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Early View

Review

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COPD mortality and exacerbations in the placebo group of clinical trials over two decades – a systematic review and meta-regression

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Introduction

COPD is currently a leading cause of death and an important cause of complications worldwide [1] [2]. The prevalence is on the rise in many countries [1]. Exacerbations are a critical event in patients with COPD and are followed by worsening of lung function, reduced quality of life, and increased mortality [3]. Mortality is particularly high after an exacerbation leading to hospital admission [4].

Previously, we reported on COPD exacerbation rate in a systematic review and meta-regression of the placebo groups in randomized controlled trials [5]. We found a decrease in exacerbations over two decades to a clinically relevant extent and independent of important prognostic factors. The reason for this finding was unclear but adjunct therapies such as vaccination, better treatment of comorbidities, less air pollution or healthier lifestyle might have contributed. Since exacerbations are related to increased mortality, we reasoned that not only exacerbations but also mortality may have decreased in the last decades.

In the last years, two large randomized controlled COPD trials were published. Both trials showed reduction in the specified secondary endpoint mortality with inhaled triple therapy (i.e. inhaled corticosteroid and a dual bronchodilator) [6] [7]. It can be speculated, that the reduction in COPD exacerbations in these two large studies might have determined the observed survival gain. Indeed, we demonstrated a strong relationship (Regression analysis: $R^2 = 0.70$, $p= 0.018$) between annual exacerbation rate and annual mortality rate for the different treatment groups in the two trials [8]. This was, however, only an exploration of two recent studies with limited validity. To our knowledge the association of exacerbations and mortality in the clinical COPD trials published has not been analysed previously.

We thus performed a meta-regression of the placebo groups in randomized controlled trials published until 2020 and reporting exacerbations as well as mortality as an outcome. The objective was to evaluate whether there is a time trend in COPD mortality and whether this was affected by baseline characteristics or inhaled corticosteroids. Furthermore, we aimed to explore whether annual exacerbation rate and annual mortality were correlated in the included studies.

Methods

The present systematic review is conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. We updated the search performed for a previous review [5] that was registered with PROSPERO (CRD42018118823, 2018) [10].

Literature review

A comprehensive literature search has been conducted using the databases MEDLINE via PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL). The search terms including relevant Medical Subject Headings and keywords are (COPD OR chronic obstructive pulmonary disease OR COLD OR chronic obstructive lung disease OR "Pulmonary Disease, Chronic Obstructive"[MeSH]) AND (double-blind OR double blind) AND exacerba*. The results have been filtered for “Clinical Trial” and “Randomized Controlled Trial”. In order to also retrieve studies that have only recently been added to the database and may not be completely indexed, we repeated the search using only the limit “published in the last 180 days”. We checked reference lists of included studies and relevant reviews to identify any additional relevant articles that were not captured by the search. The date of the last search was September 23rd, 2020.

The search results were independently screened by two reviewers (LS, JH) using the following inclusion criteria: (i) the study deals with adult COPD patients; (ii) the study has a placebo control group; (iii) the study design uses parallel group or a cross-over design; (iv) the trial is double-blind and randomized; (v) exacerbation rates are quoted or can be calculated from the data presented; (vi) at least 100 patients (intention-to-treat population) are included into the study; (vii) the study has a treatment duration of at least 12 weeks.
Title and abstract were screened and studies that clearly do not meet the inclusion criteria were excluded. Any disagreements between the reviewers were resolved by a third reviewer (CR). For all remaining studies, full texts were reviewed and the decision about inclusion or exclusion of a study was discussed with another independent reviewer (SA).

Data extraction and quality assessment

From the placebo groups of the included studies, we extracted data on patients' demographics, trial eligibility criteria, exacerbation rate, the corresponding uncertainties and overdispersion and deaths in a standardized data sheet and were checked by at least one other author (CR, JH). As exacerbation was not treated as a primary endpoint in some of the studies (see Table S2), the reporting of exacerbation rates was rather heterogeneous [11]. The joint use of the reported information on exacerbation events in a common statistical model is described in detail in the previously published systematic review [5, 12]. The concurrent use of inhaled corticosteroids (ICS) has been accepted in order to be considered as placebo group for our analysis. Details on sensitivity analyses and ICS proportion was reported previously [5]. As in the previous study we identified two variables that changed over time (SGRQ and FEV1, see Figure 2).

Study quality was rated by dual assessment (CR, JH) using the Oxford Quality Scale score [13]. Discrepancies were resolved by a third reviewer (TF).

Data analysis

The data model employed is similar to the one used in our previous investigation [5]. Briefly, the mortality rate is modelled based on a Poisson distribution for the event counts (numbers of patient deaths in a study arm). Covariables are included in the model by assuming a linear effect on the logarithmic rate parameter, and study-specific random effects are included in order to account for between-study heterogeneity. Bayesian methods are used for inference; prior distributions for the unknown parameters are uniform (between log(0.001) and log(1000)) for the intercept, normal (mean zero and standard deviation 10) for the slope, and half-normal (scale 1.0) for the heterogeneity standard deviation. Models are fitted using Markov chain Monte Carlo (MCMC) methods using JAGS and the "rjags" R package. For the analysis regarding exacerbation rates, we used the same models as employed previously [5, 12]. In order to investigate potential correlation between exacerbation rates and mortality, we simultaneously fitted regression models for both endpoints, adding a correlation parameter ρ to allow for dependence between the study-specific random effects for both endpoints. Parameter estimates are given in terms of medians and 95% credible intervals (CIs). Using a Bayesian framework, two-sided posterior tail probabilities p_B are quoted for the regression parameters instead of p-values; values below 5% are considered statistically significant.

Results

The search update resulted in only a single additional eligible study [14] published since our previous literature search (see Table S1) that had yielded a total of 55 studies [5]. Data on patient mortality were available and extracted for all 56 studies. The systematic review process is illustrated in the flow chart in Figure 1. The included 56 studies comprised 14.166 patients in the placebo arms.

Figure 2 illustrates the two regression analyses for exacerbation rates as well as mortality. The first (top panel) is nearly identical to the one reported in [5] except for the inclusion of one additional study (#56, published in 2020). The resulting parameter estimates are also very similar, showing an annual reduction by 6.5% (95% CI [4.3%, 8.7%]). Annualized mortalities are overall lower than exacerbation rates, and uncertainties are correspondingly greater, but the data also show a declining trend. With an estimated annual decrease by 6.1% (95% CI [-0.6%, 12.6%]), the decline is of a similar magnitude as for the exacerbation rate, but the 95% interval is wider and also includes a constant mortality rate (0% decrease) as a possibility (p=0.073). The parameter estimates are also shown in Table 1.

Since the different types of placebo groups considered here (with or without the concomitant use of ICSs) might exhibit differing mortalities, we also considered both subgroups of studies separately. For the group of studies allowing for ICSs (35 studies) we get a somewhat more moderate estimate for the rate reduction of 1.9% (95% CI [-8.3, 10.8%]), and for the group of "true" placebos (21 studies) the reduction is estimated at 8.5% (95% CI [-2.6%, 19.1%]).

While we did not find a significant change in mortality over time, we investigated whether the tendency would persist if we adjust for covariables that have also shifted over time and that hence might explain a change in mortality. We considered the St. George's Respiratory Questionnaire (SGRQ) score as well as the forced expiratory volume in 1 second (FEV_1) as possible additional covariables in the regression analysis as these two correlated with time. In both cases the estimated change in mortality is slightly reduced while the uncertainty is increased (see Figure 2).

