys of its kind worldwide.[6,14-19] We hypothesised that the relationship between asthma and associated risk factors has changed over a 50-year period. The outcome reported was the change in odds ratio between asthma and an associated risk factor during a given period. The risk factors considered were male sex, socioeconomic status, family history of asthma and parental smoking.

Methods

Study design

Parents of children in Scottish primary school years 5–7 (aged 8-13 years) attending schools within the 1964 Aberdeen city boundaries were invited to participate in May 1964,[14] 1989[15] and subsequently at 5 year intervals to 2014.[6,16-19] Questionnaires were distributed by school staff to parents via their children and returned to the school. Ethics and governance approval was obtained in each study year in accordance with the requirements at the time.

Measures

Each survey included the following questions: 'Has your child wheezed or had a whistle in the chest in the past three years?', 'Has your child ever had asthma?' and 'Has your child ever had eczema?'. The following question was included from 1989 onwards 'Does anyone living in the same house as your child smoke?' and the following from 1994 onwards 'Has either parent ever had asthma?' A quintile measure of socioeconomic status (SES) was derived for each child from the most appropriate measure available in the database for that study year. The Scottish Index of Multiple Deprivation (SIMD)[20] was used for the 2004–2014 surveys, the Carstairs index[21] was used for the 1989–1999 surveys and the 1964 ASAS investigators used an in-house 100-point ordinal scale based on father's occupation. On this deprivation scale, the most deprived quintile was coded 1 and the least deprived quintile was coded 5.

Data analysis

Statistical analysis was conducted using SPSS version 22 (IBM, Armonk, NY) and SAS version 9 (SAS Institute, Cary, NC) software.

Multiple imputation of missing values

As in previous ASAS studies ,[6,18.19] imputation was conducted for responses from the 2004, 2009 and 2014 surveys in cases where parents answered the wheeze question but did not answer one or both of the asthma or eczema questions (typically 10% of responses). Fifty random sample multiple imputation was used. No missing data imputation of other variables was conducted and listwise deletion of remaining missing values was used.

Ecological analysis

First the odds ratios for each risk factor for each survey were calculated using logistic regression. An additional set of identical models with wheeze in the last 3 years rather than asthma as the outcome measure was also created. A lifetime history of asthma (the outcome) was investigated using a 2 knot structural change model with a knot after 1964 and after 1999. These time-points were chosen to coincide with the relatively low lifetime asthma prevalence in 1964, rising prevalence 1989 and 1999 and static/falling prevalence from 2004 onwards.

Four main models were constructed: The first was an investigation of the associations of child asthma with child eczema, parental smoking and asthma adjusted for age, sex and deprivation, without accounting for time. This model assessed the relative contribution of these risk factors to asthma prevalence across the dataset irrespective of time. Three models were then developed to reflect the differing relationships of the risk factors and asthma over time (Supplementary table 1). Model A assessed the change in relationship between asthma and eczema, sex and socioeconomic status across the three time periods controlling for the potential confounders age, gender and SES. Model B incorporated all variables from Model A plus parental smoking, and was limited to data from 1989 to 2014. Model C incorporated all variables in model B plus parental asthma and included data from 1994 to 2014. The outcome reported was the change in odds ratio between asthma and an associated risk factor during a given period.

Population attributable risk

Population attributable risk (PAR) for asthma was determined using this equation:

$PAR = P_e (RR_e-1) \; / \; [1 + P_e (RR_e-1)]$, where P_e is the prevalence of the exposure (i.e. eczema, parental asthma, parental smoking, male gender and being in the poorest socioeconomic quintile relative to the most affluent quintile) and RR_e is the relative risk of asthma due to that exposure.

Results

Study participants

There were 23,241 children invited to participate and data were available for 17,439 (75%) of whom 15,858 were aged 8-13 years including 15,108 with complete data. Fig 1 presents the number of children included in the analyses. Demographic characteristics of the sample recruited in each study year are provided in Table 1. Across the seven study populations, there were statistically significant but minor differences in age and socioeconomic status but not sex. There were 15,108 children included in model A, 12,901 in model B and 9,480 in model C.

