

REVIEW ARTICLE

Exposure to farming environments in childhood and asthma and wheeze in rural populations: a systematic review with meta-analysis

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Abstract

Asthma is a chronic respiratory disorder that has become substantially more common over the past decades. One environmental factor for which particularly strong associations with asthma and allergic diseases have been described is exposure to farming environments in childhood. The aim of this systematic review was to update and extend existing narrative reviews, test for heterogeneity of effect across studies, and conduct a meta-analysis to report a summary effect measure. Published relevant literature was searched through PubMed including all articles added to PubMed before September 1, 2011. Articles were included if they reported an epidemiological study on the exposure to a farming environment in childhood and subsequent wheeze or asthma. Heterogeneity of effect measures across studies was evaluated using Cochran's Q and I^2 . Random-effects meta-analysis was performed to summarize effect measures for various outcome definitions. In total, 357 retrieved abstracts revealed 52 original articles from 39 studies with data considered for the meta-analysis. Most studies were conducted among children or on childhood onset of disease. Most data were published on doctor-diagnosed asthma or current wheeze. The meta-analysis showed substantial heterogeneity across studies with similar outcome definitions. Nonetheless, the combined effects were statistically significant and showed an approximate 25% lower asthma prevalence among exposed subjects compared with unexposed subjects. The protective 'farm-effect' on asthma was reported in numerous studies. Its underlying factors ought to be studied, and promising efforts have been already made. However, the heterogeneity of the effect across studies should also be investigated because whatever causes it is a potential threat to valid synthesis of evidence and to the detection of specific protective factors.

Asthma is a chronic respiratory disease that has been on the rise around the world in the past century (1). One environmental factor for which particularly strong associations with asthma are described in the literature is exposure to a farming environment in childhood. An early report noted a

significant negative correlation between living on a farm and prevalence of allergic rhinitis among Swedish conscripts (2). Ten years later, Braun-Fahrlander et al. (3) investigated the effect size of living on a farm with childhood asthma and allergic disease. Since then, this so called 'farm-effect' has

Abbreviations

4-H club, A youth organization. The name represents four personal development areas of focus for the organization: head, heart, hands, and health; 95% CI, 95% confidence interval; ALEX, Allergy and Endotoxin Study; E3N, Etude Epidémiologique des Femmes de la Mutuelle Générale de l'Education Nationale; ECRHS, European Community Respiratory Health Survey; GABRIELA, The GABRIEL Advanced Surveys. GABRIEL is the name of the larger project and is not an acronym; ICD, International Classification of Diseases; IR, incidence risk ratio; ISAAC, International study of Asthma and Allergies in Childhood; min, minimum; max, maximum; NLSCY, Canadian National Longitudinal Survey of Children and Youth; OR, odds ratio; PARSIFAL, Prevention of Allergy Risk factors for Sensitization In children related to Farming and Anthroposophic Lifestyle; PECOS, Prairie Ecosystem Study; PR, prevalence ratio; Q1, first quartile; Q3, third quartile; RR, incidence rate ratio; SCARPOL, Swiss Study on Childhood Allergy and Respiratory symptoms with Respect to Air Pollution.

been extensively reported for atopy, allergic disease, and asthma (4). The majority of studies have addressed childhood asthma but there are some studies among adults or on adult onset of disease as well (4).

An editorial to three of the earlier publications on the protective effect of exposure to farming environments on asthma mentioned that the protective effect on asthma was less consistent than that for hay fever (5). This notion has been picked up in various publications thereafter (6–12).

The ‘farm-effect’ on atopic eczema and allergic rhinitis but not asthma was addressed by a systematic review and meta-analysis of the literature up to 2007 (13). The authors described that there was significant heterogeneity between studies. Nonetheless, the authors conclude that ‘farm living had a substantial protective influence on the development of allergic stigmata’ (13). For asthma, a systematic review of the literature up to 2004 was published as a side note in an original article (14). Here, a test for heterogeneity across studies was not statistically significant (14). Both systematic reviews lack detail about the included studies and investigation of publication bias, and the one on asthma does not give information about the search terms used.

Although several authors comprehensively reviewed the evidence for the ‘farm-effect’ on asthma (4, 6, 15), to date, no sufficient systematic review with meta-analysis has been published on this matter. Furthermore, the claim of inconsistency has not been explored in detail using a meta-analytical approach.

This systematic review aims to update and extend the existing narrative reviews and the one systematic review on the ‘farm-effect’ on asthma. Objectives are to assemble evidence from epidemiological studies on the ‘farm-effect’ on wheeze and asthma, test for heterogeneity of effect across studies, and conduct a meta-analysis to report a summary effect measure.

Methods

Search strategy

The search of publications from epidemiological studies was conducted on September 1, 2011, using PubMed (of the US National Library of Medicine, <http://www.ncbi.nlm.nih.gov/pubmed>) which comprises citations from MEDLINE, life science journals, and online books. The search term was ‘(farming OR farm) AND (asthma OR wheeze) AND (Humans[Mesh])’ the latter term indicating the setting of limits to human studies in PubMed. No time period or other restrictions (e.g., language, age of subjects) were made. No lower limit was set for the time period of publication or entry into PubMed. The earliest publication dated back to September 1969.

A second search was conducted also on September 1, 2011, with the modification that the limit to human studies with the last MeSH Term omitted to allow for articles that were not yet assigned MeSH terms by PubMed. Only articles added to PubMed in 2010 and 2011 were searched by adding ‘AND 2010:2011/08/31[edat]’. Non-human studies were excluded based on the abstract and not counted as search hits.

Reference lists of all publications containing relevant content including reviews, editorials, commentaries, or letters were compared with the already retrieved hits. References that had not yet been evaluated were hand-searched and fed into the evaluation process.

Inclusion and exclusion

All retrieved abstracts were read, and a given publication was deemed relevant if the abstract gave any indication that asthma or asthma symptoms such as wheeze may have been studied with regard to childhood farm exposure in rural populations. Childhood was operationalized as the period of life from birth to the 18th birthday. Review articles, editorials, commentaries, or letters were categorized as relevant if the abstract indicated that they contained text on asthma or asthma symptoms as well as farm exposure. Full text of all relevant publications was again evaluated for relevant content or references with potentially relevant content.

Publications that described only adult or occupational exposure to farming were excluded. Farming students were regarded as occupationally exposed, even if they were below 18 yr of age.

Original articles that did not describe data on wheeze or asthma in relation to exposure to farming in childhood were excluded.

Of the remainder, only original articles in which exposure to farming in childhood was operationalized in at least one of the following ways were included in the meta-analysis:

- Acquiring data on whether the study participant lives or lived on a farm or in a farming environment in childhood (regardless of the specified period of childhood).
- Acquiring data on whether the paternal or maternal occupation is farming.

Other original articles that operationalized exposure to farming in childhood in a different way (e.g., exposure during pregnancy, exposure to livestock, and keeping livestock) or other publications (e.g., reviews) were not included in the meta-analysis.

Data extraction

Information on the study design and setting, age of the participants, the exposure and outcome definitions, modeled confounders, and point estimates together with 95% confidence intervals (95% CI) or p-values as well as the type of point estimate (odds ratio [OR], prevalence ratio, incidence risk ratio, incidence rate ratio) were extracted. Further information that was regarded as relevant was collected.

For publications for which no measure of association was published, crude odds ratios were recalculated from published numbers or published numbers in combination with published prevalences if possible. All measures of association were extracted together with their 95% CI with a precision of two decimals.

If multivariate models contained other, more specific indicators of farm exposure (e.g., exposure to livestock and regular stay in barns), the adjusted estimates were not extracted

because the effect of the broader proxy for farm exposure will in general be attenuated and no longer comparable with other studies.

Data analysis

To obtain the standard error of the log(OR) for meta-analysis, the standard error was recalculated from the lower and the upper limit of the 95% CI, and the arithmetic mean of both estimates was used. The displayed confidence intervals are based on the recalculated standard error and may deviate from published confidence intervals.

The extracted data were categorized to be from a 'childhood study' if it was assessed either among children or among adults but on childhood onset of disease. Studies among adults with either no indication for onset of disease or adult onset of disease were classified as 'adulthood studies'.

In case of multiple publications of the same study, the publications were checked for consistency with regard to the same or similar associations. If there were multiple publications of the same association from one study, one was selected for meta-analysis based on the higher methodological quality (see Data S1).

To assess evidence of publication bias, funnel plots were drawn, and Egger's test for small-study effects (p_{Egger}) was performed (16, 17). For this, all adjusted point estimates (regardless of methodological issues or definition of exposure and outcome) were included. If there was only a crude estimate for an association, this was included. This means that multiple estimates from a single publication and also multiple publications per study are included. Estimates for different outcomes were labeled with different symbols in the funnel plots.

Combined effect measures and measures of heterogeneity between studies were derived by random-effects meta-analysis using the 'Dersimonian-Laird' method. The p -value from the chi-squared test for heterogeneity (p_{het}) and the value for I^2 and its 95% confidence interval were calculated (18). I^2 describes the percentage of total variation across studies, which is owing to heterogeneity rather than chance (18). Heterogeneity was explored with regard to methodological issues, exposure and disease definitions, and average birth cohort of the study population.

Statistical analyses were performed, and forest plots were created with SAS 9.2 (The SAS Institute, Cary, NC, USA). Funnel plots and Egger's test for small-study effects were created with STATA SE 10.1 (StataCorp LP, College Station, TX, USA).

Results

The evaluation process is depicted in Fig. 1. In total, 357 abstracts were retrieved in the literature search. The first search yielded 341 abstracts, and the second search yielded 16 additional abstracts on human studies. Eight of those 16 contained relevant full text. Details on reasons for inclusion and exclusion are given in the Data S1.

Criteria for the meta-analysis were fulfilled by 51 full texts describing results from 39 studies (Table 1). The studies are

numbered by their appearance in PubMed except one article not indexed in PubMed, which is placed at the end of the list (study #39). Details on these studies' design, study population, methodological quality, as well as exposure and disease assessment are given in the Data S1.

Most studies were cross-sectional or performed cross-sectional analyses reporting ORs. Table 2 displays how many studies gave information on childhood and adulthood disease and how often certain exposure and disease indicators were used. Furthermore, the range of exposure and disease prevalence is described. Prevalence of exposure to farming environments in childhood covered a very broad range across the studies from about 5% to 85%. For all outcomes but wheeze ever, the median disease prevalence was below 15%. Although there were some studies that reported extremely high prevalences of over 30%, most studies reported prevalences below 20%.

Definitions of asthma and wheeze varied across studies (see Data S1). Common instruments to assess wheeze or asthma were the questionnaires from the International Study of Asthma and Allergy in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS) (19–22). The definitions employed by the studies were classified as into 'current wheeze', 'wheeze ever', 'doctor diagnosed asthma', and 'asthma ever' as defined in the Data S1. Data on wheeze in the past 12 months (termed 'current wheeze') and doctor-diagnosed asthma were reported by many studies, followed by asthma ever and wheeze ever.

Inclusion of all relevant point estimates from all studies resulted in the funnel plot shown in Fig. 2. Funnel plots after stratification into childhood and adulthood studies are depicted in the Data S1. The funnel plot gave some evidence of asymmetry, particularly with more effect estimates from small studies that were strongly protective rather than showing strong positive associations. The p -value from Egger's test was $p = 0.001$ for all studies and childhood studies only. For adulthood studies, it was $p = 0.793$. Exclusion of studies that were regarded to have methodological issues did not change the plots or test results substantially. Further exclusion of crude estimates also made no difference (data not shown). Virtually, all studies calculated ORs but the standard errors did not correlate with disease prevalence, suggesting no influence of the choice of effect measure in combination with the disease prevalence (data not shown).

The initial meta-analyses were stratified into childhood and adulthood studies and carried out per asthma indicator (current wheeze, doctor-diagnosed asthma, asthma ever, and wheeze ever). All studies were included regardless of methodological issues or control for confounding. The meta-analysis was grouped by exposure definition (farm residence, parental occupation, combination of both). The result is depicted in Figs 3 and 4 for childhood studies on doctor-diagnosed asthma and current wheeze, respectively. The number of studies for the other indicators and the adult studies was low, and forest plots are given in the Data S1.

