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REVIEW

Industry-funded versus non-profit-funded critical care research: a meta-epidemiological overview

Perrine Janiaud[1], Ioana-Alinea Cristea[1,2] and John P. A. Ioannidis[1,2,3,4,5,6*]

Abstract

Purpose: To study the landscape of funding in intensive care research and assess whether the reported outcomes of industry-funded randomized controlled trials (RCTs) are more favorable.

Methods: We systematically assembled meta-analyses evaluating any type of intervention in the critical care setting and reporting the source of funding for each included RCT. Furthermore, when the intervention was a drug or biologic, we searched also the original RCT articles, when their funding information was unavailable in the meta-analysis. We then qualitatively summarized the sources of funding. For binary outcomes, separate summary odds ratios were calculated for trials with and without industry funding. We then calculated the ratio of odds ratios (RORs) and the summary ROR (sROR) across topics. ROR < 1 implies that the experimental intervention is relatively more favorable in trials with industry funding compared with trials without industry funding. For RCTs included in the ROR analysis, we also examined the conclusions of their abstract.

Results: Across 67 topics with 568 RCTs, 88 were funded by industry and another 73 had both industry and non-profit funding. Across 33 topics with binary outcomes, the sROR was 1.10 [95% CI (0.96–1.26), $I^2 = 1\%$]. Conclusions were not significantly more commonly unfavorable for the experimental arm interventions in industry-funded trials (21.3%) compared with trials without industry funding (18.2%).

Conclusion: Industry-funded RCTs are the minority in intensive care. We found no evidence that industry-funded trials in intensive care yield more favorable results or are less likely to reach unfavorable conclusions.

Keywords: Meta-epidemiology, Industry-funded, Randomized controlled trials, Sponsorship

Introduction

Clinical trials funded by industry and those funded by non-profit institutions may differ in their results and conclusions [1–5]. Several evaluations have compared trials with and without industry funding on reported efficacy, harms, conclusions, and risk of bias [6]. Most of these studies addressed single or few topics and none focused on intensive care. Between 2006 and 2012, 33% of the trials registered on Clinicaltrials.gov were funded by industry [7], but industry overall spends more on clinical research than public funders [8] and has unavoidable financial incentives to get favorable conclusions.

Industry may interfere at all steps of the research pipeline, including production of evidence (both fundamental and clinical research) [9], evidence synthesis (including ghostwriting) [9–11], and decision-making [9]. For randomized controlled trials (RCTs), industry sponsors can influence study outcomes by various means: e.g., choosing inactive or strawman comparators [12] or selectively reporting favorable results with spin [13]. The degree of financial involvement also varies. Industry may be

*Correspondence: jioannid@stanford.edu
[3] Department of Medicine, Stanford University, Stanford, CA 94305, USA
Full author information is available at the end of the article

the only funder or one among multiple funders, or it may offer drug/placebo or technical support. However, it often remains unclear in published papers whether industry sponsors have exerted a catalytic, modest, or no influence on the paper. CONSORT requires reporting of funding sources and conflicts of interest [14], but reporting remains suboptimal [15]. There is even less transparency on industry-led ghostwriting of the published reports [16].

Intensive care research is often stated to be underfunded by the National Institutes of Health (NIH) compared to the burden of critical illnesses on healthcare in the USA [17, 18] and similar issues exist also in other countries where intensive care is widely employed. Unmet needs raise the stakes for sponsors and manufacturers; yet little is known on the funding landscape of intensive care research. Here, we assessed to what extent critical care research (specifically RCTs) is funded by industry and whether there are clear differences in the results and conclusions of trials by different sponsors. Therefore, we conducted a meta-epidemiological overview of systematic reviews of RCTs conducted in critical care settings.

Methods

Search strategy and eligibility criteria

We searched PubMed (March 1, 2018) for meta-analyses and Cochrane Database Systematic Reviews (CDSRs) using the following keywords in their titles: respiratory failure, acute respiratory distress syndrome, ventilation, ventilated, critical care, intensive care, septic shock, sepsis, fluid, fluid resuscitation, hydroxyethyl starch, or albumin (Supplementary file). Recent articles published online between 2015 and 2018 were screened; for older reviews published pre-2015, only CDSRs were screened because the source of funding for included trials is rarely reported in meta-analyses published in journals.

After removing duplicates, two reviewers (PJ and IAC) screened titles/abstracts and, if needed, full texts for eligibility. Systematic reviews that included meta-analyses of RCTs evaluating an intervention in the critical care setting were eligible if they also reported funding source(s) for each included RCT. When study-level funding information was unavailable in the systematic review, we perused the full text of each RCT to identify its funding whenever the interventions pertained to drugs or biologics (excluding supplements, fluids, antiseptics, probiotics), since these interventions are likely to have interested sponsors. Reviews of non-randomized studies and those without meta-analysis were excluded.

Data extraction

For each eligible review, we screened all RCTs included in the meta-analyses to determine funding sources: industry funding only; no industry funding; mixed sources of funding (industry and non-profit institutions); intervention supplied by industry; and not reported. If not available or unclear in the systematic review, the information was extracted from the full-text RCT article. For overlapping meta-analyses, we retained the most recent one, or the largest, when publication years were identical.

For meta-analyses including both RCTs with industry funding and RCTs without industry funding and using primary binary outcomes, we extracted information on setting (ICU, surgical ICU, mixed), population (preterm, infant, child, adult), type of the intervention (device, pharmacological, procedure), type of comparator (active, placebo, no intervention), and number of primary outcome events per arm. Whenever multiple primary outcomes existed or no single outcome was clearly identified as such, we selected the primary outcome with the largest number of included studies (in ties, largest sample size; and further ties, largest number of events).