Trends in prevalence of asthma and associated risk factors for the whole population

Asthma prevalence rose from 1964 (4%) until 2004 (28%) and then fell in 2009 (22%) and again in 2014 (19%) (Fig 2).[6] Eczema prevalence initially followed that of asthma rising from 3% in 1964 to 33% in 2004, whereafter these prevalences diverged and eczema prevalence remained static.[6] Parental asthma prevalence rose in a near-linear fashion from 1994 (21%) to 2014 (34%) and parental smoking prevalence fell in a near-linear fashion from 1989 (58%) to 2014 (28%). When time was not considered, childhood asthma was positively associated with male sex, increased deprivation, eczema, parental smoking and parental asthma (Table 2). Table 3 provides odds rations for each risk factor for each survey.

Change in odds ratios of asthma with respect to risk factors over time

Independent of changes in the prevalence of asthma and associated risk factors, the odds ratio (OR) of a child with asthma also having eczema increased by 1.031 [95% CI 1.028, 1.035] between 1989 and 1999. Between 2004 and 2014, this OR increased by 1.042 [1.038, 1.047] (Table 4, model A). Similarly, the OR for a child having asthma having a parent who smoked increased between 1989 and 1999 by 1.032 [1.028, 1.036], $p<0.05$ as well as by 1.043 between 2004 and 2014 [1.038, 1.048], $p<0.001$ (Table 4, model B). The OR for a child with asthma having a parent with asthma rose by 1.027 between 1994 and 1999 [1.022, 1.031] $p<0.0001$) as well as by 1.042 between 2004 and 2014 [1.037, 1.048], $p<0.001$ (Table 4, model C). The OR for a child with asthma being male and from more deprived communities changed both between 1989 and 1999 and 2004-2014 (Table 4, models A and B), although ORs did not reach statistical significance for every deprivation quintile (Table 4).

Change in odds ratios of wheeze in the past three years with respect to risk factors over time

The OR for a child with recent wheeze increased by 1.03 between 1989-1999 and also between 2004-2014, supplementary table 2. The OR for a child with recent wheeze being male or having a parent who smoked rose by a factor of 1.01 between 1989-1999 and again for 2004-2014, supplementary table 2. Finally, the OR for a child with recent wheeze having a parent with asthma rose by 1.02 between 1989-1999 and by 1.01 between 2004-2014.

Population attributable risk

The PAR for parental asthma, smoking and poverty remained mostly unchanged during the period studied (See supplementary fig 1). There was a two-fold increase in the PAR for eczema between 1999 and 2004, a fall in PAR for male sex to zero in 2004 which had reversed by 2014 (Supplementary fig 1).

Discussion

We provide novel insight into the changing patterns of risk factors for asthma over a 50-year period. Although the magnitude of changes in odds ratio between asthma and individual risk factors was not particularly large, large changes would be unexpected and likely to have been previously identified. Instead, a summative effect of several smaller changes may partly explain the change in asthma prevalence seen in our population. The association between asthma and risk factors is often different between populations.[9] Repeat surveys of the same defined population over a long period of time may offer insight into within-population temporal changes in risk factors, which may reflect changes in environmental exposures and/or susceptibility to these exposures.