There was substantial heterogeneity with an I^2 of up to 76% within exposure groups and across all studies for all disease indicators that were investigated by more than five

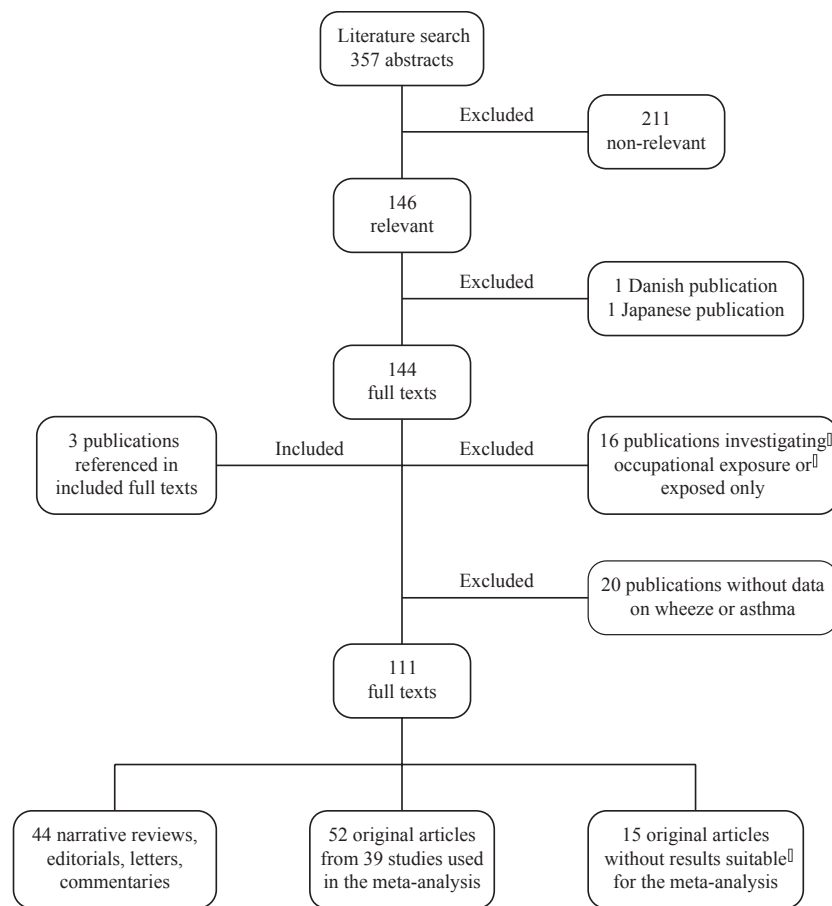


Figure 1 Flow chart of the literature search and the evaluation process.

studies. Some of these groups had lower estimates of I^2 than others but if so tended to be comprised of less studies with only one or two larger studies dominating the group. Exclusion of studies with methodological issues or restriction to studies with adjusted estimates or highly comparable disease definitions did not alter the results substantially (data not shown). Furthermore, sorting the studies by average birth cohort of the study population did not reveal a clear trend of effect estimates across birth cohorts (data not shown). When the childhood studies were restricted to methodologically sound studies conducted in and around the Alps in Europe, heterogeneity decreased (studies #4, 11.1, 22.1, 36.1–36.4 for doctor-diagnosed asthma with I^2 52% and studies #1, 4, 22.1, 36.1–36.4 for current wheeze with I^2 0%).

For doctor-diagnosed asthma and current wheeze, the combined estimate around 0.75 indicates a 25% reduction of odds of disease for children exposed to farming environments compared with the unexposed. Because the prevalence of asthma and wheeze was below 20% in the majority of studies, this translates into an approximately 25% lower prevalence of childhood disease among those exposed to farming in childhood compared with the unexposed. However, the substantial amount of heterogeneity between studies has to be recognized.

For adult studies, there was less heterogeneity between studies for doctor-diagnosed asthma but a similarly sized effect. The other outcomes were investigated only by a few childhood or adulthood studies. For all but asthma ever among childhood studies, there was a protective combined effect of exposure to farming in childhood; however, this was mostly driven by few larger studies.

Discussion

This systematic review identified a large body of evidence that had earlier been reviewed in a narrative way (4, 6, 8, 11, 12, 15, 23, 24). However, it extends beyond earlier reviews because it includes a number of additional articles (most of them only recently published), because a more rigorous assessment of the studies' methods was employed, and because meta-analyses were performed. The meta-analyses produced statistically significant summary estimates which suggest that the prevalence of asthma and wheeze may be approximately 25% lower among subjects exposed to farming environments in childhood compared with unexposed subjects. There was also substantial heterogeneity across studies with between study variance accounting for up to

Table 1 Details of studies included in the meta-analyses

No.	Ref.	Study region	Sample size*	Age (yr)†	Birth cohort‡
1	3	Switzerland	1620	6–15	1984
2.1	45	Finland	10,667	18–24	1974
3	25	Austria	2001	8–11	1987
4	46	Germany	9835	5–7	1991
5	47	Canada	9082; 1199	12–19	1984
6	48	Canada	393	<18	1986
7	26	Switzerland	1287	15	1976
8.2	49	Finland	5509	31	1966
9.1, 9.2	50	Australia	473; 963	7–12	1987
10	27	Sweden	707	7–8	1989
11.1, 11.2	42, 51	Austria, Germany, Switzerland	812	6–13	1989
12.1	52	Europe	6251	20–44	1959
12.2	53	France	600	31–59	1955
13	54	Finland	7981	13–14	1991
14	43	New Zealand	293	7–10	1993
15.1–15.3	55	Sweden	1,316,985	17	1957, 1967, 1977
16	56	USA	3090	6–14	1990
17	57	Vietnam	2641	5–13	1992
18	58	USA	4247	4–16	1993
19	59	Finland	710	6–13	1991
20	60	USA	644	1–17	1987
21	61	USA	13,490	14–17	1985
22.1	9	Europe	8263	5–13	1992
23	14	UK	4767; 879	5–11	1992
24	30	USA	309	5–11	1998
25	62	Greece	797	7–18	1988
26	63	Canada	1158	7–19	1988
27	64	The Netherlands	1798	27–64	1955
28	65	Germany	1595	18–44	1972
29	66	Canada	13,524	0–11	1988
30.1	67	New Zealand	5616	28–70	1958
30.2	68	New Zealand	1899	5–17	1996
31	28	Austria	33,808	6–10	1997
32	69	Canada	477; 212	5–9	1993
33	70	USA	25,814	20–88	1941
34.1, 34.2	71	The Netherlands	877	18–65	1964
35	29	Sweden	1261	16–20	1990
36.1–36.5	72–75	Europe	103,219	6–12	1997
37.1, 37.2	76	France	54,018	40–65	1937
38.1	77	Denmark	999	16–26	1972
38.2	78	Denmark	122 cases, 116 controls	16–26	1972
39	79	Canada	1704	5–11	1985

*Sample size of the study population that underlies the estimates used in the meta-analysis. Sometimes estimates were from different subpopulations indicated by multiple sample sizes.

†Age at baseline for cohort studies. Age ranges were approximated for some studies. More details in Data S1.

‡Mean birth cohort of the study population approximated from the mean age and study period (or year of publication if study period was unknown).

76% of the total variance. This is in stark contrast to heterogeneity across studies on the ‘farm-effect’ on childhood atopy. Based on the data displayed in a recent review (4), the corresponding estimate is only 12% (95% CI 0–52%; calculations not shown). The heterogeneity of reports on the ‘farm-effect’ on asthma was only partly explained by

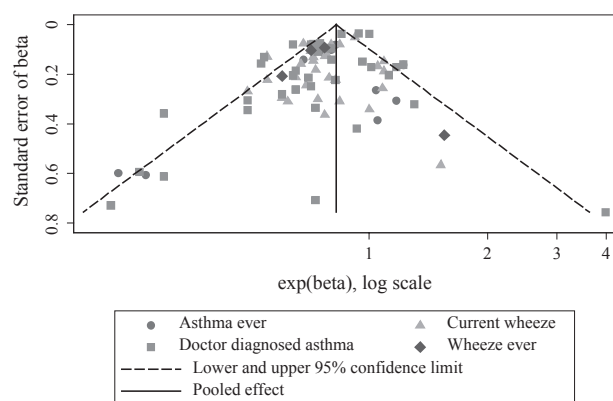
methodologically questionable estimates, control for confounding, or heterogeneous exposure and disease definitions.

A limitation is that the search was only performed in Pub-Med. However, effort was made to prevent location bias by employing a broad search term without language restriction, circumventing the use of MeSH terms, and evaluating

Table 2 Frequency of reports and distribution of reported exposure and disease prevalence among the studies considered in the meta-analysis*

	Total (n = 39)		Childhood studies (n = 29)		Adulthood studies (n = 10)	
	n	Median (min; max)	n	Median (min; max)	n	Median (min; max)
Exposure indicators						
Living on a farm	19	28.6 (6.0; 83.9)	13	28.6 (14.1; 83.9)	8	42.5 (6.0; 60.9)
Parental occupation	12	19.2 (3.4; 85.6)	11	19.1 (3.4; 85.6)	2	22.9 (22.9; 22.9)
Combination	6	13.7 (11.1; 36.7)	6	13.7 (11.1; 36.7)	1	12.1 (12.1; 12.1)
Disease indicators						
Wheeze in the past 12 months	25	13.9 (4.3; 33.2)	22	14.2 (4.3; 33.2)	5	13.7 (10.5; 23.4)
Wheeze ever	5	30.9 (16.6; 32.4)	5	30.9 (16.6; 32.4)	0	
Asthma ever	10	10.2 (3.5; 33.4)	8	8.8 (3.5; 33.4)	3	12.9 (11.1; 14.7)
Doctor-diagnosed asthma	29	8.7 (0.9; 18.7)	22	10.2 (1.6; 18.7)	9	4.7 (0.9; 9.5)

*The median, minimum, and maximum prevalence of exposure or disease from contributing studies is given in %. Studies can report on more than one item within onset, exposure, or disease. Study #30 reported on children and their parents and assessed living on farm in childhood for the parents whereas for the children the exposure was defined by parental occupation.

**Figure 2** Funnel plot of estimates from publications included in the meta-analysis, labeled according to the outcome definition.

references from retrieved articles, in particular from numerous review articles, commentaries, and editorials by experts in the field.

The relevant publications contained in the majority more than one relevant point estimate. Furthermore, multiple publications per study occurred. However, multiple publication bias is unlikely to affect the meta-analysis because a substantial number of studies, also smaller studies, with just one publication were retrieved.

To assess publication bias, a funnel plot was drawn that included all point estimates on all relevant outcomes from all publications, regardless from which publication they were derived. The reasoning was that this would resemble the whole published body of evidence which should be tested for publication bias. Egger's test suggested that there were small studies showing strong effects. Furthermore, the funnel plot gave some evidence of asymmetry, particularly with regard to five strongly protective associations from five small studies (25–29) and just one strong positive association from another small study (30). However, the latter was subject to

methodological issues and of the five small studies with strong protective effects two provided crude estimates (31, 32) and another was on a very strict outcome definition (28). It seems unlikely that the combined effect and the heterogeneity detected in the meta-analysis are fully owing to publication bias.

Fifteen publications reported on the association of exposure to farming in childhood with wheeze or asthma but were not included in the meta-analysis (details in the Data S1). They were assumed to be incomparable with studies which use a broader proxy for farm exposure or avoid inclusion of urban populations. Another reason was that non-significant findings were quoted in the text without reporting of effect estimates. This may provide some evidence of publication bias. However, increased risk of asthma as well as inverse or null associations were quoted in these articles which makes a strong influence on the results of the meta-analysis unlikely.

The exposure definitions were broad proxies for exposure to farming environments in childhood and associations with specific farm exposures such as exposure to livestock have been explicitly excluded. Evidence from various studies pointed toward the contact with livestock and possibly associated fodder and to the consumption of unpasteurized cow's milk. This is not reviewed here because it is covered extensively in previous reviews (4, 11, 15). As the studies included in this meta-analysis vary with regard to the farming environments investigated albeit being conducted among rural populations, a different distribution of the factors that truly underlie the 'farm-effect' across studies could be the reason for the detected heterogeneity. Furthermore, the composition of the unexposed subjects may play a role as the exposure contrast varied across studies.

It has been argued that the farms in regions close to or in the Alps in Switzerland, Austria, and Germany may show particularly protective effects because they are small in scale and traditional farms with just livestock, in particular cattle, and because the children living there are in very close contact to the farm life (4). When the meta-analysis was restricted to childhood studies conducted in these areas, the heterogeneity

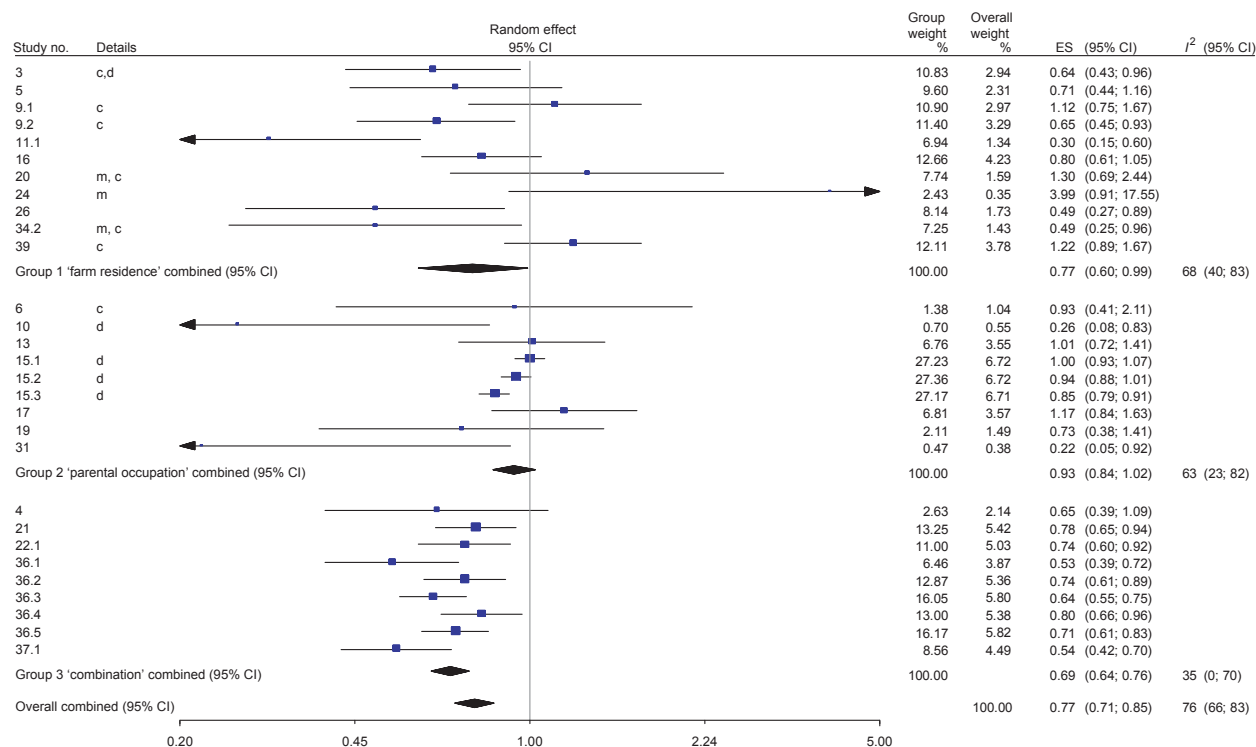


Figure 3 Forest plot for the association between farm exposure in childhood and doctor-diagnosed asthma from childhood studies. The random-effects meta-analysis is grouped by different exposure definitions (farm residence, parental occupation, combination of both). Combined estimates are per group and overall. Within group weights and overall weights are displayed. The symbols of the effect estimates of each study are scaled according to the overall weight. Study #: the study number provided in Table 1; details: m = methodological issues (detailed in Data S1), c = crude estimate, d = differing disease definition from the categorization described in the Data S1; ES: effect size; I^2 : measure of heterogeneity, given in %.

for current wheeze decreased. However, these meta-analyses were dominated by the large GABIELA study. Nonetheless, this may lend further support to the notion of heterogeneity owing to specific farm environments.

