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Title: The prevalence of atopic dermatitis beyond childhood: A systematic review and meta-analysis of longitudinal studies

Running Title: Atopic dermatitis prevalence does not decline after childhood

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ABSTRACT

There are sparse and conflicting data regarding the long-term clinical course of atopic dermatitis (AD). Although often described as a primarily childhood disease, newer population-based estimates suggest the prevalence of pediatric and adult disease may be similar. Our objective was to determine whether there is a decline in the prevalence of AD in population-based cohorts of patients followed longitudinally beyond childhood. We conducted a systematic review and meta-analysis including studies assessing AD prevalence across 3 or more points in time. The primary outcome was weighted overall risk difference

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(percentage decrease in AD prevalence). Of 2,080 references reviewed, 7 studies with 13,515 participants were included. Participants were assessed at 3-6 time points, ranging from age 3 months to 26 years. The percentage decrease in prevalence after age 12 was 1%, which was not significantly different from zero (95% confidence interval -2% to 5%). Similar results were found with other age cut-offs. In conclusion, the prevalence of AD in longitudinal birth cohort studies is similar in childhood and early adulthood.

INTRODUCTION

Atopic dermatitis, also known as atopic eczema or simply eczema,¹ is one of the most common and burdensome diseases of childhood, yet little is known about the long-term clinical course of the disease.² Textbooks and review articles suggest that most individuals develop disease within the first two years of life, experience episodic symptoms throughout childhood, and improve by adolescence; yet, sparse and conflicting data exist regarding the proportion of individuals whose disease resolves and little is known about predictors of disease persistence or adult-onset disease.³⁻⁵ Challenging the traditional notion of AD as a predominantly childhood disease, a growing body of research on the pathophysiology of AD points to genetic causes of altered skin barrier and immune dysfunction that predispose to episodic disease throughout life.^{6,7} Additionally, population-based estimates from cross-sectional surveys suggest that AD may be as common in adults as in children.⁸ If AD prevalence does not decline over time, there are important implications for patient counseling, management, and future research.

The clinical course of AD has been particularly challenging to study because the condition is heterogeneous and intermittent. Individuals have different clinical presentations, and many will have periods without symptoms or skin lesions. Clinical trials generally focus on short-

term disease control, and cross-sectional studies offer a snapshot of the population and hence, cannot be used to generate prognostic information for individuals. Thanks to growing interest in atopic diseases, a number of longitudinal cohort studies included measures of AD disease activity at multiple time points in the same individuals, enabling the estimation of changes in AD prevalence as a given population ages. The primary objective of this paper is to systematically review and analyze longitudinal studies of AD that include repeated measurements in the same cohort during and after childhood to test the hypothesis that the prevalence of AD does not decrease with age.

METHODS

Data Source and Searches

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational studies in Epidemiology (MOOSE) guidance.^{9,10} Our research protocol was registered on PROSPERO and was publically available prior to the study start date (registration ID: 42016033553).

PubMed and EMBASE were searched from database inception to October 2015 using pre-specified search terms, MeSH (medical subject heading) headings and keywords, developed in consultation with a professional medical librarian. Search terms are described in Appendix

1. Reference lists of included studies were also screened for additional potentially relevant articles.

This study was exempt from IRB review because it included only published data and is not considered Human Subjects Research by the UCSF IRB (<http://irb.ucsf.edu/not-human-subjects-research>).

Study selection

We included studies of patients with AD as diagnosed by a physician or using a standardized definition such as the UK working party diagnostic criteria for AD or the International Study of Asthma and Allergies in Children ISAAC criteria.^{11,12} Because our objective was to examine changes in AD prevalence within a given cohort as populations aged, we included only longitudinal cohort studies that assessed AD activity in the same patients at 3 or more distinct time points, to account for the episodic nature of AD and allow for observation of any non-linear patterns of change. Further, to capture AD prevalence beyond childhood, studies were required to include at least 1 assessment with participants over the age of 12 years. We chose this cut-off because prior studies suggested high rates of ‘remission’ in adolescence and a longitudinal prospective study suggested that prevalence declines most rapidly between ages 8 to 11.^{13,14} We excluded studies that were clinic-based, or focused on patients with localized forms AD (e.g., hand eczema). We did not select studies on the basis of interventions and our search included studies in all available languages.

Data Extraction and Quality Assessment

Title and abstract screening followed by full-text screening was performed independently and in duplicate to ascertain whether studies met eligibility criteria. Extracted variables included study information (authors, year of publication); cohort information (country of study, cohort name, method of participant recruitment); study size (number of patients at study start/end, and alternate measures of loss to follow up); patient characteristics (sex, race/ethnicity, other demographic information); AD diagnostic criteria; and finally, method and age of AD prevalence assessment.

Methodological quality was assessed using the Newcastle-Ottawa Scale for cohort studies.¹⁵

The risk of bias and scoring criteria used in the present review are described in Appendix

Table 2. Screening, data extraction, and risk of bias assessment were all performed in

duplicate by 2 authors (AY, JO) and discrepancies were resolved by group consensus (AY, JO, KA, SML).

Data Synthesis and Analysis

The primary outcome was percentage change in AD prevalence by age, and all measured time points were included. Secondary outcomes included the prevalence of other atopic conditions (asthma, hayfever), treatment information, and severity data. Corresponding authors of included studies were contacted via e-mail to verify extracted study prevalence data used for the analyses.

We tabulated and plotted the AD prevalence by age for each study. We then calculated the standardized difference in mean prevalence before and after age 12 years (using all time points from each study), and report individual study differences and the mean weighted risk difference. We tested for heterogeneity with the chi-square test and measured inconsistency using the I^2 statistic, which represents the percentage of total variation across studies.¹⁶

Because of the methodologic and clinical heterogeneity inherent in the data, we used random effects models for all meta-analyses.

Pre-planned sensitivity analyses were conducted to assess the impact of varying the age cut-offs. The primary analysis was repeated using different age cut-offs: <10 years vs ≥ 10 years; < 8 years vs ≥ 8 years. These analyses were performed to test whether our choice of an age 12 cut-off affected the results. We repeated the analysis comparing those aged <2 years to 3-

11 years, and those aged 2-12 years vs > 12 years to test whether including very young children (when the diagnosis of AD can be more challenging) affected our results. Additional stratified analyses were performed to explore sources of heterogeneity, including analyses by age, by country, by loss to follow-up, by number of measurements and a 'jackknife' analysis that eliminated 1 study at a time. Egger's test was used to evaluate for publication bias.¹⁷ All analyses were performed with Stata (Version 14, Stata Corporation, College Station, TX).

