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The effect of farming environment on asthma; time dependent or universal?

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Abstract
The increasing prevalence of asthma is linked to westernization and urbanization. Farm environments have been associated with a lower risk of asthma development. However, this may not be universal, as the association differs across birth cohorts and farming methods. The aim of this study was to investigate the associations of farm upbringing with asthma in different generations and at different times in history. The study population consisted of three generations: 13,868 subjects participating in the ECRHS in 2010, their 9,638 parents, and their 8,885 offspring participating in RHINESSA in 2013. Information on place of upbringing and self-reported ever asthma was provided via questionnaires. Logistic regression was performed including subgroup analysis stratified by generation and birthyear into ten-year-intervals. The prevalence of asthma increased from 8% among grandparents to 13% among parents and to 18% among offspring. An overall analysis showed an inverse association of farm upbringing on the risk of asthma (OR = 0.64; 95%CI 0.55–0.74). Subgroup analysis stratified into ten-year-intervals showed a tendency towards a more pronounced inverse association between growing up on a farm and asthma among subjects born in the 1940s (0.74; 0.48–1.12), 1950s (0.70; 0.54–0.90) and 1960s (0.70; 0.52–0.93). For subjects born in 1970 and thereafter this association appeared less consistent. While growing up on a farm was associated with a reduced risk of developing asthma in participants born between 1945–1999, this was mainly driven by generations born from 1945 to 1973.

Keywords Asthma · ECRHS · RHINESSA · RHINE · Farm opbringing

Introduction

The prevalence of asthma increased noticeably in the late twentieth century [1]. Large geographical variations in the prevalence of asthma have been observed [2, 3], and generally, the rising prevalence has been linked to westernization and urbanization [4]. However Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) recently found that the prevalence was stabilizing or even declining in some high prevalence countries, while the prevalence kept increasing in countries with lower symptom prevalence [5].

One favored theory behind the increasing prevalence of allergic diseases including asthma is "the microbial diversity hypothesis" suggesting that changes in type and level of microbial exposure have influenced the development of immune function [4, 6]. It has been shown that a diverse microbial exposure is able to impact the innate immune system, eventually leading to activation and expansion of regulatory T (T_{Reg}) cells. T_{reg} cells balance the adaptive immune response by reducing the allergen induced activation of Th_2 cells and the Th_2 cell dependent IgE production [7] driving the immune response into a Th_1 direction with less tendency to develop atopic diseases [8]. Livestock is an important source of a diverse microbial environment [9, 10]. Several studies reported a reduced risk of asthma when growing up on a farm [9, 11–17], however one study from Leynaert et al. found that childhood farming environment was associated with a reduced risk of atopic sensitization

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in adulthood, but had no relation to the risk of asthma or wheeze [18].

There is also evidence that the association between farm upbringing and the risk of developing inflammatory diseases may vary throughout history. In a Swedish population, Bråbäck et al. found a reduced risk of developing asthma among children of farmers, compared with children of parents with other occupations. When analyzing each birth cohort separately, a protective effect of parental farming was only seen in subjects born after 1961 [17]. A study of inflammatory bowel disease (IBD) also found the protective effect from farming environment stronger in younger generations. Timm et al. found that subjects who lived their first 5 years of life on a livestock farm had markedly less IBD in adulthood, as compared to those who grew up in a city or village. The protective effect of farming environment was significant only among subjects born after 1952 [19]. Another study investigated environmental exposures and immune profiles in 60 Amish children growing up in traditional farming environments and Hutterite children living on modern, industrialized farms in the US. This study found that the prevalence of asthma was substantially lower among Amish (5.2%) than among Hutterite children (21.3%) [20].

Thus, the literature suggests that the association of farm upbringing with asthma may not be universal, as this seems to differ across birth cohorts and farming practices. There is a need for more studies to understand the inconsistent findings in the association between childhood farm upbringing and development of asthma. We hypothesized that the inverse association between farm upbringing and asthma was strongest among younger generations due to larger differences in microbial exposure between city and farm environment over time. Therefore, we aimed to study the association between childhood farm upbringing and asthma development at different times in history and investigate whether this association was time dependent or universal.