The described studies also varied in their control of confounding. For some studies, only crude associations were available. Age, gender, and familial allergies were controlled for in most studies that published adjusted associations. The number of siblings was accounted for by some. For the 1966 Finnish birth cohort (study #8), there was evidence from the two included publications that inclusion of additional covariates into a multivariate model may have a large effect on the observed association. Residual confounding or 'overadjustment' may apply to any published association and distort the conclusion from this meta-analysis.

Most of the studies were cross-sectional and retrospectively assessed exposure to farming in childhood. However, the place of upbringing as well as the father's or mother's occupation is likely to be recalled correctly. Furthermore, distorted responses owing to, for example, social desirability or attribution to development of asthma are unlikely. Thus, with regard to exposure, information bias cannot substantially influence the detected associations.

One study (#5) used ISAAC questions in the full study population and French ECRHS questions in an

exposure-stratified random subsample. Interestingly, 12.7% among the exposed reported current wheeze in the ISAAC questionnaire, while 17.1% did when questioned with the ECRHS questionnaire. This increase can only be explained by selection bias, if all of the approximately 20% who were not assessed in the subsample were non-wheezers or had lost their wheeze. This seems unlikely and shows that different instruments will produce different disease prevalence estimates which may influence the detection of an association between exposure and disease. This may be especially true if different languages have to be used (36).

A lot of studies published on doctor-diagnosed asthma, most often self-reported but sometimes assessed from routine data sources. There are reports that diagnostic labeling differs across doctors and that a diagnostic label is often given with delay after onset of disease or possibly not at all (37, 38). However, heterogeneity may not only arise from varying diagnostic labeling and symptom expression and perception. There may be sub-phenotypes of wheeze and asthma that are particularly affected by the 'farm-effect'. Two childhood studies reported on stratification by atopy and did not see a different 'farm-effect' on atopics and non-atopics; however, the study populations were possibly too small to detect interaction (42, 43). Conversely, the 'farm-effect' on childhood wheeze was confined to non-atopic subjects after stratification

in the large GABRIELA study (44). Apart from this strong interaction, this study was the first to show a 'farm-effect' on transient early wheeze (44). Ege et al. (10) compared atopic and non-atopic children with doctor-diagnosed asthma, separately, to all non-asthmatics regardless of atopy. They found some evidence for specific farm exposures that only pertain to atopic or non-atopic subjects. However, this approach may lead to spurious associations because of the atopic subjects within the non-asthmatic reference group. In general, 'farm-effects' on sub-phenotypes may drive the associations with asthma – depending on the prevalence of the sub-phenotypes and strength of effects – which may also increase heterogeneity across studies.

Further work should be invested to summarize the evidence for the 'farm-effect' on atopy and allergic diseases. Sub-phenotypes, such as asthma among atopic and non-atopic subjects, separately, or childhood wheeze phenotypes need to be investigated more carefully and full information on reference groups should always be provided. The understanding of the published studies' settings and the correlation of published indicators for disease needs to be enhanced to reveal potential sources of heterogeneity.

The underlying causes in this complex environment should be unraveled because they may advance understanding of the disease and provide suggestions for cure or prevention.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.

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Online Supplement to “Exposure to farming environments in childhood and asthma and wheeze in rural populations: a systematic review with meta-analysis.”

Methods

Search strategy

The search was conducted in PubMed with the term “(farming OR farm) AND (asthma OR wheeze) AND (Humans[Mesh])”, the latter term indicating the setting of limits to human studies. The search term was automatically translated by PubMed into the fuller “(farming[All Fields] OR farm[All Fields]) AND (("asthma"[MeSH Terms] OR "asthma"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheeze"[All Fields])) AND "humans"[MeSH Terms]”.

Inclusion and exclusion

In total, 211 (59%) were classified non-relevant. One article retrieved in the first search was non-relevant because it described an animal study although PubMed limits had been set to human studies. The most prevalent reason for non-relevance was adult/occupational exposure (55.0%) followed by other non-relevant exposures (rural vs. urban, endotoxin, or others; 26.1%) and other disease than asthma or wheeze (10.4%). Articles could be non-relevant for multiple reasons.

One article was published in Japanese(1) and one in Danish(2), both with an English abstract. These two abstracts could not strictly be classified as non-relevant but were judged likely to be. Both journals were not electronically available and the author refrained from

ordering a paper copy due to the likely non-relevant content and the lack of quick and low cost options for translation into English or German. Both articles were excluded.

For the remaining 144 (40%) relevant abstracts full text was obtained and evaluated. Most publications were in English, some in German, and one in Spanish. One article(3) lead to a publication(4) not indexed in PubMed which contained relevant content on the same study and was included. Another two articles indexed in PubMed were referenced in several publications and also included.(5; 6)

Sixteen publications solely described data from occupationally exposed subjects or exposed subjects only without an unexposed comparison group.(3; 7–21) Twenty original articles did not contain original data on the relation of farming exposure in childhood with wheeze or asthma.(22–41) There were in total 44 narrative reviews, editorials, or commentaries/letters, all of which did not uncover any new references.(42–85)

In 15 original articles, either exposure was defined differently from the criteria for exposure to farming environments in childhood or relevant associations were only commented on but no estimates were provided.(6; 86–99) Two were reports of ecologic investigations of the association.(86; 88) The first was conducted in Germany and found more doctor visits for childhood asthma in a region with very high livestock density (and concentrated animal farming operations) compared to regions with average livestock density.(86) The second investigated several aggregate exposure proxies in North Carolina, USA, and found an inverse relation to regional asthma prevalence.(88)

Some studies reported increased risk of asthma by contact to farm animals or other specific farm exposures. Data from the Children's Health Study in California, USA, indicated that early exposure to farm animals may increase risk of asthma although statistical significance was only reached when crop or dust exposure was included in the exposure definition.(87) Exposure of the pregnant mother to farm animals was also significantly associated with an increased risk of asthma in Mexico City.(89) Similarly, contact to farm

animals during pregnancy and in early life increased the odds of allergic asthma without reaching statistical significance in a Finnish/Russian study.(93) In a Canadian study specific farm exposures including haying, harvesting, and feeding livestock were also positively associated with asthma but only emptying or filling to grain bins reached statistical significance.(94) The authors state in the abstract that “the prevalence of asthma did not differ by home location (farm/non-farm)”.

But also null or inverse associations were reported. A study on childhood asthma in Spain found a protective effect of contact with farm animals in the first year of life on atopy and the authors stated in the text: “These protective factors for sensitisation were not protective for asthma, rhinitis or eczema (data not shown).”(97) In a follow-up of a breastfeeding intervention trial in Belarus, contact with farm animals was significantly inversely related to current wheeze.(95) Likewise, a Chilean study found strongly reduced odds of childhood asthma among those with regular contact with farm animals.(98) Radon et al report data on adults living in Northern Germany who had regular visits to animal buildings in childhood.(6) They found an effect on nasal allergies but the picture was much less clear for atopic and non-atopic asthma symptoms which were investigated with non-asthmatics as the reference. The only significant protective effect was for atopic asthma symptoms with exposure in the fourth to sixth year of life.

A study from Mongolia found a protective but not significant ‘farm-effect’ on asthma among a rural population compared to an urban population and argued, that virtually all subjects in the rural region are exposed to animal husbandry from early life on.(90) Similarly, a study conducted in China, reported significantly reduced prevalence of wheeze and asthma comparing rural to urban children.(96) Almost all rural children had reported to have lived on a farm at some point in life, but this association was not displayed and also confounding was not corrected for. Furthermore, exposure to livestock farming was positively associated with current wheeze.

A study among Greek schoolchildren assessed whether parents were employed in farming and reported “no association between full-time, part-time or any occupation with farming and diagnosed asthma, wheezing, hay fever, eczema or allergic sensitization” without giving effect estimates.(91) For a study of candidate genes for asthma among Danish farming students, the authors noted “Potential confounders (being born and raised on a farm, smoking, and case–control status) had ORs close to one in multiple logistic regression models...” without giving detailed estimates.(92) Also, in a report on a study in Helsinki, Finland, authors reported that “Incidence of allergic rhinoconjunctivitis was significantly lower among those who had lived in the countryside or on a farm during the first 5 years of life compared to those who had not..., while this was not true for asthma.” without giving an effect estimate.(99)

Data extraction

For all retrieved abstracts information was collected on relevance and in case of non-relevance the reason (categorized into adult/occupational exposure, animal study, experimental study, case study, study on other disease than asthma, pharmacologic study, other exposure than exposure to farming). For relevant abstracts information from full text was collected. In case of non-relevance based on the content of the full text the reason was documented (adult/occupational exposure, non-exposed not assessed, or no data on wheeze or asthma).

Study design

Most studies were cross-sectional or performed cross-sectional analyses reporting odds ratios.

There were two birth cohort studies. For the 1966 Finnish birth cohort study (study #8) it was unclear at what time point exposure was assessed but disease was assessed at age 31 as lifetime prevalence and so estimates from this study were judged to be comparable to other studies and were included. Another birth cohort study in Tyrol, Austria (study #31), seems to have investigated associations with cumulative incidence of hospitalizations for atopic asthma among children aged six years or older using logistic regression. This estimate was included in the meta-analysis.

One prospective cohort study (study #29) reported on cumulative incidence of doctor diagnosed asthma over a 2-year period, another study (#32) published on cumulative incidence of wheeze using longitudinal analyses of two repeat surveys 3 years apart. A third prospective cohort study (#38) investigated the incidence rate of asthma using a case-control study with incidence density sampling. These three studies were not included in the meta-analysis because the period of incidence assessment did not match any periods of (retrospectively assessed) lifetime prevalence from the other studies.

Two studies (numbers 10 and 15) reported prevalence ratios whereas the others reported odds ratios. The prevalence ratios were included along with the odds ratios without any correction or transformation. The highest outcome prevalence from both studies was 12% and so the prevalence ratios are assumed to be very similar to the odds ratios, had they been calculated.

Some studies employed a complex survey design, mostly a disproportionate exposure stratified random sampling, but not all appropriately accounted for the design in the analyses. Depending on the relation between the stratification variable, the exposure, and the outcome this will introduce confounding. For some studies, only crude estimates were available. Some studies used reference categories that were judged to be different from most other studies. For all these studies, the originally reported estimates of association are primarily included in the meta-analysis and, if warranted, subsequently excluded.

122 *Exposure and outcome: definitions and prevalences*

123 Definitions of asthma and wheeze varied across studies. Common instruments to
124 assess wheeze or asthma were the questionnaires from the International Study of Asthma and
125 Allergy in Childhood (ISAAC) and the European Community Respiratory Health Survey
126 (ECRHS).(100–103) The definitions employed by the studies were classified as into “current
127 wheeze”, “wheeze ever”, “doctor diagnosed asthma”, and “asthma ever” as follows and
128 described in table E1.2:

- 129 ● wheeze ever: a positive answer to the ISAAC question “Has your child ever had
130 wheezing or whistling in the chest at any time in the past?” or a similarly worded
131 question
- 132 ● current wheeze: a positive answer to the ISAAC question “Has your child had
133 wheezing or whistling in the chest in the last 12 months?”, the ECRHS question
134 “Have you had wheezing or whistling in your chest at any time in the last 12
135 months?”, or similarly worded questions
- 136 ● asthma ever: a positive answer to the ISAAC question “Has your child ever had
137 asthma?” or a similarly worded question
- 138 ● doctor diagnosed asthma: a positive response to the ISAAC question “Did a
139 doctor ever diagnose any of the following diseases in your child? (a) asthma; (b)
140 asthmatic, spastic or obstructive bronchitis” allowing for combinations of (a) and
141 (b) or similarly worded questions
- 142 ● current asthma (ECRHS): a positive response to either “Have you had an attack of
143 asthma in the last 12 months?” or “Are you currently taking any medicine
144 (including inhalers, aerosols or tablets) for asthma?”

145 Some studies used combinations of these indicators such as asthma diagnosis plus
146 current wheeze or other indicators including lung function, bronchial provocation, or tests of

atopic sensitization. If the combination contained an indication that a doctor had diagnosed asthma, this was counted as doctor diagnosed asthma. The same is true for studies that ascertained asthma diagnosis from hospital charts, routine data sources, or by conducting a clinical examination (e.g. including lung function). If the combination of items restricted the diseased to a certain subpopulation that was not reflected by the majority of studies (e.g. all subjects with wheeze among those not diagnosed with asthma (study #2.1)) associations with this item were not included in the meta-analyses.

Three studies reported age ranges spanning over the arbitrary cut-off for childhood of 18 years. For one study almost all participants were below 18 years of age and this study was counted as a study on childhood onset of disease. Conversely, for the other two studies over half of the subjects were 18 years of age or older and these were counted as studies on adulthood disease. Three studies reported on both, childhood and adulthood disease in the same or separate publications.(104–107) For the other studies among adults, data on age at onset of disease was not published.

