



Asthma and selective migration from farming environments in a three-generation cohort study

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Abstract

Individuals raised on a farm appear to have less asthma than individual raised elsewhere. However, selective migration might contribute to this as may also the suggested protection from farm environment. This study investigated if parents with asthma are less likely to raise their children on a farm. This study involved three generations: 6045 participants in ECRHS/RHINE cohorts (born 1945–1973, denoted G1), their 10,121 parents (denoted G0) and their 8260 offspring participating in RHINESSA (born 1963–1998, denoted G2). G2-offspring provided information on parents not participating in ECRHS/RHINE. Asthma status and place of upbringing for all three generations were reported in questionnaires by G1 in 2010–2012 and by G2 in 2013–2016. Binary regressions with farm upbringing as outcome were performed to explore associations between parental asthma and offspring farm upbringing in G0–G1 and G1–G2. Having at least one parent with asthma was not associated with offspring farm upbringing, either in G1–G2 (RR 1.11, 95% CI 0.81–1.52) or in G0–G1 (RR 0.99, 0.85–1.15). G1 parents with asthma born in a city tended to move and raise their G2 offspring on a farm (RR 2.00, 1.12–3.55), while G1 parents with asthma born on a farm were less likely to raise their G2 offspring on a farm (RR 0.34, 0.11–1.06). This pattern was not observed in analyses of G0–G1. This study suggests that the protective effect from farm upbringing on subsequent asthma development could not be explained by selective migration. Intriguingly, asthmatic parents appeared to change environment when having children.

Keywords Asthma · Farming · Selective migration · ECRHS · RHINE · RHINESSA

Background

Numerous studies suggest that being born and raised on a farm reduces the risk of asthma [1–4]. The protective effect from farm upbringing has been ascribed to a greater or more diverse microbial exposure in the farm environment, complementing the hygiene hypothesis which proposes that immunological competence is impaired after low microbial stimulation in early life [2, 5, 6]. However, findings in this field have been inconsistent [7, 8], and one important

concern has been the possibility for selective migration over generations. One could therefore question if the apparently protective effect from farm upbringing is a result of asthmatic parents avoiding the farm environment rich in airway irritants such as endotoxin, allergens and organic dust [9] and raising their children in the cities. This would leave the farm effect as the mere product of selective migration rather than a biological effect of the farm environment. One thing is to claim that farm upbringing could explain less asthma in adulthood; another thing is if a healthy selection among farm dwellers contributes to curb heredity of asthma among their children.

Evidence of potential healthy selection patterns in farming is scarce, inconsistent and does not take both parents into account. One study found that 35–39-year-old men were less likely to take over the family farm if they had asthma at conscript examination, and one study found that asthmatics

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were less likely to become pig farmers [10, 11]. In contrast, another study found similar prevalence of asthma among farming students and their siblings, and one study found similar prevalence of family history of asthma among farmers' and non-farmers' children [12, 13].

It seems plausible that selective migration may persist across generations. However, the inherent challenges in investigating this among humans are evident, and to our knowledge, no studies have analysed selection with regard to farming in multiple generations. Using the unique opportunity from a multi-generation study, we aimed to investigate if asthmatic parents were less likely than non-asthmatic parents to raise their children on a farm.

Methods

Study population

The present study is embedded in the ECRHS (European Community Respiratory Health Survey), the RHINE (Respiratory Health In Northern Europe) and the RHINESSA (Respiratory Health In Northern Europe, Spain and Australia) cohort studies (see Figure S1). The ECRHS was initiated in 1988–1992 and included 1500 men and 1500 women born 1945–1973 randomly selected by each of the study centres [14]. The RHINE was a sub-study in five Northern European countries with extended questionnaires [15]. In the present study, we only consider seven countries with ten centres which constitute the RHINESSA study, comprising offspring of the ECRHS/RHINE participants: Denmark (Aarhus), Norway (Bergen), Sweden (Uppsala, Umeå, Gothenburg), Iceland (Reykjavik), Estonia (Tartu), Spain (Huelva, Albacete) and Australia (Melbourne).

