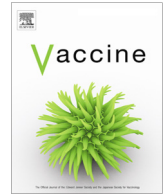




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Review

Vaccines do not cause atopic dermatitis: A systematic review and meta-analysis

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ABSTRACT

Background: Previous studies found conflicting results about the association of vaccinations and likelihood of atopic dermatitis (AD).

Objectives: To determine whether vaccinations increase the likelihood of AD.

Methods: A systematic review was performed of all published studies in MEDLINE, EMBASE, LILACS, Scopus, and Web of Science databases. At least 2 reviewers conducted title/abstract, full-text review, and data extraction. Quality of evidence was assessed using the Newcastle-Ottawa Scale (NOS).

Results: Forty-four studies met inclusion criteria; 37 had sufficient data for meta-analysis. There were no associations any vaccine regimen (random-effects logistic regression: odds ratio [95% confidence interval]: 0.961 [0.822–1.124]; n = 21 studies) BCG (0.927 [0.701–1.226]; n = 8), pertussis (0.790 [0.416–1.499]; n = 4), single (1.031 [0.920–1.155]; n = 17) or multiple vaccines (0.902 [0.608–1.338]; n = 7) with likelihood of AD. This remained true in studies with high-quality (NOS $\geq$ 7) (OR [95% CI]: 0.941 [0.793–1.117]; n = 13 studies) or low-quality (NOS < 7) (OR [95% CI]: 1.058 [0.669–1.674]; n = 8 studies).

Limitations: No randomized controlled trials.

Conclusions: No vaccine regimen was consistently associated with developing AD.

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Contents

1. Introduction	00
2. Methods	00
2.1. Search strategy	00
2.2. Selection and data extraction	00
2.3. Results	00
2.4. Study characteristics	00
2.5. Assessment of AD and vaccination status	00
2.6. Pooled meta-analysis	00
2.6.1. Any vaccine, BCG and pertussis	00
2.6.2. Multiple vaccines	00
2.7. Qualitative analysis	00
3. Discussion	00
4. Contributors	00

Abbreviations: AD, Atopic dermatitis; TB, tuberculosis; BCG, bacille Calmette-Guérin; HIB, Haemophilus Influenzae type B; NOS, Newcastle-Ottawa Scale; CI, confidence interval; OR, odds ratio.

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5. Financial disclosures	00
6. Funding support	00
CRediT authorship contribution statement	00
Declaration of Competing Interest	00
Appendix A. Supplementary data	00
References	00

1. Introduction

The 'hygiene hypothesis' was first introduced in 1989 and postulated that the increased allergic diseases in industrialized countries is associated with decreased infectious diseases [1,2]. The proposed mechanism behind the 'hygiene hypothesis' is that decreased exposure to pathogens shifts the lymphocyte population from a Th1 predisposition to increased Th2 activity and therefore atopic disease [3,4]. By extension, vaccination has been implicated as a potential factor in the hygiene hypothesis.

Vaccination has played an important role in decreasing the amount and spread of communicable disease throughout the world; however, there has been concern whether vaccination is related to the development of allergic or autoimmune disease [5]. In particular, vaccination during infancy can prevent harmful infections, but may also prevent downstream immune responses that may have a protective effect against AD and allergic disease [6]. This topic is particularly timely during the SARS-Cov-2 pandemic and ongoing development of novel vaccines. Yet, previous studies found conflicting results about the relationship of AD and vaccination [7,8]. We hypothesized that vaccines had little effect on the development of AD. Due to the potential link between vaccines, AD and atopic disease, we conducted a systematic review and meta-analysis to discover the relationship between immunization and AD.

2. Methods

This review was registered with Prospero (CRD42020171535).

2.1. Search strategy

The following databases were searched through March 1, 2020: MEDLINE via OVID (1946-present), EMBASE 1947-present), LILACS (1981-present), SCOPUS (1996-present), and Web of Science for AD terms combined with either vaccination terms, type of vaccine terms, or vaccine adjuvant terms. Search strategies were modified from those previously used in Cochrane reviews, see Supplemental Material. Studies from all years and countries published in press, online, or in print were included. All search results with titles and abstracts written in any language were considered. Institutional review board approval was not required as these data were collected from the published literature.

2.2. Selection and data extraction

Studies with primary epidemiologic data reporting the prevalence of AD in patients receiving a vaccination or related vaccination adjuvant were included. Papers assessing adverse events, protective effects, or no effects of vaccines on AD status were included. Studies were excluded if hand eczema was the specific type of eczema referred to. Eczema vaccinatum studies were also excluded. Relevant studies in foreign languages (Japanese) were translated using Google Translate.

Studies were excluded if they contained <10 individuals. The most recent and complete study was included in analysis if duplicate data was encountered. Data extraction was performed independently by reviewers (MA, AA, CM, ME) and any differences were resolved by discussion. Data items collected included: funding source; timeframe of study; study design; type of vaccination; age at which vaccination was administered; vaccination status; method of assessment of AD and vaccination status; country of study; total number of patients in study; number of patients with AD; number of females in the study; and similar data points in control patients, if present. Analysis of study quality for studies eligible for sensitivity analysis was performed using Newcastle-Ottawa Scale (NOS).

Statistical analyses were performed with OpenMeta for Sierra (version 10.12, Brown University, Providence, RI). Prevalence of AD in patients receiving vaccinations were analyzed. Pooled meta-analyses were performed on all studies with a control group. Sensitivity analyses were performed on studies of good quality (classified as those with NOS score ≥ 6), and specific vaccination subtypes if three or more data were available to run analyses on. Forest-plots were generated using random-effects estimates because of heterogeneity for analysis.

2.3. Results

The literature search yielded 6,515 non-duplicate articles; 6,457 did not meet inclusion criteria, 4 contained repeated data sets, and 11 could not be obtained after multiple attempts. Forty-four articles met inclusion criteria, of which thirty-seven were used in quantitative meta-analyses (Fig. 1).

2.4. Study characteristics

Studies were published from 1997 to 2018 [7–50], and included cross-sectional studies ($n = 26$, 59%) [7–14,16,17,20,21,26,29,31–33,35,38–42,44,48,50], longitudinal studies ($n = 12$, 27.3%) [15,22–25,27,28,30,34,36,47,49], case-control studies ($n = 3$, 68.2%) [43,45,46], prospective observational study ($n = 2$, 4.55%) [18,19], and randomized control trials (RCT; $n = 1$, 2.27%) [37].

The studies were conducted in Europe ($n = 25$; 56.82%) [7,11–14,17–20,25–27,29,31,33,34,37,38,40–42,45–48], Asia ($n = 5$; 11.36%) [9,32,44,49,50], Australia/ Oceania ($n = 5$; 11.36%) [22,24,28,30,36], North America ($n = 3$; 6.8%) [8,39,43], Africa ($n = 1$; 2.27%) [23], and multiple continents ($n = 5$; 11.36%) [10,15,16,21,35]. Most studies were written in English ($n = 43$; 97.7%) [7–49], and one was written in Japanese (2.27%) [50].

Funding for studies was provided by federal funding ($n = 10$; 22.73%) [18,19,26,28,32,33,35,47–49], pharmaceutical companies ($n = 1$, 2.27%) [21], foundations ($n = 6$; 13.64%) [15,22,30,34,36,46], or combination of sources ($n = 10$; 22.73%) [16,17,23,24,27,37,39–41]. Some studies were unfunded ($n = 5$; 11.36%) [8,13,14,20,25], and others had did not specify funding ($n = 12$; 27.27%) [7,9,10,12,29,31,38,42–45,50].

Target populations included children ($n = 40$; 90.91%) [7–13,15–29,31–35,37,38,40–50], adults ($n = 1$; 2.27%) [30] or both ($n = 3$;

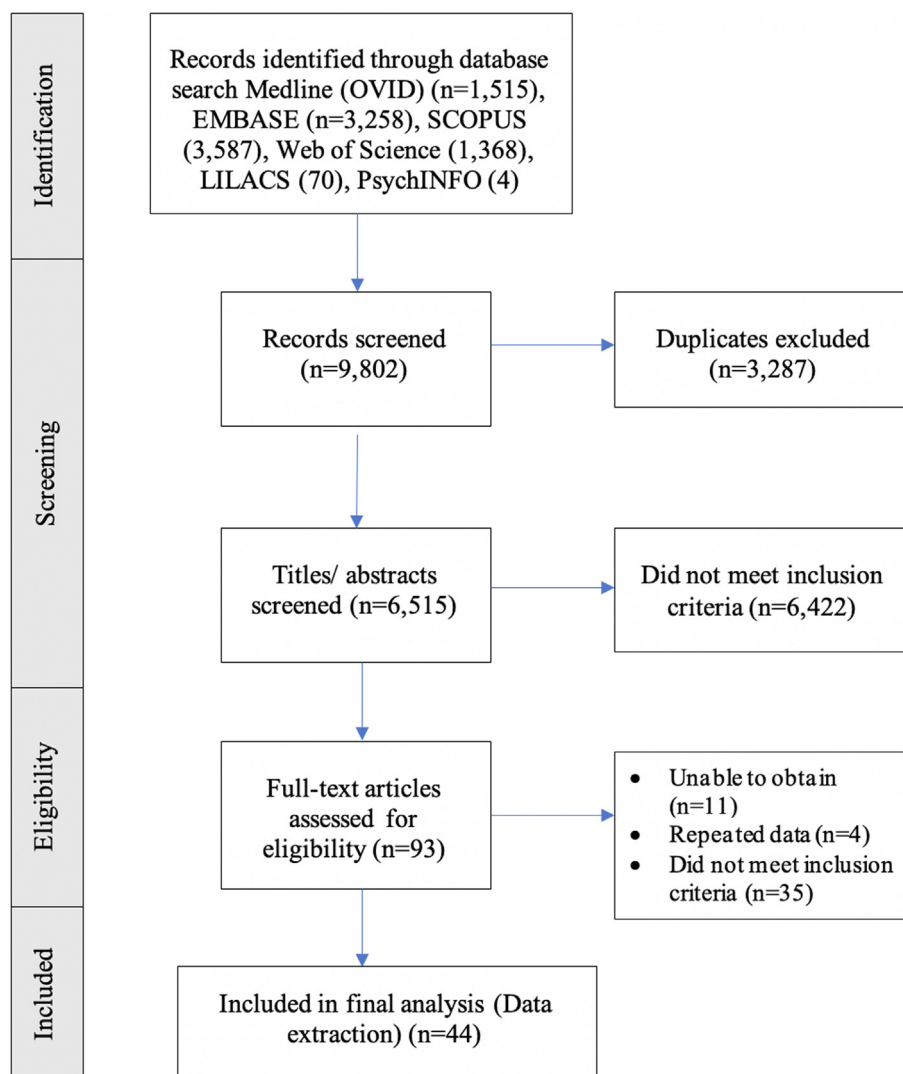


Fig. 1. PRISMA diagram.

6.82%) [14,36,39]. Twenty-five studies (56.82%) included a cohort with < 50% females [8,9,12,13,19,20,22,25–28,30–32,34,36–38,41,43–47,49], eleven studies (25%) had 50% or more females [14,15,17,21,23,24,29,33,39,42,50], and eight (18.18%) did not specify sex characteristics of the cohort [7,10,11,16,18,35,40,48].

Associations of AD were investigated with the following vaccines: Bacille Calmette–Guérin (BCG) (n = 17; 38.64%) [9,11,15–17,19–21,23,27–29,32,33,44–46], diphtheria-tetanus-pertussis (DTP/DTaP/DTWP) (n = 5; 11.36%) [10,24,30,34,50], Haemophilus influenzae type B vaccine (HIB) (n = 4; 9.09%) [13,18,21,26], pertussis vaccination (acellular [aP] or whole cell [wP]) (n = 10; 22.73%) [7,18,21,29,30,33,35–37,48], measles (n = 6; 13.64%) [10,14,18,21,35,40], measles-mumps-rubella (n = 4; 9.09%) [31,38,39,47], rubella (n = 3; 6.82%) [14,18,21], mumps (n = 2; 4.55%) [18,21], diphtheria (n = 3; 6.82%), [21,30,36] tetanus (n = 3; 6.82%) [21,30,36] smallpox (n = 3; 6.82%) [14,30,36], polio (n = 3; 6.82%) [21,30,36], typhoid fever (n = 1; 2.27%) [14], varicella zoster vaccine (n = 1; 2.27%) [43], multiple combination vaccination (n = 5; 11.36%) [12,22,25,41,49], other vaccination (n = 3; 6.82%) [10,29,31], or unspecified vaccination (n = 2; 4.55%) [8,42].