Multiple publications or stratification of associations

There were 11 studies (numbers 2, 8, 9, 11, 12, 15, 22, 30, 34, 36, and 38) with multiple publications of the same or very similar associations which are discussed in the following.

For the study of Finnish university students (study #2), there were two publications.(108; 109) The first(108) described the full study population while the second(109) described data on a small subset of participants in only one study region that was invited for in-depth clinical assessment (spirometry and skin prick tests). The second employed a much stricter definition of asthma diagnosis as an outcome, including a specialist's interview and spirometry. Furthermore, the exposure reference was broadened to include subjects from an urban area. The second publication quotes an adjusted OR of

0.22 (0.07;0.70) for the strict asthma definition while the first publication gives an adjusted OR of 0.70 (0.46;1.06) for doctor diagnosed asthma. The latter was harmonizing more with other reported studies in terms of exposure and disease definition and was used in the meta-analysis.

For the 1966 Finnish birth cohort (study #8) two publications were available.(110; 111) The first(110) employed more restrictions on the study population (available data for length of gestation, birth weight, and asthma) while both restricted to subjects with data on atopy. This led to an approximately 10% smaller sample size for the first publication. The exposure (paternal/parental occupation) and disease definition (doctor diagnosed asthma) were described in a similar way, but the second publication included additional confounders (residential density, place of residence, maternal BMI, maternal education, birth height [instead of birth weight], mother's age of menarche). The adjusted OR from the first publication is 0.71 (0.53;0.95); the adjusted OR from the second is 0.96 (0.72;1.29). The first publication was primarily on effects of gestational age while the second was focused on exposure to farming in childhood, thus only the second was included.

A study in New South Wales (study #9) reported associations stratified by study region.(112) Each of the two study regions is included as a separate study in the meta-analyses.

For the ALEX study (Study #11), three publications were included.(113–115) Only the first(113) gave adjusted estimates for doctor diagnosed asthma which are used in the meta-analyses. The other two allowed only calculation of crude estimates for doctor diagnosed asthma and current wheeze from published numbers. The crude OR for current wheeze were similar from both (0.53 (0.29;0.97) for #11.2 and 0.56 (0.30;1.05) for #11.3). Since the third publication(115) was only on a subpopulation who contributed DNA, the crude OR from the second publication(114) was used in the meta-analyses.

Two publications from the ECRHS are counted to be from one study (study #12).(116; 117) However, the first publication(116) is on combined data from 13 centres in 5 countries from the cross-sectional ECRHS I.(102; 103) The second publication(117) is only on two French centres and reports data from ECRHS II, a follow-up of ECRHS I participants.(118) The two French centres are supposedly included in the first publication although names of the 13 centres were not detailed. So, the reported associations are not strictly independent. They are, however, included in the meta-analysis as separate studies because they report on different outcomes and the first only offers crude while the second published adjusted estimates.

A study among Swedish conscripts (study #15) published associations stratified for the birth cohorts 1952-61, 1962-71, and 1972-81. The resulting associations are included as three separate studies.

There were four relevant publications of the PARAFIAL study (study #22).(119–122) The first publication(119) reports a combined adjusted OR for doctor diagnosed asthma from the five centres (0.74 (0.60;0.92)) and points out heterogeneous disease prevalence across centres. The second publication(120) reports a significantly different crude OR for doctor diagnosed asthma for Germany (0.45 (0.32;0.64)) compared to the combined crude OR from the remaining centres (0.92 (0.72;1.17), which is not heterogeneous across the four contributing centres). Both publications used the same study population and exposure and disease definitions. In the third publication(121) additional covariates were modeled (breastfeeding, BMI, food avoidance) without an effect on previously reported associations. The fourth publication(122) was on a subsample that provided DNA and reported a crude OR of 0.50 (0.36;0.70) for doctor diagnosed asthma in contrast to the crude OR of 0.70 (0.58;0.85) for the same association from the first publication. The associations reported in the first publication are primarily used in the meta-analysis.

For a study conducted on the North Island of New Zealand among families (study #30), a first publication(104) describes data for the parents only while a second publication(105) describes data for the children only. These publications were included as separate studies in the meta-analysis.

A study among agricultural workers in The Netherlands (study #34) reported on doctor diagnosed asthma stratified by age at onset in one publication.(106) The same was done by the E3N study (study #37).(107) The resulting associations were included as separate studies (one as a childhood study the other as an adulthood study) in the meta-analyses.

The GABRIEL Advanced Surveys (GABRIELA, study #36) have been published in four publications.(123–126) The estimates used in the meta-analysis are unpublished data from one publication (authored by the author of the present meta-analysis).(126) GABRIELA consists of five study regions and these regions were included as separate studies in the meta-analyses although only the associations for current wheeze differed across regions whereas the associations for doctor diagnosed asthma did not.

There were three publications for a cohort study among Danish farming students (study #38). The first was retrieved via checked references and reported estimates from baseline(5) and the second reported data on asthma incidence from the follow-up.(127) Both were considered for the meta-analysis. The third investigated genetic associations and only commented in the text that “Potential confounders (being born and raised on a farm, smoking, and case–control status) had ORs close to one in multiple logistic regression models...” without giving detailed estimates.(92)

Overview of the publications that contained data relevant for the meta-analysis

The studies are sorted according to the appearance of their first publication in PubMed that was relevant for the meta-analyses. An exception is study #39 which is not indexed in Pubmed and appended at the end of the table. In fact, it was one of the first ones published. Within a study, the publications are sorted according to their appearance in PubMed.

Table E1.1 gives detail on the study design, methodological issues, and sample size. Each study is assigned a number (#) and multiple publications within studies are enumerated with the first decimal. For each publication the appropriate reference is indicated (ref.). Table E1.2 shows the age of the participants in years, the exposure definition and its prevalence (% exposed) as well as the disease definitions and their prevalence (% diseased) and the confounders accounted for in multivariate models. The age is sometimes given as a range from minimum to maximum, sometimes as mean $\pm$ SD, and sometimes as both.

Where appropriate, text was copied from the publications to avoid confusion by changing the wording. To keep the table legible, no double quotes were used in these instances. However, the appropriate reference is indicated for each row of the table. Squared brackets indicate comments to the original authors' description by the author of this work.

Shaded areas for studies with multiple publications indicate that there was no information other than that denoted in the row before. For non-shaded empty cells no information was available or had to be given.

Table E1.1: Detail on study design, methodological issues and sample size of the studies relevant for the meta-analyses

#	ref.	study	design	details	methodological issues	sample size ¹
1	(128)	SCARPOL	multi-centre cross-sectional surveys conducted in Nov-Mar 1992/93 and repeated in 1995/96 among children not in the 1st survey	data reported on 3 rural (Grabs, Langnau, Payerne) out of 10 surveyed Swiss communities, data from both surveys pooled; pooling based on no systematic differences in prevalence rates of respiratory and allergic symptoms or in atopic sensitization rates between the two surveys;	unclear which subgroups of the surveys were compared to justify pooling (full, rural, full 1st and children in 2nd but not 1st, stratified by age); but associations are adjusted by age and the issue is regarded minor;	N=1,620; restricted to Swiss nationals; participation rates close to or above 80% except 6-7 year olds from Payerne
2.1	(108)	Finnish university students	cross-sectional survey among all Finnish first-year university students in winter 1995/96,	data on full sample		N=10,667; participation rate 75.1%
2.2	(109)			data on disproportionate disease (asthma and/or wheeze) stratified random sample (frequency matched for gender) in Turku to investigate SPT and LUFU in winter 1996/1997	weighted approaches to account for the stratified sampling for prevalences; authors state: "Weighting by sampling did not change the results of risk factor analyses."	n=296 (participation rates 78% among diseased, 66% among non-diseased)
3	(129)	Salzburg, Austria	cross-sectional survey in the county of Salzburg, Austria in Jan-May 1997.	All school children from the district Lungnau (district with the highest proportion of farmers) and 17 schools with reasonable size from the other five districts of the county; Most of the county is rural area with a high proportion of farmers. Farms are usually small and run by the members of the family and only occasionally by farm workers. Ninety percent of Austrian farmers have livestock or poultry.		overall N=2,283; overall participation rate 95.4%; study population restricted to Austrian nationals (n=2,001)
4	(130)	rural Bavaria, Germany	cross-sectional study in rural Bavaria (Niederbayern,			overall N=10,163; overall participation rate 76.2%; study

			Oberpfalz), Germany, among all children attending obligatory school entry health examinations from Feb-Aug 1997			population restricted to Austrian nationals (n=9,835)
5	(131)	Quebec, Canada	cross-sectional survey among school children of 14 secondary schools in rural areas surrounding Quebec City	farm environment and ISAAC questionnaire assessed in full cohort; disproportionate exposure stratified subsample (all exposed and half the number of unexposed) frequency matched for school class and gender to assess ECHRS based questionnaire and objective outcomes (SPT, AHR, n=1,594 invited) “the principal industry is farming, primarily dairy farming, cattle raising, and swine confinement”	ISAAC (language unclear) and French ECRHS questionnaires produce dissimilar prevalence estimates; frequency matching was insufficient after drop-out and gender had still to be corrected for in regression models	full cohort N=9,082 (participation rate 93.1%); exposure stratified subsample n=1,199 (participation rate 75.2%)
6	(132)	PECOS	cross-sectional survey in a rural agricultural area (3 small towns and 3 surrounding rural municipalities) in Saskatchewan, Canada in Nov 1995	crude odds ratios for children were recalculated from prevalences; odds ratios for adults were not included because for them no data on exposure to farming in childhood was published	no adjustments for household clustering were made; this issue is regarded minor because the estimate is statistically non-significant and accounting for clustering is likely to increase the standard error not substantially (not many subjects per cluster in this study).	549 households (participation rate 43.6%); within those: n=393 children (<=17 yrs), n=1014 adults
7	(133)	Grabs, Switzerland	consecutive yearly surveys among school children in their 8th year, 1983-1999		no correction for siblings (family clustering) or year of assessment (asthma prevalence ranges from 1.6% to 16.1%); only 3 exposed children had asthma, so not enough sample size for meaningful adjustment; these issues are regarded major because family clustering may largely affect variance estimation and uncertainty is very large;	N=1,287 (participation rate 98.5%)
8.1	(110)	1966 Finnish	birth cohort study of live	coverage at baseline 96%; data on	unclear when exposure was	at baseline N=12,058; in 1997

		birth cohort	births in 1966 in Oulu and Lapland, Finland; analyses are possibly cross-sectional	asthma retrospectively assessed in self-reported questionnaires in 1997	assessed, if it was also retrospectively assessed at age 31 this would be a cross-sectional study;	n=6,025 participants (71.1% of invited); study population restricted to subjects with data on length of gestation, birth weight, atopy and asthma (n=5,192).
8.2	(111)					after restriction by valid skin prick test n=5,509 participants in 1997
9.1	(112)	New South Wales, Australia	cross-sectional survey in primary schools of two rural Australian towns (Moree and Wagga Wagga, New South Wales) in summer 1997;	data published stratified: Moree (high prevalence of crop farming (83.9% wheat, 46.2% cotton, 9.1% livestock), 29.6% living on a farm)		n=1,436 (participation rate 67%); n=473 (Moree)
9.2	(112)			Wagga Wagga (lower prevalence of crop farming (50.9% wheat, 1.9% cotton, 26.1% livestock), 15.4% living on a farm)		n=963 (Wagga Wagga)
10	(134)	Gotland, Sweden	cross-sectional study (termed closed birth-cohort study) of all children born on Gotland, Sweden, in 1989 assessed by questionnaire in Dec 1996-Mar 1997;	35% of the Gotland population are involved in farming; 85% of farms keep livestock or poultry	the authors call their study birth cohort study and use Mantel-Haenszel methods to compute adjusted risk ratios; all data was assessed in the same questionnaire among children born in the same year; birth registry information was only used to restrict the study population; data are cross-sectional, estimates are prevalence ratios	overall N=805 (participation rate 94.2%); study population was restricted to n=707 who were born on Gotland and lived on the island for their first year of life and who had no inconsistent farm exposure (current but not previously in life)
11.1	(113)	ALEX	cross-sectional multi-centre survey in Austria, Germany, and Switzerland in Mar-Jul 1999	n=1406 gave consent for further blood and dust sampling; disproportionate exposure stratified random subsample were invited (n=901);	exposure stratified sampling was not corrected for in the multivariate models; the issue is regarded minor because the exposure definition for the analyses matches the one for sampling;	overall N=2,618 assessed with questionnaire (participation rate 74.7%), study population restricted to n=812 nationals of the respective study country participating in the subsample
11.2	(114)					
11.3	(115)					n=668 after restriction to participants who contributed DNA (only Austria and Germany)
12.1	(116)	ECRHS	cross-sectional multi-centre	simple random sampling of	Test for heterogeneity of the	n=6,251 (median response rate to

			two-stage survey conducted between 1988? and 1994?;	second stage; additional symptomatic sample not used for this publication; combined data from 13 centres from 5 countries (in which farming was assessed) [unclear which 13 centres, the five countries have in total 17 centres]	association between farm exposure in childhood and the risk of allergic disorders in adulthood did not show any evidence for heterogeneity between countries.	the postal questionnaire was 78.1%; median response rate to Stage II was 64.9%.)
12.2	(117)	French ECRHS II	cross-sectional survey of ECRHS I participants in Paris and Grenoble (France) in 1999 and 2001		unclear how information from ECRHS I was taken into account; study population likely to be already included in ECRHS I estimate; this issue is regarded minor because the studies report on different outcomes.	n=600 (participation rate not detailed and cannot be deducted)
13	(135)	ISAAC (Finland)	cross-sectional multi-centre survey in Helsinki area, Turku and Pori county, Kuopio county, and Lapland county in 1994-1995	The fieldwork in the Helsinki area was partially conducted in spring during the pollen season, significantly affecting the 12-mo symptom prevalence of allergic rhinitis. Therefore, the Helsinki area was excluded from the present study in order to avoid reporting bias.		n=7,981 (response rates in all regions >95%)
14	(136)	Dannevirke, New Zealand	cross-sectional survey among school children	timing unclear, published in 2002	“The low overall response rate of 60% was due to poor response rates (<50%) in two schools from low socioeconomic areas with predominantly nonfarm children. Thus selection bias cannot be excluded as an explanation for the positive associations we found for current farm abode with symptoms and disease.”; This is regarded major because only crude estimates could be used due to the inclusion of specific farm exposures in the multivariate model;	n=293 (participation rate 59.3%)
15	(137)	Swedish conscripts	survey of Swedish conscripts (males) from the birth cohorts 1952-1981; data on exposure	data summarized from 1952-61, 1962-71, 1972-81; data on disease and on exposure were assessed		n=1,316,985