This study involves three generations: Participants in the ECRHS/RHINE (G1), their parents (G0, information given by G1) and their children (G2). Furthermore, we include information via the G2 children on the parent, who was not part of ECRHS/RHINE study.

Data measurement

G1 participants provided information via the ECRHS/RHINE III questionnaires in 2010–2012 and G2 provided information via the RHINESSA questionnaires in 2013–2016, Table S1.

G0 and G1 asthma status was defined as ever asthma corresponding to an affirmative answer to “Do you/your mother/your father have or have you/they ever had asthma?”. G1 participants provided this information about themselves and their parents (G0), and G2 provided this information on the G1 not part of the ECRHS/RHINE cohort. G1 and G2 place of upbringing was defined from answers to the question

“What term best describes the place you/your mother/your father lived most of the time before the age of five years?” with 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 same phrasing was used when offspring reported on behalf of parents and grandparents. Data were analyzed as “farm” in which we merged farm with livestock and farm without livestock, and “city” with the remaining four response categories. A recent paper analyzing the 6 response categories separately in G1 did not detect a significantly different effect from farms with or without livestock and consequently they were merged in the present analyses [1].

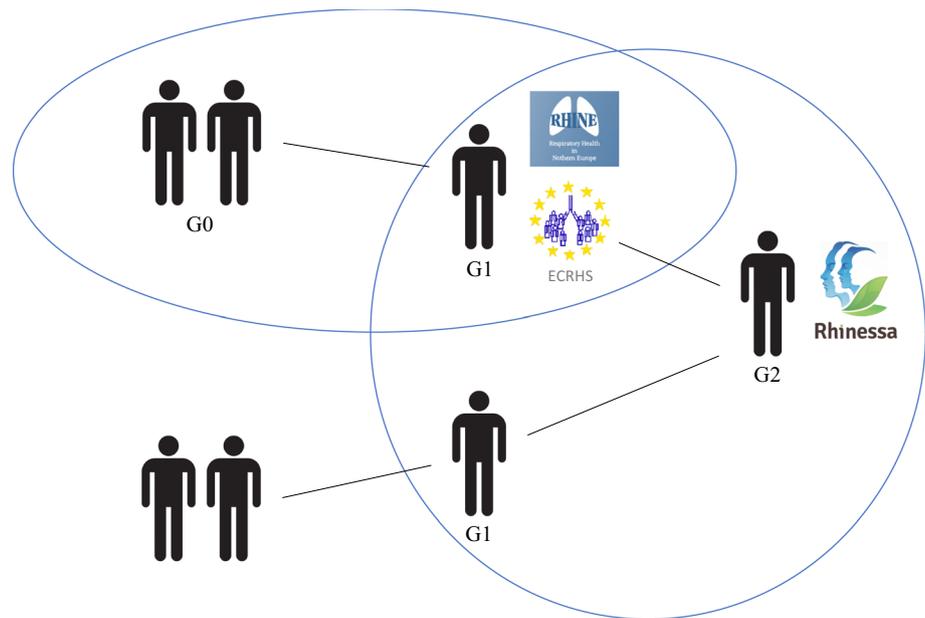
A formal forward–backward translation was performed in all languages to ensure homogeneity between study centres.

Statistical analyses

Data were analysed by binary regression models with log-link estimating relative risks (RR) and corresponding 95% confidence intervals (CIs) with farm upbringing as outcome adjusted for potential confounders. Potential confounders were selected using directed acyclic graphs (DAG) depicting the causal network of interest [16] (see Figure S2). The DAG was based on current evidence and assumptions, and included the following variables: parental smoking, parental and grandparental socioeconomic status and parental place of upbringing. In the statistical model we included the minimal adjustment set for the total effect of parental asthma on offspring place of upbringing was mother's place of upbringing and father's place of upbringing. Furthermore, due to varying prevalence of farm upbringing between different study centres, it was determined a priori also to adjust for centre.