For RCTs funded by industry (fully or mixed source) or supplied by industry, we identified whether interventions involved in the comparison were manufactured by the industry sponsor. Three scenarios were identified: one arm of the comparison contains a sponsor-manufactured intervention (SMI), both arms contain SMIs, and none of the arms contain SMIs. All comparisons were coined so that experimental arms were always an SMI versus a control. When both arms contained SMIs, the SMI considered as the experimental arm was chosen to be the most expensive one, and, when both arms contained equally expensive interventions or this was unclear, the SMI considered the experimental intervention was chosen to be the most recent one (as suggested by the original article). When trials were industry-funded but had no SMI involved in the comparison that we examined, they were excluded from quantitative analysis as they are not informative about sponsor bias.

Data synthesis and statistical analysis

Sources of funding were summarized across all eligible topics. For topics where trials with or without industry funding could be compared for binary outcomes, we prespecified two large categories in the primary analysis: with industry funding (industry only or mixed) versus without industry funding (non-profit institution and only intervention supplied by industry). RCTs without reported funding were excluded.

For each topic that included both trials with and without industry funding, separate summary odds ratios (ORs) were calculated for the two categories of funding

using random-effects model inverse variance weighting. In trials with zero event cells in the 2 × 2 table, a standard 0.5 correction was added [19]. For consistency, intervention and outcome data were coded so that OR < 1 indicates that the experimental SMI-containing intervention is better than the control.

To compare the relative treatment effect of RCTs with versus without industry funding, we calculated the ratio of odds ratios (RORs) for each topic, the summary OR of trials with industry funding divided by the summary OR of trials without industry funding. ROR < 1 implies the experimental intervention is relatively more favorable in trials with industry funding compared with trials without industry funding. We then calculated the summary ROR (sROR) across all topics using fixed effect [20] and random effects [21]. We assessed between-topic heterogeneity using I^2 and its 95% confidence interval (CI) and between-topic variance τ^2 [22]. We also assessed the magnitude of the difference by checking how often OR estimates with and without industry funding differed by twofold or more (ROR ≥ 2 or ≤ 0.5).

We conducted sensitivity analyses including only mortality outcomes; recoding trials for which the intervention was supplied by industry as "with industry funding"; excluding trials with 0 events in both arms; and retaining only trials with one SMI versus a control (excluding trials supplied by industry and trials with SMIs in both arms).

To explore the influence of trials not reporting their funding, we carried out secondary analyses comparing these trials versus trials with industry funding and trials not reporting their funding versus trials without industry funding. We also compared industry-funded and not reported trials combined together versus trials without industry funding. As previously, for all secondary analyses the sRORs were also calculated using fixed effect and random effects and I^2 and τ^2 were also assessed.

Conclusions of RCTs

In a further exploratory analysis, we evaluated the conclusions of the abstracts of the trials with industry funding and of those without industry funding for topics that were eligible for ROR analyses. Conclusions were considered as "negative" (unfavorable) if trials concluded that the experimental SMI was less effective, more harmful or not more effective (for superiority trials) without mentioning any potential positive trade-offs [e.g., good safety, lesser cost, possible benefit in subgroups/specific patients, worth studying further (in more long-term and/or larger studies) for potential benefits] or it was squarely stated that it is not recommended. All other scenarios were classified as "positive" conclusions, including those where the experimental SMI was equally effective as an active comparator, those where positive trade-offs were mentioned, and those where it was more effective than comparators.

Results were reported in 2 × 2 tables. We calculated the arcsine difference of having a negative conclusion for each topic and then the summary arcsine (AS) estimate across topics using random effects. The arcsine transformation enables one to obtain a more robust estimate while including 0 cells in the analysis without continuity corrections [23]. AS > 0 implies that conclusions are more favorable in industry-funded trials.

Results

Search results

The search on PubMed yielded 220 CDSRs and 440 meta-analyses published in journals in 2015–2018 (Fig. 1). After exclusions, 67 systematic reviews were eligible of which 37 reported the sources of funding of the included RCTs and 30 did not but evaluated a drug intervention and for which we could retrieve sources of funding of each trial by perusing the respective full-text articles of RCTs. Across the 67 topics, there were a total of 568 RCTs. Of those, 88 (15.5%) were funded by industry, 73 (12.9%) were funded by both industry and other funding sources, 167 (29.4%) had only not-for-profit funding, 20 (3.5%) had not-for-profit funding but were supplied by industry, 144 (25.4%) did not report sources of funding, and 76 (13.4%) were excluded because of non-English language or access barrier (Table 1). Nine RCTs stated that they did not receive any funding for their study, and we have included them among the trials with only not-for-profit funding, since unavoidable expenses (e.g., personnel salary and overheads) can be assumed to have been covered by investigators and/or their institutions.

Topics that did not have both trials with and without industry funding

Twenty-five otherwise eligible topics could not be assessed for a comparison of trials with versus without industry funding because they only included trials with the same source of declared funding (Table 2). For 17 topics none of the trials had industry funding, for one topic all the trials had industry funding, and for another one all trials were funded both by industry and not-for-profit sources. The 25 topics include a total of 113 RCTs of which 20.3% (23/113) did not report their source of funding.