Methods

Study population

Data were collected as part of three cohort studies: ECRHS (The European Community Respiratory Health Survey), RHINE (Respiratory Health in Northern Europe) and Respiratory Health in Northern Europe, Spain and Australia (RHINESSA). The original ECRHS study included information on around 140,000 young adults aged between 20–44 years from 48 study centers across Europe and other parts of the world [2].

The RHINE study was a sub-study following up on the seven study centers located in Northern Europe: Denmark (Aarhus), Norway (Bergen), Sweden (Gothenburg, Umeå, Uppsala), Iceland (Reykjavik) and Estonia (Tartu) [21]. RHINE is the original random population based ECRHS study from the five Northern European Countries. For Spain and Australia only subgroups with clinical investigations are included. This is due to the fact that only the Northern European ECRHS centers performed a follow-up of the total ECRHS population. RHINE and ECRHS originate from the same study population, and the age is similar for the ECRHS and RHINE.

The RHINESSA study included adult offspring from ten ECRHS/RHINE centers: Denmark (Aarhus), Norway (Bergen), Sweden (Gothenburg, Umeå, Uppsala), Iceland (Reykjavik), Estonia (Tartu), Spain (Albacete, Huelva) and Australia (Melbourne) [22]. The local Science Ethics Committees approved the study for each study centre, and informed consent was obtained from all study participants.

Data collection

Data on parents and offspring were provided via the ECRHS/RHINE III questionnaire in 2010 and the RHINESSA questionnaire in 2013–2015, respectively. Offspring also provided information on their other parent not participating in ECRHS, smoking status of parents when offspring were children and grandparental place of upbringing. Moreover, parents provided information on grandparental asthma and smoking status when parents were children (Table S1 in supplementary materials).

Information on place of upbringing was reported via the question: "What term best describes the place you (your father, your mother, your grandparents) lived most of the time before the age of five years?" with the following response categories: (1) farm with livestock, (2) farm without livestock, (3) village in a rural area, (4) small town, (5) suburb of city, and (6) inner city. The groups were merged into three levels: 1 + 2 as "farm upbringing", 3 + 4 as "rural upbringing" and 5 + 6 as "urban upbringing". Information on asthma status was defined from the question: "Do you have, or have you ever had asthma?".

Possible confounders were selected based on evidence from the literature: sex, parental smoking in offspring childhood, parental asthma, and study centre. Parental asthma was defined by either parent ever suffering from asthma and was merged into a combined parental asthma variable in two categories: (1) ≥ 1 parent with asthma, and (2) no parents with asthma. Parental smoking was defined as regular smoking by either parent during childhood and presented in the categories: (1) no parent smoked, (2) one parent smoked, (3) both parents smoked or (4) don't know. Information on subjects' own smoking was categorized as never, current or ex-smoker.

Statistical methods

Data were analyzed in logistic regression models and presented as odds ratios (ORs) with corresponding 95% confidence intervals (95% CI). Clusters within families were taken into account by use of robust standard errors. Subgroup analyses included stratification by generation and by birthyear into ten-year-intervals to investigate whether the association between farm upbringing and asthma has changed over time. Also, stratification by self-reported hay fever (considered as a marker of atopy) was included to investigate the allergic and nonallergic phenotype of asthma among parents and offspring. Formal interaction between place of upbringing and generation and birthyear, respectively, was performed by adding an interaction term to the logistic regression model. A complete case analysis was made on subjects with complete information to investigate magnitude of confounding.

Regarding the grandparents, only information on place of upbringing and asthma status was available and analyses on this generation are therefore only presented as unadjusted.

Statistical analyses were carried out using STATA 16.1 (StataCorp, College Station, TX).

Results

The study population consisted of 32,391 eligible subjects. Basic characteristics of study population included in ECRHS/RHINE (Parents) and RHINESSA (offspring) are shown in Table 1. The ECRHS/RHINE study included n = 13,868 responders and among them n = 12,617 had no

Table 1 Characteristics of the study population: Parents participating in the ECRHS and their offspring participating in RHINESSA