Identical analyses were conducted investigating the association between parental asthma and offspring upbringing in the two parent–offspring sets G0–G1 and G1–G2, respectively, as illustrated by the blue circles in Fig. 1. Analyses were clustered by family. In order to examine centre specific effects, the analyses were presented for each study centre separately. To investigate moving patterns, analyses were stratified by the previous generation's place of upbringing. Sensitivity analyses also included repetition of analyses with direct reporting of offspring asthma and place of upbringing from the one parent in the ECRHS/RHINE instead of the indirect report by the offspring in the RHINESSA to investigate the robustness of the results. Furthermore, sub-analyses were performed on parental hay fever and offspring farm upbringing in a clinical subsample of the ECRHS/RHINE with information on both parents' hay fever among G0–G1, and with information on only one parent's hay fever (the ECRHS/RHINE participant) among G1–G2.

Fig. 1 Illustration of the three generations under study from the left: G0 (included in the study based on information from G1 and G2), G1 (where either mother or father was a participant in the ECRHS/RHINE cohort) and G2 (RHINESSA participants). The G1 parent who was not part of the ECRHS/RHINE cohort was included in the study based on information from G2. The blue circles illustrate the two subsets of analyses denoted G0–G1 and G1–G2, respectively



Statistical analyses were performed using Stata 15 (STATA Corp., College Station, TX, USA).

Results

Basic characteristics of the study populations ECRHS/RHINE (G1, $N=6045$) and RHINESSA (G2, $N=8260$) are shown in Table 1. G2 offspring born on a farm were comparable to city offspring with regard to birth year and parental asthma (Table 1). The same was observed in the G1 population. Farm-brought up offspring (G2) were more likely to have their father brought up in farms than their mothers; this difference was not observed in G1. Place of upbringing varied markedly over generations with 32% G0 participants from farms, 17% G1 participants from farms and 4% G2 participants from farms (Fig. 2).

In binary regression, parental asthma was not associated with offspring farm upbringing either among G1–G2 (RR 1.11, 95% CI 0.81–1.52) or among G0–G1 (RR 0.99, 95% CI 0.85–1.15), Tables 2 and 3. Sensitivity analyses on G1–G2 using direct reports from the ECRHS/RHINE participants instead of indirect reports from the RHINESSA participants revealed similar results (RR 1.21, 95% CI 0.80–1.82). Centre-specific estimates in general showed the same picture among both G0–G1 and G1–G2. Only Reykjavik and Melbourne stood out, showing that Icelandic G1 individuals with asthma were more likely to raise their offspring on a farm (RR 2.74, 95% CI 1.21–6.20), and the same was observed for Australian G0 individuals with asthma (RR 2.51, 95% CI 1.25–5.05), Tables 2 and 3.

When investigating moving patterns, G1 parents with asthma born in a city tended to move and raised their G2

offspring on a farm (RR 2.00, 95% CI 1.12–3.55), in contrast with G1 parents with asthma born on a farm who were less likely to raise their G2 offspring on a farm (RR 0.34, 95% CI 0.11–1.06), Table 4 and Fig. 3. This pattern was not observed in the G0–G1 analyses as G0 asthma was not associated with G1 farm upbringing when stratifying by G0 place of upbringing, Table 5 and Fig. 3.

Analyses on a clinical subsample of 1350 ECRHS participants showed that parental eczema, skin allergy, nasal allergy or hay fever were not associated with offspring farm upbringing among G0–G1 (RR 0.81, 95% CI 0.64–1.05). We revealed similar results in a sub-analysis of 4695 G2 offspring in the RHINESSA with information on only one parent's hay fever and nasal allergies among G1–G2 (RR 0.96, 95% CI 0.68–1.35).