Topics where the industry sponsor did not manufacture any of the compared interventions

In another two topics, both trials with and without industry funding were available, but the industry funder did not manufacture any of the interventions for the comparison that we assessed. In one case, we were interested

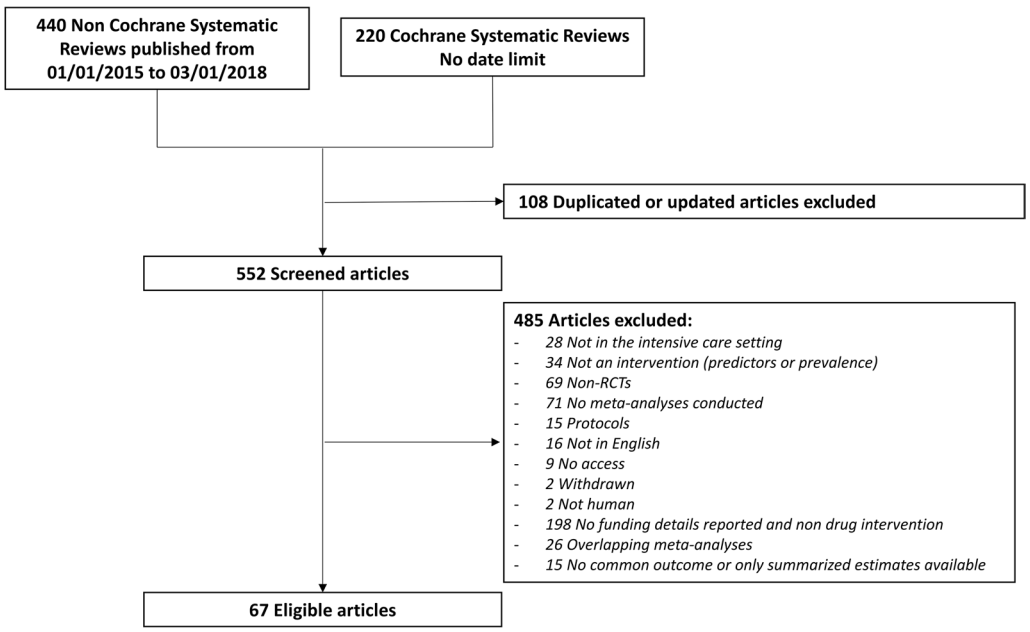

Fig. 1 Flowchart of the literature search and screening

in the comparison of midazolam versus placebo, but an AstraZeneca-funded trial included a third arm of morphine (manufactured by the company) (eTable 1). Four other trials in other topics did not have SMIs in the two compared arms, but for their topics there existed also other industry-funded RCTs involving SMIs in the comparisons (eTable 1).

Topics using a continuous outcome

An additional seven topics were excluded from the ROR analysis because they only had primary continuous outcomes, covering 79 RCTs of which 35 were with industry funding (fully and mixed sources) and 22 were without industry funding (non-profit and supplied by industry) (eTable 2). The outcomes assessed were ventilation duration and other related outcomes such as weaning time or ICU length-of-stay and biological measurement such as cytokine levels.

Trials included in the ROR analyses

Thirty-three topics covering 363 RCTs were included in the comparison of the relative treatment effect of trials with versus those without industry funding. Their summary characteristics appear in Table 1 and detailed topic-specific results appear in Table 3. Out of the 126 RCTs with a connection with industry (fully funded, mixed source, or supplied by industry), 113 had only one SMI in the comparison and 13 had both arms with SMIs (in 5/13 trials the comparison involved a combination of two drugs versus a single drug by the same sponsor; in 5/13 trials the comparison addressed strategies of ventilation, tracheostomy, antibiotics, or sedation and the sponsor manufactured ventilators, tracheostomy equipment, antibiotics, and sedatives, respectively; in 2/13 trials the sponsor manufactured the fluids compared head-to-head; in the remaining trial, two companies sponsored the trial comparing their products head-to-head) (eTable 1).

Primary analysis

The sROR across the 33 topics was 1.10 [95% CI (0.96; 1.26)] with no strong evidence of heterogeneity [$I^2 = 1\%$, 95% CI (0–40%), $\tau^2 = 0.001$, p value = 0.46] (Table 4 and Fig. 2). Within single topics, the 95% CIs of ROR excluded 1.00 in three topics [24–26]. Early tracheotomy significantly reduced mortality in a trial funded by a manufacturer of tracheotomy equipment [OR 0.29; 95% CI (0.14–0.61)] while there was a non-significant reduction in trials without industry funding [OR 0.82; 95% CI (0.58–1.16)] [24]. Conversely, corticosteroids [26] and levosimendan [25] for sepsis and septic shock reduced mortality in trials without industry funding [OR 0.49; 95% CI (0.22–1.07) and OR 0.75; 95% (0.57–0.99), respectively] while there was a non-significant increase in deaths in trials with industry funding [OR 1.23; 95% CI (0.86–1.77) and OR 1.12; 95% (0.86–1.46), respectively].

For seven topics, the point estimates of the ROR indicated a relative difference between with and without

Table 1 General characteristics

At topic level	All 67 eligible topics		The 33 topics included in the sROR analysis	
	N=67		*N*=33	
Type of interventions				
Drug intervention	45	67.2%	24	72.7%
Devices	12	17.9%	5	15.2%
Procedure	10	14.9%	4	12.1%
Type of comparator				
Active	34	50.7%	13	39.4%
Placebo or no intervention	31	46.3%	18	54.5%
Active, placebo or no intervention	2	3%	2	6.1%
At RCT level	**All 67 eligible topics**		**The 33 topics included in the sROR analysis**	
	N=568		*N*=363	
Number of RCTs by sponsors				
Industry	88	15.5%	61	16.8%
Industry and non-profit organization	73	12.9%	52	14.3%
Non-profit organization	167[a]	29.4%	100[b]	27.5%
Supplied by industry	20	3.5%	13	3.6%
NR	144	25.4%	104	28.7%
NA	76	13.4%	33	9.1%
Population included in RCTs				
Adults	464	81.7%	286	78.8%
Children	16	2.8%	9	2.5%
Neonates	29	5.1%	21	5.8%
Preterm	17	3%	17	4.7%
NR	42	7.4%	30	8.3%
Number of subjects included				
Median (interquartile range)	63 (40–133)		71 (41–172)	
Total included	92,034		71,283	
Industry	29,029		23,047	
Industry and non-profit organization	15,038		14,068	
Non-profit organization	26,783		18,497	
Supplied by industry	3393		2821	
NR	11,555		9125	
NA	6236		3725	

NR not reported, *NA* original article not accessible or not in English

[a] Nine of which reported that they did not receive any funding to conduct their trial

[b] Six of which reported that they did not receive any funding to conduct their trial

industry funding trials of at least twofold. Five topics had an ROR ≤ 0.5 [24, 27–30] while six topics had an ROR ≥ 2 [25, 31–35]. Uncertainty in the ROR estimates was typically substantial.