	Parents (ECRHS/RHINE)				Offspring (RHINESSA)			
	All	Farm upbringing	Rural upbringing	Urban upbringing	All	Farm upbringing	Rural upbringing	Urban upbringing
	n = 13,868	n = 2133 (15%)	n = 5345 (39%)	n = 6390 (46%)	n = 8885	n = 368 (4%)	n = 2669 (30%)	n = 5848 (66%)
Asthma, n (%)	1742 (13)	208 (10)	716 (13)	818 (13)	1632 (18)	60 (16)	481 (18)	1091 (19)
Birth year, mean (min;max)*	1958 (1945;1973)	1956 (1945;1973)	1958 (1945;1973)	1959 (1945;1973)	1984 (1950;1999)	1984 (1953;1999)	1984 (1954;1999)	1985 (1950;1999)
Sex, n (% Female)*	7301 (53)	1162 (54)	2879 (54)	3260 (51)	5153 (58)	223 (61)	1540 (58)	3390 (58)
Smoking, n (%)								
Never smoker	6378 (46)	1026 (48)	2567 (48)	2785 (44)	5732 (65)	244 (66)	1788 (67)	3700 (63)
Current smoker	2424 (17)	369 (17)	860 (16)	1195 (19)	1142 (13)	43 (12)	307 (12)	792 (14)
Ex-smoker	4733 (34)	679 (32)	1807 (34)	2247 (35)	1742 (20)	68 (18)	485 (18)	1189 (20)
Missing	333 (2)	59 (3)	111 (2)	163 (3)	269 (3)	13 (4)	89 (3)	167 (3)
Parental smoking, n (%)								
No parents smoked	4425 (32)	872 (41)	1741 (33)	1812 (28)	4343 (49)	198 (54)	1343 (50)	2802 (48)
One parent smoked	5256 (38)	808 (38)	2037 (38)	2411 (38)	2307 (26)	87 (24)	666 (25)	1554 (27)
Both parents smoked	3503 (25)	338 (16)	1325 (25)	1840 (29)	1911 (22)	68 (18)	561 (21)	1282 (22)
Don't know	665 (5)	115 (5)	238 (4)	312 (5)	297 (3)	11 (3)	95 (4)	191 (3)
Missing	19 (0.14)	0 (0)	4 (0.07)	15 (0.23)	27 (0.30)	4 (1.09)	4 (0.15)	19 (0.32)
Parental asthma status, n (%)								
Parent with asthma	1977 (14)	305 (14)	737 (14)	935 (15)	1066 (12)	34 (9)	242 (9)	790 (14)
No parent with asthma	10.650 (77)	1710 (80)	4217 (79)	4723 (74)	4781 (54)	171 (46)	1229 (46)	3381 (58)
Missing	1241 (9)	118 (6)	391 (7)	732 (11)	3038 (34)	163 (44)	1198 (45)	1677 (29)

RHINE (Respiratory Health in Northern Europe), ECRHS (European Community Respiratory Health Survey), RHINESSA (Respiratory Health in Northern Europe, Spain and Australia)

*N varies due to missing variables

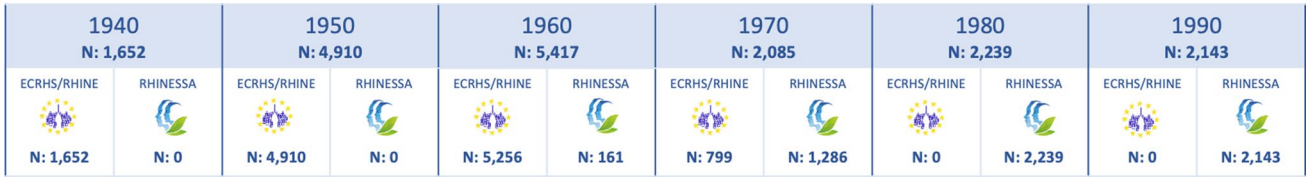

Fig. 1 Number of subject with no missing data from ECRHs/RHINE and RHINESSA in the different birth cohorts

Table 2 Characteristics of the study population: Grandparents, who were parents of participants of ECRHS and grandparents of participants in RHINESSA

	Grandparents			
	All	Farm upbringing	Rural upbringing	Urban upbringing
	n = 9638	n = 2562 (27%)	n = 4030 (42%)	n = 3046 (32%)
Asthma, n (%)	806 (8)	204 (8)	327 (8)	275 (9)
Sex, n (% Female)	4891 (51)	1286 (50)	2111 (52)	1494 (49)

missing data. The RHINESSA cohort included n = 8,885 responders and among them n = 5,829 had no missing data. Figure 1 shows number of subjects with no missing data from ECRHS/RHINE and RHINNESA in the different birth cohorts. Among the total of 18,456 subjects with no missing data (12,618 parents), the mean number of participating offspring per parent was 0.46 (range 0 – 6). Information on grandparents (*n = 9,638*) regarding place of upbringing, asthma and sex are shown in Table 2.