Including dependence between mortality and exacerbation rates in the model yielded an estimated correlation coefficient ρ of 0.18 (95% CI [-0.24, 0.56]), indicating a tendency for a positive relationship (i.e., larger exacerbation rates tend to be associated with greater mortality), while the effect magnitude is not large nor certain (see also Figure 2).

model	parameter	estimate [95% CI]	percentage change	p_B
all placebos	intercept β_0	-4.077 [-4.878, -3.434]		
(56 studies)	slope β_1 (year)	-0.063 [-0.134, 0.006]	-6.1 [-12.6, 0.6]	0.073
	heterogeneity τ	0.951 [0.629, 1.426]		
ICS-placebos only	intercept β_0	-4.670 [-5.951, -3.720]		
(35 studies)	slope β_1 (year)	-0.019 [-0.115, 0.079]	-1.9 [-10.8, 8.3]	0.689
	heterogeneity τ	0.875 [0.423, 1.564]		
true placebos only	intercept β_0	-3.620 [-4.756, -2.721]		
(21 studies)	slope β_1 (year)	-0.089 [-0.212, 0.026]	-8.5 [-19.1, 2.6]	0.116
	heterogeneity τ	0.988 [0.554, 1.737]		
SGRQ-adjusted	intercept β_0	-8.117 [-15.186, 0.513]		
(28 studies)	slope β_1 (year)	-0.010 [-0.140, 0.118]	-1.0 [-13.0, 12.5]	0.873
	slope β_2 (SGRQ)	0.078 [-0.095, 0.218]	8.1 [-9.1, 24.4]	0.362
	heterogeneity τ	0.957 [0.551, 1.628]		
FEV1-adjusted	intercept β_0	-1.571 [-4.408, 1.509]		
(51 studies)	slope β_1 (year)	-0.027 [-0.110, 0.063]	-2.6 [-10.4, 6.5]	0.535
	slope β_2 (FEV1)	-0.058 [-0.130, 0.004]	-5.6 [-12.2, 0.4]	0.069
	heterogeneity τ	0.942 [0.610, 1.438]		

Table 1: Parameter estimates from the regression analyses, for the main analysis as well as for the sensitivity analyses based on the subsets of "true" and "ICS-" placebos only, or when adjusting for confounders. The parameters originally refer to the mortality rate on the logarithmic scale, the slope parameters are expressed in terms of an annual percentage change; these are shown in a separate column, where applicable. Bayesian posterior tail probabilities (p_B) are also provided for the regression coefficients instead of frequentist two-sided p-values. Between-study heterogeneity is quantified in terms of the standard deviation parameter τ.

Discussion

Although not statistically significant, our data revealed an annual reduction of mortality by about 6%, that was similar in magnitude as compared to the decrease in exacerbation rate reported previously. This could at least partially be due the fact that the more recent studies tended to include less severely affected patients. Mortality is a relatively rare event as compared to acute exacerbations and therefore larger samples sizes are necessary to detect statistically significant differences. Furthermore, the residual correlation of exacerbation rate with mortality after adjustment for a common time trend was not statistically significant. Interestingly temporal trends have also been investigated in other disease areas. For instance, a decline in relapse rate as well as disability worsening has been observed in randomized controlled trials in multiple sclerosis [15-17]. Furthermore, temporal trends in mortality and readmission after acute heart failure were reported recently [18].

It is not trivial whether the reduction of exacerbations by inhaled treatment transforms to reduced mortality in this patient group. Since COPD exacerbations are followed by worsening lung function, reduced quality of life, and increased mortality [1, 19] a causal relation is conceivable [20]. Furthermore, exacerbations increase the risk of myocardial infarction, stroke, and death [20]. Indeed, many patients with COPD die directly from cardiovascular disease, especially frequent exacerbators [7, 21].

So far, efficacy of inhaled treatments has never been demonstrated based on effects on mortality as primary endpoint in randomized controlled COPD trials. For instance, the largest randomized controlled COPD trial ever, the SUMMIT trial investigating all-cause mortality as the primary endpoint was negative despite the trial being enriched by patients with cardiovascular disease [22]. This negative finding was in part attributed to the inclusion of patients with less severe respiratory disease [23] [24]. Thus it is consequent, that the current GOLD report noticed a lack of convincing evidence for a survival benefit with inhaled COPD therapy despite relevant improvements in lung function, exacerbations and patient reported outcomes [25].

The decrease in mortality over time we observed in our data, albeit insignificant, is in line with the results of a previous large population study. The Chronic Respiratory Disease Collaborators reported that the global age standardised mortality rate for COPD dropped by 43% between 1990 and 2017 [2]. As the authors discussed these data might be explained by changes in smoking prevalence or the environment. Ambiguities in diagnoses and data reporting also may have added.

Our data showed a weak association between exacerbations and mortality explaining only about 4% of the variance. Thus, our data are unable to support a meaningful relation between exacerbations and mortality. Due to the limitations discussed below, such as a low number of mortality events and the lack of individual patient data, our findings are also unable to disprove a causal association. Furthermore, low correlation across the patients' placebo populations does not mean that a treatment wouldn't be able to reduce exacerbations and mortality at the same time.

To the best of our knowledge this is the first meta-regression analysis of randomized clinical trials investigating a time trend in COPD mortality. Network meta-analyses are commonly used to indirectly compare treatments that have not been compared directly in a clinical trial. The interpretation rests on the assumption of a relatively stable rate of the investigated endpoint over time. Indeed, large trials have been performed in COPD for over two decades and thus network meta-analysis included studies over a 20-year period [26]. Our results of a decrease in mortality rate over time, albeit insignificant, raises concern on the robustness of such work.

Recently it was suggested that the observed mortality reduction with inhaled triple therapy was mediated mainly by the ICS [7]. The beneficial effect on cardiovascular outcomes with ICS is a possible explanation [27]. Indeed, in a very recent network meta-analysis ICS/LAMA/LABA and ICS/LABA unlike other combinations were associated with reduced mortality as compared to placebo [26]. Albeit not significant, our findings showed a reduced time trend in the ICS treated patients as compared to the group without ICS. This finding may support a protective effect of ICS on mortality compared to the patients not treated by ICS. However, again the observed difference was insignificant due to the low event number. Interestingly, in our previous analysis on exacerbation rate, the time trend was very similar in the ICS and the non ICS group [5].

There is ambiguity in the definition of what exactly constitutes an exacerbation mainly in the older studies. Indeed, the use of different conventions may make substantial differences [28]. This is especially true for mild exacerbations. In the more recent trials standardized definitions especially for moderate and severe exacerbations were used [10], which increased the comparability of events.
Our approach was to use data for moderate to severe exacerbations, if more than one category of exacerbations was reported. However, the incomplete reporting of exacerbations mainly in the older trials did not allow for a distinct analysis according to the severity of exacerbations.

Limitations and strengths:
The mortality rate in patients with COPD is much lower as compared to the exacerbation rate. For instance, the exacerbation rate in recent large randomized trials was about one per patient and year, while the mortality rate was only 1-2% per patient and year [6] [7]. Therefore, the time trend in mortality relies on fewer events as compared to the time trend in exacerbations and thus is associated with larger uncertainties. We further acknowledge that we present only data aggregated at study-level and not individual patient data. Furthermore, patients included in clinical trials might not be representative for a general COPD population. Finally, it should be kept in mind that the correlation demonstrates an association and not necessarily a causal relationship. Potentially the correlation could be explained by a time trend in a variable we were unable to control for.
The main strength of our study lies in the long period of time evaluated, the thorough quantity of studies included and the adjustment for a number of well-known confounders including baseline symptoms and lung function.

In conclusion the present analysis of more than 50 clinical trials in COPD patients showed that mortality rate did decline about 6% per year. This decline is of similar magnitude as compared to the decline of exacerbation rate but did not reach statistical significance. Nevertheless, our findings indicate that care is needed in the design of new trials given the observed shifts in study populations. In future trials, these planning risks might be mitigated by the application of adaptive designs [29]. Furthermore, one needs to be cautious when comparing results from older trials with more recent ones e.g. indirectly comparing treatments in network meta-analyses. The association between exacerbation rate and mortality rate was weak as well as insignificant and does not allow for inferences.