Discussion

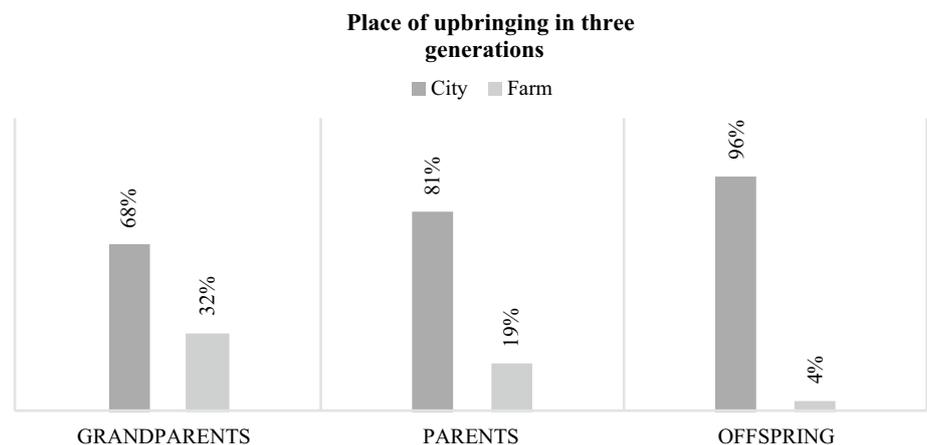
Key results

In this three-generation study, parental asthma was not associated with offspring farm upbringing in either of the two parent–offspring sets G0–G1 and G1–G2. Therefore, this study is not consistent with the hypothesis that the protective effect from farm upbringing on asthma may be due to selective migration from farming environments over generations. However, asthmatic G1 parents were more likely to raise their offspring in another environment than where they grew up themselves, while asthmatic G0 parents did not tend to change residential area.

Table 1 Characteristics of the study population in the RHINE/ECRHS (G1) and the RHINESSA (G2)

	G2 (RHINESSA)				G1 (RHINE/ECRHS)*			
	All	Farm upbringing	City upbringing	Missing	All	Farm upbringing	City upbringing	Missing
	N = 8260	N = 335	N = 7794	N = 131	N = 6045	N = 909	N = 4168	N = 968
Birth year, mean (min.;max.)	1984 (1963;1998)	1984 (1964;1997)	1984 (1963;1998)	1985 (1965;1998)	1956 (1945;1973)	1954 (1946;1973)	1956 (1945;1973)	1956 (1945;1972)
Sex, N (% F)	4781 (58%)	207 (62%)	4505 (58%)	69 (53%)	3311 (55%)	519 (57%)	2297 (55%)	495 (51%)
Parental asthma status, N (%)								
No parents with asthma	6389 (77%)	259 (77%)	6112 (78%)	18 (13%)	5321 (88%)	786 (86%)	3572 (86%)	963 (99%)
At least one parent with asthma	1598 (19%)	74 (22%)	1518 (20%)	6 (5%)	723 (12%)	123 (14%)	596 (14%)	4 (1%)
Missing	273 (3%)	2 (1%)	164 (2%)	107 (82%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Maternal upbringing [^] , N (%)								
Farm	1222 (15%)	131 (39%)	1086 (14%)	5 (4%)	1606 (27%)	573 (63%)	758 (18%)	275 (28%)
City	6831 (83%)	202 (60%)	6616 (85%)	13 (10%)	3539 (58%)	264 (29%)	2783 (67%)	492 (51%)
Missing	207 (2%)	2 (1%)	92 (1%)	113 (86%)	900 (15%)	72 (8%)	627 (15%)	201 (21%)
Paternal upbringing [^] , N (%)								
Farm	1277 (16%)	205 (61%)	1069 (14%)	3 (2%)	1613 (27%)	617 (68%)	742 (18%)	254 (26%)
City	6621 (80%)	123 (37%)	6484 (83%)	14 (11%)	3367 (56%)	207 (23%)	2682 (64%)	478 (49%)
Missing	362 (4%)	7 (2%)	241 (3%)	114 (87%)	1065 (18%)	85 (9%)	744 (18%)	236 (25%)

[^]As reported by G2 in RHINESSA, *For the RHINE/ECHRHS cohort i.e. “parental asthma” refers to asthma of their parents meaning G0

Fig. 2 Bar chart depicting the prevalence of farm and city upbringing in three generations in RHINESSA

Strengths and limitations

The multi-generation design is the most important strength of this study. To our knowledge, this is also the first study to investigate asthma and selective migration over generations taking both parents' asthma status into account.