Parents were comparable across exposure groups with regard to asthma, birthyear, sex, smoking and parental asthma. Parental smoking was less frequent among subjects with farm upbringing. Offspring were comparable across exposure groups regarding asthma, birthyear, sex, smoking and parental smoking. Among offspring, subjects missing information on parental asthma were more pronounced in rural and farm children (45% and 44%, respectively) compared to children raised in the city (29%).

The prevalence of ever asthma increased from 8% among grandparents to 13% among parents and to 18% among offspring. In parallel, the proportions of subjects raised on a farm have declined markedly from 27% among grandparents to 15% among parents and to 4% among offspring.

A pooled analysis including all eligible subjects across generations (Table 3) showed an inverse association between growing up on a farm and the risk of developing asthma (OR = 0.64; 95%CI 0.55–0.74) compared to growing up in a city. There was no evidence of a difference in risk of asthma between individuals growing up in a rural setting compared to city (OR = 0.97; 95%CI 0.89–1.06).

Crude logistic regression analysis on place of upbringing and asthma stratified by generation (Table 4) showed tendency towards decreased risk of asthma among grandparents with a farm upbringing (OR = 0.87; 95%CI 0.72–1.06). Regarding the parents, both crude (OR = 0.74; 95%CI 0.63–0.86) and adjusted (OR = 0.73; 95%CI 0.62–0.87) analysis showed that farm upbringing was inversely associated with the risk of developing asthma. Crude estimates (OR = 0.85; 95%CI 0.64–1.13) showed a tendency for reduced risk of asthma when growing up on a farm among offspring, but this association was no longer apparent in adjusted analysis (OR = 1.03; 95%CI 0.71–1.51).

Table 3 Odds ratios and corresponding 95% confidence intervals for ever asthma according to place of upbringing

	All	
	n = 32,391	n = 18,456
	Crude	Adjusted*
City	1	1
Rural	0.87 (0.81–0.93)	0.97 (0.89–1.06)
Farm	0.62 (0.55–0.69)	0.64 (0.55–0.74)

Drop in numbers of subjects from crude to adjusted analysis are mainly due to missing data on covariates on the entire grandparental generation G0 (n = 9638), but also missing data among parents G1 (n = 1250) and offspring G2 (n = 3047)

*Adjusted for sex, parental smoking in offspring childhood, parental asthma and study centre

Subgroup analysis stratified by birthyear into ten-year-intervals showed a tendency that the association between growing up on a farm and reduced risk of asthma was stronger among subjects born in the 1940s (OR = 0.74; 95%CI 0.48–1.12), 1950s (OR = 0.70; 95%CI 0.54–0.90) and 1960s (OR = 0.70; 95%CI 0.52–0.93). For subjects in the 1970s and thereafter this association appeared more variable and with wider confidence intervals, especially in the 1980s (Table 5 and Fig. 2).

Interaction analysis found no formal interaction on either place of upbringing and generation (P-value = 0.14) or place

Table 4 Odds ratios and corresponding 95% confidence intervals for ever asthma according to place of upbringing stratified by generation

	Grandparents		Parents		Offspring	
	n = 9638		n = 13,868	n = 12,618	n = 8885	n = 5838
	Crude	Adjusted	Crude	Adjusted*	Crude	Adjusted*
City	1	–	1	1	1	1
Rural	0.89 (0.75–1.06)	–	1.05 (0.95–1.17)	1.11 (0.99–1.24)	0.96 (0.85–1.08)	1.03 (0.88–1.20)
Farm	0.87 (0.72–1.06)	–	0.74 (0.63–0.86)	0.73 (0.62–0.87)	0.85 (0.64–1.13)	1.03 (0.71–1.51)

*Adjusted for sex, parental smoking in offspring childhood, parental asthma and study centre.

of upbringing and birthyear (P-value = 0.52) upon the effect on asthma.