2.5. Assessment of AD and vaccination status

AD was assessed by parental questionnaire or self-report (n = 21; 47.73%) [8,10–13,15,17,20,23,25–30,32,36,38,41,42,44], physician diagnosis (n = 11; 25%) [9,19,21,24,34,35,37,40,43,46,49], medical records (n = 4; 9.09%) [7,31,39,48], or a combination of physician diagnosis and self-report (n = 7; 15.91%) [14,16,18,22,33,45,47]. Vaccination status was determined by medical chart review (n = 24; 54.55%) [7,11,18–21,23,24,26–29,31–34,38,39,41,43,47–50], parental questionnaire or self-report (n = 14; 31.82%) [8,12–14,16,17,22,25,30,35,36,40,42,44], physician report (n = 4; 9.09%) [15,37,45,46], and other methods (n = 2; 4.55%) [9,10].

2.6. Pooled meta-analysis

2.6.1. Any vaccine, BCG and pertussis

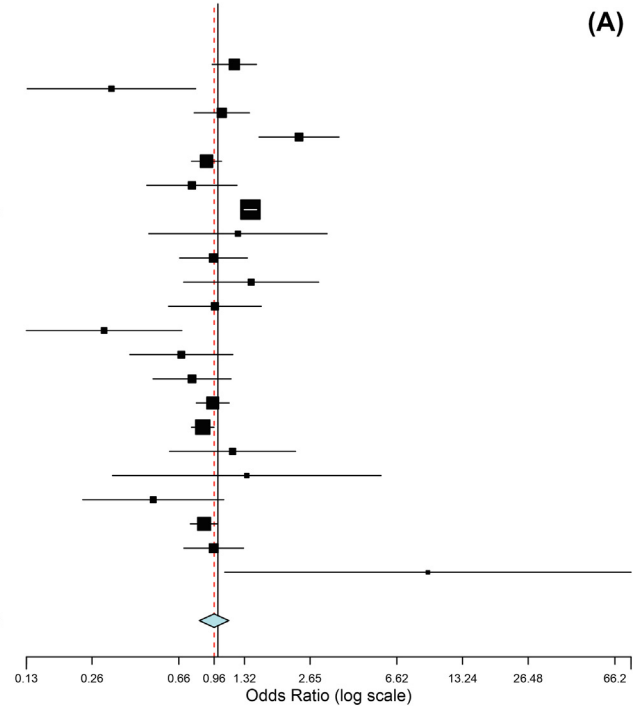
Across all studies, the pooled random-effects prevalence (95% CI) of AD was 14.6% (13.0–16.2%; n = 34 studies) in patients who received any vaccine (Supplemental Fig. 1A), 14.0% (10.2–17.8%;

n = 14 studies) in those who received BCG vaccine (Supplemental Fig. 1B), 14.7% (5.9–23.5%; n = 7 studies) in those who received pertussis vaccine (Supplemental Fig. 1C), and 15% (12.1–17.8%; n = 21 studies) in unvaccinated patients (Supplemental Fig. 1D).

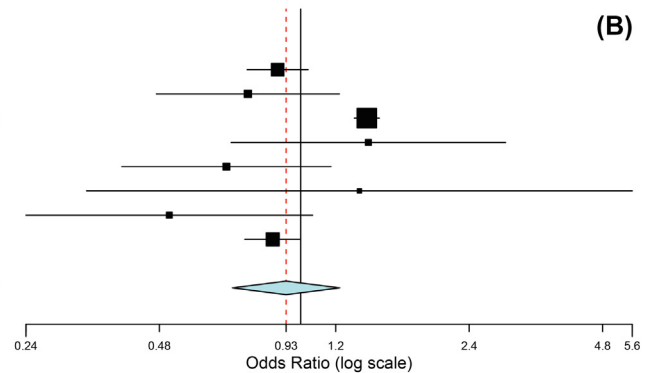
In sensitivity analysis, the pooled random-effects prevalence (95% CI) of AD was 14.4% (13.0–15.9%; n = 23 studies) in high-quality studies (NOS score ≥ 7) (Supplemental Fig. 1E) and 14.4% (9.1–19.7%; n = 11 studies) in lower-quality studies (NOS < 7) (Supplemental Fig. 1F); and 16.0% (13.7–18.4%; n = 21 studies) in Europe (Supplemental Fig. 1G), 7.7% (3.9–11.5%; n = 5 studies) in Asia (Supplemental Fig. 1H), 28.9%

(20.7–37.1%; n = 3 studies) in Australia/ Oceania (Supplemental Fig. 1I), and 13.7% (3.3–24.2%; n = 2 studies) in North America (Supplemental Fig. 1J); and 19.8% (14.5–25.1%; n = 6 studies) in studies with patients age 0–3 years (Supplemental Fig. 1K), 9.1% (7.2–11.1%; n = 7 studies) in studies with patients age 0–7 years (Supplemental Fig. 1L), 15.7% (10.5–21.0%; n = 5 studies) in studies with patients age 0–12 years (Supplemental Fig. 1M), 11.7% (8.6–14.8%; n = 9 studies) in studies with patients age 0–15 years (Supplemental Fig. 1N), and 18.3% (11.7–25.0%; n = 5 studies) in studies with patients with maximum age ≥ 16 years (Supplemental Fig. 1O).

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Bernsen, R (A) 2006 [12]	1.190 (0.942, 1.503)	271/1201	132/671
Bernsen, R 2003 [7]	0.325 (0.134, 0.791)	82/1680	6/44
Bernsen, R (B) 2006 [13]	1.042 (0.779, 1.396)	153/652	95/418
Enriquez, R 2005 [8]	2.356 (1.546, 3.591)	55/293	46/515
Garcia-Marcos, L 2005 [17]	0.887 (0.757, 1.039)	527/6762	246/2828
Gruber, C 2001 [19]	0.760 (0.472, 1.223)	27/92	241/682
Gruber, C 2002 [20]	1.410 (1.321, 1.505)	2548/20383	1695/18425
Kemp, T 1997 [22]	1.236 (0.482, 3.167)	398/950	7/19
Kummeling, I 2007 [25]	0.955 (0.668, 1.365)	529/2255	43/177
Mohrenschlager, M 2007 [33]	1.421 (0.697, 2.899)	62/1230	9/250
Mohrenschlager, M 2007 [33]	0.969 (0.595, 1.580)	45/977	27/569
Martignon, G 2005 [29]	0.301 (0.132, 0.683)	182/694	13/24
Miyake, Y 2008 [32]	0.680 (0.395, 1.170)	391/5567	15/150
Olesen, A 2003 [38]	0.761 (0.504, 1.149)	298/7178	26/483
Rosenlund, H 2009 [40]	0.947 (0.796, 1.126)	748/7383	177/1664
Schlaud, M 2017 [41]	0.852 (0.757, 0.960)	552/7263	648/7364
Schmitz, R 2011 [42]	1.168 (0.601, 2.271)	1935/13366	10/79
Singh, M 2013 [44]	1.357 (0.329, 5.598)	48/9492	2/536
Steenhuis, T 2008 [45]	0.505 (0.240, 1.064)	27/61	33/54
Thostesen, L 2017 [46]	0.865 (0.748, 1.000)	466/2052	495/1952
Timmermann, C 2015 [47]	0.957 (0.699, 1.311)	110/541	88/418
Yoneyama, H 2000 [50]	9.188 (1.075, 78.493)	7/39	1/43
Overall ($I^2=85.26\%$, $P<0.001$)	0.961 (0.822, 1.124)	9461/90111	4055/37365



Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Garcia-Marcos, L 2005 [17]	0.887 (0.757, 1.039)	527/6762	246/2828
Gruber, C 2001 [19]	0.760 (0.472, 1.223)	27/92	241/682
Gruber, C 2002 [20]	1.410 (1.321, 1.505)	2548/20383	1695/18425
Mohrenschlager, M 2007 [33]	1.421 (0.697, 2.899)	62/1230	9/250
Miyake, Y 2008 [32]	0.680 (0.395, 1.170)	391/5567	15/150
Singh, M 2013 [44]	1.357 (0.329, 5.598)	48/9492	2/536
Steenhuis, T 2008 [45]	0.505 (0.240, 1.064)	27/61	33/54
Thostesen, L 2017 [46]	0.865 (0.748, 1.000)	466/2052	495/1952
Overall ($I^2=90.02\%$, $P<0.001$)	0.927 (0.701, 1.226)	4096/45639	2736/24877



Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Gruber, C 2003 [18]	0.590 (0.385, 0.904)	34/366	78/527
Mohrenschlager, M 2007 [33]	0.969 (0.595, 1.580)	45/977	27/569
Nakajima, K 2007 [36]	1.516 (1.420, 1.618)	6940/68712	1132/16406
Bernsen, R 2003 [7]	0.325 (0.134, 0.791)	82/1680	6/44
Overall ($I^2=90.70\%$, $P<0.001$)	0.790 (0.416, 1.499)	7101/71735	1243/17546

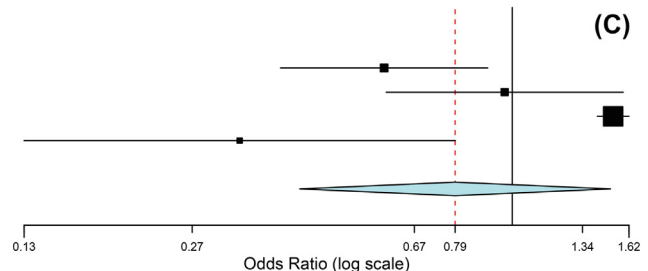


Fig. 2. Forest-plots of the prevalence of atopic dermatitis in persons with (A) any vaccination (B) bacille Calmette-Guerin (BCG) vaccine for tuberculosis, (C) pertussis, (D) multiple vaccines and (E). 95% confidence intervals (squares), pooled proportions (diamond) are presented.

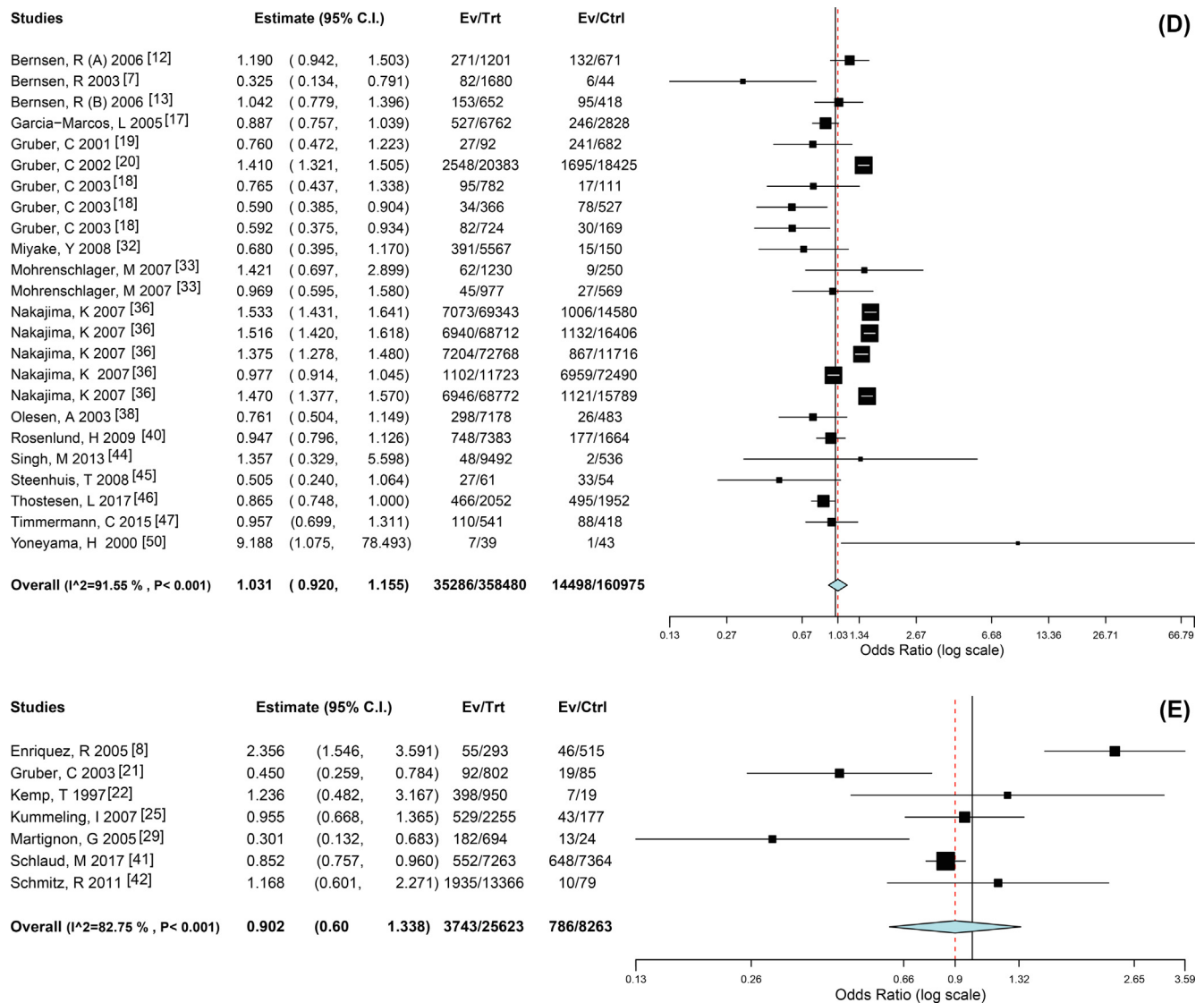


Fig. 2 (continued)

Among studies that included an unvaccinated control group, patients who were vaccinated with any of the studied vaccine regimens did not have significantly different odds of AD compared to those who were unvaccinated (OR [95% CI]: 0.961 [0.822–1.124]; $n = 21$ studies) (Fig. 2A), nor did those who received BCG (0.927 [0.701–1.226]; $n = 8$) (Fig. 2B) or pertussis (0.790 [0.416–1.499]; $n = 4$) (Fig. 2C) in particular. This remained true in high-quality studies ($NOS \geq 7$) (OR [95% CI]: 0.941 [0.793–1.117]; $n = 13$ studies) or low-quality studies ($NOS < 7$) (OR [95% CI]: 1.058 [0.669–1.674]; $n = 8$ studies), across all regions and age groups (Supplemental Fig. 2A, B).