Sensitivity analyses

The sensitivity analysis excluding trials supplied by industry and trials with an SMI in both arms of the comparison resulted in sROR = 1.22 [95% CI (1.02–1.45)] with significantly more favorable outcomes in trials without industry funding compared with trials with industry finding. There was no evidence of heterogeneity [$I^2 = 3\%$, 95% CI (0–44%), $\tau^2 = 0.0065$, p value = 0.42]. The other sensitivity analyses did not substantially change the results observed in the primary analysis (Table 4, eFig. 3 and eTable 3).

Secondary analyses

Trials that did not report their source of funding had an sROR of 0.88 [95% CI (0.71–1.07); $I^2 = 0\%$, 95% CI

Table 2 Topics reporting the same source of funding across all randomized controlled trials with declared funding

Author	Year	Indication	Outcome	Funding type	Total trials included in meta-analysis	Trials with no reported funding	Trials with access barrier	Total sample size
Monro-Somerville	2017	Effect of high-flow nasal cannula oxygen therapy on mortality and intubation rate in acute respiratory failure	Hospital mortality	Industry	5	0	0	1932
Stephens	2018	Early sedation depth in mechanically ventilated patients	Mortality	Industry and non-profit	2	0	0	97
Shah	2017	Inhaled versus systemic corticosteroids for preventing bronchopulmonary dysplasia (BPD) in ventilated very low birth weight preterm neonates	BPD at 36 weeks	Supplied by industry	3	0	0	429
Afshari	2017	Aerosolized prostacyclins for acute respiratory distress syndrome	Overall mortality	Non-profit	2	0	0	81
Alarcon	2017	Elevation of the head in people with severe traumatic brain injury	Mortality at the end of study follow-up	Non-profit	3	0	0	20
Avni	2015	Vasopressors for the treatment of septic shock	28-day mortality	Non-profit	11	2	6	1718
Borthwick	2017	High-volume hemofiltration for sepsis	Mortality	Non-profit	2	0	0	156
Bradt	2014	Music interventions for mechanically ventilated patients	State anxiety	Non-profit	5	2	0	288
Chacko	2015	Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury or acute respiratory distress syndrome	Mortality in hospital	Non-profit	3	1	0	1089

Table 2 continued

Author	Year	Indication	Outcome	Funding type	Total trials included in meta-analysis	Trials with no reported funding	Trials with access barrier	Total sample size
Dervan	2017	Methadone to facilitate opioid weaning in pediatric critical care patients	Proportion developing withdrawal	Non-profit	2	1	0	115
Hu	2015	Non-pharmacological interventions for sleep promotion	Total sleep time	Non-profit	2	1	0	116
Huang	2017	Dexmedetomidine for one-lung ventilation in adults undergoing thoracic surgery	Intraoperative oxygenation index	Non-profit	7	0	4	269
Korang	2016	Noninvasive positive pressure ventilation for acute asthma in children	Serious adverse events	Non-profit	2	0	0	40
Morag	2016	Cycled light for preterm and low birth weight infants	Daily weight gain during neonatal care	Non-profit	2	0	0	128
Pandor	2015	Pre-hospital noninvasive ventilation for acute respiratory failure	Mortality	Non-profit	10	2	0	800
Rose	2017	Cough augmentation techniques for extubation or weaning	Extubation success	Non-profit	2	1	0	95
Stuani	2017	Underfeeding versus full enteral feeding in critically ill patients with acute respiratory failure	Overall mortality	Non-profit	5	2	0	1532
Wu	2015	Albuterol in the treatment of acute respiratory distress syndrome	Mortality	Non-profit	3	0	0	646
Yang	2017	Early application of low-dose glucocorticoid improves acute respiratory distress syndrome	Mortality	Non-profit	8	4	1	1218

Table 2 continued

Author	Year	Indication	Outcome	Funding type	Total trials included in meta-analysis	Trials with no reported funding	Trials with access barrier	Total sample size
Faria	2015	Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery	Rate of tracheal intubation	NR	2	2	0	269
Peng	2017	Delirium risk of dexmedetomidine and midazolam	Incidence of delirium	NR	6[a]	1	5	356
Suresh	2001	Superoxide dismutase for preventing chronic lung disease in mechanically ventilated preterm infants	Death before discharge	NR	2	2	0	78
Wang	2015	Mannitol for acute severe traumatic brain injury	Mortality	NR	2	2	0	53
Liu	2016	Thymosin alpha1 for sepsis	28-day mortality	NA	10[a]	0	10	530
Zheng	2018	Xuebijing combined with ulinastatin for patients with sepsis	Mortality	NA	11[a]	0	11	741