An analysis of asthma according to farm upbringing stratified by study centre showed an overall homogeneity among all centres apart from Albacete, which separated out (Fig. 3 and Table S2 in supplementary materials). Data from Huelva were too sparse and therefore not included in the Fig. 3. Estimates for allergic and non-allergic asthma from subgroup analysis stratified by self-reported hay fever were similar with those seen in the subgroup analysis stratified by generation, however with lower statistical power especially in the generation of offspring (Table S3 in supplementary materials).

Stratification by sex showed no difference between females and males (Table S4 in supplementary materials), so sex was assessed not to be affecting the association between farm upbringing and asthma.

Discussion

Key results

In this three-generation study, the prevalence of self-reported asthma increased across generations. Overall, growing up on a farm was associated with a reduced risk of developing asthma in participants born from 1945–1999. However, this association was mainly driven by the parent generation born from 1945 to 1973. When stratified by birthyear into ten-year-intervals, a more pronounced inverse association between growing up on a farm and the risk of developing asthma was seen among the older generation born in the 1940s-1960s, while the association appeared more variable in the younger generations born during the 1970s and thereafter. No formal interaction was found between either place of upbringing and generation, or place of upbringing and birthyear upon the effect on asthma.

The association between farm upbringing and ever asthma stratified by generation showed a relatively large shift between crude and adjusted estimates among offspring. This difference was not observed among parents. A complete case analysis on offspring with complete information (n = 5,838) showed a crude estimate (OR = 1.01; 95%CI 0.69–1.47), which did not differ markedly from the adjusted estimate (OR = 1.03; CI95% 0.71–1.51). This suggest that little residual confounding was removed when adjusting for sex, parental smoking in offspring childhood, parental asthma and study centre. Instead, the difference in crude and adjusted may potentially be attributed to the differences in subjects with missing information on covariates and subjects with a complete set of data.

The association between farm upbringing and asthma stratified by birthyear into ten-year-intervals appeared variable and with wide confidence intervals among subjects born after 1970. Especially in the 1980s the confidence interval appeared very wide. This was assessed not to be related to the number of subjects as this did not differ markedly (*n = 2240)* compared to the number of subjects in the other strata with narrower confidence intervals. Considering the crude and adjusted estimates of each stratum it appeared that the estimates changed substantially more in the 1980s than in any of the other strata. A complete case analysis on subjects born in the 1980s resulted in a crude estimate (OR = 1.58; 95%CI 0.89–2.81), not substantially different from the adjusted estimate (OR = 1.68; 95%CI 0.93–3.02), which suggests that the difference in crude and adjusted estimates also here may potentially be attributable to differences in the subjects with missing information on covariates and subjects included in the complete case analysis. A complete case analysis (Table S5 in supplementary materials) and original analysis (Table 5) reported quite similar estimates and do not change the interpretation of our results.

The analysis stratified by study centre showed overall homogeneity among all study centers except Albacete, for which the risk of asthma appeared higher among subjects with farm upbringing compared with subjects growing up in the city. The subgroup of subjects from Albacete, who were born on a farm consisted of 29 subjects, of whom only 8 reported asthma (data not shown). Generally, stratifying by center caused a reduced number of subjects in each stratum, and thus, centre estimates should be interpreted with the

Table 5 Odds ratios and corresponding 95% confidence intervals for ever asthma according to place of upbringing stratified by birthyear in ten-years-intervals

	1940s		1950s		1960s		1970s		1980s		1990s	
	N = 1867	N = 1652	N = 5450	N = 4910	N = 6008	N = 5417	N = 2967	N = 2085	N = 3453	N = 2239	N = 2977	N = 2143
	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted	Crude	Adjusted
City	1	1	1	1	1	1	1	1	1	1	1	1
Rural	0.76 (0.55–1.04)	0.76 (0.54–1.08)	1.08 (0.91–1.28)	1.12 (0.93–1.35)	1.05 (0.90–1.23)	1.12 (0.95–1.32)	1.08 (0.88–1.34)	1.24 (0.96–1.59)	1.02 (0.84–1.25)	1.13 (0.87–1.46)	0.86 (0.70–1.05)	0.82 (0.64–1.05)
Farm	0.70 (0.47–1.04)	0.74 (0.48–1.12)	0.73 (0.58–0.93)	0.70 (0.54–0.90)	0.71 (0.54–0.93)	0.70 (0.52–0.93)	0.72 (0.43–1.20)	0.89 (0.49–1.60)	1.22 (0.80–1.86)	1.68 (0.93–3.02)	0.61 (0.35–1.05)	0.61 (0.32–1.18)