RESULTS

The search yielded 2,080 records. After full text review of 28 manuscripts, 7 studies were selected for inclusion.^{14,18-23} The study flow diagram (Figure 1) lists the reasons 21 studies were excluded.

Study characteristics

Table 1 outlines the characteristics of each study in detail. The included studies followed 13,515 individuals. All geographical locations could be broadly classified as Northern European: studies were conducted in Sweden, Iceland, Germany, Denmark, and the UK (3 studies). All studies began follow-up at birth, and most were initiated the 1980s, with the exception of Williams *et al* study which began follow up in 1958, and Ballardini *et al*, which began follow-up in 1994-96. Each study measured prevalence at 3-6 separate time points, which ranged between patient ages 3 months to 26 years. The annual period prevalence of AD was assessed via questionnaire in all studies, with the addition of physical exam at some time points in three studies. The diagnostic criteria varied slightly by study and are outlined in detail in Appendix Table 3. Data were largely unavailable for the secondary outcomes: only 4 studies reported data on the prevalence of other atopic outcomes, and the methods for

assessment and reporting differed. None of the studies reported data on treatment or severity of AD (Table 1).

Prevalence estimates

The annual period prevalence of AD ranged from 6% at age 26 years²² to 34% at age 12 years.²¹ Study-specific figures are presented graphically in Figure 2 and the exact numbers used in the meta-analysis are included in Appendix Table 4.

Multiple studies found AD was more prevalent among teenage females, though the data were mixed. Gough *et al.* observed that AD prevalence tended to increase with age in the female population, and decrease amongst males. Similarly, in Burr *et al* and Ziyab *et al*, AD prevalence in females rose from age 15-23 years and 10-18 years respectively, while declining in males over the same time period. In contrast, Finnbogadottir *et al*, and Ballardini *et al*, did not find any difference between AD prevalence between males or females across all time points.

Risk difference

The primary outcome was the percentage change in prevalence after age 12 years. This ranged from -0.05 (meaning there was a 5% increase in the prevalence after age 12 years, 95% CI -0.03, -0.04)¹⁴ to 0.10 (a 10% decrease in prevalence after age 12y, 95% CI: 0.06, 0.15).²⁰ The overall mean weighted percentage difference in prevalence was not significantly different from 0 (0.01, a 1% decrease, 95% CI 0.02, -0.050). We found similar results when we explored multiple age cut-offs in sensitivity analyses (Appendix Table 5), and Eggers test showed no significant publication bias ($p = 0.314$). Because of the small number of included studies, funnel plots were not created.

Heterogeneity

There was significant heterogeneity in the primary analysis (I^2 96.3%). Multiple sensitivity analyses were performed to explore the impact of study design features on the degree of heterogeneity and the outcome. First, we considered differences in the age structure of the cohorts: the Ballardini *et al* study only followed individuals until age 12 years, while all the other studies followed individuals through ages 18-26 years. Excluding this single study only reduced the I^2 to 93.4%. Secondly, we considered the possibility of chronological trends: the Williams *et al* study included older individuals who were born in 1958 (2-3 decades prior to the other cohorts); excluding this study reduced the I^2 to 81.9%. Next, we examined whether the disease definition impacted the heterogeneity: Finnobogadottir *et al* was the only study to require eczematous symptoms to have begun in early childhood, which would have excluded individuals with older-onset disease from their AD classification and could have made the risk difference seem especially large. Excluding this study from the meta-analysis did not change the I^2 ; it remained at 96.3%. In all of these aforementioned analyses, our overall conclusion, that there was no significant change in the prevalence of AD after age 12 years remained robust. Finally, we tested whether the origin of the study (UK vs. non-UK), and the number of times AD was measured (3-4, 4-5, or 5-6) affected our estimates. In both cases, there were only mild reductions in heterogeneity (see Appendix Table 5 and Figures 1 and 2).

Risk of bias

The included studies had variable risk of bias with Newcastle-Ottawa scores ranging from 3-7 of a total maximum score of 9. One of the criteria, demonstration that the outcome of interest (i.e. AD diagnosis) was not present at the start of the study, was not relevant given that all of the included studies were birth cohorts. In terms of selection, most (7/9) cohorts were representative of the general population. The Gough *et al* and Burr *et al* studies included

only healthy newborn children with family histories of atopic disease, and therefore may overestimate AD prevalence. Moreover, the Burr cohort was followed after a randomized controlled trial of milk protein over the first 4 months of life which may introduce a bias since families willing to participate in a RCT may be different from those who decline. The ascertainment of AD was sometimes self-reported, but always based on a standardized questionnaire or examination applied to all participants (Appendix Table 6). In the Burr *et al* study, the definition of AD used varied over time and could have introduced bias: they measured the point prevalence of AD through age 7 years, then annual period prevalence from ages 15 and 23 years, which could make AD rates appear higher during adulthood. A sensitivity analysis excluding this study did not change the results (Appendix Table 5). All studies had good comparability due to equivalent measurements between AD and non-AD controls, and all studies included had an adequate length of follow-up. Loss to follow-up was >30% for 3/7 studies; excluding these studies did not affect our results (Appendix Table 5).

Analyses of repeated measures among individuals

Four studies examined whether individuals reporting AD symptoms at each age had a history of prior disease. All found that there was substantial turnover with many new and remitting cases throughout the study period. However, studies were inconsistent in providing study definitions of disease “remission” and “persistence” (Appendix Table 3). In 1 study, persistence was defined as AD at 2 or more observation points at any time within the study;¹⁸ another required subjects to have AD over the course of all study assessments, and across consecutive observation points.²³ This inconsistency in the definition of AD persistence and reporting makes it difficult to compare results across studies.

Multiple studies reported the proportion of patients with new-onset disease at each age of measurement. Incidence rates were highest in early childhood, but remained above zero throughout the teens and early 20s. Williams *et al* found that of the 870 cases with examined or reported AD onset by the age of 16 years, 66% had onset by the age of 7 years. Nissen *et al*, found the highest proportions of new-onset AD onset before age 1.5, and Ballardini *et al* reported that over all time periods, the total proportion of new (vs repeated cases) was 53%.