References of the reviews are available in the supplementary information

NA original article not accessible or not in English

[a] All included trials in the reviews were in Chinese

Table 3 Individual ROR and OR with and without industry funding for each topic

Author	Year	Indication	SMI	Control	Outcome	Trials with industry funding	Trials without industry funding	ROR *p* value	ROR	OR with industry funding	OR without industry funding
Aitken	2015	Mechanical ventilated	Protocol-directed sedation	Non-protocol-directed sedation	Hospital mortality	1	1	0.21	1.56 (0.78; 3.15)	1.21 (0.72; 2.04)	0.78 (0.49; 1.24)
Andriolo	2017	Sepsis	Procalcitonin-guided algorithm	No intervention	Mortality at longest FU	3	1	0.69	1.21 (0.47; 3.09)	1.03 (0.65; 1.65)	0.86 (0.38; 1.94)
Barrington	2017	Respiratory failure neonates	Nitric oxide	Placebo or no intervention	Death before hospital discharge	3	6	0.96	1.02 (0.44; 2.38)	0.97 (0.49; 1.94)	0.95 (0.58; 1.55)
Barrington	2017	Respiratory failure preterm	Nitric oxide	Placebo or no intervention	Death before hospital discharge	9	4	0.50	1.2 (0.71; 2.04)	1.05 (0.82; 1.36)	0.88 (0.55; 1.4)
Bednarczyk	2017	Fluid resuscitation	Dynamic assessment	No intervention	Mortality	5	7	0.66	1.24 (0.47; 3.26)	0.66 (0.28; 1.58)	0.53 (0.35; 0.82)
Beitland	2015	Adult ICU patients	Low molecular heparin	Unfractionated heparin	Any deep vein thrombosis	2	1	0.81	0.9 (0.37; 2.17)	0.76 (0.33; 1.77)	0.85 (0.67; 1.07)
Bellu	2008	Mechanically ventilated infants	Opioids	Placebo or no intervention	Neonatal mortality	1	3	0.21	0.13 (0.01; 3.03)	0.16 (0.01; 3.51)	1.19 (0.81; 1.73)
Busani	2016	Septic shock	Polyclonal intravenous immunoglobulin	Fluids or no intervention	Mortality	6	2	0.29	3.8 (0.32; 45.2)	0.91 (0.65; 1.27)	0.24 (0.02; 2.77)
Fujii	2018	Sepsis and septic shock	Polymyxin B-immobilized hemoperfusion	No intervention	28-day mortality	4	1	0.56	1.93 (0.21; 17.34)	1.07 (0.68; 1.7)	0.56 (0.06; 4.76)
Gebistorf	2016	ARDS child and adult	Nitric oxide	Placebo or no intervention	Overall mortality	5	5	1.00	1 (0.6; 1.67)	1.06 (0.77; 1.45)	1.06 (0.71; 1.58)
Gillies	2017	Mechanically ventilated adults	Heated humidifiers	Heat and moisture exchangers	Artificial airway occlusion	5	1	0.47	0.28 (0.01; 7.79)	2.04 (0.48; 8.72)	7.15 (0.37; 139.77)
Guay	2015	Intraoperative acute lung injury in adults	Low tidal volume ventilation	High tidal volume ventilation	Mortality within 30 days after the surgery	1	7	0.62	2.82 (0.05; 159.58)	1.9 (0.04; 100.63)	0.68 (0.32; 1.42)
Kuriyama	2015	Mechanically ventilated adults	Closed tracheal suctioning systems	Open tracheal suctioning systems	Incidence of ventilator-associated pneumonia	2	3	0.29	2.69 (0.43; 16.72)	0.64 (0.34; 1.19)	0.24 (0.04; 1.31)

Table 3 continued

Author	Year	Indication	SMI	Control	Outcome	Trials with industry funding	Trials without industry funding	ROR *p* value	ROR	OR with industry funding	OR without industry funding
Liberati	2009	Adult ICU patients	Antibiotics	No prophylaxis	Mortality	9	2	0.51	0.73 (0.29; 1.83)	0.83 (0.69; 1)	1.13 (0.46; 2.78)
Liu	2017	Sepsis	Ulinastatin combined with thymosin alpha2	Placebo or no intervention	28-day mortality	1	1	0.61	0.69 (0.17; 2.85)	0.31 (0.09; 1.02)	0.45 (0.21; 0.95)
Lu	2017	Sepsis	Omega-3	Placebo	Mortality	6	3	0.72	1.25 (0.39; 3.99)	0.87 (0.52; 1.48)	0.7 (0.25; 1.98)
Moeller	2016	Resuscitation	Gelatin-containing plasma expanders	Crystalloids or albumin	Mortality	4	5	0.86	1.06 (0.56; 1.98)	1.4 (0.83; 2.37)	1.32 (0.94; 1.87)
Nagendran	2017	ARDS	Statins	Placebo	28-day mortality	1	4	0.91	1.04 (0.58; 1.84)	1.11 (0.79; 1.56)	1.07 (0.67; 1.71)
Osadnik	2017	Acute hypercapnic respiratory failure COPD adults	Noninvasive ventilation	No intervention	Endotracheal intubation	1	9	0.16	0.17 (0.02; 1.96)	0.05 (0; 0.54)	0.29 (0.19; 0.43)
Porhomayon	2015	ICU survivors	Light sedation	Heavy or standard sedation	Delirium	2	5	0.75	1.26 (0.32; 4.99)	1.02 (0.33; 3.18)	0.81 (0.37; 1.77)
Putzu	2017	ARD and sepsis in adults	Continuous veno-venous hemofiltration	No intervention	Mortality at longest follow-up	2	2	0.95	0.87 (0.02; 42.85)	0.27 (0.01; 11.97)	0.31 (0.13; 0.76)
Serpa	2017	Resuscitation in adults	Balanced saline	Isotonic saline	In-hospital mortality	2	2	0.88	0.84 (0.08; 8.52)	0.87 (0.65; 1.17)	1.03 (0.1; 10.26)
Shah	2017	Chronic lung disorders in infants	Corticosteroids	Placebo or no intervention	Chronic lung disease at 36 weeks post-menstrual age (among survivors)	2	2	0.39	0.74 (0.38; 1.46)	0.62 (0.46; 0.85)	0.83 (0.46; 1.53)
Siempos	2015	Mechanical ventilated	Early tracheostomy	Late tracheostomy	Mortality	1	6	0.01	0.35 (0.15; 0.81)	0.29 (0.14; 0.61)	0.82 (0.58; 1.16)
Sjovall	2017	Sepsis	Combination of antibiotics	One antibiotic	All-cause mortality	7	1	0.92	1.02 (0.66; 1.58)	1.18 (0.92; 1.52)	1.16 (0.81; 1.66)
Sole-Lleonart	2017	Mechanical ventilated	Nebulized antibiotics	Intravenous antibiotics	Nephrotoxicity	1	1	0.07	0.05 (0; 1.21)	0.06 (0; 1.24)	1.18 (0.47; 2.97)
Sud	2016	ARDS	High frequency oscillatory ventilation	Conventional or pressure controlled ventilation	Hospital or 30-day mortality	4	3	0.21	2.48 (0.61; 10.19)	1.03 (0.55; 1.94)	0.41 (0.12; 1.46)