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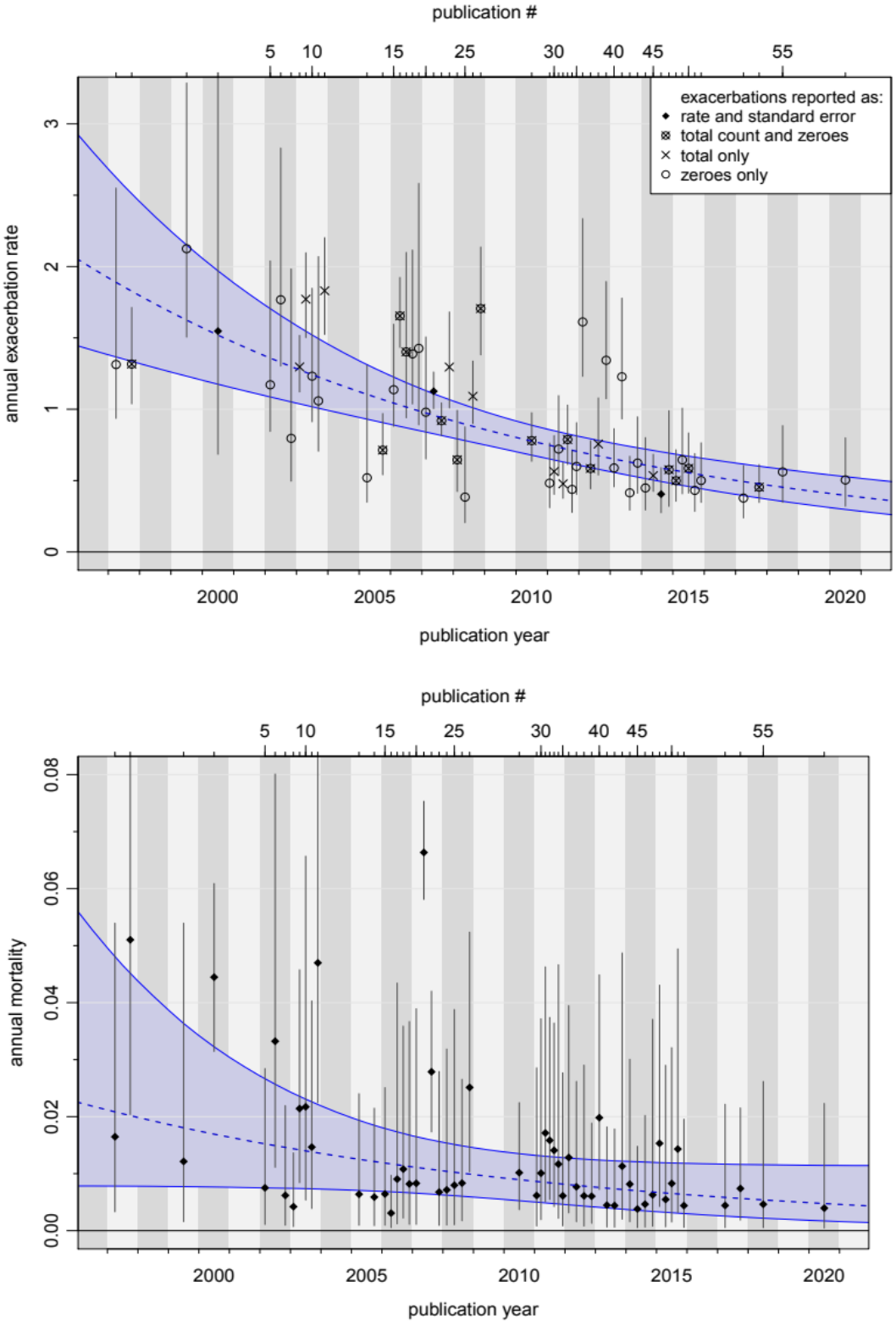


Figure 1: The estimated time trends in annualized exacerbation rates (top panel) as well as mortality rates (bottom panel). The analysis of exacerbation rates includes one additional study (#56) compared to the previous results (Andreas et al., 2019) and essentially confirms the earlier findings. The investigation of mortality suggests a similar trend.

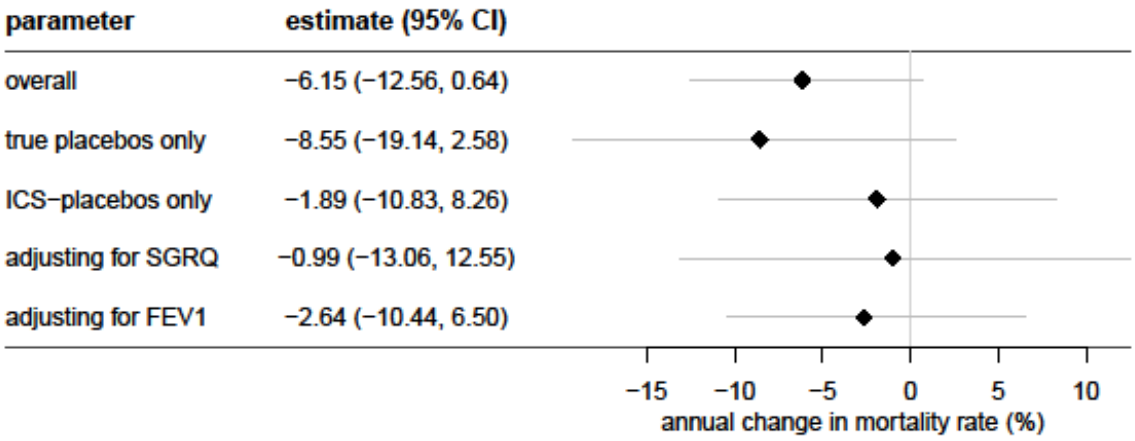
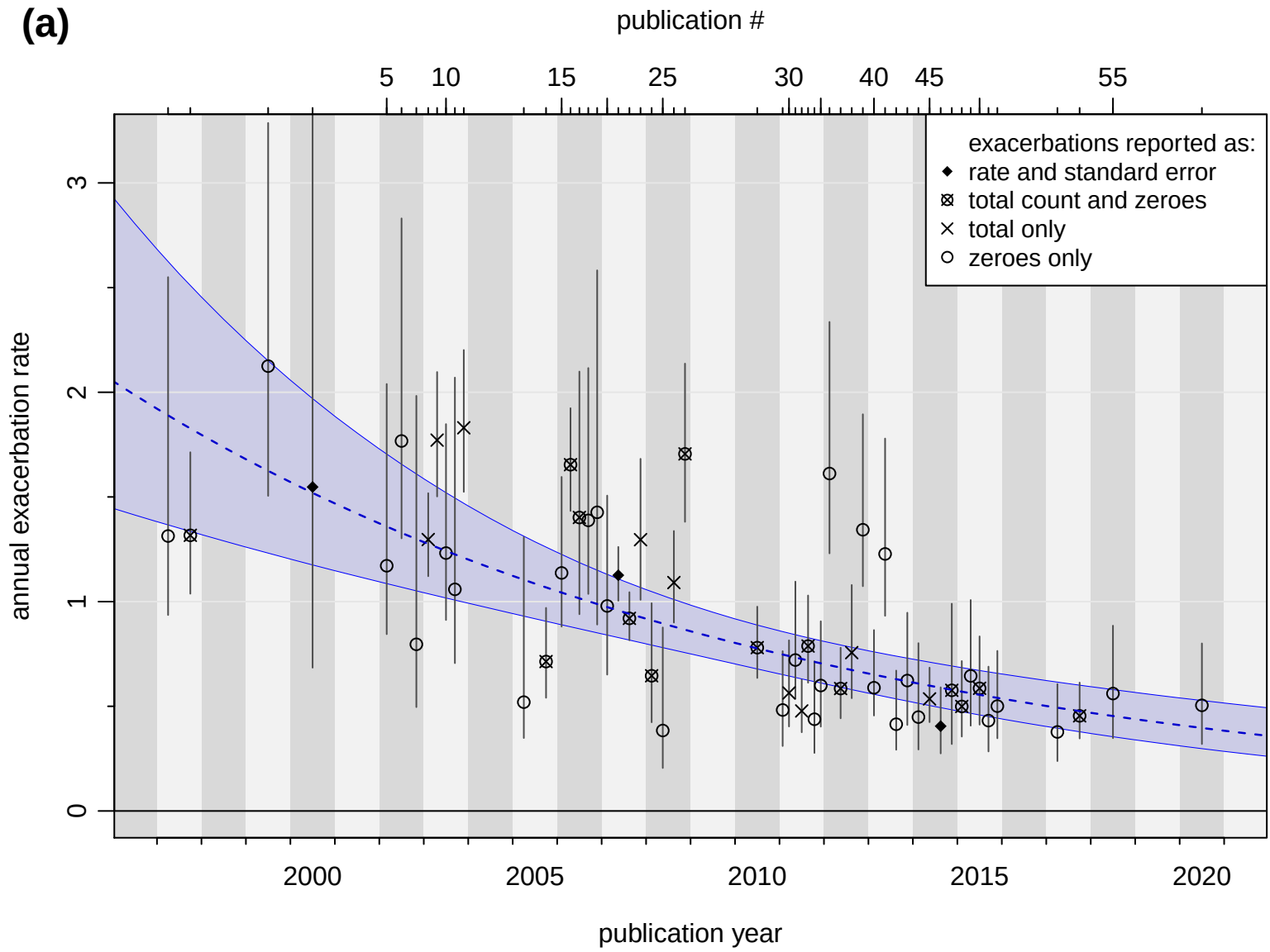