*Adjusted for sex, parental smoking in offspring childhood, parental asthma and study centre

limited power in mind. Center analysis stratified by birthyear into ten-year-intervals was not possible due to power issues.

Interpretation

In line with the findings of this study, a register-based study by Bråbäck et al. [17] involving male subjects born between 1952–1981 found an increasing prevalence of asthma from 2.0% in cohorts born 1952–1956 to 7.2% in cohorts born 1977–1981. A cohort study by Timm et al. [19] involved subjects born between 1945 and 1971. Both of these studies found the protective effect of farm upbringing on the risk of developing inflammatory diseases to be a rather modern phenomenon. However, this three-generation study including subjects born between 1945–1999 showed an overall consistent association between farm upbringing and asthma, except for subjects born during the 1980s.

One study by Ober et al. found that the prevalence of asthma was substantially lower in Amish children growing up in families using traditional farming methods compared to Hutterite children, with families practicing a modern and industrialized farming method. Otherwise, Hutterite and Amish children were similar with respect to ancestry and lifestyle [20]. However, these observations were not consistent with the results of our study as the association between asthma prevalence and farm upbringing did not differ substantially between 1940 and 1990s despite considerable changes in the farming methods during these years. A limitation of this study is that the exposure measure is relatively crude and does not include detailed information on i.e. direct contact with farm animals or the age of such exposure. Stratification by type of farm was not possible, since of all subjects growing up on a farm only 484 reported a farm without livestock. For 2,017 farm with livestock was reported.

Strengths and limitations

An important strength of this study is the large three-generation study design conducted in Europe and Australia. To the best of our knowledge, this is also the first three-generation study to investigate the association between farm upbringing and asthma at different times in history.

The response rates and drop-outs of the cohort studies have been considerable, leading to a risk of selection bias. At baseline 86% of the invited RHINE cohort answered the questionnaire. After 20 years of follow-up, the response rate was 53% [23]. Only one third of the invited RHINESSA cohort answered the questionnaire (personal communication, Signe Timm). A study on long-term participation and follow-up found the baseline prevalence of asthma similar for long-term follow-up participants compared to non-participants. In RHINE, only minor differences in more