Table 3 continued

Author	Year	Indication	SMI	Control	Outcome	Trials with industry funding	Trials without industry funding	ROR *p* value	ROR	OR with industry funding	OR without industry funding
Umemura	2016	Sepsis	Anticoagulants	Placebo or no intervention	Mortality	9	7	0.87	1.03 (0.75; 1.41)	0.96 (0.87; 1.07)	0.94 (0.7; 1.26)
Volbeda	2015	Sepsis	Corticosteroids	Placebo or no intervention	Mortality	8	10	0.04	1.49 (1.02; 2.17)	1.12 (0.86; 1.46)	0.75 (0.57; 0.99)
Wang	2017	Septic shock	Levosimendan	Dobutamine, placebo or no intervention	Mortality	1	4	0.04	2.54 (1.06; 6.07)	1.23 (0.86; 1.77)	0.49 (0.22; 1.07)
Zhang	2015	Sepsis	Antipyretic therapy	Placebo or no intervention	Mortality	2	2	0.75	1.45 (0.15; 14.47)	0.96 (0.11; 8.64)	0.66 (0.34; 1.3)
Zhang	2017	ARDS	*N*-Acetyl-cysteine	Placebo	Short-term mortality	3	1	0.10	4.82 (0.76; 30.69)	0.8 (0.38; 1.71)	0.17 (0.03; 0.9)

References of the reviews are available in the supplementary information

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disorder, *FU* follow-up, *ICU* intensive care unit

(0–30%)] versus trials without industry funding. Trials that did not report their source of funding also had an sROR of 0.88 [95% CI (0.74–1.04); $I^2 = 15\%$, 95% CI (0–48%)] versus trials with industry funding.

For trials that did not report their source of funding or had industry funding versus those without industry funding, the sROR was 0.98 [95% CI (0.85–1.13); $I^2 = 1\%$, 95% CI (0–45%)]. Results of secondary analyses are available in eTable 4 and eFig. 4.

Conclusions in abstracts

Excluding seven trials without abstracts and one that did not conclude on the SMI, 23 among 108 RCTs with industry funding (21.3%), as opposed to 20 among 110 RCTs (18.2%) without industry funding had negative conclusions (as defined in the "Methods" section). The AS estimate of having negative conclusion with versus without industry funding was 0.04, 95% CI (− 0.09 to 0.17).

Discussion

Randomized controlled trials in the intensive care setting seem to be led primarily by public and non-profit institutions while a sizeable minority has been funded by industry. Evidence on several clinically important topics includes no RCTs sponsored by industry. Topics such as assessing head elevation for severe brain injury [36], music to calm mechanically ventilated patients [37], cycled lights in neonatal intensive care units [38], or cough augmentation techniques for extubation [39] are procedures where the lack of industry funding is easily explained. Such procedures do not necessarily involve equipment or products manufactured by the biopharmaceutical, biotechnology, or other health-related industry. However, in cases such as low-dose corticosteroids for acute respiratory distress syndromes we cannot exclude the possibility that the trials not reporting their source of funding were potentially funded by industry, but this had not been disclosed [40]. We found only one topic where all the available published trials with reported funding disclosed industry support, the evaluation of high-flow nasal cannula in adult acute respiratory failure [41]. In the RCTs funded by industry, the typical pattern was comparison of an SMI versus a control. However, we also observed some variations, e.g., where companies sponsored trials in which both arms included their sponsored products, either as part of the comparison of interest or as backbone treatment given to all patients. As shown before, these trial designs promote the interests of the sponsor regardless of the results [12]. Head-to-head comparisons of products by different sponsors co-sponsoring the same trial are very rare [12, 42].

On average, our primary analysis did not show more favorable treatment effects for the primary outcome in

Table 4 Summary RORs for all analysis

	Topics	*N* trials with industry funding	*N* trials without industry funding	sROR random effects	I^2 (%; 95% CI)	τ^2	sROR fixed effect
Primary analysis	33	113	113	1.10 (0.96; 1.26)	1% (0%; 40%)	0.001	1.10 (0.96; 1.26)
Sensitivity analyses							
Mortality outcomes only	26	100	90	1.14 (0.98; 1.31)	0% (0%; 38%)	0	1.14 (0.98; 1.31)
Supplied by industry merged with industry-funded trials	32	118	100	1.12 (0.9; 1.4)	36% (1%; 58%)	0.109	1.17 (1.01; 1.36)
Without 0 events in both arms	32	106	101	1.10 (0.95; 1.27)	2% (0%; 41%)	0.0035	1.10 (0.96; 1.26)
Without trials supplied by industry and without trials with SMI in both arms	28	102	85	1.22 (1.02; 1.45)	3% (0%; 44%)	0.0065	1.22 (1.03; 1.44)