Our findings provide insight into the apparently inconsistent associations between asthma and associated risk factors when whole-population data are considered. The first apparent inconsistency is the relationship between asthma and eczema, where there is a well-established association which is thought to reflect a common underlying allergic immune phenotype, but where we and another group have seen population-level dissociation between prevalences of asthma and eczema over time.[5,6] Our results suggest that the association between asthma and eczema is becoming stronger at the individual level, and implies that the fall in asthma seen in our population may be explained by a greater fall in asthma not associated with eczema (i.e. non-atopic asthma) relative to atopic asthma. The proportion of asthma in ASAS attributable to atopy (as evidenced by eczema) between 1964 and 1999 is consistent with the figure of 34% reported in 1999 by Pearce *et al*,[22] while the NHANES III survey[23] (1988-1994) reported a PAR of 55% for 6-19 year olds which is consistent with the results in the present study from 2004 onwards. The relationship between asthma and atopy is complex and our data suggest that this relationship evolves over time. The second apparent inconsistency is that exposure to parental smoking is a recognised risk factor for asthma,[9] but the prevalence of parental smoking in our population (and elsewhere) fell whilst asthma prevalence was rising between 1964 and 1989. Although the 2006 smoking ban in Scotland was associated with a reduction in exacerbations of existing asthma,[24] we see no change in the population risk for asthma attributable to parental smoking, suggesting that increased individual susceptibility is offsetting the benefit from reduced exposure for the whole population. Protecting children from second hand smoke exposure is becoming more important as parental smoking becomes less prevalent.

We have previously reported a gender convergence in asthma prevalence in 2004[25] and here proportion of asthma attributable to male sex between 1964 and 2004 fell to zero, but then rose to 2014. Since the gender ratio has remained static over time, the change in asthma risk attributable to sex is most likely explained by changing diagnostic trends, i.e. since 2004 boys are increasingly more likely to be diagnosed. Additionally, a small increase in susceptibility to asthma in boys (present since 1989) may have added to the increased population risk attributable to male sex since 2004. The 1993 British Thoracic Society Guideline (BTSG)[26] made childhood asthma a diagnosis of exclusion and asthma prevalence rose during this time. The 2008 BTS/SIGN asthma guideline[27] recognised the "greyness" of diagnosing childhood asthma and provided clinicians with hints for actively diagnosing childhood asthma and fall in childhood asthma prevalence seen in our 2009 might be partly explained by the move from "diagnosis of exclusion" to "diagnosis by criteria" subsequent to the 2008 guideline. An alternative (and not exclusive) explanation for the changing relationship between asthma and risk factors may be changes in the characteristics of asthma itself.

Hereditary factors are thought to contribute towards approximately 50% of asthma susceptibility[28] and between 1989 and 1999 we observed an increase in parental and child asthma prevalence as well as an increased association between them. Between 2004 and 2014, there was a divergence in child and parental asthma prevalence and the relationship between them remained static. One explanation for this divergence is that alterations in the intrinsic susceptibility of, children during the preschool years may have occurred over this period of time, and changes in early environmental encounters (e.g. diet, second hand smoke) may yield a lower burden of asthma in children relative to their parents.

Our analysis separately considered asthma and recent wheeze as outcomes since although asthma is characterised by wheeze, some children with wheeze may not reach an asthma diagnosis. However the results from the analysis of asthma and recent wheeze were mostly consistent. In the model which included all variables (model C), the change in odds ratio for a child with asthma or wheeze also being male and having parents who smoked were very similar. Although the change in odds ratio for a child with asthma also having parental asthma or eczema were similar between 1989 and 1999 for wheeze, the odds ratio for

wheeze but not asthma being associated with eczema continued to rise between 2004 and 2014 whilst the odds ratio for a child with asthma having a parent with asthma rose by 4% between 2004 and 2014 compared to 1% for wheeze. These subtle differences for asthma and wheeze may reflect trends in reporting of symptoms.

A study of this length faces some inevitable limitations. Firstly, there were regulatory changes over the history of ASAS. From ASAS 2004 onwards, reminders could no longer be sent to non-respondents due to the Data Protection Act, which has been identified as a significant contributing factor to falling response rates in UK epidemiological studies in recent years.[29] While it is possible that the falling response rate might have introduced bias into the characteristics of the populations studied since 2004 onwards, the consistency of results in models A (where data from all surveys were included) and C (where results from 1964 and 1989 were not included and results post 1999 would have greater weight) for associations between childhood asthma and male sex, deprivation and eczema indicates that falling response rates in recent years have not substantially affected the results. Secondly, there has been substantial social change in the UK between 1964 and 2014. Smoking was socially acceptable in 1964 and the dangers of secondhand smoke were not understood, so parental smoking was not measured in the 1964 survey. Moreover, concepts of SES and its measurement have changed between 1964 and 2014 meaning that a composite measure had to be constructed from the most appropriate available measure in each year's data. Additionally, we do not have data for all potential risk factors for asthma. The 50 year perspective provided by our serial surveys has allowed us to explore the relationship between asthma and risk factors over time. The changing nature of these relationships suggests modification of environmental exposures, e.g. exposure to second hand smoke, can reduce population risk or susceptibility for developing asthma.

