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REVIEW

Overall bias and sample sizes were unchanged in ICU trials over time: a meta-epidemiological study

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Abstract

Objective: To assess time trends in risk of bias (RoB) and sample sizes in randomized clinical trials (RCTs) of adult intensive care unit (ICU) patients.

Study Design and Setting: A meta-epidemiological study of RCTs from Cochrane systematic reviews assessing interventions in adult ICU patients. Using run charts, we assessed time trends in the annual proportion of RCTs with overall low RoB, the annual median sample sizes, and the annual proportion of RCTs with low, unclear, and high RoB in individual bias domains.

Results: We included 604 RCTs published between 1977 and 2018 from 53 Cochrane systematic reviews. Only 6.8% of the RCTs had overall low RoB. We observed only random variation in the annual proportions of RCTs with overall low RoB, in the annual median sample sizes and in most individual bias domains. For ''allocation concealment,'' we observed an increase in the proportion of low RoB RCTs and a decrease in the unclear RoB RCTs.

Conclusions: Few RCTs in adult ICU patients had overall low RoB. We found no evidence of an increase in RCTs with overall low RoB or in the median sample sizes over time. The only individual RoB domain with better ratings over time was ''allocation concealment.''

Keywords: Risk of bias; Sample size; Intensive care; Intensive care unit; Research methodology; Randomized clinical trials

1. Introduction

The most reliable assessments of benefits and harms of health care interventions derive from randomized clinical trials (RCTs) and systematic reviews of RCTs [1]. Flaws in trial design, conduct, or analysis may introduce bias and produce misleading results [2]. Assessment of risk of bias is typically done within seven bias domains according to the Cochrane Handbook [2]. Meta-epidemiological studies indicate that RCTs with high risk of bias in any domain overestimate intervention effect estimates compared to RCTs with low risk of bias [3–7]. In addition to risk of bias, RCTs with small sample sizes produce imprecise effect estimates and are at risk of random errors (i.e., chance findings) [8], and as a result of publication bias, they tend to overestimate intervention effect estimates compared with RCTs with larger sample sizes [9]. Within the intensive care unit (ICU) setting, smaller trials have been shown to report larger effect estimates compared with larger trials, in part due to lower methodological quality [10]. Biased data and data from small trials may therefore result in unwarranted clinical practice recommendations of futile or even harmful healthcare interventions with widespread consequences for patients and society [11]. Over time, the risk of bias in RCTs has decreased both generally [12,13] and within specific fields [14]. However, the temporal development of risk of bias in RCTs of ICU interventions is unknown. We therefore conducted a meta-epidemiological study in which we aimed to assess

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Ethical approval: Not required.

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What is new?

Key findings

- We found no evidence of improvement over time in randomized clinical trials (RCTs) of intensive care unit (ICU) interventions with respect to overall risk of bias and sample sizes.

What this adds to what was known?

- There is evidence that the overall risk of bias regardless of medical subspecialty has decreased over time, but until now, the specific status within the ICU setting was unclear. Our study gives an overview of the development of overall risk of bias, risk of bias in individual bias domains, and samples sizes over time within RCTs of ICU interventions.

What is the implication and what should change now?

- Our findings raise concern that the general methodological quality of RCTs within the ICU setting has not improved over time. Researchers, clinicians, and policymakers must take care not to draw incorrect conclusions about interventions to avoid the implementation of costly, futile, or even harmful interventions, and substantial efforts are necessary to increase the methodological quality of RCTs in the ICU setting.

time trends in risk of bias and in sample sizes in RCTs of ICU interventions. We hypothesized that the increased focus on methodological rigor and implementation of research guidelines such as the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [15] and the Consolidated Standards of Reporting Trials (CONSORT) [16] statements have led to lower risk of bias and increased sample sizes over time in RCTs assessing ICU interventions.

2. Methods

2.1. Protocol and registration

This meta-epidemiological study was conducted in accordance with the prepublished protocol and statistical analysis plan [17]. We adhered to the recommendations by the Cochrane Collaboration [2], and we have prepared this manuscript in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis statement where applicable (completed checklist is included in the electronic supplementary material [ESM] available at the publisher's website) [18]. Deviations from the protocol were minor and are described in Table S1 in the ESM.