Multiple studies found that individuals with early-onset AD were more likely to have symptoms at older ages. In Williams *et al*, patients with early onset AD by age 1 year were more likely to have AD age 23 years, $p < 0.001$). Similar findings were presented by Burr *et al*, whereby AD onset by age 1 year was associated with AD at age 7 and 15 years, and for those with AD at 7 or 15 years, there was an association with AD at age 23 years. In Ziyab *et al*, of the patients that developed AD by age 2 years, 16.9% of patients had AD present at all time points by age 18 years; by contrast, in children who developed AD by age 4 years, the proportion with AD at all time points was only 10.9%

DISCUSSION

In this systematic review and meta-analysis of 7 birth cohort studies including over 13,000 individuals, we found no significant difference in AD prevalence before and after childhood. Our finding fills a gap in the literature about AD in adolescence and early adulthood. It also highlights the importance of longitudinal analyses to understand the natural history of an episodic condition. In the studies included in our review that report on the consistency of individual responses over time, the presence of AD symptoms was neither constant nor monotonic. Instead, individuals commonly reported years with symptoms of AD, followed by years without symptoms, then reported symptoms again. Because studies did not consistently

report repeated measures of disease activity or severity among individuals, we are unable to conclude whether AD tends to get better or worse over time. Nonetheless, the available data suggest that the reason for steady prevalence estimates across ages is due to a combination of active disease in both childhood and early adulthood among some individuals, remission or clearance of disease, and later onset disease among others.

Comparison with other studies

A recent review focused on “AD persistence” concluded that “80% did not persist by 8 years”.²⁴ It measured the change in the average proportion of a population reporting AD symptoms upon second measurement at any age. Upon first glance, these findings may seem contrary to ours. However, the authors caveat, that “it is possible that some of the patients reported to have AD remittance had unobserved recurrences later in life.” Thus, although their results are not directly comparable to ours because they included studies with variable populations, definitions of AD, and timing of follow up; their findings also highlight the episodic nature of the condition.

Our results concur with previous work showing high rates of AD persistence in a longitudinal cohort of children and young adults treated with pimecrolimus, which may be biased towards more persistent disease.²⁵ This study did not meet inclusion criteria for this review because enrollment was clinic-based and it included only patients with AD which didn’t allow for estimates of disease prevalence. The population-based ISAAC studies calculated AD prevalence at 2 age points in sites around the world, but were cross-sectional in nature and did not follow the same individuals over time. There was variation in prevalence by site and by age, but as with our findings, the average prevalence at both time points was similar (7.9% at age 6-7 and 7.3% at age 13-14).²⁶

It is important to highlight that diagnostic definitions may impact prevalence estimates, possibly biasing towards smaller numbers at older ages. Notably, the one study that required symptom onset occur in “early childhood” for the definition of AD found the sharpest decline in prevalence,²⁰ possibly because new-onset cases at later ages were not included. Other, more commonly used definitions of AD, such as the classic Hanifin and Rajka criteria and the widely used UK Working Party Criteria, assign extra points if the AD diagnosis is made in early childhood.^{11,27} Subsequently, studies using these criteria may report smaller numbers of individuals with later-onset disease, which should be taken into account when considering estimates of adult AD.

Strengths and limitations

Major strengths of our review and meta-analysis include the comprehensive search, careful selection and critical appraisal of studies, and inclusion of large representative cohorts followed from birth over 2-3 decades. Of note, we did not specify the initial age of follow up in our review; it was coincidental that all of the studies that met inclusion criteria were designed as birth cohort studies. Limitations also warrant discussion. First, there is variability in the terminology used to describe AD: “atopic dermatitis,” “atopic eczema,” and “eczema” are all used to refer to the condition.²⁸ In some settings, “eczema” is considered a less specific term that may include other types of dermatitis. Therefore, we carefully reviewed the diagnostic criteria used in each study (Appendix Table 3) and assessed the impact on our results as described above. Second, we found a high level of statistical heterogeneity between studies. This might be due in part to the use of a risk difference as our outcome measure, as risk differences are often less homogeneous.^{16,29} We used a model with random-effects to help account for the statistical heterogeneity, and found no appreciable

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differences in the results after multiple analyses to address differences in the methods for and timing of AD ascertainment between studies (Appendix Table 5). Nonetheless, our results should be interpreted with caution and replicated as additional follow-up data from longitudinal cohorts becomes available. Third, most studies lacked important information on secondary outcomes including treatment use, disease severity and other atopic conditions. These data may impact the clinical course and are important to report. Fourth, as is common for studies that follow large cohorts of patients over decades, attrition was substantial, ranging from 10-39%. Most of the studies (7 of 9) were not designed to specifically study AD, and none were organized through clinic visits so dropout was likely random with respect to AD and would therefore be unlikely to bias prevalence estimates. However, other factors differentially associated with attrition such as race/ethnicity and socioeconomic status may also be associated with AD resulting in selection bias.³⁰ These data should be reported in future longitudinal studies. Finally, all of the studies identified were from Northern European countries, and patients were only followed into the third decade of life. Additional work is needed to understand the clinical course throughout adulthood and in more diverse settings.

Conclusions and implications for practice and research

Our finding of similar AD prevalence before and after childhood supports the emerging paradigm of AD as a lifelong genetic predisposition to episodic skin lesions.³ We were unable to address the unresolved question of whether early onset disease is the same as late onset disease. Studies examining predictors of individual disease course are a high priority for additional research and can help to elucidate the relationship between genetic susceptibility and environmental influences on the epidemiological trends described herein.