Figure 2: Parameter estimates corresponding to the annual change in mortality rate for the sensitivity analyses in comparison to the main analysis (see also Table 1). All estimates suggest a decline in mortality over time of slightly differing magnitude, but in all cases the 95% CIs also include 0%, i.e., the possibility of no change. FEV1 (Forced Expiratory Pressure in one Second), ICS (inhaled corticosteroids), SGRQ (Saint Georg's Respiratory Questionnaire).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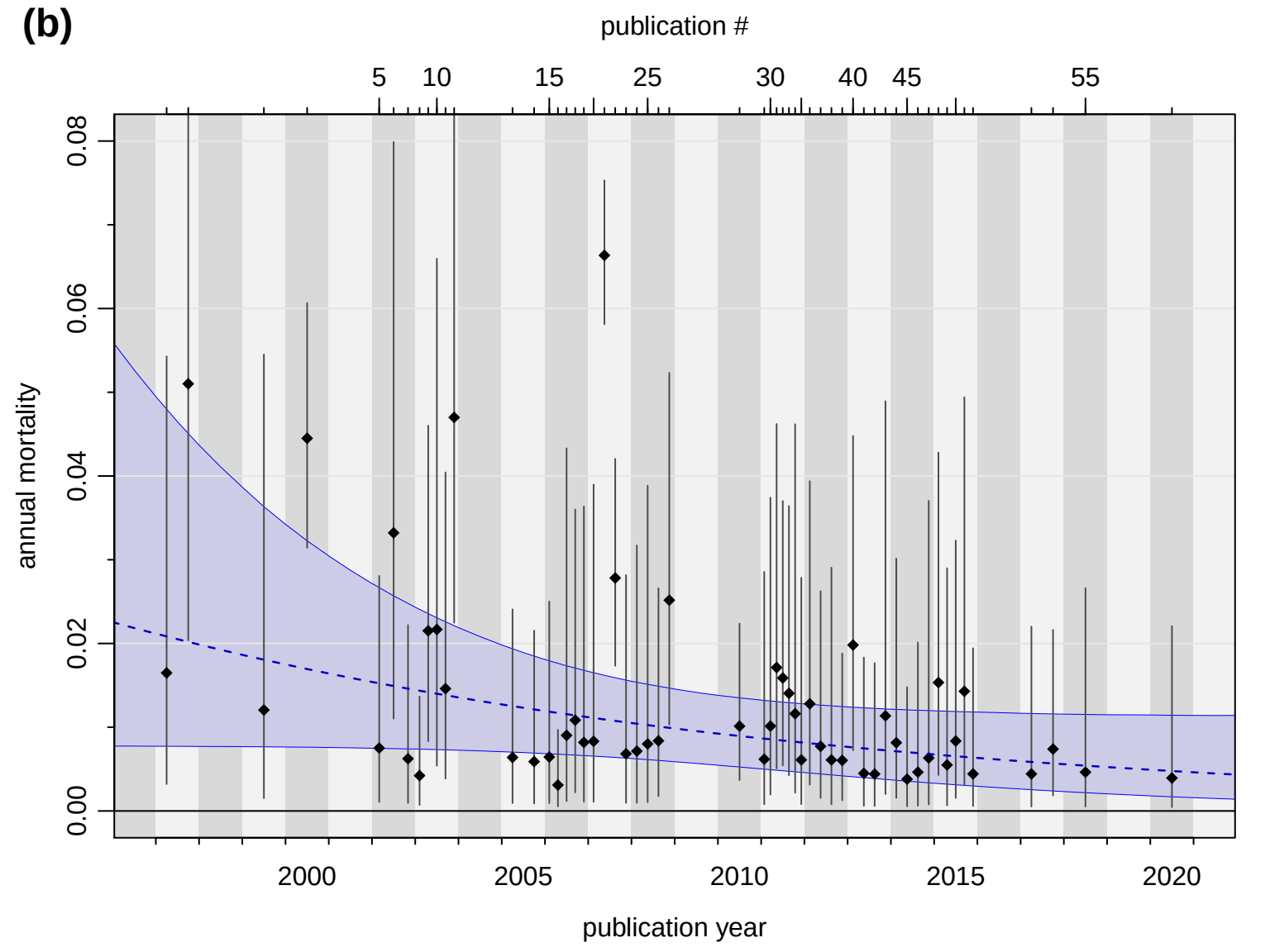
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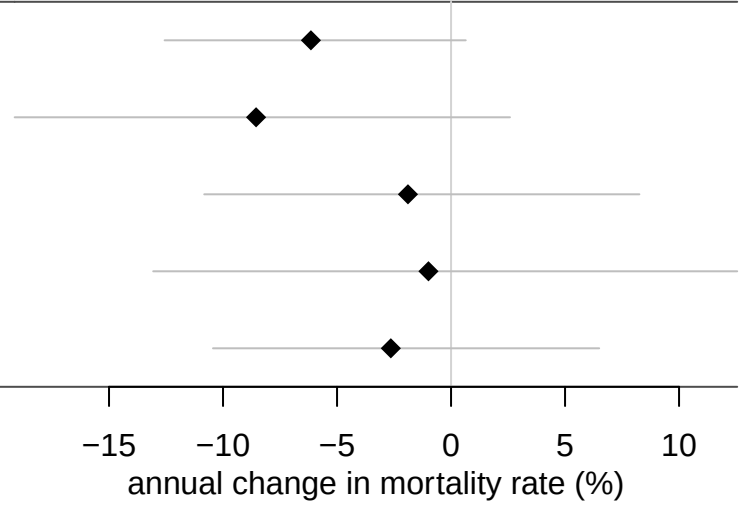
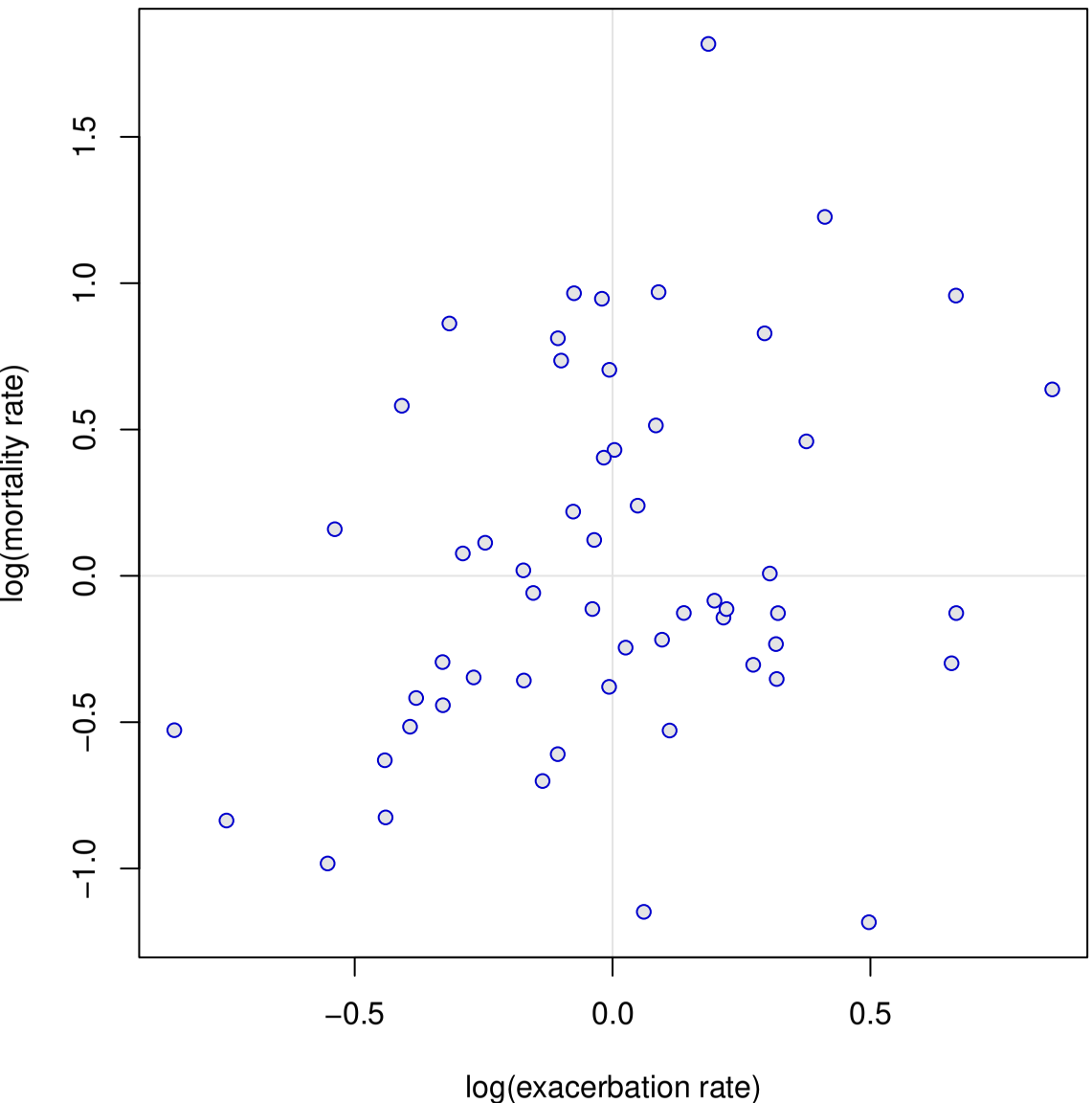
parameter	estimate (95% CI)
overall	−6.15 (−12.56, 0.64)
true placebos only	−8.55 (−19.14, 2.58)
ICS−placebos only	−1.89 (−10.83, 8.26)
adjusting for SGRQ	−0.99 (−13.06, 12.55)
adjusting for FEV1	−2.64 (−10.44, 6.50)