2.6.2. Multiple vaccines

The pooled prevalence of AD in patients receiving multiple vaccines was 15.2% (13.0–17.5%; $n = 10$ studies) (Supplemental Fig. 1P) vs. 16.9% (14.4–19.5%; $n = 28$ studies) in those who received a single vaccine (Supplemental Fig. 1Q). The odds of AD were not significantly different in patients receiving single (OR [95% CI]: 1.031 [0.920–1.155]; $n = 17$) or multiple vaccines (0.902 [0.608–1.338]; $n = 7$) (Fig. 2D) compared to unvaccinated controls.

2.7. Qualitative analysis

Seven studies provided insufficient data for pooled meta-analysis and were included in a qualitative analysis. Three found no association of vaccines with AD [16,21,26], one found some association of vaccination with AD [14], and two found associations of preventable infections with AD [27,35].

A cross-sectional study of 23,901 schoolchildren (ages 8–12 years) investigated TB infection vs. BCG vaccination either before or after the first year of life and found no association of BCG vaccination with AD [16]. In contrast, TB infection was associated with increased self-reported flexural eczema in the past year (adjusted OR [95% CI]: 3.21 [2.01–5.12]), flexural eczema on physical examination (4.04 [1.71–9.56]), severe eczema (6.31 [2.19–18.17]), as well as wheeze (2.27 [1.52–3.41]), severe asthma (4.02 [2.17–7.47]), and hay fever symptoms (2.23 [1.22–4.09]). Another cross-sectional study of 1608 British children followed until age 13–17 years found no association of BCG vaccination with AD or asthma [27].

A study of 2,184 infants with an established diagnosis of AD found that vaccinations with diphtheria, tetanus, pertussis, polio,

varicella, BCG, meningococci and pneumococci were not associated with AD severity or allergic sensitization when given before the first year of life [21].

A cross-sectional study of 18,617 Polish patients found a slightly higher risk of self-reported AD in patients vaccinated against typhoid fever (OR: 1.13, $p = 0.005$), smallpox (OR: 1.18, $p = 0.003$) and rubella (OR: 1.34, $p < 0.0001$), but no associations with AD diagnosed by a doctor [14]. Of note, potentially confounding variables were not controlled for in this study.

No association was found for Hemophilus influenza B vaccination and AD in an East German cohort of 1,943 school children (OR [95% CI]: 1.25 [0.94–1.67]) [26]. A cross-sectional study of 54,943 children ages 8–12 years found that measles infections was associated with increased self-reported AD and wheeze overall, whereas, pertussis infection was associated with a higher prevalence of self-reported AD, particularly in non-affluent countries, as well as wheeze and rhinoconjunctivitis [35].

In a study of 256 individuals with atopic dermatitis and 422 healthy controls in New York, children with wild type varicella zoster virus infection, when compared with varicella vaccination, had lower odds of developing AD (OR [95% CI]: 0.55 [0.34–0.89]). In addition, the patients with infection who did eventually develop AD required fewer pediatric sick visits for management of their AD, suggesting that infection protects against AD and decreases the severity of AD [43].

3. Discussion

This SR of 44 studies and meta-analysis of 37 studies found no consistent associations of vaccination by any regimen, and particularly BCG, pertussis, or multiple vaccines with AD in pooled meta-analysis. Only one study found increased self-reported AD in those vaccinated against typhoid fever, smallpox and rubella [14] and another study found varicella infection was more protective against developing AD than vaccination [43]. Taken together, no specific vaccine regimen was associated with AD, although, some studies found mixed results about whether some preventable infections are associated with increased or decreased AD. Providers caring for patients who may be considered high risk for developing AD should take this information into account when considering vaccination regimens. Immunization should not be delayed or withheld, and parents should be informed the risk of AD is not increased from vaccination. Patients at risk for AD should be especially encouraged to receive age-appropriate vaccinations as patients who go on to develop AD and suffer natural infection from certain preventable disease, including varicella, are more prone to complications such as cellulitis, hemorrhagic varicella, Kaposi varicelliform eruption and superimposed soft tissue infections [51].

Strengths of this study include a comprehensive search strategy, with no limitations in language or time period. Additionally, we used random-effects models to address study heterogeneity and sensitivity analyses by vaccine type, study quality, and age groups. However, there are potential limitations to this study. The majority of studies included were cross-sectional, and there were no randomized control trials comparing development of AD in children who were vs. were not vaccinated. Additionally, most of the studies were conducted in North America and Europe, and may not be generalizable to all regions of the world. There were limited studies from some regions, e.g. Africa. Most studies did not stratify analyses by race/ethnicity, precluding assessment of racial/ethnic differences in vaccine responses or racial/ethnic disparities in vaccination coverage. None of the studies specifically addressed adjuvants used in vaccines, but it is doubtful that adjuvants have a major impact on risk of AD since there was no association between vaccinations overall and development of AD.

In conclusion, no vaccine regimen was consistently associated with developing AD. Based on these results and the crucial importance of immunizations in preventing a wide array of deadly infectious diseases, we recommend that all children with AD receive age-appropriate vaccinations.

4. Contributors

Jl Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

5. Financial disclosures

None

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CRediT authorship contribution statement

Marissa Ayasse: Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Adnan Ahmed:** Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing. **Catherine McCullum:** Investigation, Data curation, Writing - original draft, Writing - review & editing. **Maria L. Espinosa:** Investigation, Data curation, Writing - original draft, Writing - review & editing. **Amy S. Paller:** Investigation, Writing - review & editing. **Jonathan I. Silverberg:** Conceptualization, Methodology, Software, Resources, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

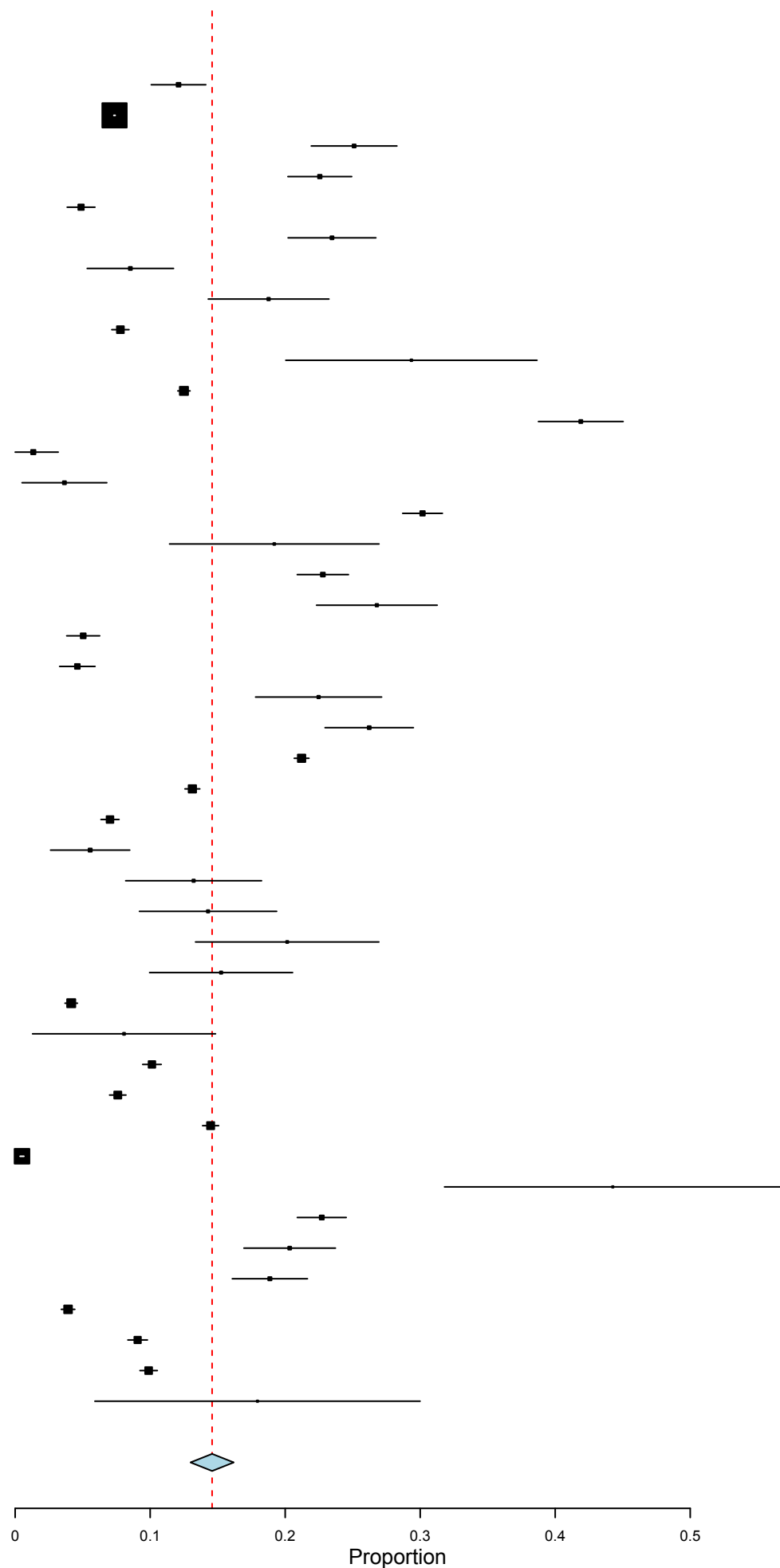
Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2021.02.036>.