			and disease at age 17 assessed from routine data sources	from the routine data documented nearest in time together making the analyses cross-sectional		
16	(138)	Iowa, USA	cross-sectional survey among rural Iowa school children (Keokuk county, Louisa county) in Jan-Feb 2000, Oct-Nov 2000, and Mar-Jun2001	approx. 12,000 subjects living in each county within 9 cities in Lousia and 12 cities in Keokuk county (Wikipedia)		n=3,090 (participation rate 86.6%)
17	(139)	Dong Anh, Vietnam	cross-sectional study in Apr 2001 of school children from Dong Anh (Vietnam)	“predominantly agrarian community with a growing industrial sector and a well-developed infrastructure including municipal treated water and sewage system”		n=2,641 (participation rate 65.5%)
18	(140)	Wisconsin, USA	cross-sectional survey among rural school children in Jun-Oct 2003	the study area has a maximum town size of 25,000 inhabitants	very low participation rate; unclear asthma definition, dissimilar wording used throughout the manuscript; the participation is regarded a minor issue because the authors argue convincingly against substantial bias;	n=4,481 (participation rate 12.8%), study population n=4,247 after exclusion of invalid responses
19	(141)	Kuopio, Finland	cross-sectional survey with exposure stratified random sampling among school children in mainly rural areas around Kuopio	exposure definition for sampling was paternal occupation (farmer), possibly from the population registry;	exposure definition seems to overlap 100% with sampling definition, thus no weights for associations needed;	full stratified random sample n=1,521; after restriction to children whose mother lived at the same address and random selection of 1 child per family n=924 were invited; study population n=710 (participation rate 76.8%)
20	(142)	Keokuk County Rural Health Study	cross-sectional survey of a rural population (Keokuk county, Iowa, USA) conducted 1994-1998 using stratified random sampling of households in farm, rural non-farm, and town locations (the largest town has less than 2,500 inhabitants).	children ≥ 8 years of age were invited for clinical examination; household clusters were corrected for; additional estimates for currently living on a farm yes vs no are available	stratified sampling was not corrected for in the published data and own calculations; this issue is regarded major because although the exposure definition for analyses is likely to overlap strongly with the definition used in sampling the direction of the bias cannot be predicted;	n=644 children out of n=1,004 households

21	(143)	Minnesota, USA	longitudinal study of rural Minnesota (USA) high school students grade 9-11; only data from the initial survey Jun–Aug 2001 were used			n=13,490 (participation rate 89.1%)
22.1	(119)	PARSIFAL	cross sectional study in Austria, Germany, the Netherlands, Sweden and Switzerland in Mar 2001-Jul 2002 using disproportionate exposure stratified random sampling in two countries	In Switzerland and Sweden only a random sample of non-farm children was included. In Austria, sampling was performed by school teachers; the study has an anthroposophic component (also exposed vs. unexposed) that is not reported here	no weights for the stratified random sampling available	overall N=15,137 (participation rate 69.1%), after exclusion of children outside age limits and without information on sex and of the anthroposophic component n=2,823 farm children and n=5,440 non-farm children remained
22.2	(120)					
22.3	(121)					
22.4	(122)				possible selection bias for those who contributed DNA	n=1,307 farm children and n=654 non-farm children who contributed DNA
23	(144)	Study of Asthma and Allergy in Shropshire	cross-sectional two-stage survey among rural primary school children in Shropshire (UK) using disproportionate exposure stratified random sampling	screening questionnaire in stage 1, clinical examinations in stage 2	stratified sampling accounted for in the analyses; laborers' children excluded from the analyses; timing, age, and wheeze definition unclear	n=4,767 in stage 1 (participation rate 66.0%), n=879 in stage 2 (participation rate 60.3%)
24	(145)	Iowa, USA	cross-sectional study in two schools in rural Iowa, one of them close to a "concentrated animal feeding operation" (the study school)		the published adjusted OR for asthma is most likely inflated due to collinearity between living on a farm and school and living in a rural area; this issue is regarded major because the sample size is low, there are six covariates in the model, and only 6.8% of the participants from the control school are living on a farm;	study school n=61 (participation rate 52.6%), control school n=248 (participation rate 54.4%)
25	(146)	Crete, Greece	cross-sectional survey among all schoolchildren aged 7–18 years and living in four previously unsurveyed areas of rural Crete in 2001	On Crete, no cows are farmed and animals are kept outdoors throughout almost the entire year; moreover, goat's milk is universally boiled before it is		n=797 (participation rate 93%)

				drunk, being otherwise considered unpalatable; age-specific prevalences are given in comparison to other farming studies		
26	(147)	British Columbia, Canada	cross-sectional survey among all 4-H club members (a youth organization) in five regions in British Columbia (Canada) in Jul-Aug 2001, a 50% sample in the remaining two largest regions was contacted in May 2002		family clusters accounted for in the association analyses	n=1158; SPT (n=317) in one region only (Jul 2001 to Jan 2002);
27	(148)	Organic farmers, The Netherlands	cross-sectional survey among conventional and organic farmers and their spouses working on a farm in the Netherlands in Mar-Jun 2001		low participation rate; this issue is regarded minor because the authors argue convincingly against substantial selection bias	n=1054 farmers and n=869 spouses (participation rate 38.1%), after restriction to age and farming pattern (purely organic, purely conventional) in total n=1798
28	(149)	Lower Saxony Lung Study	cross sectional survey among adults in Lower Saxony, Germany, in 2002-2004;		low participation rate; this issue is regarded minor because the authors argue convincingly against substantial selection bias	overall N=10,252, random subsample invited for questionnaire and clinical examination (n=7,080); n=2,812 returned the questionnaire and gave informed consent for BHR (participation rate 39.7%*), after exclusion due to medical reasons BHR was measured in n=1,980 of which n=1,935 were born in Germany; final study population were n=1,595 with complete data (22.5% of the originally invited)
29	(150)	NLSCY	prospective cohort study of children with baseline in 1994/95 conducted by Statistics Canada in the 10 provinces in Canada, follow-up in 1996/97		complex design accounted for in the analyses	baseline N=22,831, n=14,318 children at follow-up (participation rate 62.7%), after exclusion due to missing data for asthma at baseline or FU1 and asthmatics at baseline n=13,524;
30.1	(104)	North Island,	Cross-sectional study;	Subjects were asked to complete a	family clusters accounted for in the	n=2,509 farming families

		New Zealand	Farming families living in the lower half of the North Island were randomly selected from a national database of farms in New Zealand. A rural control group of non-farmers from the same region (adults aged 25–49) was randomly chosen from the New Zealand Electoral Roll.	postal survey for themselves and their children aged 5–17 years (if any). Data on adults is reported.	analyses, for “growing up on a farm” correction for the exposure stratified sampling was made by adjusting for “farmer”	(participation rate 77.8%), n=1,001 non-farming families (participation rate 67.0%), in total 4,288 farmers, 1,328 non-farmers with n=1,333 farmer’s children and n=566 non-farmer’s children
30.2	(105)			Data on children is reported		
31	(151)	Tyrol, Austria	birth cohort study of all infants liveborn Apr 1994-Dec 1999 in Tyrol, Austria		asthma ascertainment based on hospitalizations; authors modeled logistic regression but call estimates relative risk, unclear whether a transformation was applied	N=33,808 (participation rate 74.1%)
32	(152)	Estevan and Swift Current, Saskatchewan, Canada	longitudinal analysis of participants in two repeat cross-sectional surveys among school children in a primarily agricultural town in 2000 and 2003	Students in grades 1 to 3 in 2000 were potentially studied again in 2003 in grades 4 to 6, creating a prospective cohort.	farm exposure detailed in methods does not match description in the tables (Farm visits in the first 12 months of life ≤ 3 vs. >3)	N=477 at baseline (grades 1-3, participation rate 94%), after exclusion of subjects with wheeze or asthma at baseline n=212 had been followed up (participation rate 67.1%)
33	(153)	Agricultural Health Study	prospective cohort study among pesticide applicators and their spouses in Iowa and North Carolina, USA, with baseline in 1993-1997	data presented as cross-sectional at baseline		N=32,347 spouses enrolled at baseline, after restriction on sex, age, asthma after age 19 years, and complete data n=25,814 farm women remained
34	(106)	Agricultural workers, The Netherlands	cross-sectional study among workers involved in processing and trade of agricultural products and among (organic) farmers in Feb-Dec 2006	Questionnaires were sent to all employees of 23 participating companies, a representative sample of companies in four agricultural sectors (onion trade, flower bulb trade, animal feed industry and vegetable seed industry)	prevalences and crude estimates are not adjusted for the exposure stratified sampling; this issue is regarded major because although the exposure definition for analyses is likely to overlap with the definition used in sampling the direction of the bias cannot be predicted;	n=877 (participation rate for agricultural workers 90%, for farmers 61%)
35	(154)	West Gothia, Sweden	cross-sectional survey in West Gothia including the city of Gothenburg in 2008 using disproportionate	data reported on the subset of 16-20yr olds	unclear description of the multivariate model; correction for the exposure stratified sampling was made by adjusting for study area	n=1,261 (participation rate 49.7%)

			stratified (city/non-city) sampling			
36.1	(123–126)	GABRIELA	cross-sectional multi-centre survey among school children from Austria, Germany, Poland, and Switzerland with three phases using disproportionate exposure and disease stratified random sampling for Phase 2 and 3; data reported is from Phase 1 in Nov 2006-Apr 2007	data for Austria	The author is one of the principal investigators of GABRIELA. At the time of this project the estimates used had not been published but similar estimates have been published. The author took the liberty of producing estimates that would harmonize with other studies presented here in terms of exposure and outcome definitions and that would not deviate largely from what is and will be published.	Overall N=103,219 (participation rate 57.7%); Austria n=12,291 after restriction to Austrian nationals
36.2				data for Switzerland		n=14,817 after restriction to Swiss nationals but no exclusion of late responders
36.3				data for Munich, Germany		n=20,349 after restriction to German nationals
36.4				data for Ulm, Germany		n=19,233 after restriction to German nationals
36.5				data for Poland		n=23,331
37	(107)	E3N	prospective cohort study among female members of a national health insurance plan that covers mainly teachers with baseline in 1990 and follow-up every two years	Standardized questions on asthma and data on farming lifestyle during childhood were included in the seventh follow-up questionnaire in 2003. [Data reported is of cross-sectional nature.]; Because approximately one third of the women were born during the Second World War and because living conditions on farms might have been quite different before, during and after the war, we stratified our analyses according to the year of birth (n=17,961 born before the war, i.e., between 1925 and 1938; n=18,651 born during the war,		N=98,995 at baseline, n=74,525 completed baseline, 1993 and 2003 follow-up (participation rate 75.3%), after exclusion due to missing data or extreme values for diet n=54,018 were analyzed

				i.e., between 1939 and 1945; and n=17,406 born after the war, i.e., between 1946 and 1950);		
38.1	(5)	Farming-students, Denmark	prospective cohort study among Danish farming students using an exposure stratified recruitment (farming students, conscripts), baseline in 1992-1994 and yearly follow-ups for 5 years.	data reported is for baseline; the stratified sampling is accounted for by inclusion of the stratification variable as a covariate in multivariate models;	the exposure assessment was implemented late in the cohort and only 1,166 (59%) of the farming students answered to the question “Were you born and raised on a farm”; this issue is regarded minor because the authors argue convincingly against selection bias	n=999 farming students (40.3% of the originally approached N=2,478, after restriction to male sex, age below 26yrs, data on exposure and covariates)
38.2	(127)	Farming-students, Denmark	An asthma case-control study was nested into the cohort using incidence density sampling	data reported is for nested case-control study	Among farming students there are n=107 cases and n=102 controls, among conscripts there are n=15 cases and n=14 controls. Although not stated explicitly in the text the stratified sampling may have been also applied to the case-control study. Since farm-students/conscripts is not associated with case/control it is unlikely to influence the association between exposure and case/control	n=122 asthma cases, n=116 controls
39	(4)	Saskatchewan, Canada	cross-sectional survey among school children in Saskatchewan, Canada, in 1993			n=1704 (participation rate 71.8%)

¹ of the study population unless further detailed

268 **Table E1.2: Detail on age of the participants and exposure and disease assessment of the studies relevant for the meta-analyses**