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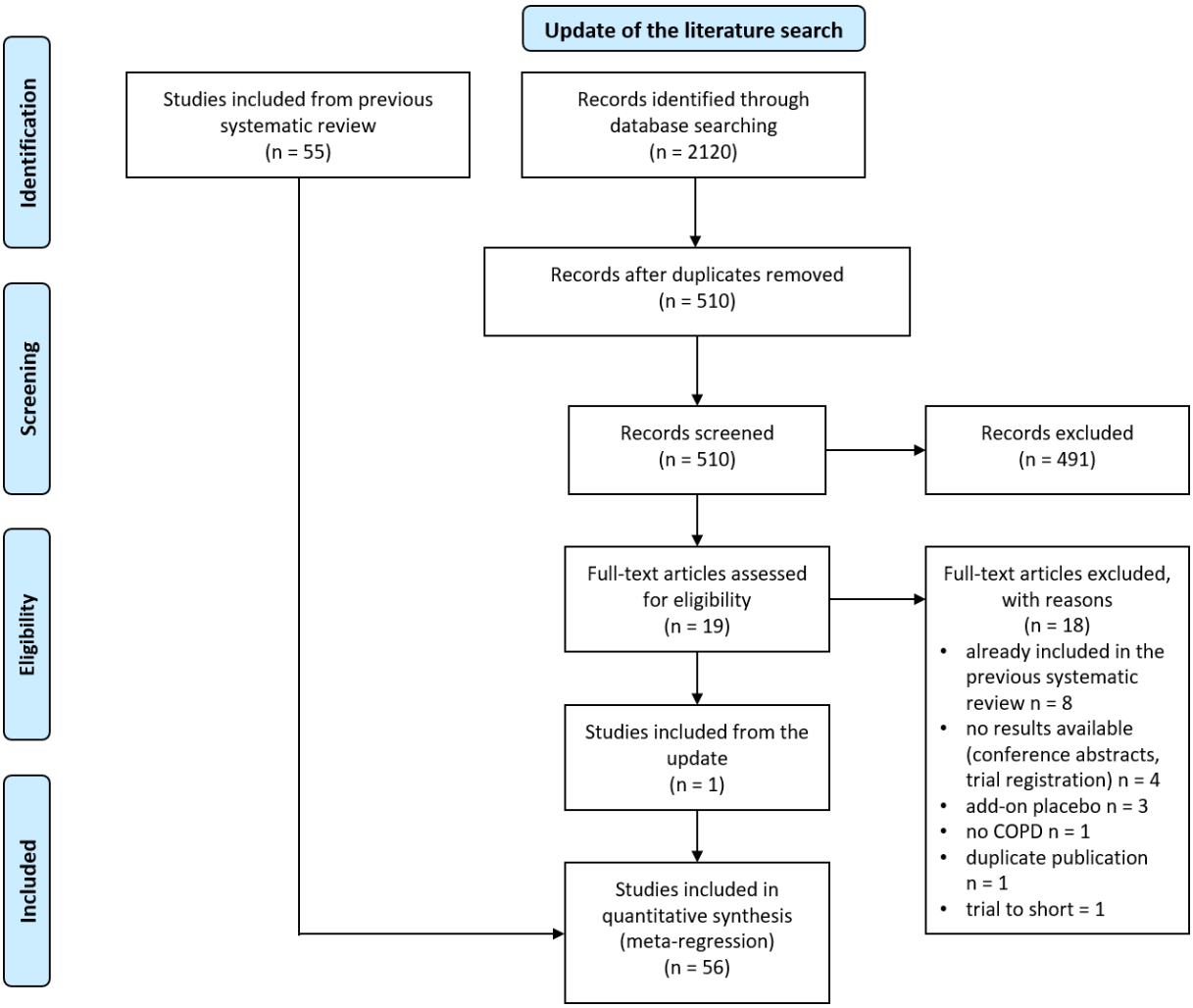
−0.5
−1.0
−0.5
0.0
0.5
log(exacerbation rate)


Identification
Screening
Eligibility
Included
Update of the literature search
Studies included from previous systematic review (n = 55)
Records identified through database searching (n = 2120)
Records after duplicates removed (n = 510)
Records screened (n = 510)
Records excluded (n = 491)
Full-text articles assessed for eligibility (n = 19)
Full-text articles excluded, with reasons (n = 18)
• already included in the previous systematic review n = 8
• no results available (conference abstracts, trial registration) n = 4
• add-on placebo n = 3
• no COPD n = 1
• duplicate publication n = 1
• trial to short = 1
Studies included from the update (n = 1)
Studies included in quantitative synthesis (meta-regression) (n = 56)