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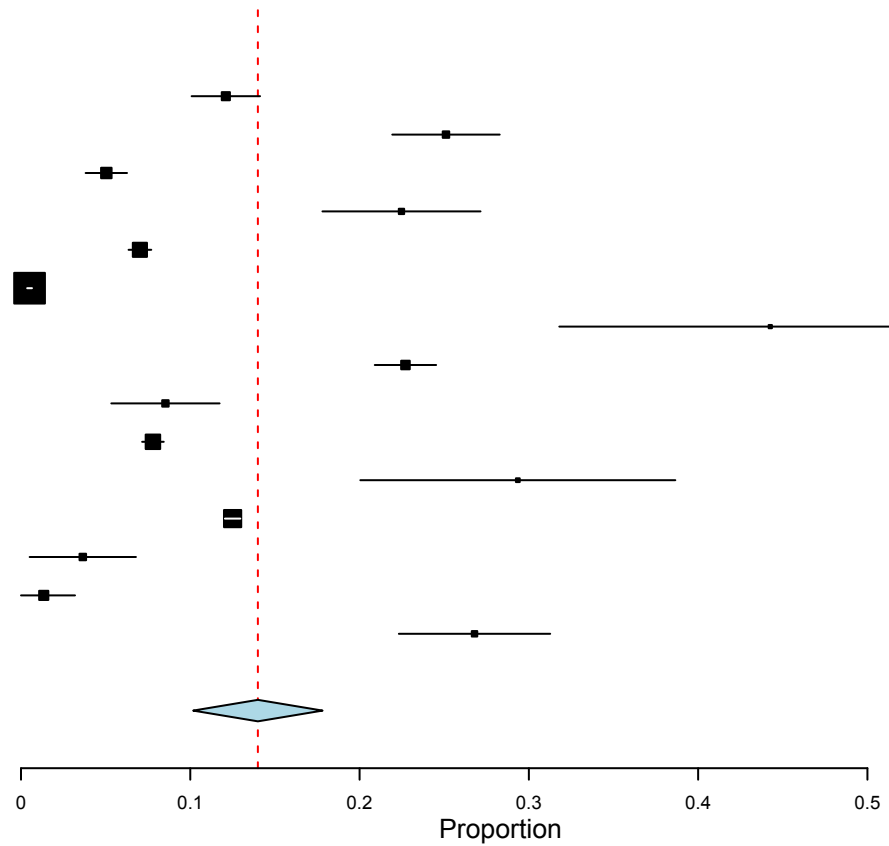
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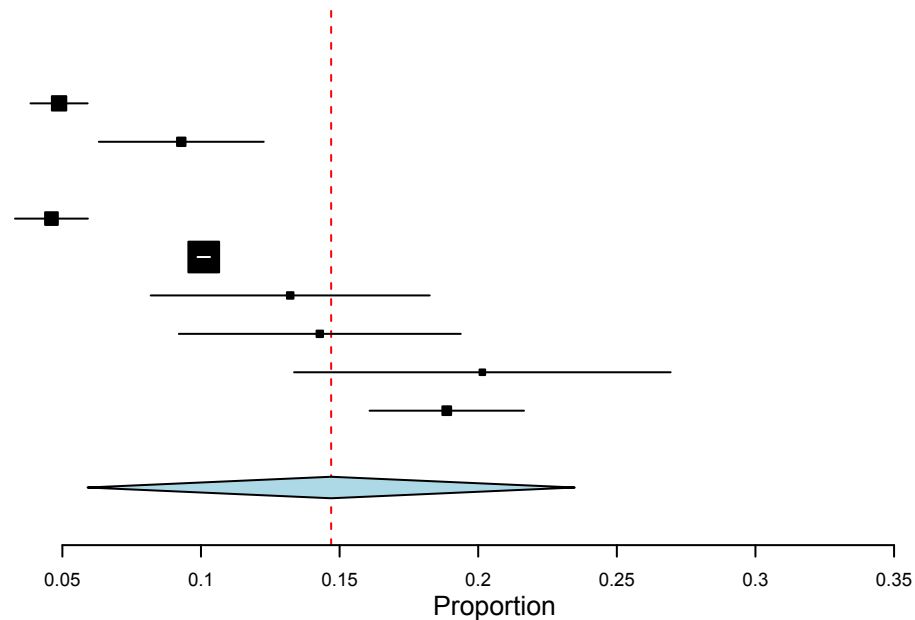
Studies	Estimate (95% C.I.)			Ev/Trt
Ahmadiafshar, A 2005 [9]	0.121	(0.101,	0.141)	121/1000
Anderson, H 2001 [10]	0.074	(0.073,	0.074)	69130/939300
Annus, T 2004 [11]	0.251	(0.219,	0.283)	180/717
Bernsen, R (A) 2006 [12]	0.226	(0.202,	0.249)	271/1201
Bernsen, R 2003 [7]	0.049	(0.039,	0.059)	82/1680
Bernsen, R (B) 2006 [13]	0.235	(0.202,	0.267)	153/65
Eifan, A 2009 [15]	0.085	(0.053,	0.117)	2
Enriquez, R 2005 [8]	0.188	(0.143,	0.232)	25/29
Garcia-Marcos, L 2005 [17]	0.078	(0.072,	0.084)	527/6762
Gruber, C 2001 [19]	0.293	(0.200,	0.387)	527/292
Gruber, C 2002 [20]	0.125	(0.120,	0.130)	2548/20383
Kemp, T 1997 [22]	0.419	(0.388,	0.450)	398/950
Kiraly, N 2013 [23]	0.013	(0.000,	0.032)	2/149
Kiraly, N 2013 [23]	0.036	(0.005,	0.068)	5/137
Kiraly, N 2016 [24]	0.302	(0.287,	0.316)	1127/3735
Kiraly, N 2016 [24]	0.192	(0.114,	0.269)	19/99
Kummeling, I 2007 [25]	0.228	(0.209,	0.247)	428/1878
Kummeling, I 2007 [25]	0.268	(0.223,	0.313)	101/377
Mohrenschlager, M 2007 [33]	0.050	(0.038,	0.063)	62/1230
Mohrenschlager, M 2007 [33]	0.046	(0.033,	0.059)	45/977
Marks, G 2003 [28]	0.225	(0.178,	0.271)	69/307
Martignon, G 2005 [29]	0.262	(0.230,	0.295)	182/694
McKeever, T 2004 [31]	0.212	(0.207,	0.218)	4559/21489
McKeever, T 2004 [31]	0.131	(0.126,	0.137)	1884/14353
Miyake, Y 2008 [32]	0.070	(0.064,	0.077)	391/5567
Mrozek-Budzyn, D 2018 [34]	0.056	(0.026,	0.085)	13/234
Nilsson, L 2003 [37]	0.132	(0.082,	0.183)	23/174
Nilsson, L 2003 [37]	0.143	(0.092,	0.194)	26/182
Nilsson, L 2003 [37]	0.201	(0.134,	0.269)	27/134
Nilsson, L 2003 [37]	0.153	(0.100,	0.206)	27/177
Olesen, A 2003 [38]	0.042	(0.037,	0.046)	298/7178
Patel, R 2013 [39]	0.081	(0.013,	0.148)	5/62
Rosenlund, H 2009 [40]	0.101	(0.094,	0.108)	748/7383
Schlaud, M 2017 [41]	0.076	(0.070,	0.082)	552/7263
Schmitz, R 2011 [42]	0.145	(0.139,	0.151)	1935/13366
Singh, M 2013 [44]	0.005	(0.004,	0.006)	48/9492
Steenhuis, T 2008 [45]	0.443	(0.318,	0.567)	27/61
Thostesen, L 2017 [46]	0.227	(0.209,	0.245)	466/2052
Timmermann, C 2015 [47]	0.203	(0.169,	0.237)	110/541
Venter, C 2016 [48]	0.189	(0.161,	0.217)	143/758
Wang, I 2012 [49]	0.039	(0.034,	0.044)	224/5717
Wang, I 2012 [49]	0.091	(0.083,	0.098)	544/5997
Wang, I 2012 [49]	0.099	(0.092,	0.105)	816/8254
Yoneyama, H 2000 [50]	0.179	(0.059,	0.300)	7/39
Overall (I²=99.73 % , P< 0.001)	0.146	(0.130,	0.162)	88430/1093379



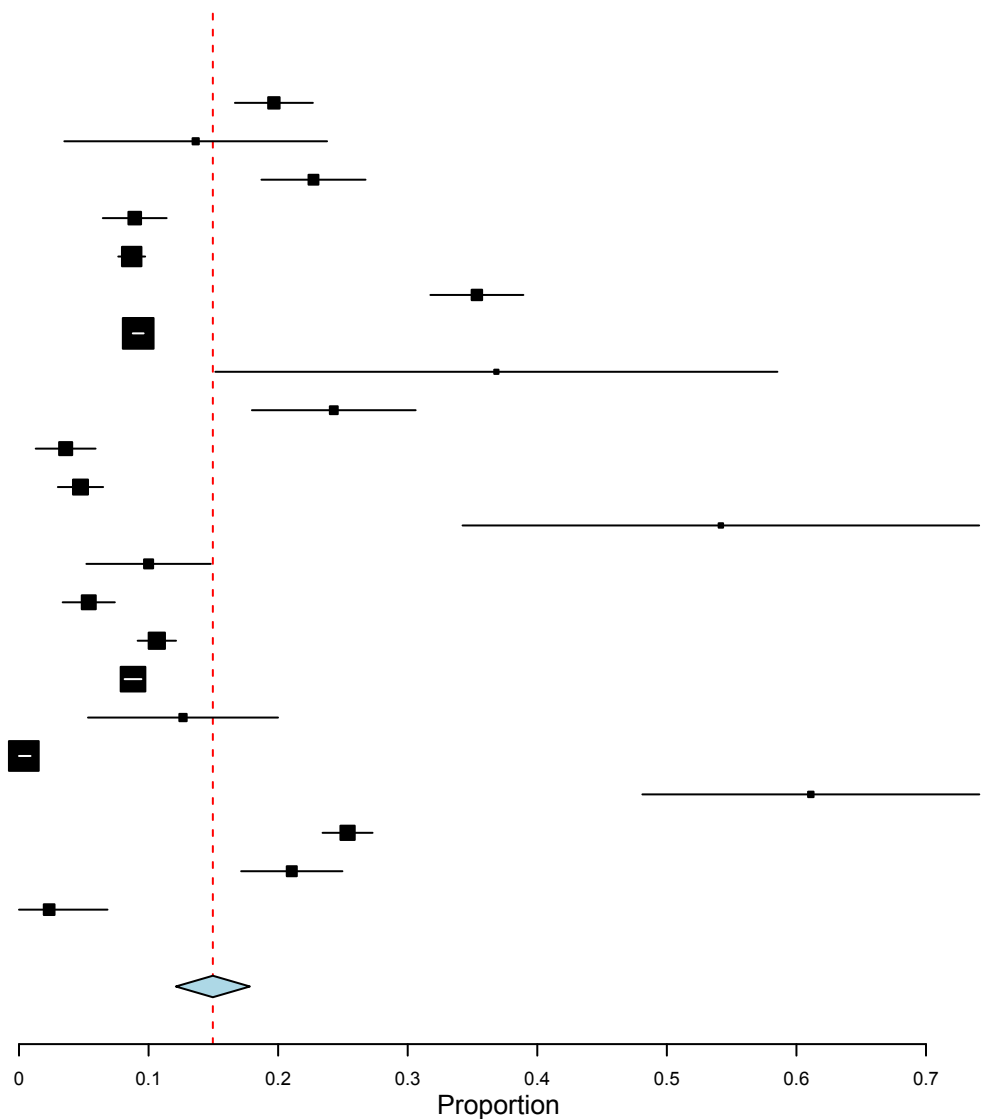
Studies	Estimate (95% C.I.)			Ev/Trt
Ahmadiafshar, A 2005 [9]	0.121	(0.101,	0.141)	121/1000
Annus, T 2004 [11]	0.251	(0.219,	0.283)	180/717
Mohrenschlager, M 2007 [33]	0.050	(0.038,	0.063)	62/1230
Marks, G 2003 [28]	0.225	(0.178,	0.271)	69/307
Miyake, Y 2008 [32]	0.070	(0.064,	0.077)	391/5567
Singh, M 2013 [44]	0.005	(0.004,	0.006)	48/9492
Steenhuis, T 2008 [45]	0.443	(0.318,	0.567)	27/61
Thostesen, L 2017 [46]	0.227	(0.209,	0.245)	466/2052
Eifan, A 2009 [15]	0.085	(0.053,	0.117)	25/293
Garcia-Marcos, L 2005 [17]	0.078	(0.072,	0.084)	527/6762
Gruber, C 2001 [19]	0.293	(0.200,	0.387)	27/92
Gruber, C 2002 [20]	0.125	(0.120,	0.130)	2548/20383
Kiraly, N 2013 [23]	0.036	(0.005,	0.068)	5/137
Kiraly, N 2013 [23]	0.013	(0.000,	0.032)	2/149
Kummeling, I 2007 [25]	0.268	(0.223,	0.313)	101/377
Overall ($I^2=99.66\%$, $P<0.001$)	0.140	(0.102,	0.178)	4599/48619