2.2. Eligibility criteria

Eligible trials were parallel-group RCTs including crossover trials and quasirandomized trials of interventions in adult ICU patients included in Cochrane systematic reviews. First, we used an electronic search strategy (described in section 2.6) to identify relevant Cochrane systematic reviews. Eligible reviews included (1) adult ICU patients; (2) evaluated interventions used in the ICU; (3) assessed risk of bias in all seven Cochrane risk of bias domains: "random sequence generation," "allocation concealment," "blinding of participants and personnel," "blinding of outcome assessment," "incomplete outcome data," "selective reporting," and "other sources of bias" according to the Cochrane Handbook [2], and (4) included at least one meta-analysis (to ensure that it would be possible to extract sample sizes) [2]. Second, we included all eligible trials that fulfilled criteria 1 and 2 from the included Cochrane systematic reviews. Trials including both adults and children or both ICU and non-ICU patients were excluded unless data for adult ICU patients could be extracted separately. Furthermore, we excluded trials using anything other than patients as the unit of analysis, for example, intravascular catheters. An overview of the trial selection process is presented in Fig. 1.

2.3. Population

The population was adult patients (as defined in the individual Cochrane systematic reviews) admitted to the ICU regardless of diagnosis, condition, or length of stay. We assumed that patients were adults unless otherwise specified. If the setting was unclear, we assumed that patients were ICU patients if they were treated with typical ICU interventions (e.g., invasive monitoring, mechanical ventilation, or vasopressors).

2.4. Interventions and comparators

We included all interventions and comparators used during stay in the ICU (including interventions that started prior to ICU admission and continued in the ICU) and classified interventions assessed in each review into three categories: drug interventions, management interventions, and medical device interventions. If a Cochrane systematic review assessed more than one intervention type, we classified each RCT into the appropriate categories.

2.5. Outcome measures

The primary outcome was the time trend in the annual proportion (based on year of publication) of RCTs with overall low risk of bias, defined as low risk of bias in all seven Cochrane bias domains.

Secondary outcomes were the time trend in the annual median sample sizes, and time trends in the annual proportion of trials with low, unclear, and high risk of bias in the individual Cochrane bias domains.

2.6. Search strategy

The Cochrane Database of Systematic Reviews (http://onlinelibrary.wiley.com/cochranelibrary/search) was independently searched by two authors (C.T.A. and A.G.) using the search string: "'intensive care'' OR ''ICU'' OR ''intensive therapy unit'' OR ''ITU'' OR ''critically ill'' OR ''critical care.'' The search was conducted on 15 September 2018, limited to title, abstract, and keywords and filtered to include reviews published from March 2011 and onwards corresponding to the most recent version of the Cochrane Handbook and the Cochrane Risk of Bias tool [2]. We refrained from searching other resources and did not establish contact with original RCT authors, as this is mandatory in Cochrane systematic reviews [2]. We updated the search on 5 February 2019.

2.7. Study selection

Potentially eligible Cochrane systematic reviews were assessed in full-text according to the criteria stated previously. Individual RCTs included in eligible Cochrane systematic reviews were assessed for inclusion based on data presented in the full Cochrane systematic review. This was performed independently and in duplicate by two authors (C.T.A. and A.G.) and disagreements were resolved through discussion, if necessary, with a third author (M.H.M.).

2.8. Data extraction and management

Two authors (C.T.A. and A.G.) performed duplicate and independent extraction of preaggregated data from the included Cochrane systematic reviews using predefined and pilot-tested electronic case report forms. We extracted data on predefined variables including review and RCT characteristics, risk of bias adjudications in the seven Cochrane domains, and sample sizes [17]. If an RCT was included in more than one Cochrane systematic review, or if risk of bias was rated separately for different outcomes (e.g., separate adjudications for subjective and objective outcomes), we used the most conservative (i.e., worst rated) bias adjudication for each bias domain. We defined sample size as the number of randomized patients in each RCT. If this was not specified in the Cochrane systematic review, we calculated the sample size as the sum of patients randomized to the intervention and control groups. All extracted data were electronically cross-referenced, and discrepancies were checked and resolved by consulting the original Cochrane systematic reviews (C.T.A. and A.G.) and if necessary by discussion with a third author (M.H.M.).