id.all	id.true.placebo	id.ics.placebo	study	dataType	oqs	year	N	duration	meanFU	ageMean	malePercent	smokerPercent	packYearMean	fev1Mean	sgrqMean	rate	rateStdErr	exacerbations	zeroes	deaths
1		1	BoydEtAl1997	zeroes_only	3	1997	227	0.3077	0.2932	61	75	40							168	1
2	1		ColletEtAl1997	total+zeroes	5	1997	190	0.5	0.484	66.9	71.1	31. Jan		44		Jan 14		105	107	6
3		2	MahlerEtAl1999	zeroes_only	4	1999	143	0.2308	0.2117	63.19	76.2		60.2	40.8					96	0
4	2		BurgeEtAl2000	rate+StdErr	5	2000	370	3	20.994	63.8	74.1	39.2	44	50		01. Sep	Feb 63	1476		36
5		3	ChapmanEtAl2002	zeroes_only	4	2002	207	0.4615	0.4295		64	43			52				139	0
6		4	DonohueEtAl2002	zeroes_only	4	2002	201	0.5	0.4266	65.6	75		46		45.375				109	4
7		5	RossiEtAl2002	zeroes_only	3	2002	161	1	0.8589	63	80			49	47.2				106	0
8	3		CalverleyEtAl2003a	total_only	5	2003	361	1	0.7903	63.4	75	47	43.4	44.2	47.1	01. Mrz		371		0
9	4		CalverleyEtAl2003b	total_only	3	2003	256	1	0.7746	65	75	30	39	36	48	01. Aug		357		5
10	5		CelliEtAl2003	zeroes_only	5	2003	270	0.25	0.2276	65	71.5		48	43.6	49.6				211	2
11		6	HillerEtAl2003	zeroes_only	3	2003	145	1	0.8352	64.4	53.8	46.9	59.2	41.3					79	2
12	6		SzafranskiEtAl2003	total_only	3	2003	205	1	0.7595	65	83	34	45	36		Jan 87		291		9
13		7	CampbellEtAl2005	zeroes_only	4	2005	217	0.5	0.4536	60	73	55	37	54.1	46.7				183	0
14	7		RabeEtAl2005	total+zeroes	5	2005	280	0.4615	0.4346	63	74	45	43	55		0.6501		84	218	0
15		8	BeehEtAl2006	zeroes_only	3	2006	403	0.2308	0.2147	62.2	76.7		35	45.7					323	0
16		9	DusserEtAl2006	total+zeroes	3	2006	510	1	0.8477	65	87	24		47.6		Jan 69		731	238	0
17	8		PaggiaroEtAl2006	total+zeroes	3	2006	56	0.4615	0.4406	66	89.3	37.5		51.7	48.7	Jan 32		34	30	0
18	9		RennardEtAl2006	zeroes_only	3	2006	216	0.4615	0.4034	64.9	68	47	56.1	50.5					134	1
19		10	ZhouEtAl2006	zeroes_only	5	2006	43	1	0.9024	60.5	74.4	46.5	29. Apr	71.5					15	0
20		11	BaumgartnerEtAl2007	zeroes_only	4	2007	143	0.2308	0.2039	63.1	63.6	43.4		40.6					119	0
21	10		CalverleyEtAl2007a	rate+StdErr	4	2007	1524	3	22.596	65	76	43	48.6	44.1	49	Jan 13	0.06633	3891		231
22		12	CalverleyEtAl2007b	total+zeroes	5	2007	753	1	0.8874	64	76	35	45	41	49.7	0.918		613	391	20
23	11		ZhengEtAl2007	total_only	3	2007	148	0.4615	0.4361	66.6	86.49	23	35	47	44.5	Jan 35		87		0
24		13	AmbrosinoEtAl2008	total+zeroes	4	2008	106	0.4808	0.4229	66.9	84.6		35	40.3				26	85	0
25	12		JohanssonEtAl2008	zeroes_only	2	2008	117	0.2308	0.2308	62.2	43	63	31.6	73.2					113	0
26	13		TashkinEtAl2008b	total_only	5	2008	300	0.5	0.4327	63.2	69	39.7	40	41.28	55.6	01. Nov		144		1
27		14	TonnelEtAl2008	total+zeroes	4	2008	288	0.75	0.6489	63.5	85.4	30.2	43	46.19	48.9	Jan 83		342	158	6
28		15	DahlEtAl2010	total+zeroes	5	2010	432	1	0.8314	63	81.5		43	52	43	0.74		266	254	4
29	14		BogdanEtAl2011	zeroes_only	4	2011	208	0.2308	0.2184	66.3	89.4		47.4	52.2	44.9				190	0
30		16	ChapmanEtAl2011	total_only	3	2011	124	1	0.5385	62.8	65	51	51	56.3	45	0.54		36		1
31		17	DUrzoEtAl2011	zeroes_only	3	2011	260	0.5	0.4441	64	80.5	34.1	44.6	54.33	46.34				197	3
32		18	JonesEtAl2011a	total_only	4	2011	216	1	0.8868	61.9	81	45.4	38.4	52.9	47.3	0.46		88		4
33		19	JonesEtAl2011b	total+zeroes	4	2011	204	1	0.7701	65.2	60.8	38.7	58.2	49.4	47.1	0.8		126	123	3
34	15		LeeEtAl2011	zeroes_only	4	2011	207	0.2308	0.2206	67	94.2	33.3	45	54.9					193	1
35	16		TroostersEtAl2011	zeroes_only	4	2011	219	0.2308	0.2195	62.3	32.9	57		65.84					194	0
36	17		DohertyEtAl2012	zeroes_only	4	2012	236	0.5	0.4251	58.8	75	51	43.5	38					128	2
37		20	JonesEtAl2012	total+zeroes	3	2012	273	0.4615	0.4236	62	69.2	52.8	38.9	56.6	45.1	0.47		54	217	1
38		21	KerwinEtAl2012	total_only	3	2012	186	0.2308	0.207	65.1	51.6	46.8	52.7	54.6	45.1	0.79		30		0
39	18		TashkinEtAl2012	zeroes_only	5	2012	448	0.5	0.4296	58.8	78	48	41.95	38.55					271	1
40	19		AbrahamsEtAl2013	zeroes_only	3	2013	429	0.4615	0.425	64.4	63.9	45.2	46.4	49.1	43.2				344	5
41		22	BatemanEtAl2013	zeroes_only	4	2013	234	0.5	0.4521	64.4	72.8	40.1		55.2					141	0
42		23	DonohueEtAl2013	zeroes_only	4	2013	280	0.4615	0.3956	62.2	70	54	47.2	46.7					244	0
43		24	RennardEtAl2013	zeroes_only	3	2013	182	0.2308	0.2105	61.7	54.9	56	52.6	55.2	49.2				161	1
44		25	DonohueEtAl2014b	zeroes_only	4	2014	109	1	0.7863	60.1	67		42.8	55.1					83	1
45		26	DUrzoEtAl2014	total_only	3	2014	332	0.4615	0.4574	63.5	52.7	50.9	53.3	52.6	45.3	0.533		81		0
46		27	SinghEtAl2014b	rate+StdErr	5	2014	194	0.4615	0.4198	64.2	71.1	48.5			55	45.8	0.36	0.0791	29		0
47		28	TrivediEtAl2014	total+zeroes	5	2014	68	0.2308	0.1987	62.5	62	53	52.3		47				7	61	0
48		29	BraidoEtAl2015	total+zeroes	5	2015	142	1	0.8395	68.6	64	16. Sep		52.66		0.52		62	101	3
49		30	LeeEtAl2015	zeroes_only	5	2015	128	0.2308	0.2208	68.1	100		42.5	52.8	33.1				111	0
50		31	WangEtAl2015	total+zeroes	3	2015	154	0.5	0.4819	65	94.2	22. Jan	38.3	51.88		0.59		44	119	1
51	20		ZhengEtAl2015a	zeroes_only	4	2015	162	0.4615	0.4142	64.7	90	35	43.3	48.6					135	2
52		32	ZhengEtAl2015b	zeroes_only	4	2015	193	0.4615	0.4221	64.3	92	34	37.1						156	0
53	21		BhattEtAl2017	zeroes_only	5	2017	141	0.4615	0.38	68.2	84	38	47.8		42.59				125	0
54		33	DUrzoEtAl2017	total+zeroes	5	2017	332	1	0.6257	63.5	52.7	50.9	53.3	52.6	45.3	0.49		102	261	2
55		34	MaltaisEtAl2018	zeroes_only	3	2018	132	0.2308	0.221	60.8	65.9	43.9	44	59.7					116	0
56		35	ZhongEtAl2020	zeroes_only	5	2020	101	0.4598	0.4101	65.7	96	29	37.2	47.32					82	0

COPD mortality and exacerbations in the placebo group of clinical trials over two decades – a systematic review and meta-regression

- *Supplementary material* -

Stefan Andreas[1,2]* , Christian Röver[3], Judith Heinz[3], Christian Taube[4], Tim Friede[3]

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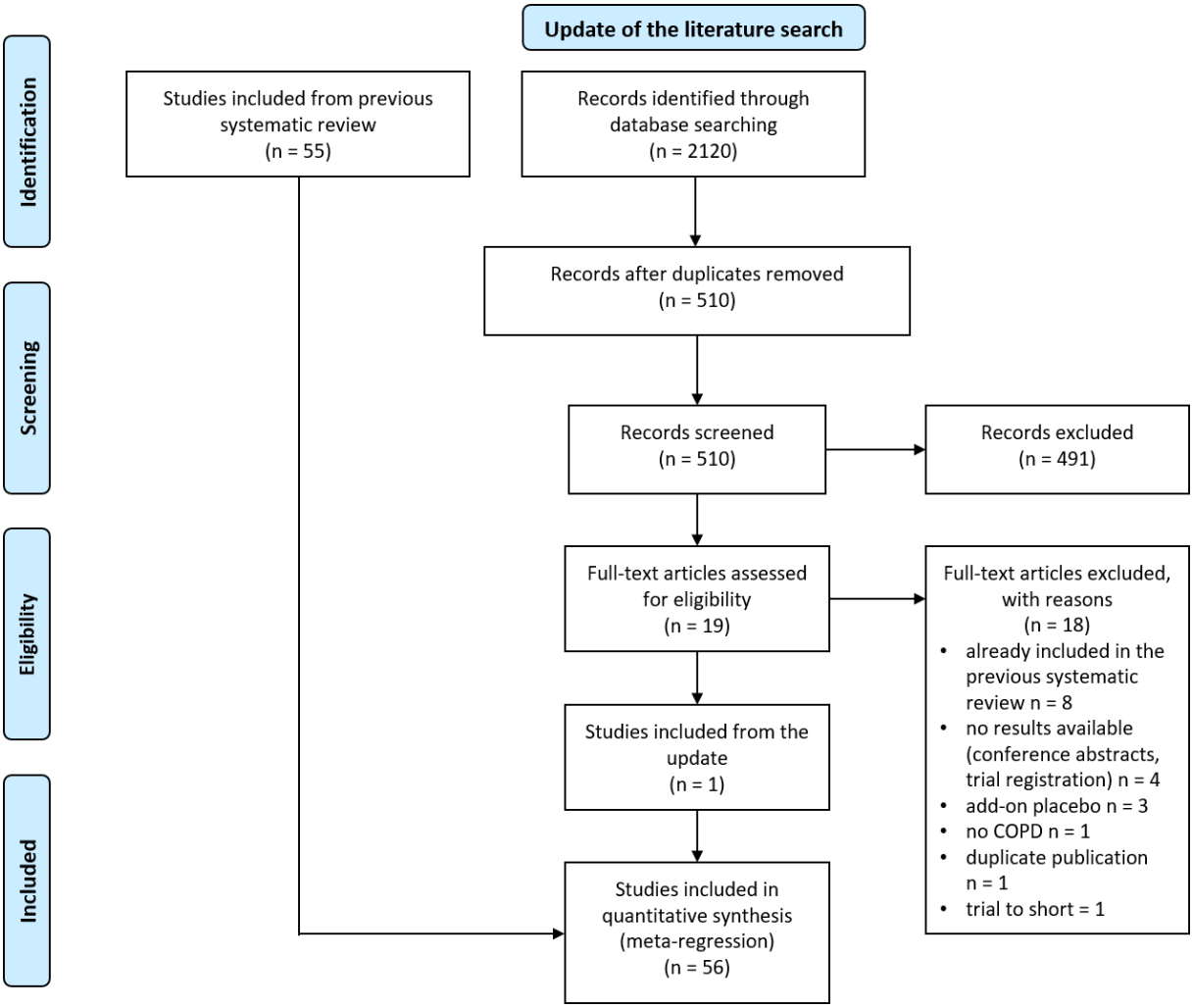
[4] Department of Pulmonary Medicine, University Hospital Essen - Ruhrlandklinik, Essen, Germany

Figure S1: The PRISMA flow chart illustrating the study selection process.