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Figure legends

Fig 1. CONSORT-style flow diagram

Fig 2. Time trends in asthma and associated risk factors 1964 to 2014

Table 1. Demographic characteristics for each year of the Aberdeen Schools Asthma Survey.

	Study year						
	1964	1989	1994	1999	2004	2009	2014
Number of questionnaires distributed	2743	3943	4198	4209	3368	2253	2527
Number of questionnaires completed	2511	3403	4034	3537	1920	1196	838
%participation	92	85	96	84	57	54	33
Completed only by	2007	3195	3157	3462	1441	831	565
8-13 year olds and all data available							
Mean age (SD) †	10.98	10.84	11.06	11.07	10.85	10.79	11.08
	(1.16)	(.92)	(.88)	(.86)	(.89)	(.88)	(.90)
% Boys	50.0 (n=1003)	51.4 (n=1746)	50.5 (n=1714)	49.5 (n=1748)	48.9 (n=840)	48.9 (n=538)	49.8 (n=391)
Median deprivation* (interquartile range)†	2(2)	2(2)	3(3)	3(3)	3(3)	2(4)	3(3)

The results presented here are previously published as separate studies. *Deprivation is in quintiles with 1 as most deprived and 5 as least deprived. † Kruskal Wallis test $p<0.001$ for difference over study years. Only children fulfilling the inclusion criteria for this analysis are included in this table (i.e those aged 9-12 within the 1964 Aberdeen city limits). In some study years, additional groups of children, not fulfilling the criteria for our current analysis, were also studied and these were included in the original study publications – these are not included in this table

Table 2. Odds ratios for asthma in association with a number of risk factors for asthma.

	Risk factor	Odds ratio	95% CI	p value
	Age (y)	1.03	0.98, 1.09	NS
	Male sex	1.34	1.21, 1.49	<0.0001
	Least affluent 1	1.30	1.12, 1.51	0.0006
Deprivation	2	1.26	1.09, 1.46	0.0015
	3	1.26	1.09, 1.45	0.0017
	4	0.95	0.73, 1.23	NS
	Most affluent 5	1	1	(Reference)
	Eczema	3.24	2.90, 3.62	<0.0001
	Obesity	1.06	0.75, 1.48	NS
	Parental smoking	1.24	1.11, 1.38	<0.0001
	Parental asthma	1.82	1.65, 2.02	<0.0001

Generalised R^2: based on 50 imputed samples; mean [min, max] 0.322 [0.320, 0.323]. The results are from analysis of 9521 individuals included in model C. The model did not consider time as a covariate. NS = not significant.

Table 3: Odds ratios [95% confidence interval] for a child having asthma for each study year following adjustment for covariates