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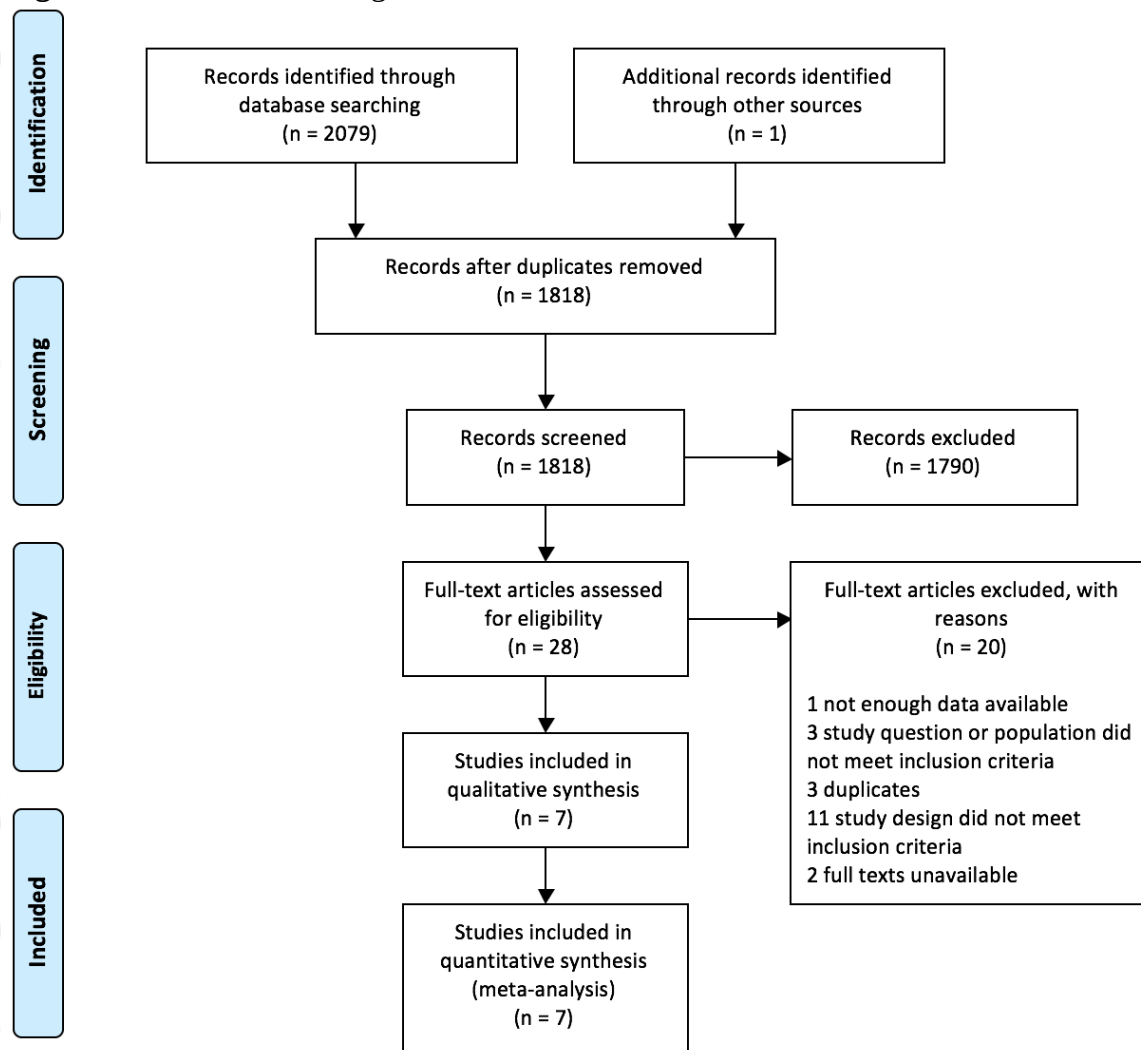
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Figure 1. PRISMA flow diagram