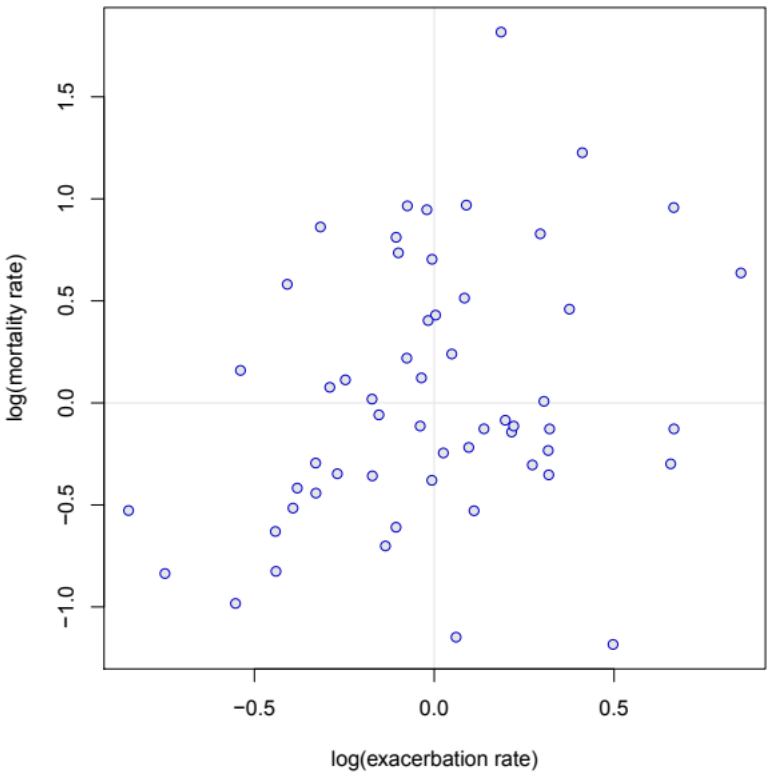


Figure S2: The residuals of the 56 studies two rate parameter estimates (annualized exacerbation and mortality rates) in the joint analysis of both endpoints. After subtracting the overall time trends, the remaining correlation of the two is rather low (estimated at ρ=0.18 (95% CI [-0.24, 0.56]).

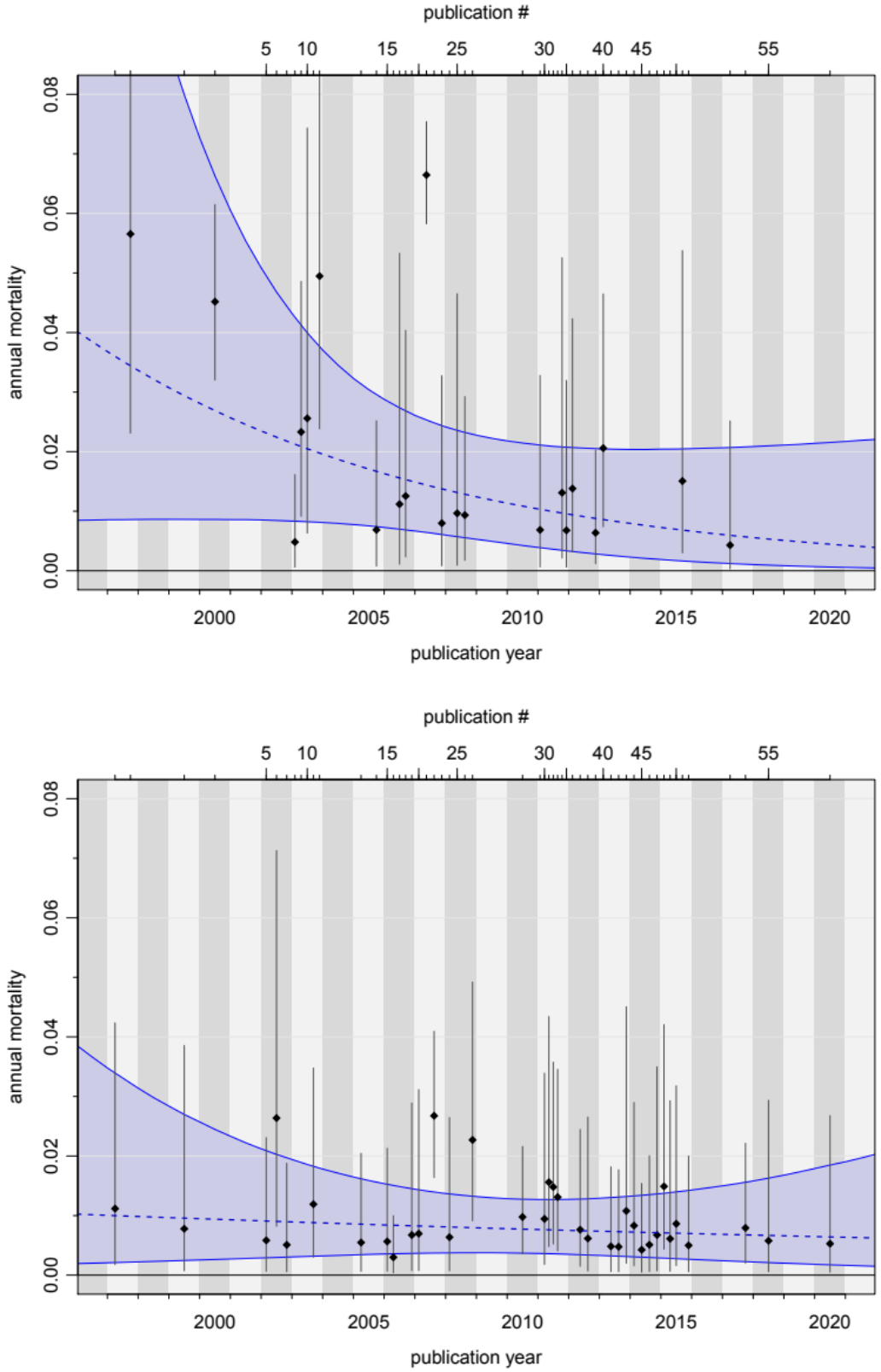


Figure S3: Regression analysis

	all studies			“true” placebos			ICS-placebos		
	N	median	range	N	median	range	N	median	range
patients	56	207	(43 - 1524)	21	219	(56 - 1524)	35	194	(43 - 753)
study duration (yr)	56	0.471	(0.231 - 3.0)	21	0.4615	(0.231 - 3.0)	35	0.5000	(0.231 - 1.0)
mean followup (yr)	56	0.431	(0.199 - 2.260)	21	0.4296	(0.218 - 2.260)	35	0.444	(0.199 - 0.902)
mean age (yr)	55	64.0	(58.8 - 68.6)	21	64.9	(58.8 - 68.2)	34	63.5	(60 - 68.6)
males (%)	56	74.7	(32.9 - 100)	21	75.0	(32.9 - 94.2)	35	73.0	(51.6 - 100)
smokers (%)	46	43.2	(16.9 - 63.0)	19	39.7	(23.0 - 63.0)	27	43.90	(16.9 - 56.0)
mean pack-years	45	44.0	(29.4 - 60.2)	18	43.75	(31.6 - 56.1)	27	44.0	(29.4 - 60.2)
mean FEV-1	51	50.0	(36.0 - 73.2)	20	47.8	(36 - 73.2)	31	52.6	(40.3 - 71.5)
mean SGRQ	28	46.5	(33.1 - 55.6)	10	47.5	(42.6 - 55.6)	18	46.07	(33.1 - 52.0)