	1964[a, b, c]	1989[a, b]	1994[a]	1999[a]	2004[d]	2009[d]	2014[d]
age	1.078 [0.88, 1.30]	0.98 [0.86, 1.11]	0.98 [0.88, 1.08]	1.06 [0.96, 1.16]	1.17 [1.01, 1.35]	1.01 [0.83, 1.24]	1.06 [0.82, 1.37]
Male	**2.46 [1.51, 4.00]***	**1.75 [1.37, 2.23]***	**1.57 [1.30, 1.89]***	**1.27 [1.08, 1.50]†**	1.11 [0.85, 1.43]	1.36 [0.95, 1.95]	**2.46 [1.48, 4.07]†**
Deprivation 1	0.86 [0.39, 1.89]	**1.96 [1.31, 2.93]***	0.90 [0.69, 1.18]	**1.41 [1.11, 1.79]†**	**1.94 [1.28, 2.96]***	**1.96 [1.16, 3.32]‡**	1.17 [0.57, 2.41]
Deprivation 2	1.23 [0.63, 2.40]	**1.63 [1.09, 2.45]‡**	0.90 [0.68, 1.15]	1.20 [0.94, 1.53]	**1.96 [1.36, 2.83]***	1.60 [0.92, 2.77]	1.39 [0.72, 2.70]
Deprivation 3	0.96 [0.44, 2.09]	**2.15 [1.41, 3.26]***	0.80 [0.62, 1.03]	**1.42 [1.15, 1.76]†**	**1.87 [1.22, 2.88]†**	**2.44 [1.34, 4.44]***	1.21 [0.56, 2.64]
Deprivation 4	1.00 [0.42, 2.37]	1.39 [0.71, 2.73]	0.90 [0.54, 1.52]	0.79 [0.48, 1.30]	1.37 [0.83, 2.29]	1.38 [0.66, 2.85]	0.28 [0.06, 1.28]
Deprivation 5	1	1	1	1	1	1	1
Childhood eczema	**12.71 [6.62, 24.41]***	**4.75 [3.63, 6.20]***	**3.07 [2.50, 3.77]***	**2.03 [1.69, 2.43]***	**7.85 [5.93, 10.40]***	**4.34 [2.89, 6.50]***	**4.82 [2.82, 8.25]***
Parental smoking	-	1.17 [0.90, 1.50]	**1.28 [1.06, 1.54]†**	1.05 [0.89, 1.24]	**1.41 [1.06, 1.89]‡**	1.11 [0.75, 1.64]	1.11 [0.61, 2.01]
Parental asthma	-	-	**1.91 [1.59, 2.30]***	**2.58 [2.19, 3.03]***	0.95 [0.70, 1.28]	1.30 [0.91, 1.85]	1.26 [0.81, 1.97]
Summary fit statistics [from 2004 for 50 imputed samples mean [min, max]							
n, asthma	n=2007, yes=84	n=3195, yes=327	n=3157, yes=604	n=3462, yes=842	n= 1441, yes= 422	n= 843, yes= 172	n=577, yes = 89
AIC [min, max]	655.37	1970.66	2918.58	3637.07	1467.91 [1441.21, 1501.77]	790.42 [782.38, 798.04]	451.26 [442.60, 459.09]
-2 Log L [min, max]	639.37	1952.66	2898.58	3617.07	1447.91 [1421.21, 1481.77]	770.42 [762.38, 778.04]	431.26 [422.60, 439.09]
R-Square [min, max]	0.029	0.048	0.057	0.063	0.19 [0.17, 0.20]	0.09 [0.85, 0.10]	0.11 [0.09, 0.12]

*p<0.001, †p<0.01, ‡p<0.05.

[a] Eczema complete; [b] No information on parental asthma; [c] No information on parental smoking; [d] imputed sampling for eczema

Deprivation is in quintiles with 5 as least deprived and 1 as most deprived, CI = confidence interval, AIC=Atkins Information Criteria, log L= log likelihood [measure of fit]

Table 4. Odds ratios and 95% confidence intervals for a child having asthma over the time period of the study following adjustment for changing prevalences of asthma and covariates