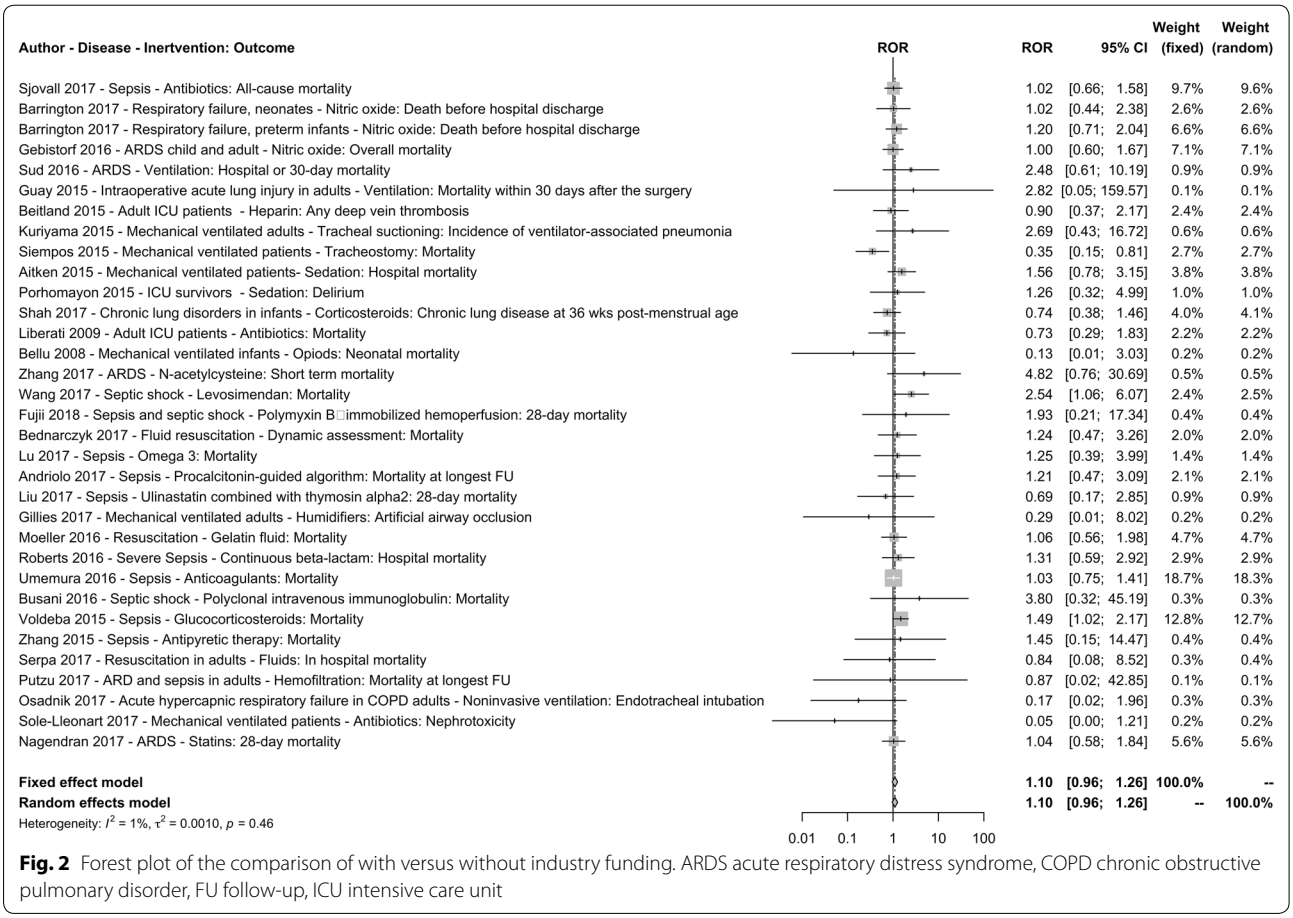

Fig. 2 Forest plot of the comparison of with versus without industry funding. ARDS acute respiratory distress syndrome, COPD chronic obstructive pulmonary disorder, FU follow-up, ICU intensive care unit

trials with versus without industry funding. One sensitivity analysis even showed significantly less favorable results for trials with industry funding. The large CIs for many of the RORs at the topic level and the twofold difference in effect sizes for 11 topics highlight substantial remaining uncertainty. Those results have to be interpreted cautiously, because most trials had a small sample size (median of 71 participants). This fact, combined with the small number of events in our included RCTs, could explain the absence of notable statistical heterogeneity

in our results; lack of power to detect heterogeneity may have resulted in low I^2 estimates [43]. The preponderance of small trials is very common across diverse medical fields [44]. Small trials leave large uncertainty and it is quite easy to manipulate their results (based on diverse analytical choices adding degrees of freedom on aspects that are not fully covered by study registration and prespecified, publically available protocols) [45] and, even more, their conclusions.

Only a small minority of the evaluated trials reached clearly unfavorable conclusions for the experimental intervention. This suggests that investigators and sponsors are unwilling to deliver a clear "negative" message, even though the majority of tested interventions in intensive care settings fail to deliver [46]. Many trials find no benefits for the primary outcome, but may still report favorable trends for secondary outcomes, subgroups or specific patients, or may conclude that further perusal of the intervention may eventually identify benefits. The proportion of trials with negative conclusions was similar in industry-funded trials and those without industry funding.