#	study	age (years)	exposure definition	% exposed	outcome definitions	% diseased	confounders
1	SCARPOL	6-7, 9-12, 13-15	Parents had to indicate whether the family was running a farm and if so, whether this was a full-time or part-time activity. Estimates are for parental occupation: farming vs non-farming.	19.0	current wheeze (ISAAC) ever asthma (ISAAC)	8.3 9.3	age, sex, parental education, maternal smoking, a family history of asthma, a family history of hay fever or eczema, number of siblings, pet ownership, indoor humidity, heating fuels
2.1	Finnish university students	18-24	(a) living on a farm at age 0-6 years, (b) living in a rural area (scattered settlement) at age 0-6 years but never on a farm (rural nonfarm category), as well as (c) living in an urban area at age 0-6 years. Estimates are for (a) vs (b).	46.8 [(a)/((a)+(b))]; 11.4 [(a)/((a)+(b)+(c))];	Self-reported wheezing during lifetime included subjects without diagnosed asthma and with positive responses to following questions: Have you at any time during your life had attacks of shortness of breath with wheezing? If yes, has your breathing been normal between the attacks? If yes, Have you had these attacks also during times you did not have a cold, flu or other chest infection? no association published Asthma: positive answers to the following questions: Have you ever had asthma? If yes, has a doctor diagnosed your asthma?	6.8 4.6	gender, parental education, passive smoking, parental asthma or atopic disease, number of older siblings, day care outside the home
2.2		18-25[?]	Estimates are for (a) vs ((b)+(c)).	9.8	At the pulmonary disease specialist's interview, current asthma was confirmed if the subject had had symptoms suggestive of asthma, such as	10.7	frequency matched for gender, adjusted for early childhood pet-keeping

					wheezing, shortness of breath, cough with wheezing, in association with typical provoking factors, such as exercise or animals, during the last 12 months, and at the same time fulfilled at least one of the following lung function criteria: 1) PD20 FEV1 $\geq$ 2.9 mg in methacholine challenge 2) FEV1 < reference value minus 1.96 SD 3) FEV% (FEV1/FVC) < reference value minus 1.96 SD (where FVC is forced vital capacity) 4) FEV1 shows a rise of at least 15% after bronchodilation.		
3	Salzburg, Austria	8-11 (9.5 $\pm$ 0.7)	With regard to farming, parents were asked 'does your child live on a farm?' and 'does your child have regular contact with livestock (cows, horses, sheep, pigs and goats) or poultry?'. Estimates are for living on a farm: yes vs. no.	14.1	current wheeze (ISAAC) ever asthma (ISAAC) A positive answer to 'did a doctor ever diagnose asthmatic, spastic or obstructive bronchitis?' suggested possible asthma; this was grouped with doctor diagnosed asthma	7.1* 3.5* 14.5*	only crude estimates available
4	rural Bavaria, Germany	5-7	Farming was assessed by asking: 'Do you live on a farm?' and if so, 'Does your family run the farm on a (a) full-time basis, (b) part-time basis, (c) small scale basis, (d) only for home consumption or (e) not at all?' Children were classified as exposed to	12.0	current wheeze (ISAAC) doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)	7.8* 6.1*	parental education, family history of atopic diseases, number of older siblings, use of wood or coal for heating or cooking

			farming if they lived on a farm and their parents were engaged in farming activity of any degree.				
5	Quebec, Canada	12-19	We identified all subjects currently living on a farm and then selected from the same school class half the number of subjects, matching for gender, among those who had never lived or worked on a farm in their lifetime. To contrast those children with and without exposure to the farm environment, we eliminated from consideration all those who had been exposed, either previously or intermittently to farming practices either by having worked or lived on a farm. Estimates are for exposure to farm environment: always vs. never	14.7*	current wheeze (ISAAC)	16.5*	only crude estimates available adjusted for gender, current smoking, number of siblings
					asthma ever (ISAAC)	7.9*	
					The report of wheezing in the last 12 months was obtained from the French version of the ECRHS questionnaire.	23.6*	
					Spirometry was carried out sitting with the subject wearing a nose clip. Acceptability of results was judged according to American Thoracic Society recommendations. Methacholine was administered by individually calibrated DeVilbiss number 40 nebulizers according to the protocol described by Yan and colleagues. Airways hyperresponsiveness (AHR) was considered to be present if the FEV1 dropped by 15% or more at the highest concentration administered. A subject was considered to have "asthma" if he demonstrated AHR on methacholine testing and reported the occurrence of wheeze in the last 12 mo.	8.7*	

6	PECOS	<=17 - >=71	household farming status determined by "Does your household operate a farm?"; only 74.8% of the farming households reside on a farm only, 6.1% of the non-farming households reside on a farm; Estimates are for farming vs. non-farming households	80.4*	Has this person ever been diagnosed by a doctor as having asthma?	10.2	only crude estimates available
7	Grabs, Switzerland	15	farm children are defined by farming as the paternal occupation, part-time farming children are children without parental farming occupation but keeping cows or children helping other farmers, all others are non-farmers. Estimates are	10.2*	asthma ever (no details)	8.3*	only crude estimates available
8.1	1966 Finnish birth cohort	31	paternal occupation; Estimates are for farmers vs. non-farmers	20.8*	ever having been diagnosed by a doctor as having asthma	8.0	sex, maternal age, maternal smoking in pregnancy, parental allergy, current vocational training, current BMI, gestational age, birth weight, parity
8.2			having a parent who was a professional farmer during infancy Estimates are for yes vs. no	22.9*	Doctor-diagnosed asthma ever	7.9*	similar to 8.1, in addition: residential density, place of residence, maternal BMI, maternal education, birth height [instead of birth weight], mother's age of menarche
9.1	New South Wales, Australia	7-12, farm: 9.47±1.04, non-farm: 9.35±1.09	Has your child ever lived for longer than 12 months on a farm?	Moree 29.4*	Has your child wheezed in the past 12 months? Has your child ever been diagnosed as having asthma	Moree 33.2* Moree 41.4*	only crude estimates available; authors mention that the association does not persist after adjusting for

					by a doctor or at a Hospital?		atopy or parental history of allergic disease
9.2				Wagga Wagga 15.4*	Has your child wheezed in the past 12 months?	Wagga Wagga 27.2*	
					Has your child ever been diagnosed as having asthma by a doctor or at a Hospital?	Wagga Wagga 38.5*	
10	Gotland, Sweden	7-8	Unclear exposure definition; Methods: "Parents were also asked questions on farming such as past and/or present farming, keeping of livestock and horses, and distance from the family houses to stable/cowshed."; Results: "children living on a farm", "children of farmers"; believed to be defined on occupation; Estimates for farmers' children vs. non-farmers' children	19.2	wheezing in the previous year without upper respiratory infection	12.0*	sex and atopic heredity (no further details on the latter given)
					"ever had asthma" or "ever had doctor diagnosis of asthma"; this was grouped with doctor diagnosed asthma	7.4*	
11.1	ALEX	grade 1-6, farm 9.42±1.63, non-farm 9.49±1.60	Does your child live on a farm? Estimates for yes vs. no	approx. 319/1406=22.7% (uncertain due to restrictions and exposure stratified random sampling)	doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis at least once (ISAAC)	not published	age, sex, study area, education of parents, family history of asthma and hay fever, number of older siblings
11.2					current wheeze (ISAAC)	farm 6.3*, non-farm 12.0*	only crude estimates available
					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis at least once (ISAAC)	farm 4.7*, non-farm 8.5*	
11.3					current wheeze (ISAAC)	farm 6.3, non-	only crude estimates

					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis at least once (ISAAC)	farm 13.1 farm 5.5, non-farm 9.4	available
12.1	ECRHS (I)	20-44	living on a farm in childhood; Estimates are for yes vs. no	8.8*	current wheeze (ECRHS) current asthma (ECRHS)	23.4* 4.9*	crude country-specific OR combined with random effects meta-analysis
12.2	French ECRHS II	44.9±7.2	living on a farm in childhood: in the first year of life, later in childhood, never; Estimates are for lived on a farm in first year of life vs never lived on a farm	12.2*	asthma ever (no details, ECRHS methodology)	14.7	age, sex, center, parental history of asthma or allergy, smoking habits, pets in childhood, severe respiratory infection in childhood
13	ISAAC (Finland)	13-14	Is your family involved in farming? Estimates are for yes vs. no	11.7	Wheezing (while at rest) in the past year (ISAAC video questionnaire) ambiguous, quotes ISAAC methodology: doctor diagnosed asthma (methods), asthma ever (results, table); this was grouped with doctor diagnosed asthma	4.3 5.6	age, gender, study area, parental education, parental atopy (history of asthma, hay fever, or eczema in either parent), number of older siblings, child's own smoking history
14	Dannevirke, New Zealand	7-10	information on residence (living in town, or on a farm, or in a rural area but not on a farm) collected for current and for first year of life Estimates are for living on a farm in the first year of life yes vs. no (including town living)	32.1*	current wheeze (ISAAC) asthma ever (ISAAC)	22.2* 33.4*	multivariate models include farm exposures and thus estimate an attenuated farm-effect
15	Swedish conscripts	17	Farming: At least one parent has a farming or animal related occupation.	The percentage of the study population with at least one parent	ICD-8/9/10 (493, J45), no details on assessment before 1968	The prevalence of asthma	only crude estimates available

			Forestry: No parent has an occupation as a farmer, but at least one parent works as a woodman. Health: No parent is a farmer or a woodman, but at least one parent is a medical doctor, nurse or has a paramedical occupation. Reference: No parent is a farmer, woodman, medical doctor, nurse or paramedic; Estimates are for Farming vs all other.	working as a farmer or a woodman decreased from 5–1.8% in the 1970s to 2.5–1.2%, respectively, in the 1990s.		increased from 2.0% in the cohorts born in 1952–1956 to 7.2% in those born in 1977–1981.	
16	Iowa, USA	6-14	whether the family lived in the town or the country, and, if in the country, whether they lived on a farm or in a rural home. Estimates are for farm vs. town; OR for farm vs. rural were calculated without CI;	27.8 for farm vs. town, 45.3 for farm vs. rural (total: farm 21.0, rural home 24.4, town 54.6)	current wheeze (ISAAC) wheeze ever (ISAAC) doctor diagnosed asthma (ISAAC)	19.1 30.9 13.4	age, sex, county of residence
17	Dong Anh, Vietnam	5-13, 8.4±1.3	parental occupation Estimates are for farmer vs non-farmer	75.1	current wheeze (ISAAC) asthma ever (ISAAC) doctor diagnosed asthma (ISAAC)	16.7 (from figure) 20.5 (from figure) 18.4 (from figure)	age, gender, education, maternal history of asthma, history of TB, household TB, stove type
18	Wisconsin, USA	10.1±3.2	Farm residence was based on a non-0 response to any one of the 3 questions regarding how long the family lived on a farm when the child was born, during the child's first 5 years of life, or when the child was older than 5	17.9*	current wheeze (ISAAC) , no association published, only noted that OR not significant wheeze ever (ISAAC) asthma ever (ISAAC)	not published 32.4* ambiguous definitions in the tables and results section	sex, exposure to second-hand tobacco smoke, household pets, breast-feeding, exposure to daycare, number of siblings in the household

			years, or a response stating that at the time of the study, the family lived on a farm. Estimates are for farm residence yes vs. no				
19	Kuopio, Finland	6-13	The children whose mothers answered 'yes' to the question 'Is your family involved in farming?' were defined as farmers' children. Estimates are for farmers' vs. non-farmers' children	not published	current wheeze (ISAAC) ambiguous, quotes ISAAC methodology: doctor diagnosed asthma (methods), asthma ever (results, table); this was grouped with doctor diagnosed asthma	farm 10.7, non-farm 14.5 farm 5.5, non-farm 6.7	age, gender, parental education, parental history of hay fever, day care attendance during the first year of life, number of older siblings
20	Keokuk County Rural Health Study	1-17, 9.6±5.0	Household type was determined at the time of the child's birth from the biologic mother's reproductive history questionnaire and through follow-up phone interviews with the biologic mother regarding residence type (farm, rural nonfarm, or home [supposedly 'town']) at the time of birth; estimates are given for 'born on a farm' yes vs no	36.5*	current wheeze (no details) doctor-diagnosed asthma (no details)	18.6* 11.5*	only crude estimates available
21	Minnesota, USA	13-21, 99.5% were 14-17	Do you live on a farm or ranch that is actively involved in agricultural production? (A farm was defined as any place producing or selling \$1,000 or more of agricultural products.) Estimates are for farm residence: yes vs. no	13.7	Have you had wheezing or whistling in your chest in the past 12 months? Has a doctor ever told you that you have asthma?	17.5 12.6	age, sex, agricultural region, household smoke, current smoking, BMI