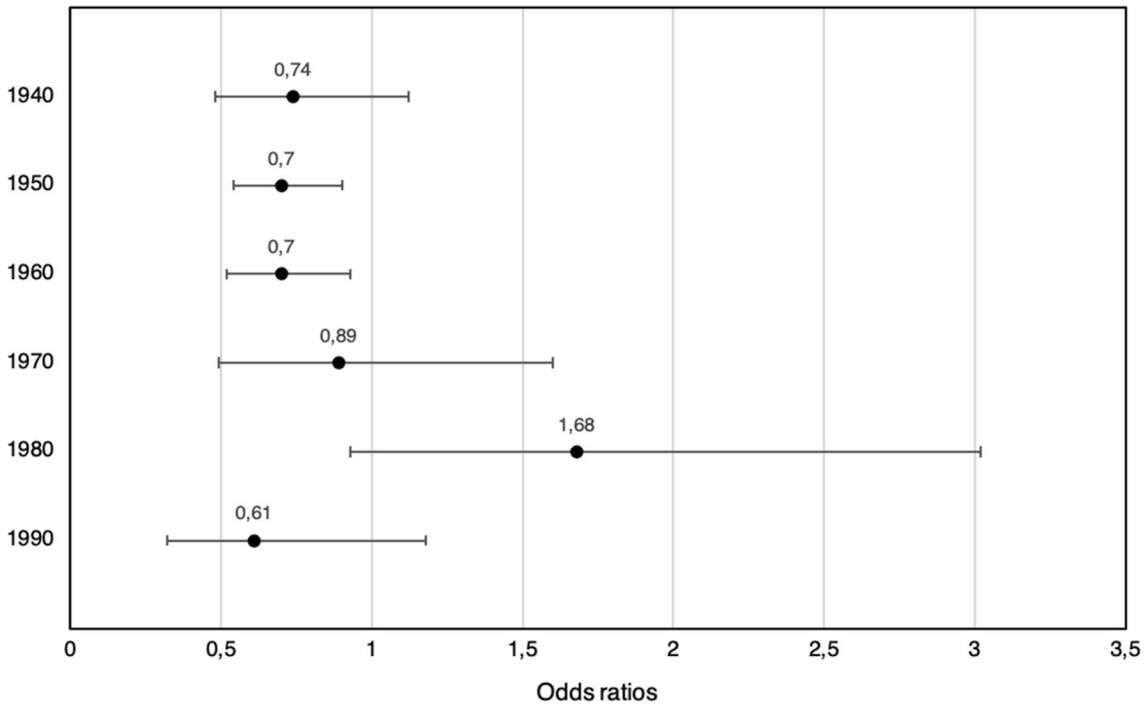

Fig. 2 Oddsratio and corresponding 95% confidence intervals for ever asthma according to farm upbringing stratified by birthyear in ten-years-intervals

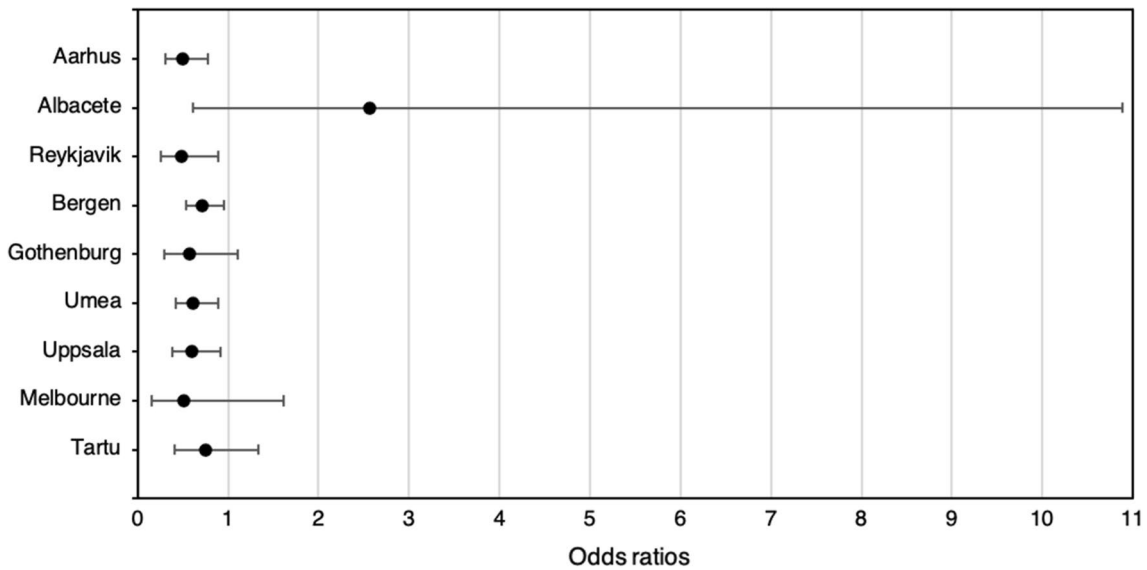

Fig. 3 Oddsratio and corresponding 95% confidence intervals for ever asthma according to farm upbringing stratified by study centre

exposure-outcome pairs were found between long-term follow-up participants and baseline participants [23]. Thus in the parental generation we do not believe the selection to be related to outcome and therefore we do not suspect selection bias. For the offspring and grandparental generations, we cannot rule out selection bias in either directions.

In this study the questionnaire data were cross-sectional, which involved a risk of recall error. The potential misclassification caused by recall error was unlikely to be differential and is more likely to lead to a potential underestimation of these associations. Furthermore, time to follow up varied between subjects as questionnaires were answered in 2010

(ECRHS) and 2013 (RHINESSA) giving information on subjects born between 1945 and 1999. Another study found that growing up on a livestock farm had a stronger protective effect on late-onset asthma diagnosed after the age of ten [21]. The youngest subjects were 14 years at time of follow up, meaning that some of these subjects could be misclassified as "not yet identified cases". This misclassification was most likely unrelated to exposure among the younger subjects, thus nondifferential causing the association to be underestimated. Additionally, the variable age of the subjects when participating in the study was problematic, as some had a long time at risk since exposure, while others had a shorter time at risk.