Multiple other evaluations have tried to assess whether industry-funded trials yield more favorable efficacy results and conclusions [6]. None of them have focused on intensive care, and most have used smaller samples of trials than our evaluation. The few assessments that addressed larger numbers of trials than we did used a qualitative categorization of favorable efficacy rather than a comparison of detailed effect size estimates within the same topic and outcome. Evaluations not accounting for topic and outcome run the risk of confounding if industry trials are performed in topics and outcomes that are more likely to show larger effect sizes and favorable results. Across 25 assessments with 2923 trials, trials funded by industry were more likely to have favorable efficacy results [relative risk (RR) 1.27, 95% CI (1.17–1.37)] [6]. Thus, the results that we observed in the intensive care trials seem substantially different than for trials in other fields. Moreover, across 29 assessments with 4583 trials, trials funded by industry were more likely to have favorable conclusions (RR 1.34, 95% CI (1.19–1.51)] [6]. Definitions of "favorable" have varied across evaluations, but the average rate of favorable conclusions in previous assessments in other fields for industry-funded trials (86.6%) seems higher than what we observed for RCTs in intensive care. The average rate of favorable conclusions in trials without industry funding was 64.4%, which seems lower than what we observed in not-for-profit-funded intensive care research.

Overall, contrary to previous evaluations in other fields, in intensive care we found no evidence for more favorable results and conclusions in industry-funded trials; if anything, the opposite trend was observed. The difference may still be due to chance. Alternatively, it could be that for several interventions in intensive care where industry-funded trials yielded unfavorable results (e.g., corticosteroids, *N*-acetylcysteine, and levosimendan), treatments were inexpensive and thus there was no strong financial bias. Or, industry-funded trials may have been better done and more protected from bias. Nevertheless, it is of note that in the previous empirical evaluations, even when adjusting results for the quality of the study and its risk of bias, trials with industry funding remained associated with more positive conclusions, suggesting that whatever differences were not easily explained with standard risk of bias tools [11].

A recent study conducted in intensive care research found that more than half its trials were funded by non-profit organization, a quarter by industry, and the rest by mixed sources of funding across a total of 391 assessed RCTs [47]. The modestly higher rate of industry funding observed in that evaluation may be due to differences in eligibility criteria (e.g., sample size greater than 100, trials published in 1990–2012). The authors found that the evidence in intensive care is increasingly being shaped by academic investigators with a decline in the number of studies with industry funding over time, and an increase in trials with non-profit funding [47]. One potential reason for the lack of interest from industry could be the specific setting of intensive care research where patients are more at risk of dying and where the complex logistics might make it more difficult to conduct a clinical trial. One proposed solution is to follow the investigator-led research model [47], by which consortia of independent investigators could help improve intensive care research and develop new mechanisms of private–public collaborations to fund it. Developing an agenda of large-scale trials with relevant clinical outcomes, publicly transparent and prespecified protocols, and protection from sponsor bias may help make major progress in intensive care research.

A substantial proportion of RCTs in intensive care do not report any information on funding. Nine trials stated that they had received no funding and, given the logistics of running an RCT, it is difficult to envision an RCT in the intensive care setting that was done without any financial support, including overheads, but it is unlikely that these trials were industry-funded. A much larger number of RCTs simply make no comment on funding. The funding, if any, of these trials remains a black box. Perhaps these trials could also have been covertly funded by industry. Alternatively, these trials could also have been funded by non-profit organizations or may have had no specific support whatsoever. However, it has been shown that articles from clinical medicine journals

compared with other fields are almost twice as likely to not include information on the funder and yet to have funding from industry [48]. There is a need to increase the enforcement of the reporting of funding source as required by the CONSORT statement [14] at the trial level but also at the systematic review level. Without such information it is difficult to apprehend the full extent of the industry involvement in clinical trials research and even to determine the needs in funding from public institutions to cover unmet needs.

Our overview has several limitations. First, we only considered trials already included in meta-analyses and this would exclude trials that have not been subjected to meta-analysis. Moreover, information on funding of RCTs is not commonly reported in journal-published meta-analyses, and despite our effort to scrutinize drug and biologic trials in their original publications, several other topics could not be assessed. Second, for consistency we only focused on binary outcomes for the ROR analysis. However, binary outcomes represent the majority of the evidence with only seven reviews excluded on this basis. Third, we did not assess the quality of the trials or compare the quality between with and without industry-funded trials. Evidence from other fields suggests that while in the past industry trials may have had quality deficits, more recent trials funded by industry do well or better in quality checklists than non-industry-funded trials [2, 49, 50]. Moreover, as we stated above, standard risk of bias tools do not seem to explain differences in favorable results and conclusions in trials with versus without industry funding [6]. Fourth, before 2015 we only covered the Cochrane Database Systematic Reviews, because journal meta-analyses rarely report the funding source of the RCTs and old meta-analyses may also not be very up-to-date about the status of the evidence. Fifth, our assessment included relatively few trials on medical devices. Medical devices are evolving rapidly owing to the development of new technologies and are less regulated compared to drug interventions [51]. Whether industry-funded trials on devices might present more favorable outcomes requires further investigation.

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Author details
[1] Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA 94305, USA. [2] Department of Clinical Psychology and Psychotherapy, Babes-Bolyai University, Cluj-Napoca, Romania. [3] Department of Medicine, Stanford University, Stanford, CA 94305, USA. [4] Department of Health Research and Policy, Stanford University, Stanford, CA 94305, USA. [5] Department of Biomedical Data Science, Stanford University, Stanford, CA 94305, USA. [6] Department of Statistics, Stanford University, Stanford, CA 94305, USA.

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Author contributions
All authors contributed to the design of the study. PJ and IAC extracted data and all authors analyzed the data and interpreted the results. PJ wrote the first draft and all authors contributed to the writing of the paper and approved the final version

Compliance with ethical standards

Conflicts of interest
All authors declare that they have no potential conflicts of interest.

Data
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