22.1	PARSIFAL	5-13	Farm children were defined as children currently living on a farm and whose family runs the farm. Estimates are for farm vs. non-farm children	not published	current wheeze (ISAAC)	farm 5.0, non-farm 7.7	[reported crude OR are adjusted for country] age, sex, country, parental education, current smoking in the household, maternal smoking during pregnancy, mother's reported asthma and/or rhinoconjunctivitis, father's reported asthma and/or rhinoconjunctivitis, older siblings.
					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)	farm 6.3, non-farm 9.1	
22.2					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)		only crude estimates available
22.3					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)		similar to 22.1 and additionally: breastfeeding, BMI, food avoidance due to familial asthma and/or allergy
22.4					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)		only crude estimates available
23	Study of Asthma and Allergy in Shropshire	primary school children [5-11, personal communication with David Strachan (Author)]	farming children whose parents live and work on a farm, laborer's children whose parents work on a farm but do not live on a farm, and control children; Estimates are for farm vs.	11.3*	current asthma symptoms (ISAAC methodology, item unclear); this was grouped with current wheeze	15.0*	age, sex, family history of atopy, number of older and younger siblings, breast-feeding

			control				
24	Iowa, USA	kindergarten through grade 5, study school 9.5yrs, control school 8.7yrs	currently living on a farm Estimates are for yes vs. no	study school 63.5, control school 6.8	current wheeze (ISAAC), no association published	study school 18.0, control school 9.7	school, living in a rural area, parental smoking, cat in the home, dog in the home
					wheeze ever (ISAAC) , no association published	study school 27.9, control school 21.4	
					doctor diagnosed asthma (ISAAC)	study school 19.7, control school 7.3	
25	Crete, Greece	7-18	Parents were defined as full-time farmers if either was a full-time farmer; part-time farming indicated that either parent was a part-time farmer but neither was involved fulltime. Only when neither the father nor the mother was involved in any kind of farming was the child considered to come from a non-farming family. Estimates are for full- and part-time farming combined vs. no farming	85.6*	current wheeze (presumably in the past 12 months, ISAAC methodology)	4.4	only crude estimates available
					wheeze ever (ISAAC)	16.6	
26	British Columbia, Canada	farm 13.8±2.8; rural no livestock 12.6±2.5	Type of residence (farm, rural non-farm and urban) was asked for current and past residence (before age 2), as well as whether they had (and types of) livestock and poultry. Rural non-farm was further categorized according to presence or absence of livestock, including horses. The farm	83.9*	current wheeze (ISAAC)	farm 12.6, non-farm 19.7	age, sex, presence of smokers in the home, parental history of allergic disease, number of older siblings, presence of dog in the home, cat in the home
					wheeze ever (ISAAC)	farm 22.7, non-farm 32.8	
					doctor-diagnosed asthma (ISAAC)	farm 12.0, non-farm 21.6	

			residences all had livestock; the three exceptions were classified as rural non-livestock. Estimates are for current farm residence vs. rural residence without livestock				
27	Organic farmers, The Netherlands	<=70, conventional farmers 45.5±9.7, organic farmers 44.2±8.4	childhood farming environment: no, crops only, livestock; Estimates are for livestock vs no	conventional 63.8 (79.2*), organic 48.5 (55.9*)	“According to the ECRHS definition, asthma was defined as a positive response to any of the following questions: “Have you had an attack of asthma in the last 12 months?”, “Have you been woken by an attack of shortness of breath at any time in the last 12 months?” and “Are you currently taking any medicine for asthma?”; this was grouped with doctor diagnosed asthma	4.7	age, sex, organic farming, asthma in parents or siblings, smoking habits, current farm type (crops/livestock), disinfectant use
28	Lower Saxony Lung Study	18-44	lived on a farm during the first 3 years of life; Estimates for yes vs. no	42.5	wheezing without a cold (no details, ECRHS methodology); this was grouped with current wheeze	10.5	age, sex, level of education, passive and active smoking, family history of allergic disease, number of siblings
					asthma diagnosis (no details, ECRHS methodology)	5.0	
29	NLSCY	0-11 at baseline	Based on street level frontage, how would you characterize land use on this block/road? (a) primarily rural, farming; (b) primarily rural, residential; (c) non-rural Estimates are for (a) vs. (b)	56.8	Does this child have asthma that has been diagnosed by a Health Professional?	5.6 (cumulative incidence over 2 years among all participants (a,b,c)), 2.3 for (a), 5.3 for (b)	age, gender, region, SES, crowding index, immigrant mother, parental smoking, parental history of asthma, child allergies, child's health status (low/high), number of pediatrician visits, number of physician visits, maternal age at birth, number of older siblings, home needing repairs, BMI

30.1	North Island, New Zealand	non-farm 42.6±7.3, farm 48.9±10.5	We also assessed whether and how long subjects had lived on a farm during childhood, and how long they worked as a farmer, i.e. 'Did you grow up on a farm?', If yes, for how many years (up to 18 years old), and 'How long have you worked as a farmer?'; Estimates are for growing up on a farm: yes vs. no	farm 65.2, non-farm 22.6	current wheeze (ECRHS)	farm 16.1, non-farm 25.4	age, sex, ethnicity, smoking, current farming (Further adjustments for number of siblings, family history of asthma, hay fever and eczema did not significantly alter the results.)
					Have you ever had asthma? (ECRHS)	farm 15.1, non-farm 23.3	
30.2		5-17, farm 11.2±3.5, non-farm 11.0±3.6	farmer's children vs. non-farmer's children	not published (stratified design)	current wheeze (ISAAC)	farm 19.5, non-farm 25.1	only crude estimates available
					asthma ever (ISAAC)	farm 28.5, non-farm 34.2	
31	Tyrol, Austria	6-10 at diagnosis	A farming environment was assumed if farm work was given as a full-time occupation. Estimates are for farming yes vs. no	3.4*	In a first step, a search was made for diagnoses 493.0 (ICD-9) and J45.0 (ICD-10) which identified 721 infants. In a second step the diagnosis was confirmed by two paediatric pulmonologists based upon a critical review of the hospital medical records. A diagnosis of asthma required a medical history of at least 3 episodes of wheezing confirmed by clinical examination on hospital admission and proof of atopy (a positive skin-prick test reaction to at least one common aeroallergen and/or elevation of specific IgE in serum). The skin-prick test reaction to common aeroallergens (grass pollen mix, hazel, birch pollen, cat	0.9*	sex, rural/suburban/urban, postnatal smoking, neonatal admission to hospital, breastfeeding, number of siblings, birth weight

					dander, D. pter., Alternaria alternata, Cladosporium herbarum) was considered positive if the wheal diameter was at least 3 mm greater than a negative control with saline solution 15 min after testing. The level of specific IgE was measured by RAST and considered elevated if the level was ≥ 3.5 kU/l for the specific allergen. A total of 367 (50.9%) children satisfied these criteria.		
32	Estevan and Swift Current, Saskatchewan, Canada	7.2 $\pm$ 0.9 at baseline	Current place of residence was defined as rural if the response to the question, "Where is your home located?" was either "farm" or "acreage" and was defined as urban when the response was "in town." A high level of farm exposure in the first year of life was considered present if a child "visited a farm more than 3 times," "visited a farm regularly," or "lived on a farm." Estimates are for farm exposure in the first year of life yes vs. no	59.0*	New-onset wheeze was defined by a positive response to either of the following questions in 2003, both of which were answered negatively in 2000: "Has this child ever had a wheeze or whistling noise that comes from the chest?" "Has your child's chest ever sounded wheezy during or after exercise/sports?"	10.4	age, sex, ETS exposure, BMI, allergic disease (allergy, hay fever or eczema), home humidifier, home fireplace
33	Agricultural Health Study	20-88, 47 $\pm$ 12	Did you spend more than half your life under age 18 on a farm? Estimates are for yes vs. no	60.9*	self-reported doctor's diagnosis of asthma	2.7	only crude estimates available
34.1	Agricultural workers, The	18-65, farm childhood yes	"Did you grow up on a farm?"	58.3*	current wheeze (ECRHS) Doctor-diagnosed asthma	11.4 adult-onset	only crude estimates available

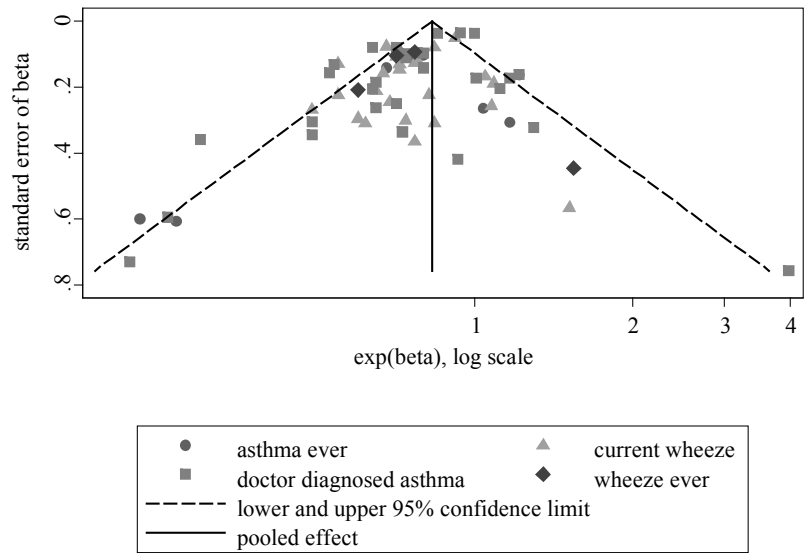
	Netherlands	46.0±9.6, no 40.5±10.5	Estimates are for yes vs. no		was defined as ever having had asthma that was confirmed by a doctor, and was stratified by time of onset (before or after 18 years of age). (ECRHS methodology)	0.9	
34.2					Doctor-diagnosed asthma	childhood-onset 4.1	
35	West Gothia, Sweden	16-20, 64% aged 18+	Did your family live on a farm during your first 5 years of life? Estimates are for yes vs. no	6.0	Have you had whistling or wheezing in the chest on any occasion during the last 12 months?	15.9	age, gender, area of domicile, smoking habits, family history of asthma and/or allergy, physician-diagnosed asthma [?], other asthma variables [?], rhinitis [?], occupational exposure to gas, dust, or fumes.
					Have you ever had asthma?, no association published	11.1	
					Have you been diagnosed as having asthma by a doctor?	9.5	
36.1	GABRIEL (4)	6-12	(a) farm children were children who lived on a farm that was currently run by the family; (b) exposed non-farm children were children who did not qualify as farm children but had regularly (at least once a week over a period of 6 months) visited stables or barns or had regularly consumed farm milk ever in life; (c) unexposed non-farm children were all remaining children; Estimates are for (a) vs. (c)	15.0	current wheeze (ISAAC) doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)	10.4 7.3	age, sex, parental education, parental smoking, family history of asthma, number of siblings
36.2				25.7	current wheeze (ISAAC) doctor diagnosed asthma at least once or asthmatic,	8.3 10.1	

					spastic or obstructive bronchitis more than once (ISAAC)		
36.3				21.4	current wheeze (ISAAC)	11.8	
					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)	10.2	
36.4				11.1	current wheeze (ISAAC)	11.6	
					doctor diagnosed asthma at least once or asthmatic, spastic or obstructive bronchitis more than once (ISAAC)	11.3	
36.5			For Poland, with more traditional rural communities and different exposure patterns, the definition of farm children was: (a) farm children were children from families who reported any animal husbandry or cultivation and lived in a village; (b) village non-farm children were all remaining children living in a village; (c) town children were all remaining children who lived in small towns (up to 15,000 inhabitants). Estimates are for (a) vs. (c)	39.8	current wheeze (ISAAC)	18.9	
					doctor diagnosed asthma at least once (ISAAC, differs from the other GABRIELA centres due to different labeling practices)	19.6	
37.1	E3N	baseline 40-65, at FU: farm 61.3±6.3, non-farm 61.4±6.4	Women were asked in 2003 whether they lived on a farm during childhood, continuously	12.1*	"Have you ever had asthma attacks?" and if yes "Was this diagnosis confirmed by a doctor?". For asthmatic	1.6	age, education level and pets in childhood

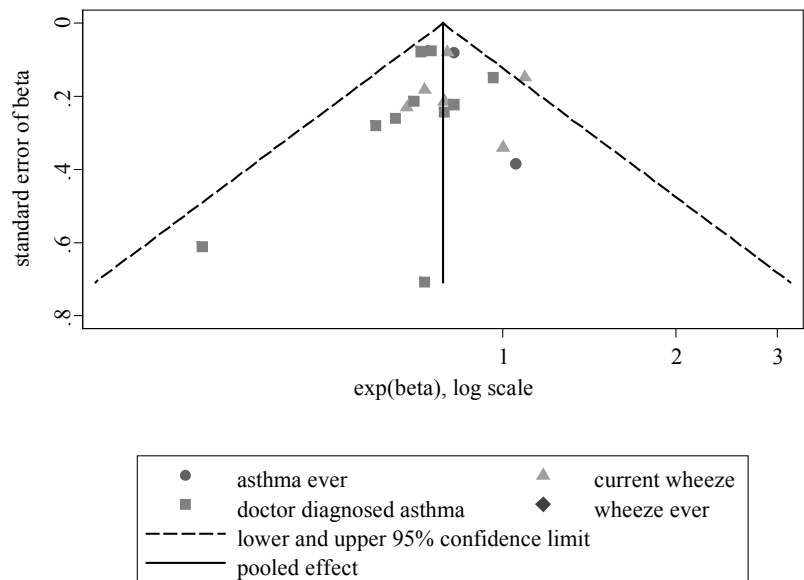
			for at least 3 months, and if yes, whether their parents were farmers. Estimates are for farmer parents yes vs. no		women, age at the first attack was recorded. Childhood asthma was defined as onset <16 years and early childhood asthma ≤ 4 years. [unclear whether early childhood asthmatics are included in the population from which estimates for childhood asthma are derived]		
37.2					Adult asthma was defined as onset ≥ 16 years.	3.2	age, education level, smoking, pets in childhood, BMI, physical activity, diet (dietary patterns and total energy intake)
38.1	Farming-students, Denmark	baseline 16-26 (mean 19.2)	Being born and raised on a farm; Estimates are for yes vs. no	50.6*	wheeze ever	8.0%*	farming student/conscript, familial history of allergy, smoking
					asthma was defined by a positive answer to at least one of 4 major questions (Have you been told by a doctor that you have asthma? Do you have asthma? Have you ever had asthma? Do you ever wheeze?) and 2 positive answers from a group of 10 symptom questions (Do you ever have chest tightness? Do you wake up in the morning with a tight chest? Do you wake up in the night with wheeze? Do you cough on waking in the morning? Do you wake with a cough? Do you wheeze when exposed to cold air? Do you wheeze with exercise? Do you wheeze when exposed to pollen? Do you wheeze by exposure to	6.9*	

					animals? Do you use asthma drugs?); this was grouped with doctor diagnosed asthma		
38.2				farming students: cases 29.5 [possibly wrong, alternatively: 24.3*], controls 48.4 [possibly wrong, alternatively 45.1*]; conscripts: cases 20.0, controls 14.3	incident asthma (definition see above)	farming students 5.4*, conscripts 3.7*	sex, disposition for asthma [no detail given], atopy, hay fever
39	Saskatchewan, Canada	asthma 8.0±1.5, no asthma 8.1±1.4	location of home Estimates are for farm/acreage vs. town	47.1*	Has your child ever been diagnosed as having asthma by a doctor or at a hospital?	10.0	only crude estimates available