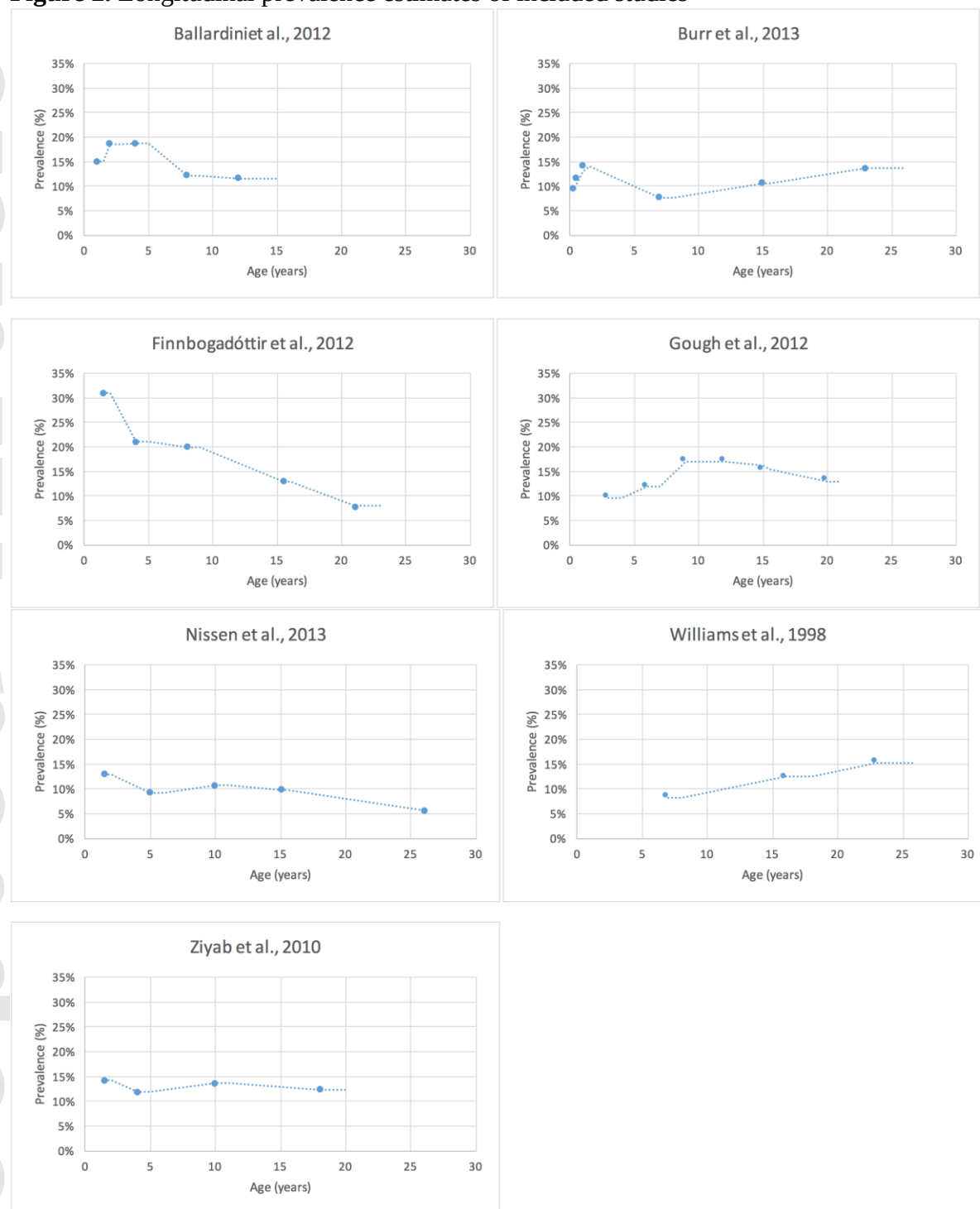
Legend: Results of search strategy

Table 1. Summary of study characteristics of included studies

Study	Country	Longitudinal Cohort		Number of patients (N)		Loss to follow-up	Sex (% male)	Prevalence			Other atopic outcomes reported (Y/N)	Treatment reported (Y/N)	Severity reported (Y/N)
		Study Cohort Name	Year of Birth	Study start	Study end			Time points (years)	Method of assessment	Period Prevalence			
Ballardini et al. ¹⁸	Sweden	BAMSE birth cohort	1994-1996	2916	2916	29% ^a	N/R	1, 2, 4, 8, 12	Questionnaire	1 year	Y	N	N
Burr et al. ¹⁹	UK	Not reported	1982-1984	497	304	39%	N/R	0.25, 0.5, 1, 7, 15, 23	Clinical exam (until age 7), Questionnaire	1 year	N	N	N
Finnbogadóttir et al. ²⁰	Iceland	Not reported	1987	179	120	33%	N/R	2, 4, 8, 16, 21	Clinical exam, Questionnaire	1 year	Y	N	N
Gough et al. ²¹	Germany	MAS-90 birth cohort	1990	1314	942	28%	52%	3, 6, 9, 12, 15, 20	Questionnaire	1 year	Y	N	N
Nissen et al. ²²	Denmark	Not reported	1985	276	193	30%	47%	2, 5, 10, 15, 26	Clinical exam	1 year	Y	N	N
Williams et al. ¹⁴	UK	National Child Development Study	1958	6877	6877	53% ^b	N/R	1-7, 11, 16, 23	Clinical exam, Questionnaire	1 year ^c	N	N	N
Ziyab et al. ²³	UK	1989 Isle of Wight birth cohort	1989	1456	1307	10% ^d	N/R	1, 2, 4, 10, 18	Questionnaire	1 year	N	N	N

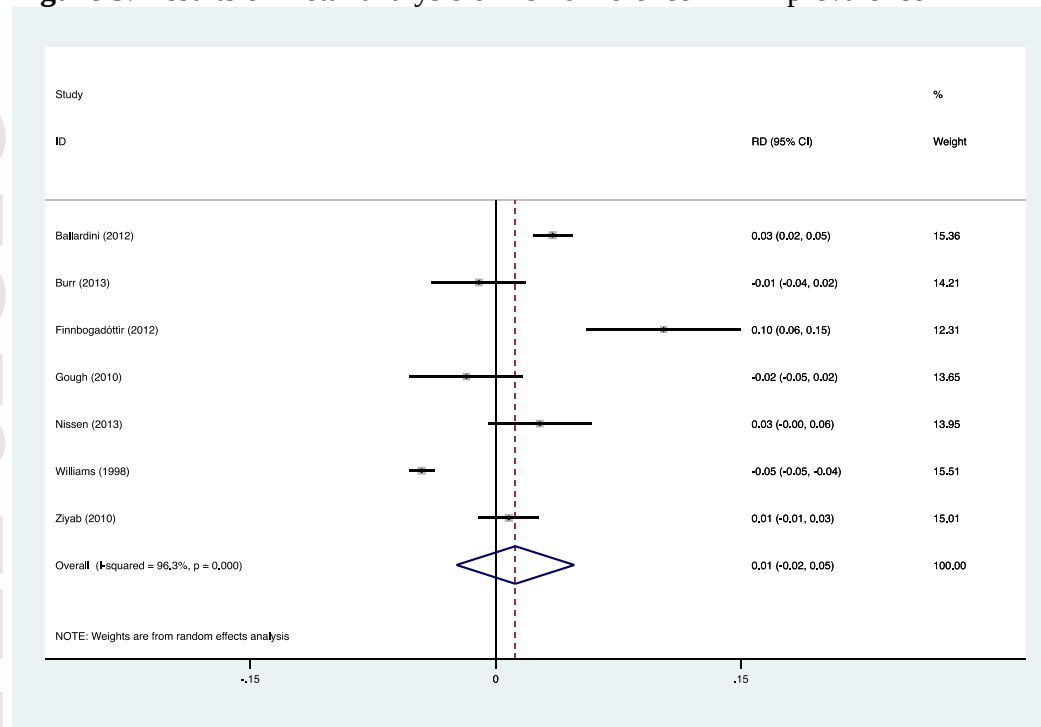
Figure Legend: A. The publication only included those with complete data on all health outcomes at every follow-up, which represented 71% of the original cohort. B. The publication only included those with complete data on all health outcomes at every follow-up, which represented 47% of the original cohort. C. At age 7, participants were asked about any AD up to age 7, at subsequent ages they were asked about AD over the past year, D. Note this was a dynamic cohort and different numbers were lost to follow up at each time point; the 10% figure represents loss to follow up at the last assessment at age 18. UK: United Kingdom, Y: Yes, N: No

Figure 2. Longitudinal prevalence estimates of included studies



Legend: Proportion of the population with AD at each age

Figure 3. Results of meta- analysis of risk difference in AD prevalence



Legend: Risk difference (RD) in prevalence in children age <12 years of age compared with children age ≥ 12 years