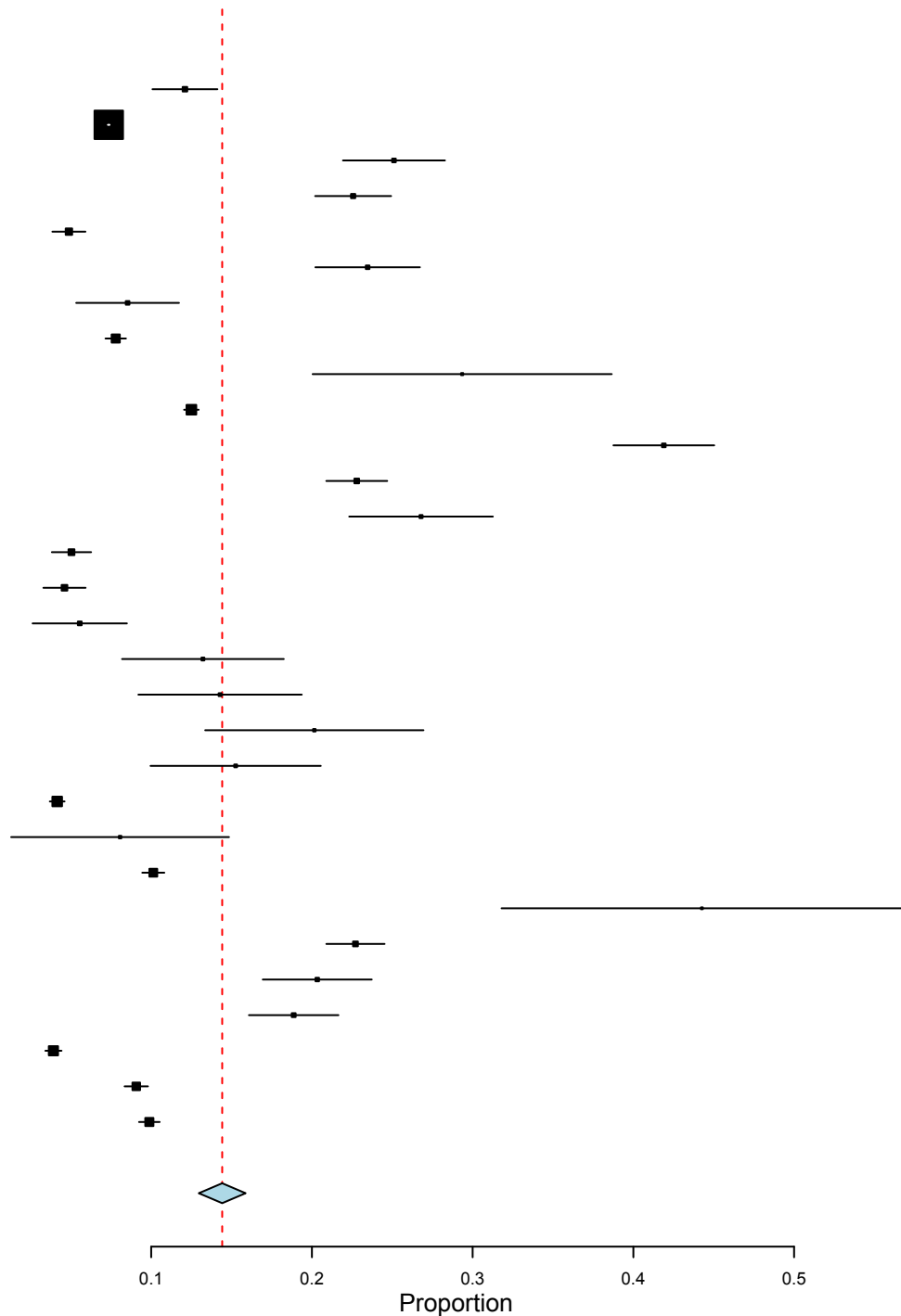
Studies	Estimate (95% C.I.)			Ev/Trt
Bernsen, R 2003 [7]	0.049	(0.039,	0.059)	82/1680
Gruber, C 2003 [18]	0.093	(0.063,	0.123)	34/366
Matheson, M 2010 [30]	0.371	(0.363,	0.379)	4829/13016
Mohrenschlager, M 2007 [33]	0.046	(0.033,	0.059)	45/977
Nakajima, K 2007 [36]	0.101	(0.099,	0.103)	6940/68712
Nilsson, L 2003 [37]	0.132	(0.082,	0.183)	23/174
Nilsson, L 2003 [37]	0.143	(0.092,	0.194)	26/182
Nilsson, L 2003 [37]	0.201	(0.134,	0.269)	27/134
Venter, C 2016 [48]	0.189	(0.161,	0.217)	143/758
Overall ($I^2=99.81\%$, $P<0.001$)	0.147	(0.059,	0.235)	12149/85999



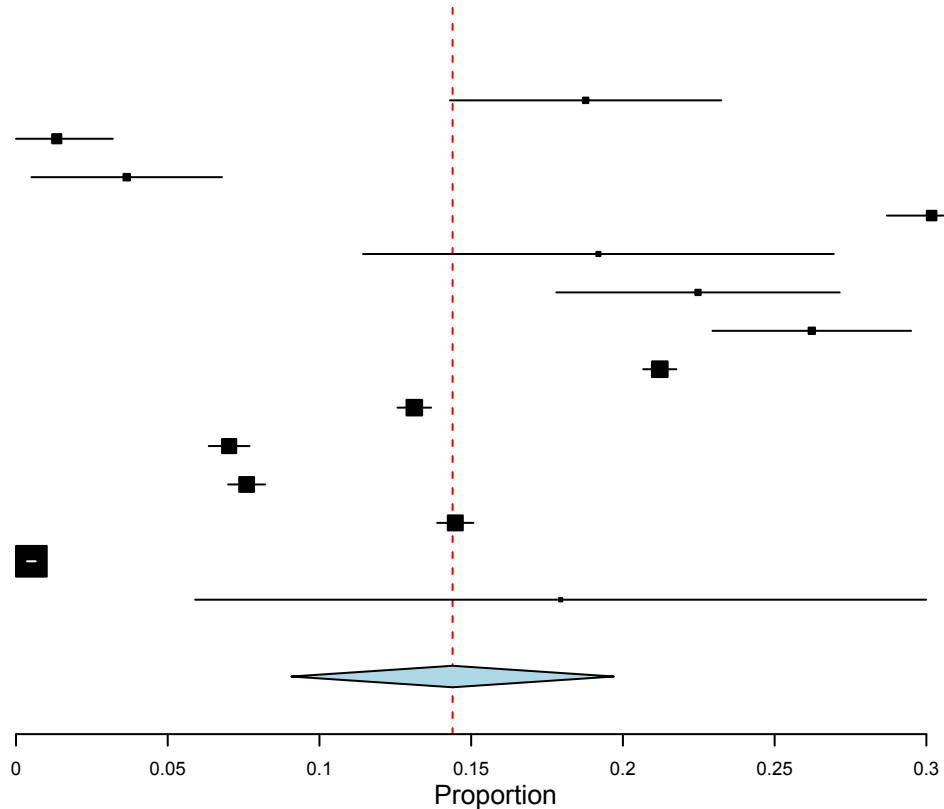
Studies	Estimate (95% C.I.)			Ev/Trt
Bernsen, R (A) 2006 [12]	0.197	(0.167,	0.227)	132/671
Bernsen, R 2003 [7]	0.136	(0.035,	0.238)	6/44
Bernsen, R (B) 2006 [13]	0.227	(0.187,	0.267)	95/418
Enriquez, R 2005 [8]	0.089	(0.065,	0.114)	46/515
Garcia-Marcos, L 2005 [17]	0.087	(0.077,	0.097)	246/2828
Gruber, C 2001 [19]	0.353	(0.317,	0.389)	241/682
Gruber, C 2002 [20]	0.092	(0.088,	0.096)	1695/18425
Kemp, T 1997 [22]	0.368	(0.152,	0.585)	7/19
Kummeling, I 2007 [25]	0.243	(0.180,	0.306)	43/177
Mohrenschlager, M 2007 [33]	0.036	(0.013,	0.059)	9/250
Mohrenschlager, M 2007 [33]	0.047	(0.030,	0.065)	27/569
Martignon, G 2005 [29]	0.542	(0.342,	0.741)	13/24
Miyake, Y 2008 [32]	0.100	(0.052,	0.148)	15/150
Olesen, A 2003 [38]	0.054	(0.034,	0.074)	26/483
Rosenlund, H 2009 [40]	0.106	(0.092,	0.121)	177/1664
Schlaud, M 2017 [41]	0.088	(0.082,	0.094)	648/7364
Schmitz, R 2011 [42]	0.127	(0.053,	0.200)	10/79
Singh, M 2013 [44]	0.004	(0.000,	0.009)	2/536
Steenhuis, T 2008 [45]	0.611	(0.481,	0.741)	33/54
Thostesen, L 2017 [46]	0.254	(0.234,	0.273)	495/1952
Timmermann, C 2015 [47]	0.211	(0.171,	0.250)	88/418
Yoneyama, H 2000 [50]	0.023	(0.000,	0.068)	1/43
Overall (I²=98.77 % , P< 0.001)	0.150	(0.121,	0.178)	4055/37365



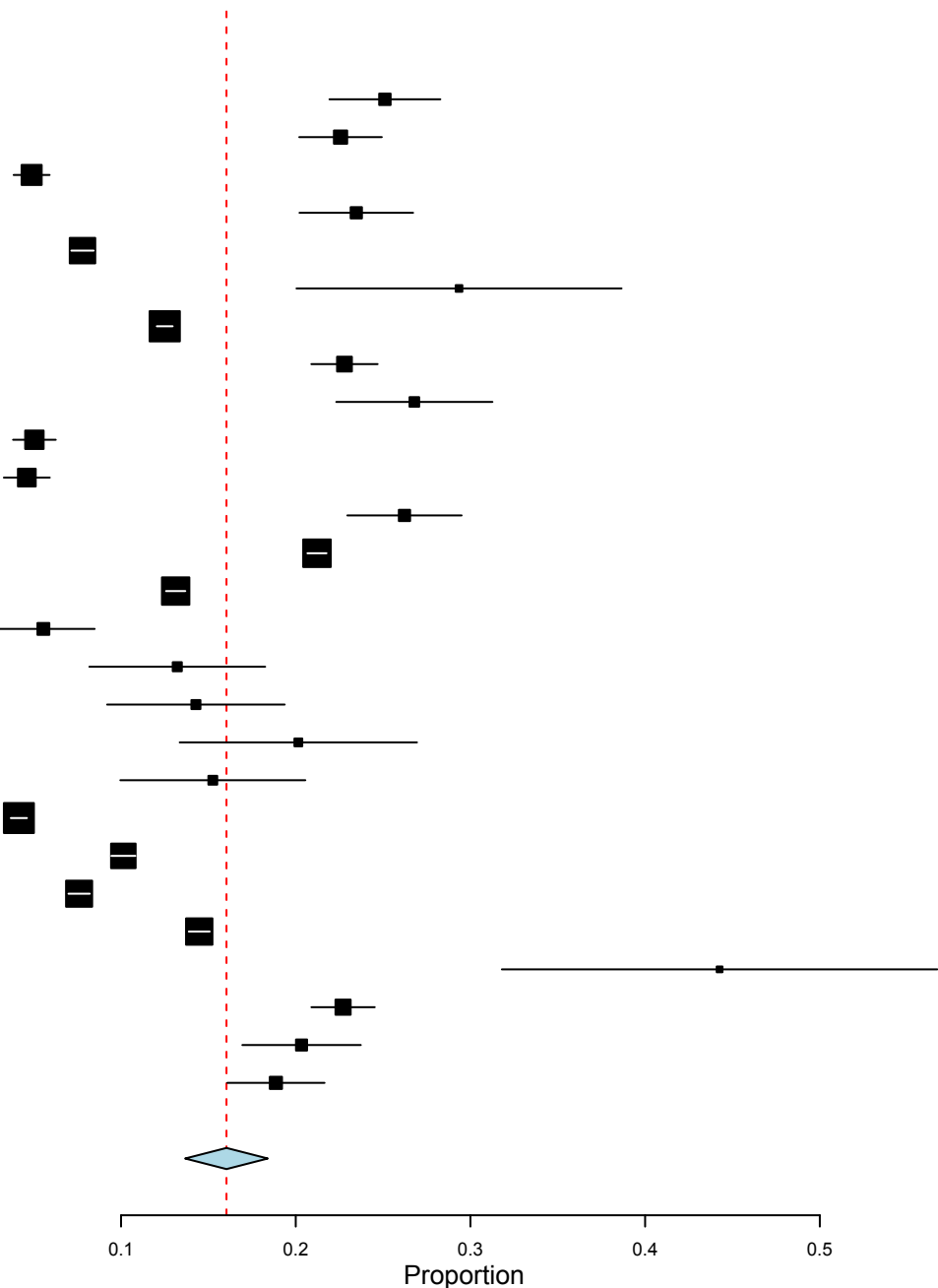
Studies	Estimate (95% C.I.)			Ev/Trt
Ahmadiafshar, A 2005 [9]	0.121	(0.101,	0.141)	121/1000
Anderson, H 2001 [10]	0.074	(0.073,	0.074)	69130/939300
Annus, T 2004 [11]	0.251	(0.219,	0.283)	180/717
Bernsen, R (A) 2006[12]	0.226	(0.202,	0.249)	271/1201
Bernsen, R 2003 [7]	0.049	(0.039,	0.059)	82/1680
Bernsen, R (B) 2006 [13]	0.235	(0.202,	0.267)	153/652
Eifan, A 2009 [15]	0.085	(0.053,	0.117)	25/293
Garcia-Marcos, L 2005 [17]	0.078	(0.072,	0.084)	527/6762
Gruber, C 2001 [19]	0.293	(0.200,	0.387)	27/92
Gruber, C 2002 [20]	0.125	(0.120,	0.130)	2548/20383
Kemp, T 1997 [22]	0.419	(0.388,	0.450)	398/950
Kummeling, I 2007 [25]	0.228	(0.209,	0.247)	428/1878
Kummeling, I 2007 [25]	0.268	(0.223,	0.313)	101/377
Mohrenschlager, M 2007 [33]	0.050	(0.038,	0.063)	62/1230
Mohrenschlager, M 2007 [33]	0.046	(0.033,	0.059)	45/977
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Rosenlund, H 2009 [40]	0.101	(0.094,	0.108)	
Steenhuis, T 2008 [45]	0.443	(0.318,	0.567)	27/61
Thostesen, L 2017 [46]	0.227	(0.209,	0.245)	466/2052
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Wang, I 2012 [49]	0.091	(0.083,	0.098)	544/5997
Wang, I 2012 [49]	0.099	(0.092,	0.105)	816/8254
Overall (I²=98.93 % , P< 0.001)	0.144	(0.130,	0.159)	77595/1016396