However, all variables were measured by questionnaires, which poses a risk of recall bias. Furthermore, several variables were reported on behalf of others. We believe that

both offspring and parents were able to report their own place of upbringing correctly; however, offspring's report on behalf of their parents may be subject to misclassification. We envisage that this misclassification may be influenced by the offspring's own place of upbringing, and it may have introduced bias to the results. However, we do not believe that the misclassification is related to the parents' asthma status and would therefore expect any bias from this to be non-differential. Reports of asthma (both self-reported and

Table 2 Risk ratios (RR) for offspring farm upbringing (outcome) according to parental asthma (exposure) in G1–G2 adjusted for G1 place of upbringing and stratified by study centre

	At least one parent with asthma		Crude RR	RR (95% CI)
	Yes (% offspring farm upb.)	No (% offspring farm upb.)		
Aarhus (DK)	169 (5.9%)	707 (4.2%)	1.39	1.55 (0.78; 3.06)
Albacete (ES)	36 (0.0%)	38 (0.0%)		
Bergen (NO)	318 (2.5%)	1330 (2.8%)	0.90	0.95 (0.46; 1.99)
Gothenburg (SE)	141 (1.4%)	792 (0.9%)	1.60	1.49 (0.32; 7.03)
Huelva (ES)	14 (0.0%)	55 (0.0%)		
Melbourne (AU)	87 (0.0%)	4 (0.0%)		
Reykjavik (IS)	231 (3.9%)	928 (1.4%)	2.78	2.74 (1.21; 6.20)
Tartu (EE)	37 (0.0%)	488 (5.5%)		
Umeå (SE)	287 (11.8%)	1009 (8.8%)	1.34	1.37 (0.96; 1.95)
Uppsala (SE)	272 (4.0%)	1020 (5.5%)	0.74	0.77 (0.42; 1.43)
All	1592 (4.6%)	6371 (4.1%)	1.10	1.11 (0.81; 1.52)

Table 3 Risk ratios (RR) for offspring farm upbringing (outcome) according to parental asthma (exposure) in G0–G1 adjusted for G0 place of upbringing and stratified by study centre

	At least one parent with asthma		Crude RR	RR (95% CI)
	Yes (% offspring farm upb.)	No (% offspring farm upb.)		
Aarhus (DK)	82 (14.6%)	492 (17.9%)	0.82	0.79 (0.48; 1.29)
Albacete (ES)	12 (8.3%)	31 (6.5%)	1.29	2.28 (0.25; 21.11)
Bergen (NO)	123 (19.5%)	758 (21.6%)	0.90	0.90 (0.61; 1.34)
Gothenburg (SE)	88 (8.0%)	609 (8.9%)	0.90	0.92 (0.45; 1.87)
Huelva (ES)	6 (0.0%)	32 (6.3%)		
Melbourne (AU)	23 (21.7%)	81 (7.4%)	2.93	2.51 (1.25; 5.05)
Reykjavik (IS)	113 (9.7%)	590 (11.0%)	0.88	0.81 (0.43; 1.50)
Tartu (EE)	31 (25.8%)	254 (28.3%)	0.91	1.07 (0.56; 2.07)
Umeå (SE)	122 (35.2%)	751 (29.0%)	1.21	1.10 (0.89; 1.35)
Uppsala (SE)	119 (10.1%)	760 (15.1%)	0.67	0.80 (0.49; 1.33)
All	719 (17.1%)	4358 (18.0%)	0.98	0.99 (0.85; 1.15)

Table 4 Risk ratios (RR) for offspring farm upbringing (outcome) according to parental asthma (exposure) in G1–G2 adjusted for study centre and the opposite parent's place of upbringing, and stratified by G1 place of upbringing

	At least one parent with asthma		Crude RR	RR (95% CI)
	Yes (% G2 offspring farm upb.)	No (% G2 offspring farm upb.)		
G1 father born in a city	940 (2.7%)	3798 (1.8%)	1.49	1.54 (0.98; 2.41)
G1 mother born in a city	928 (3.8%)	3828 (2.5%)	1.49	1.54 (1.07; 2.22)
Both born in a city	824 (2.1%)	3339 (1.0%)	1.97	2.00 (1.12; 3.55)
G1 father born on a farm	152 (13.8%)	724 (14.8%)	0.94	0.92 (0.60; 1.42)
G1 mother born on a farm	164 (6.7%)	694 (11.2%)	0.60	0.63 (0.34; 1.16)
Both born on a farm	48 (6.3%)	235 (19.1%)	0.33	0.34 (0.11; 1.06)

offspring-reported parental asthma) usually have a high specificity and a moderate sensitivity [17, 18]. If cases with asthma were incorrectly reported as healthy, this might have attenuated the results in our analyses.