Table S1. Pubmed Search

Search	Search Terms	Results
infancy/ childhood	("Dermatitis, Atopic"[Mesh] OR "Eczema"[Mesh] OR atopic dermatitis[tw] OR eczema[tw]) AND ("Infant"[Mesh] OR "Child"[Mesh] OR birth[tw] OR infants[tw] OR infancy[tw] OR neonates[tw] OR neonatal[tw] OR newborn[tw] OR newborns[tw] OR new born*[tw] OR preschool[tw] OR child[tw] OR children[tw] OR childhood[tw] OR youth[tw] OR youths[tw])	12,341
adolescence/ adulthood	("Dermatitis, Atopic"[Mesh] OR "Eczema"[Mesh] OR atopic dermatitis[tw] OR eczema[tw]) AND ("Adolescent"[Mesh] OR "Adult"[Mesh] OR adolescent[tiab] OR adolescents[tiab] OR adolescence[tiab] OR teenagers[tiab] OR teen[tiab] OR teens[tiab] OR teenage[tiab] OR adult[tw] OR adults[tw] OR adulthood[tw] OR 18 years[tw])	14,044
longitudinal/ follow up/ natural history	("Dermatitis, Atopic"[Mesh] OR "Eczema"[Mesh] OR atopic dermatitis[tw] OR eczema[tw]) AND ("Follow-Up Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Age Factors"[Mesh] OR "Recurrence"[Mesh] OR year follow up[tw] OR natural history[tw] OR longitudinal[tw] OR follow up stud*[tw] OR followup stud*[tw] OR long term follow up[tw] OR to adulthood[tw] OR persist[tw] OR persisted[tw] OR persistence[tw] OR over time[tw] OR recurrent[tw] OR recurrence[tw] OR recurrences[tw] OR recurring[tw] OR recur[tw] OR remission[tw])	4,098
epidemiology/ prevalence/ population/ birth cohort	("Dermatitis, Atopic"[Mesh] OR "Eczema"[Mesh] OR atopic dermatitis[tw] OR eczema[tw]) AND ("Prevalence"[Mesh] OR "epidemiology" [Subheading:NoExp] OR epidemiology[tw] OR epidemiologic[tw] OR epidemiological[tw] OR epidemiology[tw] OR prevalence[tw] OR population based[tw] OR birth cohort*[tw])	5,967

Table S2. Risk of bias assessment: Newcastle-Ottawa Scale

SELECTION	
1	Representativeness of the exposed cohort (maximum of 1 point): - 1 point if the study cohort is representative of other people from the same study community (i.e. general population) - 1 point if the study cohort is somewhat representative of other people from the same study community - 0 points if the study cohort was a selected subgroup of the population (i.e. only asthma patients, only males, etc.) - 0 points if there is no description of the derivation of the cohort
2	Selection of the non-exposed cohort (maximum of 1 point): - 1 point if the non-eczema cohort is drawn from the same population as the eczema patients - 0 points if the non-eczema cohort is drawn from a different source - 0 points if there is no description of the derivation of the non-eczema cohort
3	Ascertainment of exposure (maximum of 1 point): - 1 point if ascertainment of eczema outcome was from a secure record or structured interview - 0 points if ascertainment of previous eczema from written self reports - 0 points if there is no description on the ascertainment of eczema
4	Demonstration that outcome of interest (i.e. eczema diagnosis) was not present at the start of the study: - 1 point if eczema not present at study start - 0 points if not described
COMPARABILITY	
1	Comparability of cohorts on the basis of design or analysis (maximum of 2 points): - 1 point if the study controls (non-eczema) are comparable to eczema patients at each time point - 1 point if the study controls for additional factors when comparing eczema and non-eczema patients at each time point (i.e. patients lost to follow up)
OUTCOME	
1	Assessment of outcome (maximum of 1 point): - 1 point if stated that independent blinded assessments or record linkage occurred to ascertain eczema outcomes (i.e. outcome assessors unaware of study hypothesis at time of assessment) - 0 points if outcome of eczema was self reported - 0 points if method of ascertainment of eczema outcomes was not described
2	Was follow-up long enough for outcomes to occur (maximum of 1 point): - 1 point if length of follow-up was adequate (> 1 year) to ascertain outcome of eczema at each time point - 0 points if length of follow-up was not adequate to ascertain outcome of eczema
3	Adequacy of follow up of cohorts (maximum of 1 point): - 1 point if there was adequate follow up with no patients lost to follow up - 1 point if there was adequate follow up with <30% patients lost to follow up and a description of those patients that were lost to follow up - 0 points if on average, <30% of patients were lost to follow up and there was no description of those that were lost - 0 points if on average, >30% of patients were lost to follow up - 0 points if there is no statement about how many patients were lost to follow up and why

Table S3. Study definitions of eczema, remission, and persistence

Study	Study definition of eczema (study diagnostic criteria)	Study definition of remission	Study definition of persistence
Ballardini et al., 2012 ¹⁸	Dry skin, itchy rashes, with age-specific location for 2 weeks or more and/or doctor's diagnosis of eczema in the past 12 months.	Total remission: never having a specific allergy-related disease again that had been present at the previous follow-up. □ Remission and relapse: not having a specific allergy-related disease that had been present at the previous follow-up and that will be present at one or more future follow-ups.	The proportion of children who had disease at one, two, three, or more observation points among the children who had ever had the same disease.
Burr et al., 2013 ¹⁹	Children were examined by a doctor up to age 7 years, rashes were classified as noneczematous rash, a history of eczema, inactive eczema, and active eczema. At age 15 and 23 years, subjects were sent a short questionnaire including questions about eczema (from the ISAAC study). ¹⁴	Not reported	Not reported
Finnboga dóttir et al., 2012 ²⁰	Recurrent or continuous erythema, scaling, and itching in typical places, the symptoms starting in early childhood.	Not reported	Not reported
Gough et al., 2012 ²¹	An itchy rash that persisted for at least 6 months and was located in the antecubital or popliteal fossae, wrists, ankles, neck or face during the last 12 months (from the ISAAC study).	Not reported	Not reported
Nissen et al., 2013 ²²	Areas of scaly, erythematous, and itchy eczematous rash primarily of the face and scalp, behind the ears, and at the flexural folds, diagnosed by a doctor. Only eczema localized to at least two typical areas and chronically relapsing with duration of at least 3 months were recorded.	Defined as not having the disease that had been present at the previous study period(s).	Indicates the proportion of participants who had a disease in one (I), two (II), three (III), four (IV) or five (V) consecutive study periods among participants who had ever had the same disease.
Williams et al., 1998 ¹⁴	When the children were aged 7 years, parents were asked by health visitors using a “structured questionnaire” whether their child had had any eczematous rash during the first year of life or at any time after the first year. When the children were aged 11 or 16 years, parents were asked whether their child had had eczematous rashes in the past 12 months. Self-reported eczema in the last 12 months at age 23 years was also recorded. The presence of visible eczema was recorded by experienced school medical officers at the ages of 7, 11 and 16 years.	By means of a combination of visible eczema at one point and reported symptoms over the last year in order to capture both the doctors’ and the parents’ perspective in this chronic relapsing disease	Not reported
Ziyab et al., 2010 ²³	Defined as ‘ever [having] eczema’ plus an ‘itchy rash during the previous 12 months. Atopic eczema was defined as having both eczema and a positive skin prick test.	A change in the individual status from eczema to eczema free.	Persistent cases were those present over the course of all assessments (ages 1-or-2, 4, 10, and 18 years), or those from 4 years and onwards.