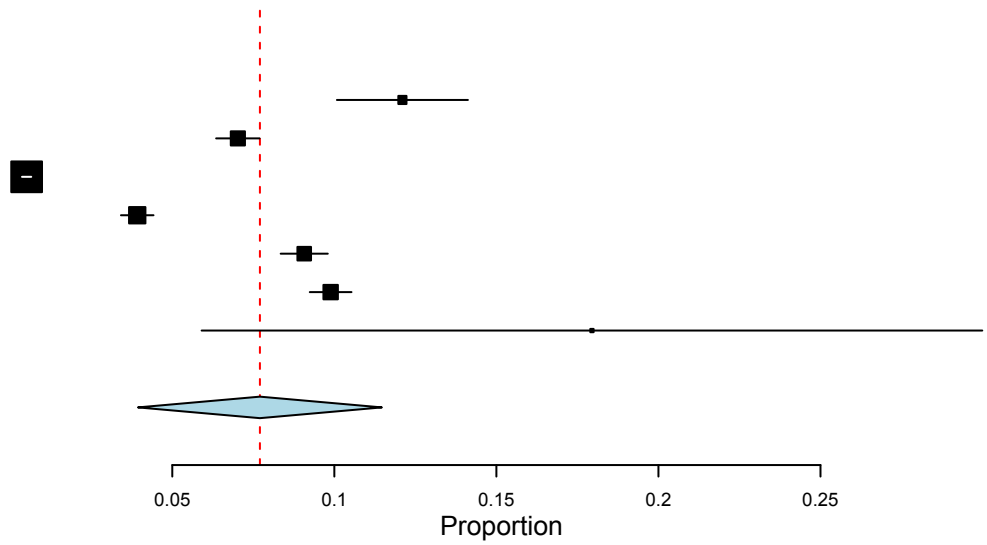
Studies	Estimate (95% C.I.)			Ev/Trt
Enriquez, R 2005 [8]	0.188	(0.143,	0.232)	55/293
Kiraly, N 2013 [23]	0.013	(0.000,	0.032)	2/149
Kiraly, N 2013 [23]	0.036	(0.005,	0.068)	5/137
Kiraly, N 2016 [24]	0.302	(0.287,	0.316)	1127/3735
Kiraly, N 2016 [24]	0.192	(0.114,	0.269)	19/99
Marks, G 2003 [28]	0.225	(0.178,	0.271)	69/307
Martignon, G 2005 [29]	0.262	(0.230,	0.295)	182/694
McKeever, T 2004 [31]	0.212	(0.207,	0.218)	4559/21489
McKeever, T 2004 [31]	0.131	(0.126,	0.137)	1884/14353
Miyake, Y 2008 [32]	0.070	(0.064,	0.077)	391/5567
Schlaud, M 2017 [41]	0.076	(0.070,	0.082)	552/7263
Schmitz, R 2011 [42]	0.145	(0.139,	0.151)	1935/13366
Singh, M 2013 [44]	0.005	(0.004,	0.006)	48/9492
Yoneyama, H 2000 [50]	0.179	(0.059,	0.300)	7/39
Overall (I²=99.87 % , P< 0.001)	0.144	(0.091,	0.197)	10835/76983



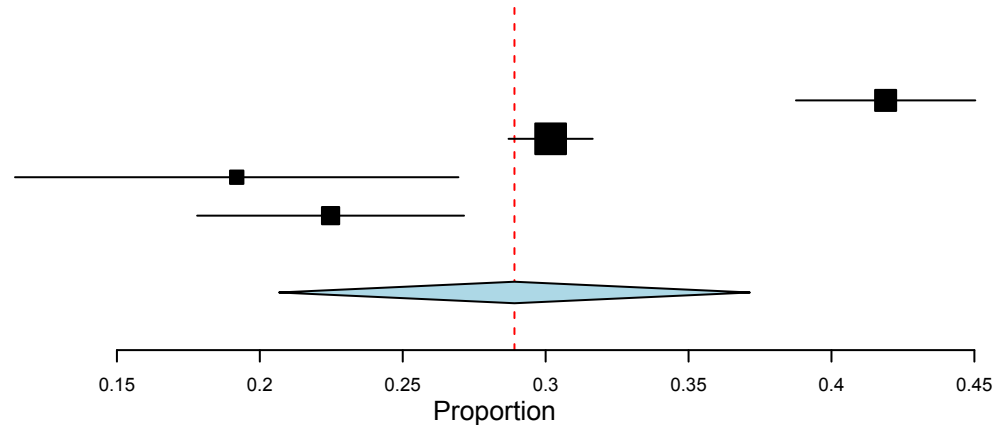
Studies	Estimate (95% C.I.)			Ev/Trt
Annus, T 2004 [11]	0.251	(0.219,	0.283)	180/717
Bernsen, R (A) 2006[12]	0.226	(0.202,	0.249)	271/1201
Bernsen, R 2003 [7]	0.049	(0.039,	0.059)	82/1680
Bernsen, R (B) 2006 [13]	0.235	(0.202,	0.267)	153/652
Garcia-Marcos, L 2005 [17]	0.078	(0.072,	0.084)	527/6762
Gruber, C 2001[19]	0.293	(0.200,	0.387)	27/92
Gruber, C 2002 [20]	0.125	(0.120,	0.130)	2548/20383
Kummeling, I 2007 [25]	0.228	(0.209,	0.247)	428/1878
Kummeling, I 2007 [25]	0.268	(0.223,	0.313)	101/377
Mohrenschlager, M 2007 [33]	0.050	(0.038,	0.063)	62/1230
Mohrenschlager, M 2007 [33]	0.046	(0.033,	0.059)	45/977
Martignon, G 2005 [29]	0.262	(0.230,	0.295)	182/694
McKeever, T 2004 [31]	0.212	(0.207,	0.218)	4559/21489
McKeever, T 2004 [31]	0.131	(0.126,	0.137)	1884/14353
Mrozek-Budzyn, D 2018 [34]	0.056	(0.026,	0.085)	13/234
Nilsson, L 2003 [37]	0.132	(0.082,	0.183)	23/174
Nilsson, L 2003 [37]	0.143	(0.092,	0.194)	26/182
Nilsson, L 2003 [37]	0.201	(0.134,	0.269)	27/134
Nilsson, L 2003 [37]	0.153	(0.100,	0.206)	27/177
Olesen, A 2003 [38]	0.042	(0.037,	0.046)	298/7178
Rosenlund, H 2009 [40]	0.101	(0.094,	0.108)	748/7383
Schlaud, M 2017 [41]	0.076	(0.070,	0.082)	552/7263
Schmitz, R 2011 [42]	0.145	(0.139,	0.151)	1935/13366
Steenhuis, T 2008 [45]	0.443	(0.318,	0.567)	27/61
Thostesen, L 2017 [46]	0.227	(0.209,	0.245)	466/2052
Timmermann, C 2015 [47]	0.203	(0.169,	0.237)	110/541
Venter, C 2016 [48]	0.189	(0.161,	0.217)	143/758
Overall ($I^2=99.30\%$, $P<0.001$)	0.160	(0.137,	0.184)	15444/111988



Studies	Estimate (95% C.I.)			Ev/Trt
Ahmadiafshar, A 2005 [9]	0.121	(0.101,	0.141)	121/1000
Miyake, Y 2008 [32]	0.070	(0.064,	0.077)	391/5567
Singh, M 2013 [44]	0.005	(0.004,	0.006)	48/9492
Wang, I 2012 [49]	0.039	(0.034,	0.044)	224/5717
Wang, I 2012 [49]	0.091	(0.083,	0.098)	544/5997
Wang, I 2012 [49]	0.099	(0.092,	0.105)	816/8254
Yoneyama, H 2000 [50]	0.179	(0.059,	0.300)	7/39
Overall ($I^2=99.65\%$, $P<0.001$)	0.077	(0.039,	0.115)	2151/36066



Studies	Estimate (95% C.I.)			Ev/Trt
Kemp, T 1997[22]	0.419	(0.388,	0.450)	398/950
Kiraly, N 2016 [24]	0.302	(0.287,	0.316)	1127/3735
Kiraly, N 2016 [24]	0.192	(0.114,	0.269)	19/99
Marks, G 2003 [28]	0.225	(0.178,	0.271)	69/307
Overall ($I^2=95.66\%$, $P<0.001$)	0.289	(0.207,	0.371)	1613/5091



Studies**Estimate (95% C.I.)****Ev/Trt**

Enriquez, R 2005 [8]

0.188

(0.143, 0.232)

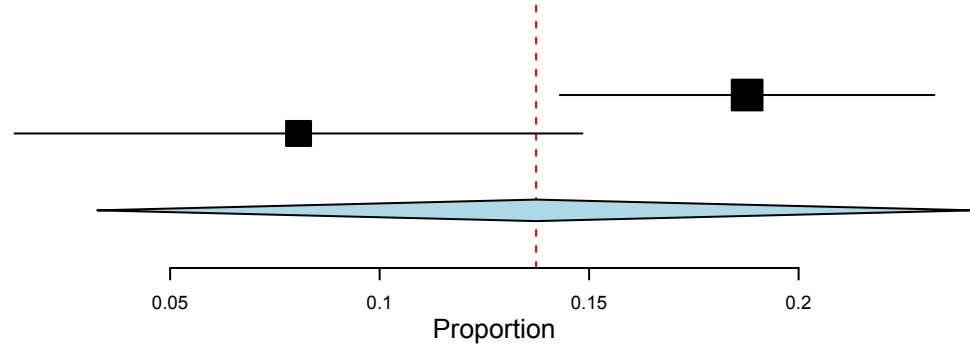
55/293

Patel, R 2013 [39]

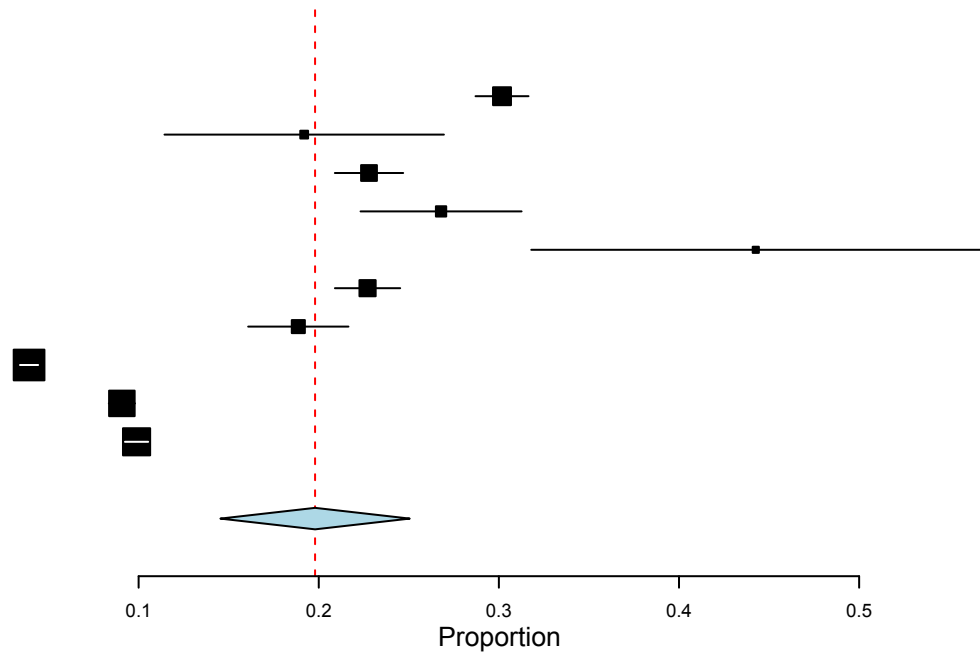
0.081

(0.013, 0.148)