Covariates		Odds ratio [95% CI] for having asthma and the covariate across a given time period Model A: n = 15108, with asthma = 2660	Model B: n = 12901, with asthma = 2538[a]		Model C: n = 9480, with asthma = 2129[b]
Constant	1964	0.998 [0.997, 0.998]*	-		-
	1989-1999	0.009 [0.005, 0.018]*	0.009 [0.005, 0.018]*	1994-1999	0.027 [0.010, 0.075]*
	2004-2014	3.821 [1.216, 12.008]‡	3.540 [1.106, 11.336]‡	2004-2014	7.106 [1.983, 25.465]‡
Asthma rate/year	1989-1999	1.078 [1.063, 1.093]*	1.077 [1.062, 1.092]*	1994-1999	1.035 [1.010, 1.061]
	2004-2014	0.910 [0.888, 0.932]*	0.912 [0.870, 0.934]*	2004-2014	0.893 [0.869, 0.917]*
Age		1.033 [0.983, 1.086]	1.028 [0.977, 1.083]		1.043 [0.985, 1.106]
Male gender	1964	1.000 [1.000, 1.001]†	-		-
	1989-1999	1.011 [1.007, 1.014]*	1.011 [1.007, 1.014]*	1994-1999	1.010 [1.006, 1.013]*
	2004-2014	1.008 [1.004, 1.013]*	1.008 [1.004, 1.013] *	2004-2014	1.007 [1.003, 1.011]‡
Deprivation 1	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	1.009 [1.004, 1.014]†	1.007 [1.002, 1.013]‡	1994-1999	1.005 [1.000, 1.011]
	2004-2014	1.016 [1.010, 1.022]*	1.013 [1.006, 1.019]*	2004-2014	1.002 [0.997, 1.008]
Deprivation 2	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	1.005 [1.000, 1.010]‡	1.005 [1.000, 1.010]	1994-1999	1.004 [0.999, 1.009]
	2004-2014	1.015 [1.010, 1.021]*	1.013 [1.007, 1.019]*	2004-2014	0.995 [0.984, 1.006]
Deprivation 3	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	1.008 [1.003, 1.012]‡	1.007 [1.002, 1.012]‡	1994-1999	1.013 [1.007, 1.022]*
	2004-2014	1.015 [1.008, 1.022]*	1.014 [1.007, 1.021]*	2004-2014	1.012 [1.006, 1.019]*
Deprivation 4	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	0.997 [0.987, 1.007]	0.996 [0.986, 1.006]	1994-1999	1.014 [1.007, 1.022]*
	2004-2014	1.004 [0.995, 1.012]	1.003 [0.995, 1.012]	2004-2014	1.002 [0.993, 1.012]
Change in the OR for a child with asthma also having eczema	1964	1.001 [1.001, 1.002]*	-		-
	1989-1999	1.031 [1.028, 1.035]*	1.005 [1.002, 1.009]‡	1994-1999	1.025 [1.021, 1.029]*

	2004-2014	1.042 [1.038, 1.047]*	1.006 [1.001, 1.011] ‡	2004-2014	1.002 [0.997, 1.007]
					-
Change in the OR for a child with asthma also having parental smokers	1964	-	-		-
	1989-1999	-	1.032 [1.028, 1.036]*	1994-1999	1.004 [1.001, 1.008]‡
	2004-2014	-	1.043 [1.038, 1.047]*	2004-2014	1.006 [1.001, 1.011]‡
Change in the OR for a child with asthma also having parents with asthma	1964	-	-		-
	1989-1999	-	-	1994-1999	1.027 [1.022, 1.031]*
	2004-2014	-	-	2004-2014	1.042 [1.037, 1.048]*

Summary fit statistics for 50 imputed samples mean [min, max]

AIC	12606.99 [12579.01, 12634.81]	11744.35 [11717.85, 11768.25]	9285.40 [9263.48, 9315.06]
-2 Log L	12558.99 [12531.01, 12586.81]	11706.35 [11679.85, 11730.25]	9243.40 [9221.48, 9273.06]
Generalised R^2	0.426 [0.425, 0.427]	0.381 [0.380, 0.382]	0.337 [0.335, 0.339]

Odds ratio [95% CI] for having asthma and the covariate across a given time period