Another limitation of this study was that outcome was assessed as self-reported ever asthma. This means that some of the older cases reporting "asthma" could instead be suffering from COPD (Chronic Obstructive Pulmonary Disease). This misclassification was assessed not to be related to place of upbringing, but as COPD is typically caused by long-term exposure to irritants such as cigarette smoke, the misclassification would be related to the age of the subjects. The potential misclassification would therefore be non-differential causing an underestimation of the association between place of upbringing and ever asthma, especially among the older generations of the study population. The same applies to subjects with early life wheeze, who could also be misclassified as subjects with"ever asthma". Another consideration regarding self-reported ever asthma is that it also relied on the subjects to see a doctor. Subjects with farm upbringing could be less prone to see a doctor, however this will be influenced by local factors in each study centre. The diagnosis of asthma might be more used by younger generations, which could contribute to the increase in asthma prevalence across generations.

Subjects were giving information on behalf of their parents and grandparents regarding place of upbringing, asthma status and smoking. A study on the agreement between offspring's and parent's reporting of parental place of upbringing showed that offspring misclassification was highly dependent on their own place of upbringing, as they tended to report the same for their parents as for themselves [24]. The potential misclassification was assessed to be unrelated to parental asthma status and therefore non-differential. Furthermore, Timm et al. performed a quantitative bias analysis presenting similar results when using direct or second-hand information in parental place of upbringing [22]. We have no information on misclassification when offspring were reporting on behalf of their grandparents but believe that this involved a comparable risk of non-differential misclassification.

As seen in Table 1 subjects with missing information regarding parental asthma among offspring were more pronounced among rural and farm children compared to children raised in the city. In adjusted analysis, subjects with missing information on covariates such as parental asthma were omitted. Among subjects with missing information, we also found a skewed distribution with regard to asthma status, meaning that this drop out was both related to exposure and outcome hence a differential dropout. The subgroup of offspring growing up on a farm consisted of 368 subjects of whom only 60 had asthma (data not shown). This meant that even small proportions of subjects could have a strong influence on the distribution.

Place of upbringing was considered as a crude measure for microbial exposure, which was a strong assumption, as not all farms were equal regarding microbial substances [10, 25]. Of all subjects growing up on a farm, 484 reported a farm without livestock. 2,017 reported a farm with livestock, of these 1,769 were parents and 248 were offspring. Information on grandparents did not differentiate farms with or without livestock. Ege et al. found that only 24% of agricultural farms did not also raise livestock and 37% of the livestock farms also performed agriculture. Both agriculture and frequent stays in animal sheds were found to have a protective effect on asthma [10]. This indicated that farms often were combining field and livestock farming, which means that distinguishing these as two separate exposures can be problematic. On basis of this, farms with or without livestock were merged under the category "farm". Farm upbringing is substantially less frequent in the later decades and is seldom in the youngest decades/offspring generation. As this reflects a general decrease in farms it may also result in less microbial exposure in the rural area. However, the associations between rural upbringing and asthma are quite inconsistent across the five included decades.

Conclusion

While growing up on a farm was associated with a reduced risk of developing asthma among all participants from three generations, this was mainly driven by the generations born from 1945 to 1973, and less consistent in persons of more recent birth cohorts. Thus, we could not identify a clear time-dependent association between farm upbringing and asthma. An additional finding was the clear increase in asthma prevalence across generations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-022-00893-2.

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Availability of data and material Data are available upon request to Cecilie Svanes, PI Bergen and Research Director of the RHINESSA project.

Declarations

Conflicts of interests MJA holds investigator-initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has undertaken an unrelated consultancy for and received assistance with conference attendance from Sanofi. He has also received a speaker's fee from GSK. The other authors have no conflicts of interest to declare that are relevant for the content of this article.

Ethical approval and consent The local Science Ethics Committees approved the study for each study centre, and informed consent was obtained from all study participants.

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