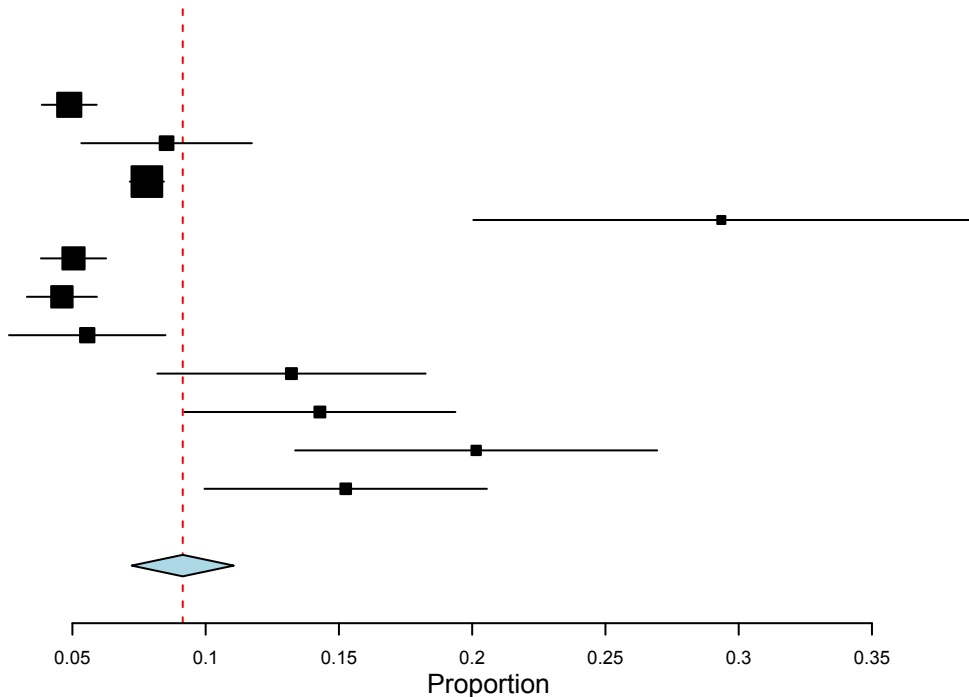
5/62

Overall ($I^2=85.03\%$, $P=0.010$)**0.137****(0.033, 0.242)****60/355**

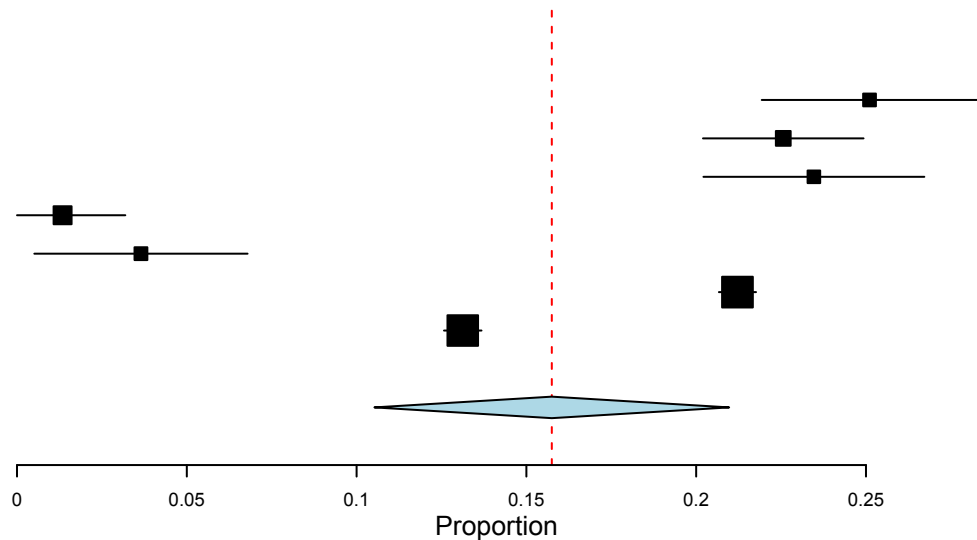
Studies	Estimate (95% C.I.)			Ev/Trt
Kiraly, N 2016 [24]	0.302	(0.287,	0.316)	1127/3735
Kiraly, N 2016 [24]	0.192	(0.114,	0.269)	19/99
Kummeling, I 2007 [25]	0.228	(0.209,	0.247)	428/1878
Kummeling, I 2007 [25]	0.268	(0.223,	0.313)	101/377
Steenhuis, T 2008 [45]	0.443	(0.318,	0.567)	27/61
Thostesen, L 2017 [46]	0.227	(0.209,	0.245)	466/2052
Venter, C 2016 [48]	0.189	(0.161,	0.217)	143/758
Wang, I 2012 [49]	0.039	(0.034,	0.044)	224/5717
Wang, I 2012 [49]	0.091	(0.083,	0.098)	544/5997
Wang, I 2012 [49]	0.099	(0.092,	0.105)	816/8254
Overall ($I^2=99.49\%$, $P<0.001$)	0.198	(0.145,	0.251)	3895/28928



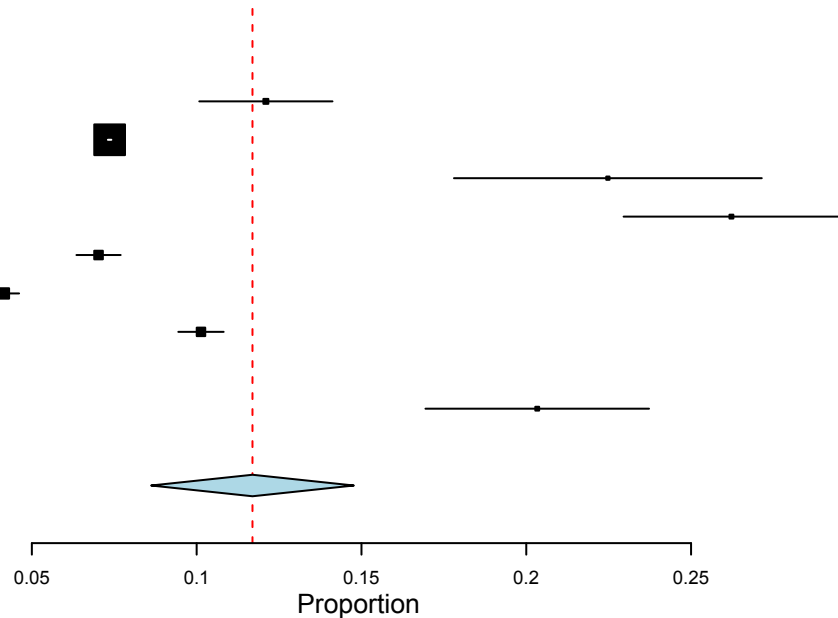
Studies	Estimate (95% C.I.)			Ev/Trt
Bernsen, R 2003 [7]	0.049	(0.039,	0.059)	82/1680
Eifan, A 2009 [15]	0.085	(0.053,	0.117)	25/293
Garcia-Marcos, L 2005 [17]	0.078	(0.072,	0.084)	527/6762
Gruber, C 2001 [19]	0.293	(0.200,	0.387)	27/92
Mohrenschlager, M 2007 [33]	0.050	(0.038,	0.063)	62/1230
Mohrenschlager, M 2007 [33]	0.046	(0.033,	0.059)	45/977
Mrozek-Budzyn, D 2018 [34]	0.056	(0.026,	0.085)	13/234
Nilsson, L 2003[37]	0.132	(0.082,	0.183)	23/174
Nilsson, L 2003[37]	0.143	(0.092,	0.194)	26/182
Nilsson, L 2003[37]	0.201	(0.134,	0.269)	27/134
Nilsson, L 2003[37]	0.153	(0.100,	0.206)	27/177
Overall ($I^2=90.45\%$, $P<0.001$)	0.091	(0.072,	0.111)	884/11935



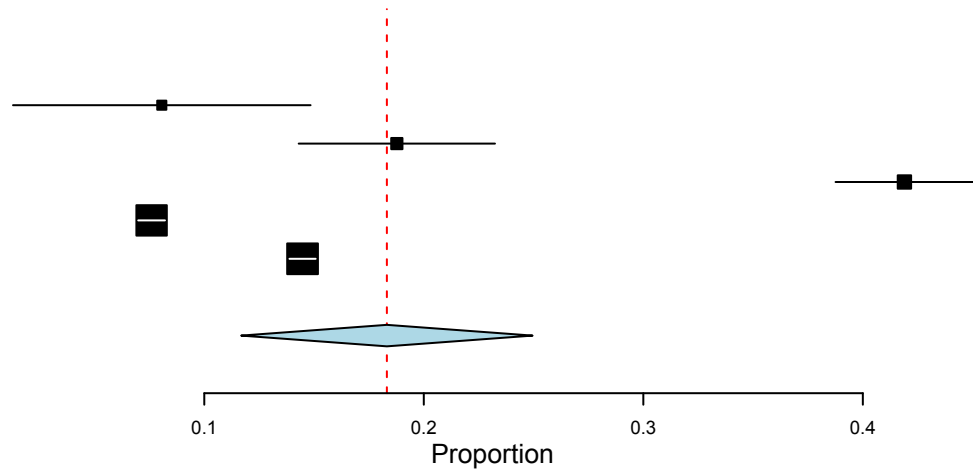
Studies	Estimate (95% C.I.)			Ev/Trt
Annus, T 2004 [11]	0.251	(0.219,	0.283)	180/717
Bernsen, R (A) 2006 [12]	0.226	(0.202,	0.249)	271/1201
Bernsen, R (B) 2006 [13]	0.235	(0.202,	0.267)	153/652
Kiraly, N 2013 [23]	0.013	(0.000,	0.032)	2/149
Kiraly, N 2013 [23]	0.036	(0.005,	0.068)	5/137
McKeever, T 2004 [31]	0.212	(0.207,	0.218)	4559/21489
McKeever, T 2004 [31]	0.131	(0.126,	0.137)	1884/14353
Overall ($I^2=99.27\%$, $P<0.001$)	0.157	(0.105,	0.210)	7054/38698