Covariates		**Model A: n = 15108, with asthma = 2660**	**Model B: n = 12901, with asthma = 2538[a]**		**Model C: n = 9480, with asthma = 2129[b]**
Constant	1964	0.998 [0.997, 0.998]*	-		-
	1989-1999	0.009 [0.005, 0.018]*	0.009 [0.005, 0.018]*	1994-1999	0.027 [0.010, 0.075]*
	2004-2014	3.821 [1.216, 12.008]‡	3.540 [1.106, 11.336]‡	2004-2014	7.106 [1.983, 25.465]‡
Asthma rate/year	1989-1999	1.078 [1.063, 1.093]*	1.077 [1.062, 1.092]*	1994-1999	1.035 [1.010, 1.061]
	2004-2014	0.910 [0.888, 0.932]*	0.912 [0.870, 0.934]*	2004-2014	0.893 [0.869, 0.917]*
Age		1.033 [0.983, 1.086]	1.028 [0.977, 1.083]		1.043 [0.985, 1.106]
Male gender	1964	1.000 [1.000, 1.001]†	-		-
	1989-1999	1.011 [1.007, 1.014]*	1.011 [1.007, 1.014]*	1994-1999	1.010 [1.006, 1.013]*
	2004-2014	1.008 [1.004, 1.013]*	1.008 [1.004, 1.013] *	2004-2014	1.007 [1.003, 1.011]‡

Deprivation 1	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	1.009 [1.004, 1.014]†	1.007 [1.002, 1.013]‡	1994-1999	1.005 [1.000, 1.011]
	2004-2014	1.016 [1.010, 1.022]*	1.013 [1.006, 1.019]*	2004-2014	1.002 [0.997, 1.008]
Deprivation 2	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	1.005 [1.000, 1.010]‡	1.005 [1.000, 1.010]	1994-1999	1.004 [0.999, 1.009]
	2004-2014	1.015 [1.010, 1.021]*	1.013 [1.007, 1.019]*	2004-2014	0.995 [0.984, 1.006]
Deprivation 3	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	1.008 [1.003, 1.012]‡	1.007 [1.002, 1.012]‡	1994-1999	1.013 [1.007, 1.022]*
	2004-2014	1.015 [1.008, 1.022]*	1.014 [1.007, 1.021]*	2004-2014	1.012 [1.006, 1.019]*
Deprivation 4	1964	1.000 [1.000, 1.000]	-		-
	1989-1999	0.997 [0.987, 1.007]	0.996 [0.986, 1.006]	1994-1999	1.014 [1.007, 1.022]*
	2004-2014	1.004 [0.995, 1.012]	1.003 [0.995, 1.012]	2004-2014	1.002 [0.993, 1.012]
Change in the OR for a	1964	1.001 [1.001, 1.002]*	-		-
child with asthma also	1989-1999	1.031 [1.028, 1.035]*	1.005 [1.002, 1.009]‡	1994-1999	1.025 [1.021, 1.029]*
having eczema	2004-2014	1.042 [1.038, 1.047]*	1.006 [1.001, 1.011] ‡	2004-2014	1.002 [0.997, 1.007]
					-
Change in the OR for a	1964	-	-		-
child with asthma also	1989-1999	-	1.032 [1.028, 1.036]*	1994-1999	1.004 [1.001, 1.008]‡
having parental smokers	2004-2014	-	1.043 [1.038, 1.047]*	2004-2014	1.006 [1.001, 1.011]‡
Change in the OR for a	1964	-	-		-
child with asthma also	1989-1999	-	-	1994-1999	1.027 [1.022, 1.031]*
having parents with	2004-2014	-	-	2004-2014	1.042 [1.037, 1.048]*
		Summary fit statistics for 50 imputed samples mean [min, max]			
AIC		12606.99 [12579.01, 12634.81]	11744.35 [11717.85, 11768.25]		9285.40 [9263.48, 9315.06]

*p<0.0001, †p<0.001, ‡p<0.05. [a] Limited to only 1989-2014, [b] Limited to only 1994-2014. Deprivation is in quintiles with 1 as most deprived and 5 as least deprived – 5 is the reference category. CI = confidence interval, AIC = Area under the Curve, Log L = log likelihood.