* recalculated from published data

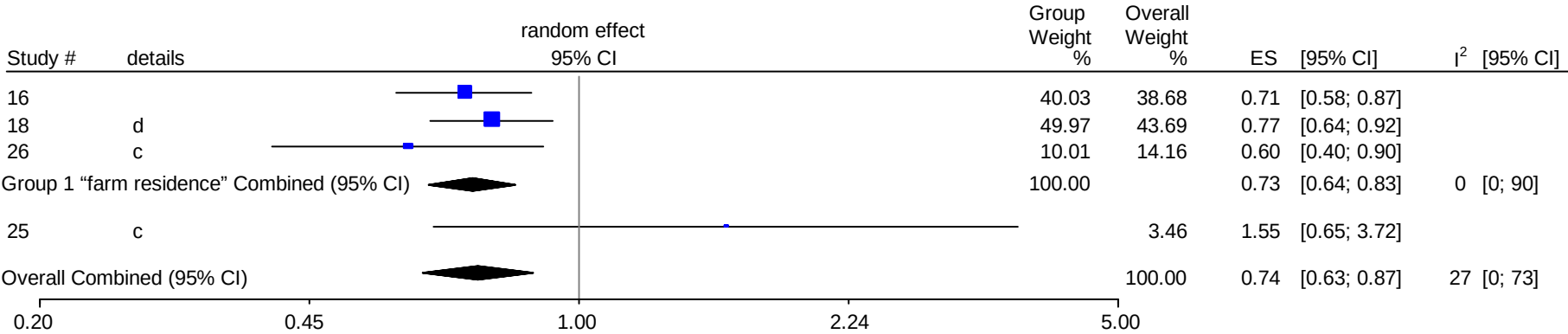


274 **Figure E1.1: Funnel plot of included estimates from childhood studies, labeled according to the**
275 **outcome definition**



276 **Figure E1.2: Funnel plot of included estimates from adulthood studies, labeled according to the**
277 **outcome definition**

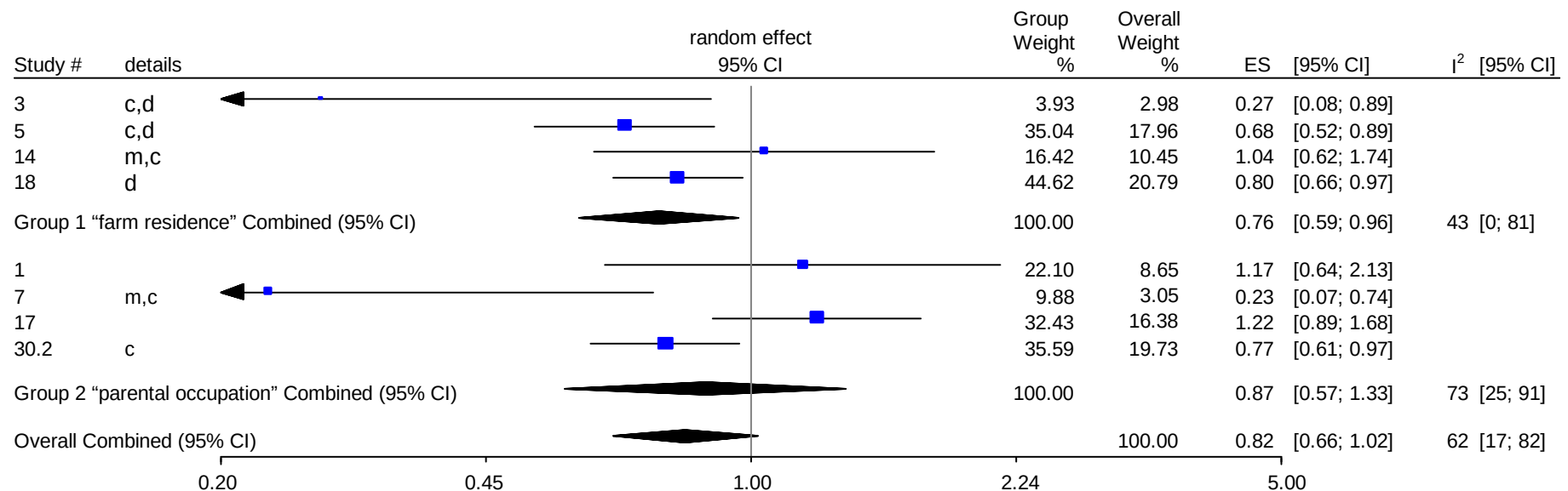
278 *Appendix 3: Forest plots for childhood and adulthood studies*



279 **Figure E2: Forest plot for the association between farm exposure in childhood and wheeze ever from childhood studies**

280 Legend to Figure E2:

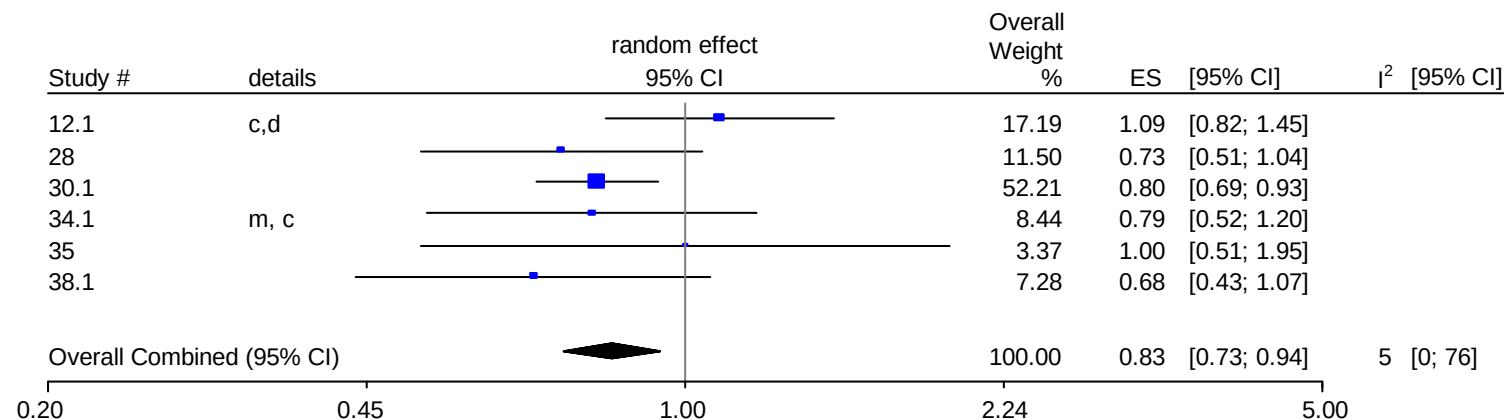
281 Study #25 belongs to group 2 “parental occupation”. The random-effects meta-analysis is grouped by different exposure definitions (farm residence, parental
282 occupation, combination of both). Combined estimates are per group and overall. Within group weights and overall weights are displayed. The symbols of the
283 effect estimates of each study are scaled according to the overall weight. *Study #*: the study number provided in table 1 and table E1.1; *details*: m=methodological
284 issues (details in table E2.1), c=crude estimate, d=differing disease definition from the categorization described in the online supplement; *ES*: effect size;
285 *I*²: measure of heterogeneity, given in %



286 **Figure E3: Forest plot for the association between farm exposure in childhood and asthma ever from childhood studies**

287 Legend to Figure E3:

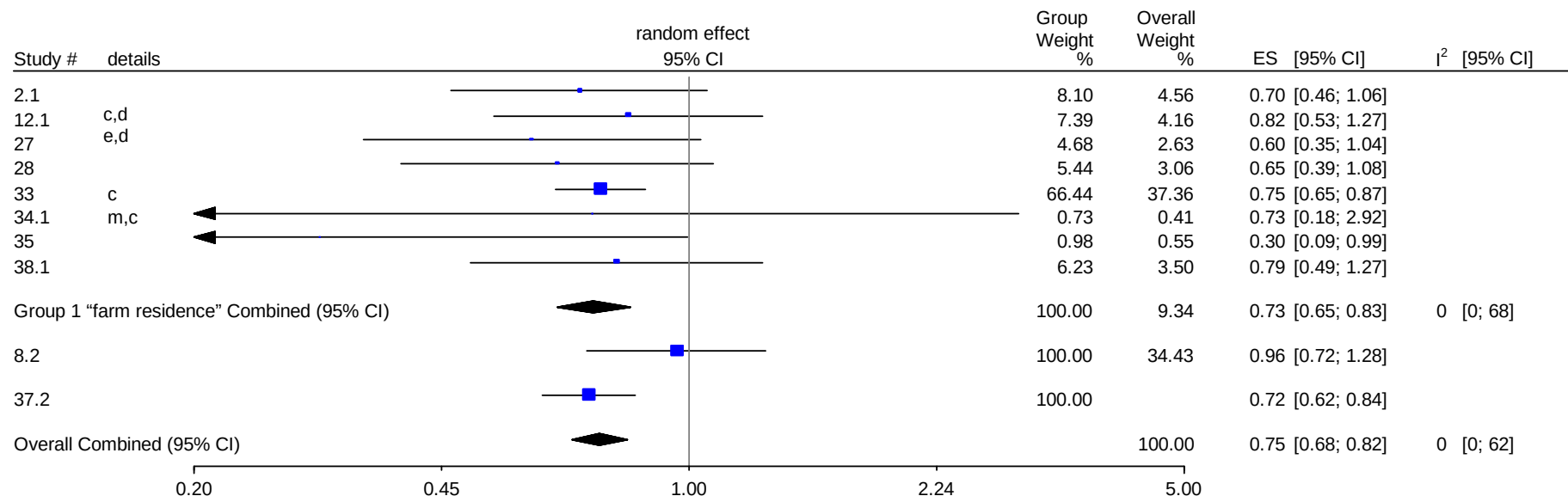
288 The random-effects meta-analysis is grouped by different exposure definitions (farm residence, parental occupation, combination of both). Combined estimates
 289 are per group and overall. Within group weights and overall weights are displayed. The symbols of the effect estimates of each study are scaled according to the
 290 overall weight. *Study #*: the study number provided in table 1 and table E1.1; *details*: m=methodological issues (details in table E2.1), c=crude estimate,
 291 d=differing disease definition from the categorization described in the online supplement; *ES*: effect size; I^2 : measure of heterogeneity, given in %



292 **Figure E4: Forest plot for the association between farm exposure in childhood and current wheeze from adulthood studies**

293 Legend to Figure E4:

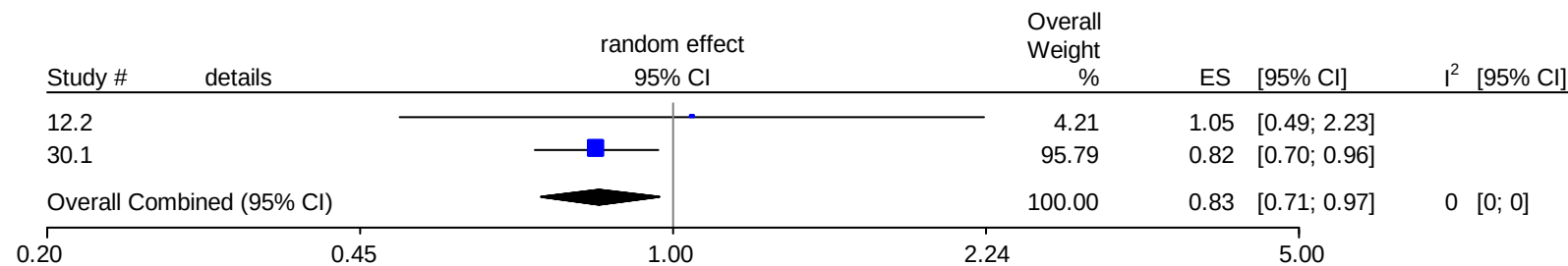
294 The random-effects meta-analysis is grouped by different exposure definitions (farm residence, parental occupation, combination of both). Combined estimates
 295 are per group and overall. Within group weights and overall weights are displayed. The symbols of the effect estimates of each study are scaled according to the
 296 overall weight. *Study #*: the study number provided in table 1 and table E1.1; *details*: m=methodological issues (details in table E2.1), c=crude estimate,
 297 **d=differing disease definition from the categorization described in the online supplement**; *ES*: effect size; I^2 : measure of heterogeneity, given in %



298 **Figure E5: Forest plot for the association between farm exposure in childhood and doctor diagnosed asthma from adulthood studies**

299 Legend to Figure E5:

300 Study #8 belongs to group 2 "parental occupation", study #37 belongs to group 3 "combination". The random-effects meta-analysis is grouped by different
 301 exposure definitions (farm residence, parental occupation, combination of both). Combined estimates are per group and overall. Within group weights and overall
 302 weights are displayed. The symbols of the effect estimates of each study are scaled according to the overall weight. *Study #*: the study number provided in table 1
 303 and table E1.1; *details*: m=methodological issues (details in table E2.1), c=crude estimate, d=differing disease definition from the categorization described
 304 in the online supplement; *ES*: effect size; *I*²: measure of heterogeneity, given in %



305 **Figure A3.5: Forest plot for the association between farm exposure in childhood and asthma ever from adulthood studies**

306 Legend to Figure A3.5:

307 All studies belong to group 1 “farm residence”. The random-effects meta-analysis is grouped by different exposure definitions (farm residence, parental
 308 occupation, combination of both). Combined estimates are per group and overall. Within group weights and overall weights are displayed. The symbols of the
 309 effect estimates of each study are scaled according to the overall weight. *Study #*: the study number provided in table 1 and table E1.1; *details*: m=methodological
 310 issues (details in table E2.1), c=crude estimate, d=differing disease definition from the categorization described in the online supplement; *ES*: effect size;
 311 *I*²: measure of heterogeneity, given in %

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