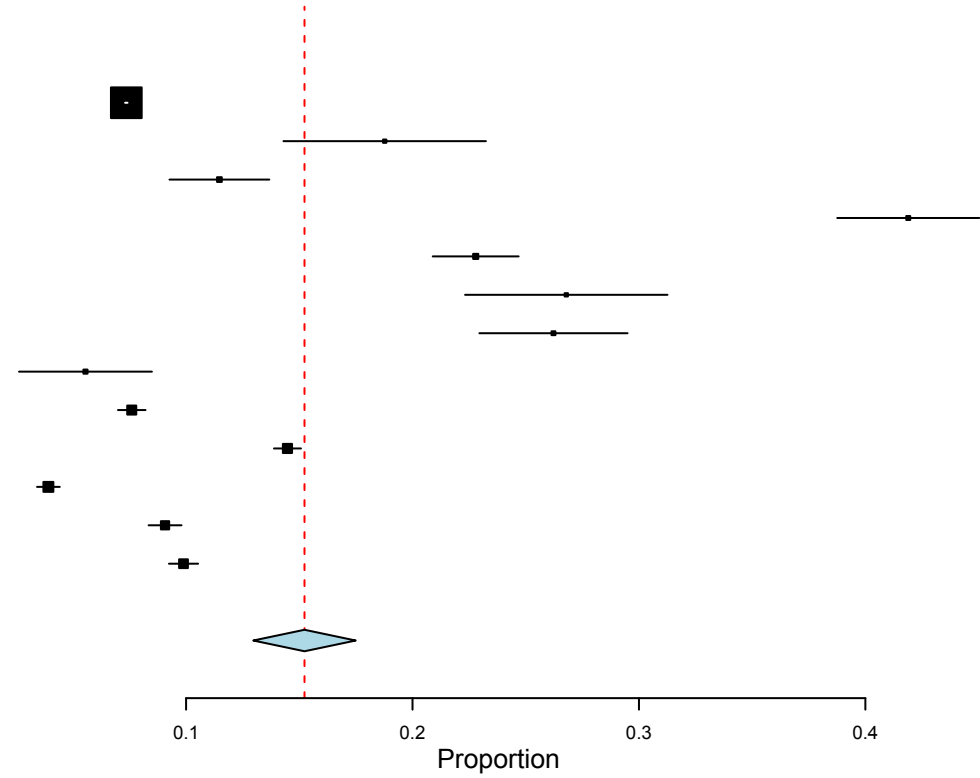
Studies	Estimate (95% C.I.)			Ev/Trt
Ahmadiafshar, A 2005 [9]	0.121	(0.101,	0.141)	121/1000
Anderson, H 2001[10]	0.074	(0.073,	0.074)	69130/939300
Marks, G 2003 [28]	0.225	(0.178,	0.271)	69/307
Martignon, G 2005 [29]	0.262	(0.230,	0.295)	182/694
Miyake, Y 2008 [32]	0.070	(0.064,	0.077)	391/5567
Olesen, A 2003 [38]	0.042	(0.037,	0.046)	298/7178
Rosenlund, H 2009 [40]	0.101	(0.094,	0.108)	748/7383
Singh, M 2013 [44]	0.005	(0.004,	0.006)	48/9492
Timmermann, C 2015 [47]	0.203	(0.169,	0.237)	110/541
Overall ($I^2=99.90\%$, $P<0.001$)	0.117	(0.086,	0.148)	71097/971462

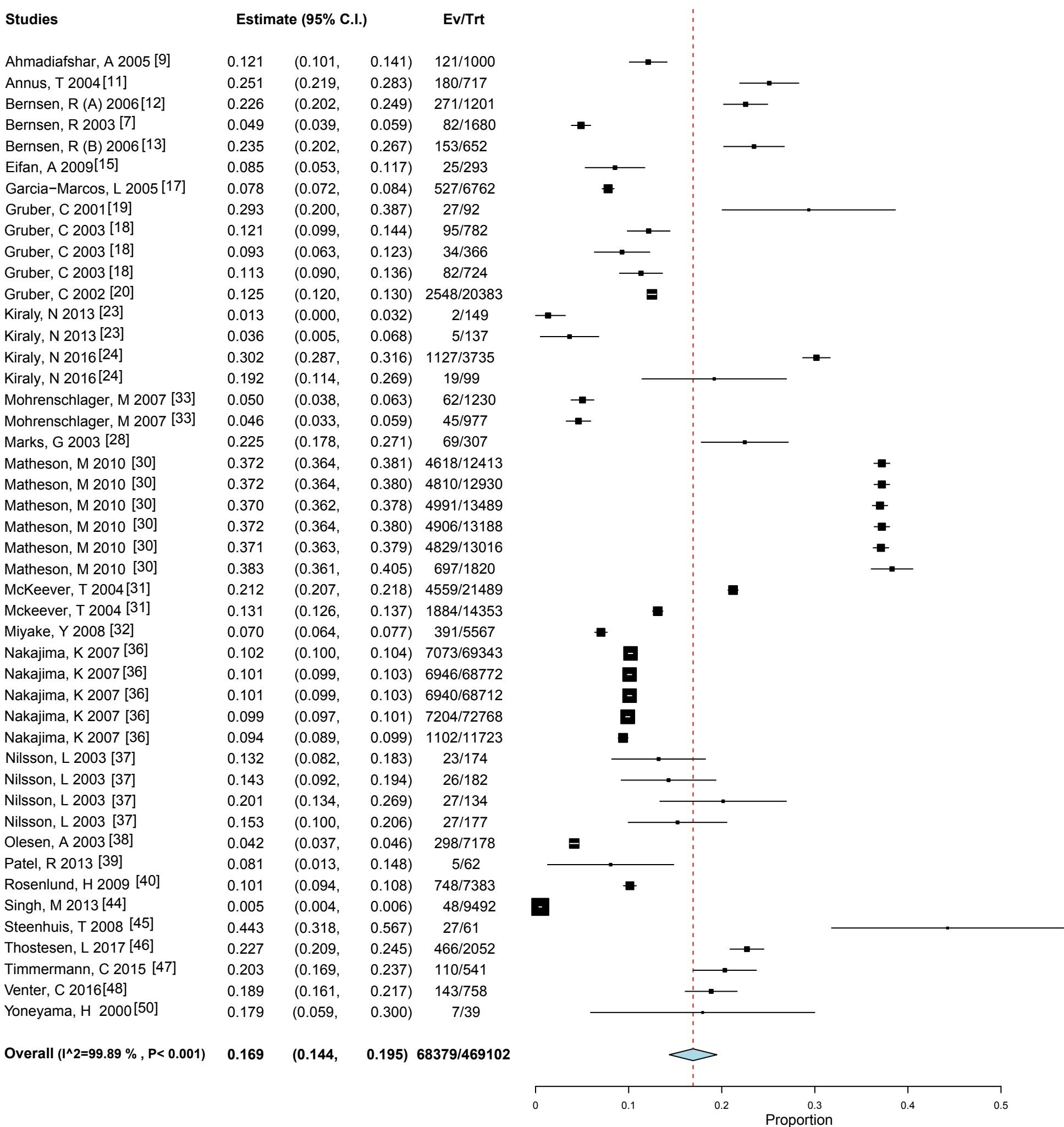


Studies	Estimate (95% C.I.)			Ev/Trt
Patel, R 2013 [39]	0.081	(0.013,	0.148)	5/62
Enriquez, R 2005 [8]	0.188	(0.143,	0.232)	55/293
Kemp, T 1997 [22]	0.419	(0.388,	0.450)	398/950
Schlaud, M 2017 [41]	0.076	(0.070,	0.082)	552/7263
Schmitz, R 2011 [42]	0.145	(0.139,	0.151)	1935/13366
Overall ($I^2=99.36\%$, $P<0.001$)	0.183	(0.117,	0.250)	2945/21934

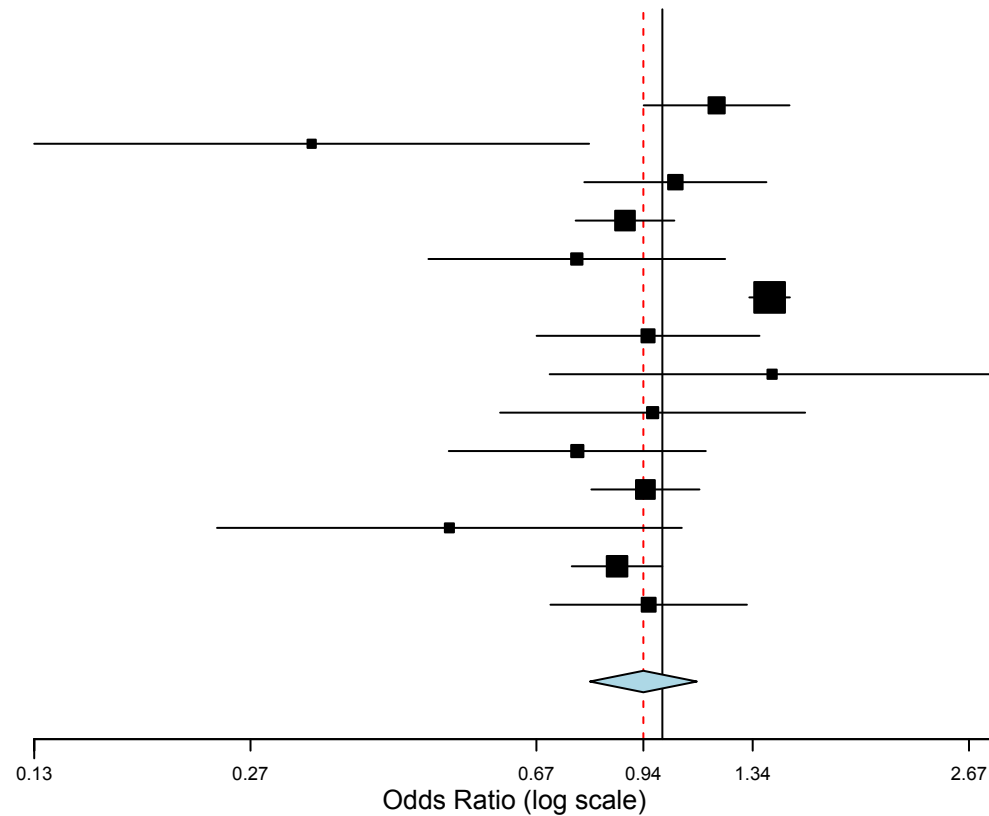


Studies	Estimate (95% C.I.)			Ev/Trt
Anderson, H 2001 [10]	0.074	(0.073,	0.074)	69130/939300
Enriquez, R 2005 [8]	0.188	(0.143,	0.232)	55/293
Gruber, C 2003 [18]	0.115	(0.093,	0.137)	92/802
Kemp, T 1997 [22]	0.419	(0.388,	0.450)	398/950
Kummeling, I 2007 [25]	0.228	(0.209,	0.247)	428/1878
Kummeling, I 2007 [25]	0.268	(0.223,	0.313)	101/377
Martignon, G 2005 [29]	0.262	(0.230,	0.295)	182/694
Mrozek-Budzyn, D 2018 [34]	0.056	(0.026,	0.085)	13/234
Schlaud, M 2017 [41]	0.076	(0.070,	0.082)	552/7263
Schmitz, R 2011 [42]	0.145	(0.139,	0.151)	1935/13366
Wang, I 2012 [49]	0.039	(0.034,	0.044)	224/5717
Wang, I 2012 [49]	0.091	(0.083,	0.098)	544/5997
Wang, I 2012 [49]	0.099	(0.092,	0.105)	816/8254
Overall (I²=99.32 % , P< 0.001)	0.152	(0.130,	0.175)	74470/985125





Studies	Estimate (95% C.I.)			Ev/Trt	Ev/Ctrl
Bernsen, R (A) 2006 [12]	1.190	(0.942,	1.503)	271/1201	132/671
Bernsen, R 2003 [7]	0.325	(0.134,	0.791)	82/1680	6/44
Bernsen, R (B) 2006 [13]	1.042	(0.779,	1.396)	153/652	95/418
García-Marcos, L 2005 [17]	0.887	(0.757,	1.039)	527/6762	246/2828
Gruber, C 2001 [19]	0.760	(0.472,	1.223)	27/92	241/682
Gruber, C 2002 [20]	1.410	(1.321,	1.505)	2548/20383	1695/18425
Kummeling, I 2007 [25]	0.955	(0.668,	1.365)	529/2255	43/177
Mohrenschlager, M 2007 [33]	1.421	(0.697,	2.899)	62/1230	9/250
Mohrenschlager, M 2007 [33]	0.969	(0.595,	1.580)	45/977	27/569
Olesen, A 2003 [38]	0.761	(0.504,	1.149)	298/7178	26/483
Rosenlund, H 2009 [40]	0.947	(0.796,	1.126)	748/7383	177/1664
Steenhuis, T 2008 [45]	0.505	(0.240,	1.064)	27/61	33/54
Thostesen, L 2017 [46]	0.865	(0.748,	1.000)	466/2052	495/1952
Timmermann, C 2015 [47]	0.957	(0.699,	1.311)	110/541	88/418
Overall (I²=85.61 % , P< 0.001)	0.941	(0.793,	1.117)	5893/52447	3313/28635



Studies	Estimate (95% C.I.)			Ev/Trt	Ev/Ctrl
Enriquez, R 2005 [8]	2.356	(1.546,	3.591)	55/293	46/515
Kemp, T 1997 [22]	1.236	(0.482,	3.167)	398/950	7/19
Martignon, G 2005 [29]	0.301	(0.132,	0.683)	182/694	13/24
Miyake, Y 2008 [32]	0.680	(0.395,	1.170)	391/5567	15/150
Schlaud, M 2017 [41]	0.852	(0.757,	0.960)	552/7263	648/7364
Schmitz, R 2011 [42]	1.168	(0.601,	2.271)	1935/13366	10/79
Singh, M 2013 [44]	1.357	(0.329,	5.598)	48/9492	2/536
Yoneyama, H 2000 [50]	9.188	(1.075,	78.493)	7/39	1/43
Overall (I²=79.74 % , P< 0.001)	1.058	(0.669,	1.674)	3568/37664	742/8730