Drop-out from the parent population was substantial (approx. 50%), and selection bias cannot be ruled out [15]. Furthermore, the response rate among offspring in

the RHINESSA was modest (34%). This may have biased our results if non-response and dropout were related both to asthma and place of upbringing. A recent non-response analysis in the RHINE cohort concluded that asthma prevalence was similar among the baseline study population and long-term responders (4.7% at baseline and 4.6% in RHINE 3) [15]. However, the original ECRHS/RHINE populations

Fig. 3 Offspring farm upbringing (outcome) according to parental asthma status (exposure) and parental place of upbringing

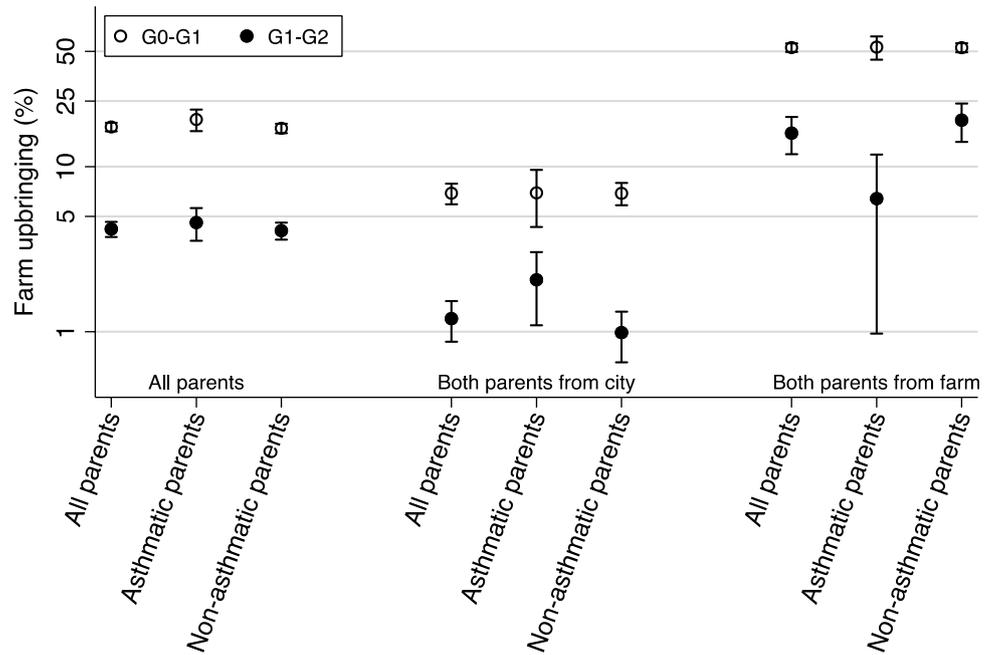


Table 5 Risk Ratios (RR) for offspring farm upbringing (outcome) according to parental asthma (exposure) in G0–G1 adjusted for study centre and the opposite parent's place of upbringing, and stratified by G0 place of upbringing