Table S1: Descriptive statistics of variables of interest

id.all	id.true.placebo	id.ics.placebo	study	dataType	oqs	year	N	duration	meanFU	ageMean	malePercent	smokerPercent	packYearMean	fev1Mean	sgrqMean	rate	rateStdErr	exacerbations	zeroes	deaths
1		1	BoydEtAl1997	zeroes_only	3	1997	227	0.3077	0.2932	61	75	40							168	1
2	1		ColletEtAl1997	total+zeroes	5	1997	190	0.5	0.484	66.9	71.1	31. Jan		44		Jan 14		105	107	6
3		2	MahlerEtAl1999	zeroes_only	4	1999	143	0.2308	0.2117	63.19	76.2		60.2	40.8					96	0
4	2		BurgeEtAl2000	rate+StdErr	5	2000	370	3	20.994	63.8	74.1	39.2	44	50		01. Sep	Feb 63	1476		36
5		3	ChapmanEtAl2002	zeroes_only	4	2002	207	0.4615	0.4295		64	43			52				139	0
6		4	DonohueEtAl2002	zeroes_only	4	2002	201	0.5	0.4266	65.6	75		46		45.375				109	4
7		5	RossiEtAl2002	zeroes_only	3	2002	161	1	0.8589	63	80			49	47.2				106	0
8	3		CalverleyEtAl2003a	total_only	5	2003	361	1	0.7903	63.4	75	47	43.4	44.2	47.1	01. Mrz		371		0
9	4		CalverleyEtAl2003b	total_only	3	2003	256	1	0.7746	65	75	30	39	36	48	01. Aug		357		5
10	5		CelliEtAl2003	zeroes_only	5	2003	270	0.25	0.2276	65	71.5		48	43.6	49.6				211	2
11		6	HillerEtAl2003	zeroes_only	3	2003	145	1	0.8352	64.4	53.8	46.9	59.2	41.3					79	2
12	6		SzafranskiEtAl2003	total_only	3	2003	205	1	0.7595	65	83	34	45	36		Jan 87		291		9
13		7	CampbellEtAl2005	zeroes_only	4	2005	217	0.5	0.4536	60	73	55	37	54.1	46.7				183	0
14	7		RabeEtAl2005	total+zeroes	5	2005	280	0.4615	0.4346	63	74	45	43	55		0.6501		84	218	0
15		8	BeehEtAl2006	zeroes_only	3	2006	403	0.2308	0.2147	62.2	76.7		35	45.7					323	0
16		9	DusserEtAl2006	total+zeroes	3	2006	510	1	0.8477	65	87	24		47.6		Jan 69		731	238	0
17	8		PaggiaroEtAl2006	total+zeroes	3	2006	56	0.4615	0.4406	66	89.3	37.5		51.7	48.7	Jan 32		34	30	0
18	9		RennardEtAl2006	zeroes_only	3	2006	216	0.4615	0.4034	64.9	68	47	56.1	50.5					134	1
19		10	ZhouEtAl2006	zeroes_only	5	2006	43	1	0.9024	60.5	74.4	46.5	29. Apr	71.5					15	0
20		11	BaumgartnerEtAl2007	zeroes_only	4	2007	143	0.2308	0.2039	63.1	63.6	43.4		40.6					119	0
21	10		CalverleyEtAl2007a	rate+StdErr	4	2007	1524	3	22.596	65	76	43	48.6	44.1	49	Jan 13	0.06633	3891		231
22		12	CalverleyEtAl2007b	total+zeroes	5	2007	753	1	0.8874	64	76	35	45	41	49.7	0.918		613	391	20
23	11		ZhengEtAl2007	total_only	3	2007	148	0.4615	0.4361	66.6	86.49	23	35	47	44.5	Jan 35		87		0
24		13	AmbrosinoEtAl2008	total+zeroes	4	2008	106	0.4808	0.4229	66.9	84.6		35	40.3				26	85	0
25	12		JohanssonEtAl2008	zeroes_only	2	2008	117	0.2308	0.2308	62.2	43	63	31.6	73.2					113	0
26	13		TashkinEtAl2008b	total_only	5	2008	300	0.5	0.4327	63.2	69	39.7	40	41.28	55.6	01. Nov		144		1
27		14	TonnelEtAl2008	total+zeroes	4	2008	288	0.75	0.6489	63.5	85.4	30.2	43	46.19	48.9	Jan 83		342	158	6
28		15	DahlEtAl2010	total+zeroes	5	2010	432	1	0.8314	63	81.5		43	52	43	0.74		266	254	4
29	14		BogdanEtAl2011	zeroes_only	4	2011	208	0.2308	0.2184	66.3	89.4		47.4	52.2	44.9				190	0
30		16	ChapmanEtAl2011	total_only	3	2011	124	1	0.5385	62.8	65	51	51	56.3	45	0.54		36		1
31		17	DUrzoEtAl2011	zeroes_only	3	2011	260	0.5	0.4441	64	80.5	34.1	44.6	54.33	46.34				197	3
32		18	JonesEtAl2011a	total_only	4	2011	216	1	0.8868	61.9	81	45.4	38.4	52.9	47.3	0.46		88		4
33		19	JonesEtAl2011b	total+zeroes	4	2011	204	1	0.7701	65.2	60.8	38.7	58.2	49.4	47.1	0.8		126	123	3
34	15		LeeEtAl2011	zeroes_only	4	2011	207	0.2308	0.2206	67	94.2	33.3	45	54.9					193	1
35	16		TroostersEtAl2011	zeroes_only	4	2011	219	0.2308	0.2195	62.3	32.9	57		65.84					194	0
36	17		DohertyEtAl2012	zeroes_only	4	2012	236	0.5	0.4251	58.8	75	51	43.5	38					128	2
37		20	JonesEtAl2012	total+zeroes	3	2012	273	0.4615	0.4236	62	69.2	52.8	38.9	56.6	45.1	0.47		54	217	1
38		21	KerwinEtAl2012	total_only	3	2012	186	0.2308	0.207	65.1	51.6	46.8	52.7	54.6	45.1	0.79		30		0
39	18		TashkinEtAl2012	zeroes_only	5	2012	448	0.5	0.4296	58.8	78	48	41.95	38.55					271	1
40	19		AbrahamsEtAl2013	zeroes_only	3	2013	429	0.4615	0.425	64.4	63.9	45.2	46.4	49.1	43.2				344	5
41		22	BatemanEtAl2013	zeroes_only	4	2013	234	0.5	0.4521	64.4	72.8	40.1		55.2					141	0
42		23	DonohueEtAl2013	zeroes_only	4	2013	280	0.4615	0.3956	62.2	70	54	47.2	46.7					244	0
43		24	RennardEtAl2013	zeroes_only	3	2013	182	0.2308	0.2105	61.7	54.9	56	52.6	55.2	49.2				161	1
44		25	DonohueEtAl2014b	zeroes_only	4	2014	109	1	0.7863	60.1	67		42.8	55.1					83	1
45		26	DUrzoEtAl2014	total_only	3	2014	332	0.4615	0.4574	63.5	52.7	50.9	53.3	52.6	45.3	0.533		81		0
46		27	SinghEtAl2014b	rate+StdErr	5	2014	194	0.4615	0.4198	64.2	71.1	48.5		55	45.8	0.36	0.0791	29		0
47		28	TrivediEtAl2014	total+zeroes	5	2014	68	0.2308	0.1987	62.5	62	53	52.3	47				7	61	0
48		29	BraidoEtAl2015	total+zeroes	5	2015	142	1	0.8395	68.6	64	16. Sep		52.66		0.52		62	101	3
49		30	LeeEtAl2015	zeroes_only	5	2015	128	0.2308	0.2208	68.1	100		42.5	52.8	33.1				111	0
50		31	WangEtAl2015	total+zeroes	3	2015	154	0.5	0.4819	65	94.2	22. Jan	38.3	51.88		0.59		44	119	1
51	20		ZhengEtAl2015a	zeroes_only	4	2015	162	0.4615	0.4142	64.7	90	35	43.3	48.6					135	2
52		32	ZhengEtAl2015b	zeroes_only	4	2015	193	0.4615	0.4221	64.3	92	34	37.1						156	0
53	21		BhattEtAl2017	zeroes_only	5	2017	141	0.4615	0.38	68.2	84	38	47.8		42.59				125	0
54		33	DUrzoEtAl2017	total+zeroes	5	2017	332	1	0.6257	63.5	52.7	50.9	53.3	52.6	45.3	0.49		102	261	2
55		34	MaltaisEtAl2018	zeroes_only	3	2018	132	0.2308	0.221	60.8	65.9	43.9	44	59.7					116	0
56		35	ZhongEtAl2020	zeroes_only	5	2020	101	0.4598	0.4101	65.7	96	29	37.2	47.32					82	0

Table S2: Summary of 56 studies