Table S4. Prevalence data from included studies

Reference	3 mo	6 mo	1 yr	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs	7 yrs	8 yrs	9 yrs	10 yrs	11 yrs	12 yrs	15 yrs	16 yrs	18 yrs	20 yrs	21 yrs	23 yrs	26 yrs
Ballardini et al ¹⁸			$\frac{440}{2916}$	$\frac{542}{2916}$		$\frac{546}{2916}$				$\frac{355}{2916}$				$\frac{339}{2916}$							
Burr et al ¹⁹	$\frac{37}{391}$	$\frac{44}{378}$	$\frac{53}{378}$						$\frac{26}{342}$						$\frac{30}{283}$					$\frac{33}{241}$	
Finnbogadóttir et al ²⁰				$\frac{55}{179}$		$\frac{34}{161}$				$\frac{27}{134}$						$\frac{16}{122}$			$\frac{10}{120}$		
Gough et al ²¹					$\frac{19}{200}$			$\frac{24}{200}$			$\frac{34}{200}$			$\frac{34}{200}$	$\frac{31}{200}$			$\frac{26}{200}$			
Nissen et al ²²				$\frac{36}{276}$			$\frac{23}{251}$					$\frac{24}{222}$			$\frac{21}{215}$						$\frac{11}{193}$
Williams et al ¹⁴									$\frac{571}{6877}$							$\frac{860}{6877}$				$\frac{1053}{6877}$	
Ziyab et al ²³				$\frac{196}{1377}$		$\frac{145}{1214}$						$\frac{186}{1359}$					$\frac{161}{1307}$				

Figure legend: mo: months; yr: year; yrs: years; when a range of years was given, numbers were rounded up

Table S5. Results of sensitivity analyses

<i>By cutoff age</i>	Overall weighted risk difference	95% confidence interval		I²
Under and over age 10	0.014	-0.022	0.049	96.30%
Under and over age 8	0.006	-0.031	0.044	97.10%
Under and over age 2*	0.014	-0.004	0.032	62.20%
Under and over age 12 (excluding those under age 2)	0.002	-0.032	0.036	94.90%
<i>By Country</i>				
Other	0.034	-0.001	0.068	82.20%
UK	-0.017	-0.055	0.022	93.40%
<i>By number of assessments</i>				
3-4 Assessments	-0.019	-0.072	0.033	96.30%
5 Assessments	0.049	0.015	0.082	74.80%
6 Assessments	-0.013	-0.036	0.009	0.00%
<i>Sensitivity Analysis - excluding one study at a time</i>				
No Ballardini	0.007	-0.028	0.043	93.40%
No Burr	0.016	-0.025	0.057	96.90%
No Finnbogadottir	-0.001	-0.037	0.036	96.30%
No Gough	0.017	-0.023	0.057	96.90%
No Nissen	0.010	-0.030	0.049	96.70%
No Williams	0.021	-0.003	0.045	81.90%
No Ziyab	0.013	-0.030	0.056	96.80%

Notes:* Gough and Williams studies excluded because they did not include children under age 2

Table S6. Newcastle-Ottawa Scale Risk of Bias Assessment

Author, year	Selection				Comparability		Outcome Assessment			Total Score
	Representa- tiveness of cohort	Selection of non- exposed	Ascertain- ment of exposure	Outcome not present at start	Controls for factor	Additi- onal factors	Assessm- ent of outcome	Length of follow-up	Adequacy of follow- up	
Ballardini et al. ¹⁸	✓	✓	✗✗	✗✗	✓	✗✗	✗✗	✓	✓	5
Burr et al.. ¹⁹	✗✗	✗✗	✓	✗✗	✓	✗✗	✗✗	✓	✗✗	3
Finnbogadóttir et al. ²⁰	✓	✓	✓	✗✗	✓	✗✗	✓	✓	✗✗	6
Gough et al. ²¹	✗✗	✗✗	✓	✗✗	✓	✗✗	✗✗	✓	✓	4
Nissen et al. ²²	✓	✓	✓	✗✗	✓	✗✗	✓	✓	✓	7
Williams et al. ¹⁴	✓	✓	✓	✗✗	✓	✗✗	✗✗	✓	✗✗	5
Ziyab et al. ²³	✓	✓	✗✗	✗✗	✓	✗✗	✗✗	✓	✓	5