	At least one grandparent with asthma		Crude RR	RR (95% CI)
	Yes (% G1 offspring farm upb.)	No (% G1 offspring farm upb.)		
G0 father born in a city	402 (7.7%)	2407 (7.2%)	1.05	1.10 (0.76; 1.58)
G0 mother born in a city	420 (8.3%)	2442 (8.8%)	0.93	0.88 (0.63; 1.23)
Both born in a city	360 (6.9%)	2174 (6.9%)	1.03	1.07 (0.74; 1.54)
G0 father born on a farm	190 (41.6%)	1141 (46.0%)	0.89	0.98 (0.83; 1.15)
G0 mother born on a farm	172 (43.6%)	1160 (41.7%)	1.02	1.02 (0.88; 1.20)
Both born on a farm	130 (53.1%)	873 (52.7%)	1.01	1.01 (0.85; 1.19)

were sampled in and around larger cities, and urban dwellers are over represented. Place of upbringing or residence may have influenced the likelihood of non-response in both the RHINE/ECRHS and the RHINESSA. A recent non-response study from Denmark suggested that participation rates among inhabitants in Copenhagen were significantly lower than in the rest of the country, and a Belgian study similarly found that odds ratio for non-participation rose with increasing level of urbanization [19, 20]. As non-response is only related to outcome (residency) and not exposure (asthma status) of interest, the potential bias from this issue would be non-differential.

Another limitation is the lack of analyses on selective migration due to allergies as the farm effect is most evident for allergic disorders such as hay fever [8, 21, 22]. However, the results of our sub-analyses showed the same picture as for asthma, although the information on parental diseases for both G0–G1 and G1–G2 analyses was incomplete. In contrast, Bråbäck et al. observed that Swedish middle-aged

men with hay fever at conscript examination were less likely to take over the family farm [10].

Interpretation

Study designs and conclusions drawn from the current evidence on selective migration due to asthma are inconsistent. In a recent Swedish study, Bråbäck et al. investigated selective migration from the farming environment among 43,234 young men from farmparents [10]. They found that at the age of 35–39 years, farm living was significantly less likely if the men had asthma at the conscript examination, and they concluded that selective migration possibly could contribute to explain the observed lower prevalence of asthma among farmers' children. In line with this finding, Vogelzang et al. observed that asthmatic adolescents were less likely to become pig farmers than non-asthmatics [11]. Conversely, Eduard et al. found a similar prevalence of asthma among Danish farm students and their

non-farming siblings, suggesting no healthy worker selection into farming [12]. Likewise, a Swedish study among 707 children on the island of Gotland found no difference in frequency of family history of asthma between farmers' and non-farmers' children [13]. Interestingly, Bråbäck et al. and Vogelzang et al. both suggested selective migration in populations comparable in calendar time to G1 in our study, while Eduard et al. and Klintberg et al. both suggested no selective migration in populations comparable to G2 in our study. Thus, the literature suggests different pictures for different generations; however, we observed the same patterns for both G0–G1 and G1–G2.

As far as we know, we are the first to report moving patterns among asthmatics independently of their residence. We interpret the differences in moving patterns between G0 and G1 as a result of the different periods in history influencing the ability to move. Student's *T* test revealed no association between asthma status and socioeconomic status in G1 ($p=0.27$), and we do therefore not believe that socioeconomic status can explain this finding. Mobility may also have varied markedly between study centres. The huge structural changes of the farms have occurred during the past five or six decades which may also have influenced the likelihood of moving. In addition, the G0 were not enlightened about the environmental influences on asthma, while we speculate that asthmatic G1 parents may suspect that their childhood exposures caused or worsened asthma and therefore tended to move. Furthermore, farmers with asthma may realize that they cannot continue as farmers because of their work-related worsening of symptoms and thus seek avoidance. A similar tendency seems to have affected pet keeping, as several studies have observed a "healthy pet-keeping effect" [23, 24].

Conclusion

This three-generation cohort study suggests that selective migration is not an important explanatory factor for the protective effect from farm upbringing on asthma, since parental asthma was not associated with offspring farm upbringing, either in analyses of the younger generations G1–G2 or analyses of the older generations G0–G1. Interestingly, individuals with asthma in G1 tended to move and raise their children in a different environment from where they grew up themselves, whereas individuals with asthma in G0 tended to stay in the same environment when raising children, probably due to differences in mobility patterns over generations.

This study contributes to the understanding of potential selection across generations for the farming effect on asthma. Further studies are needed to confirm these observations.

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Compliance with ethical standards

Conflict of interest Michael Abramson has received investigator-initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. The other authors declare no conflict of interest.

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