✓ No risk of bias (1 point), ✗✗ Risk of bias or unclear risk

Figure S1. Results of sensitivity analysis by country

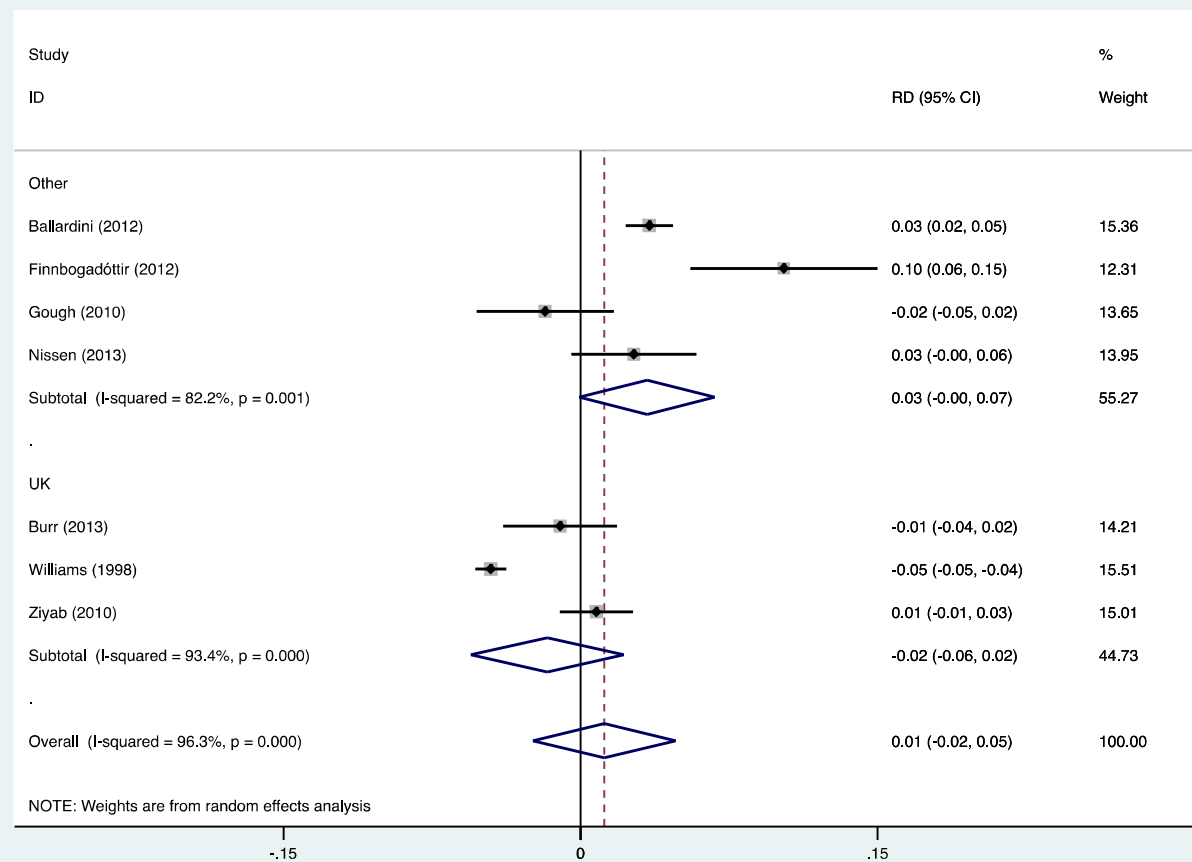


Figure S2. Results of sensitivity analyses by the number of assessments in each study

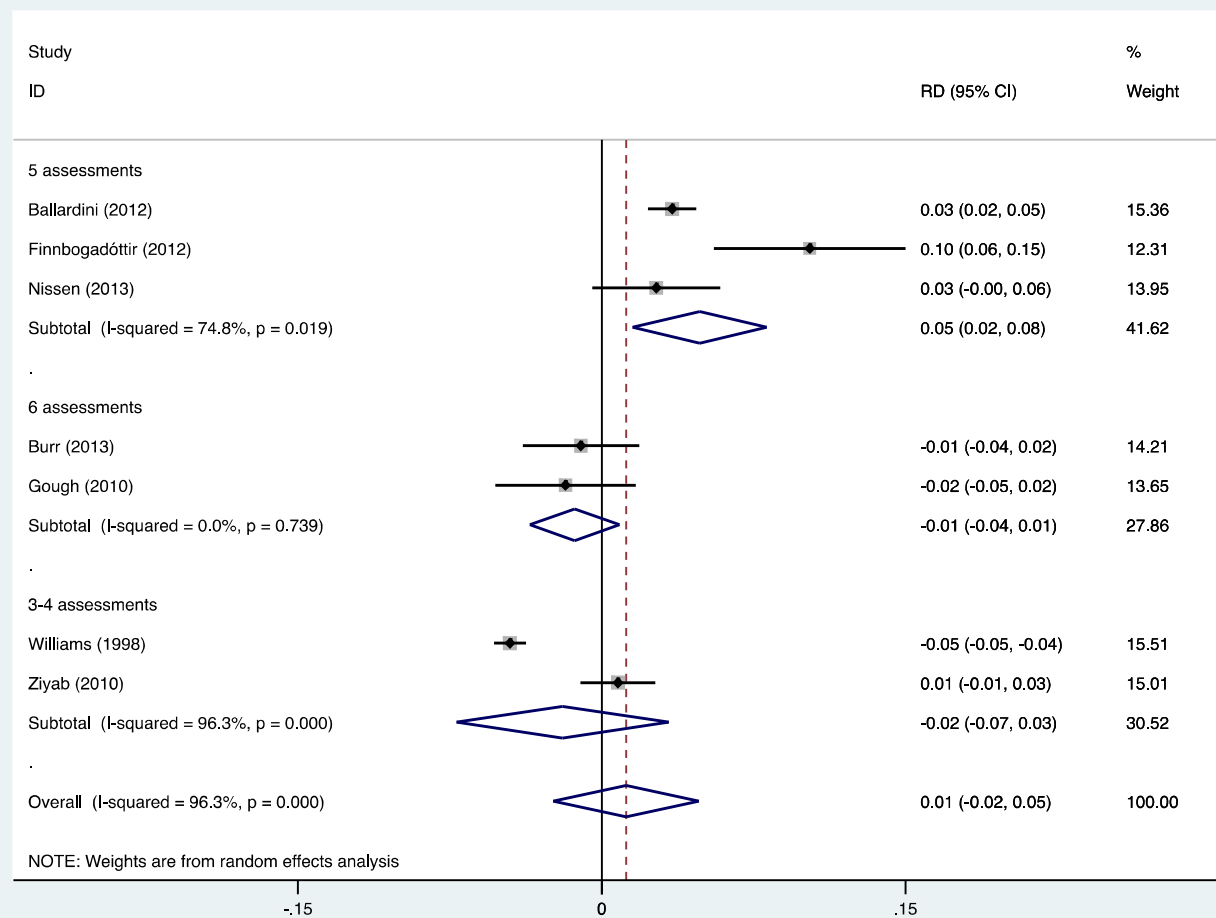


Figure S3. Results of sensitivity analysis including only studies with <30% follow-up