2.9. Risk of bias assessment

For each included RCT, we used the risk of bias adjudications (low, unclear, or high) performed by the Cochrane systematic review authors in each of the seven Cochrane bias domains stated previously. We did not use adjudications for any differently defined domains. Overall risk of bias was adjudicated as *low* in trials with low risk of bias in all seven Cochrane bias domains and as *high* in trials with unclear or high risk of bias in one or more domains.

2.10. Missing data

As we planned to use preaggregated data from Cochrane systematic reviews, we did not consult original RCT publications or contact original RCT authors for additional information as this would already have been done by the Cochrane systematic review authors where relevant. If a Cochrane systematic review included an RCT but did not specify either risk of bias assessments or sample size for said RCT, the RCT was excluded from these analyses.

2.11. Statistical analysis

2.11.1. Primary analysis and measures of effect

A detailed statistical analysis plan is outlined in the prepublished protocol [17]. In brief, we present the annual proportion of bias ratings as percentages, the annual sample sizes as medians with interquartile ranges and mean sample sizes with 95% confidence intervals (CIs). We evaluated time trends in risk of bias and sample sizes using run charts. A run chart is a graphical display of data; the x-axis is the time scale, the y-axis is the quality indicator measured (here, proportion of risk of bias ratings, median or mean sample sizes), and a centerline represents the median value of the quality indicator. If a process investigated is only affected by chance, then the data points fall randomly either above or below the median. However, if there is a consistent increase or decrease, the data points will scatter around the median in a non-random manner, which can be detected by run charts (i.e., statistically significant increase or decrease of the process evaluated as opposed to random variation only) [19]. For each run chart, we calculated the median, the number of useful observations (data points different from the median), the longest run (consecutive data points either above or below the median), the number of crossings of the median, and the prediction limits as specified by Anhøj [19,20]. Non-random variation (i.e., statistically significant variation) exists if the longest run is longer than the upper prediction limit or if the number of crossings is lower than the lower prediction limit [19].

For the primary analyses of all outcomes, we excluded years with less than five RCTs to avoid disproportionate large influence of individual RCTs.

2.11.2. Sensitivity analyses

We conducted two preplanned sensitivity analyses: (1) analyses in which all years were included irrespective of

the annual number of RCTs published and (2) analyses in each of the three intervention categories: drug, management, and medical device interventions.

2.11.3. Post hoc analyses

We conducted post hoc analyses of the annual mean sample sizes (with 95% CIs of the mean) to further explore the development of sample sizes over time. Furthermore, during the review process, two additional plots were produced; annual numbers of RCTs with overall low and high risk of bias (Fig 9.1, ESM) and annual numbers of ''small'' (sample size equal to or lower than the overall median sample size) and ''large'' RCTs (sample size higher than the overall median sample size) (Fig. 9.2, ESM)

2.11.4. Statistical analysis, data, and code

All analyses were conducted using R version 3.5.3 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) with the Tidyverse packages (www.tidyverse.org). The full dataset and the annotated analysis code are available at the Mendeley data repository (http://dx.doi.org/10.17632/mb7wt2wghs.1), and a data dictionary is available in the ESM to ensure full transparency.

3. Results

An overview of the search results and study selection process is presented in Fig. 1. In total, we included 604 RCTs from 53 Cochrane systematic reviews (Table S3, ESM) ([21–73]). Two RCTs (0.3%) had no risk of bias adjudications available and two RCTs (0.3%) had no sample size specified why they were excluded from the analyses. An overview of the number of RCTs included in each analysis is presented in Table S4 in the ESM.

3.1. Trial characteristics

The RCTs were published between 1977 and 2018. The median (interquartile range) sample size was 82.5 (42–224) patients. We included 336 (55.6%) RCTs investigating drug interventions, 148 (24.5%) investigating management interventions, and 120 (19.9%) investigating medical device interventions.

3.2. Summarized risk of bias

In total, 6.8% of the RCTs had overall low risk of bias. The distribution of risk of bias in the individual Cochrane bias domains is summarized in Fig. 2. More than half of the included RCTs had low risk of bias in ''random

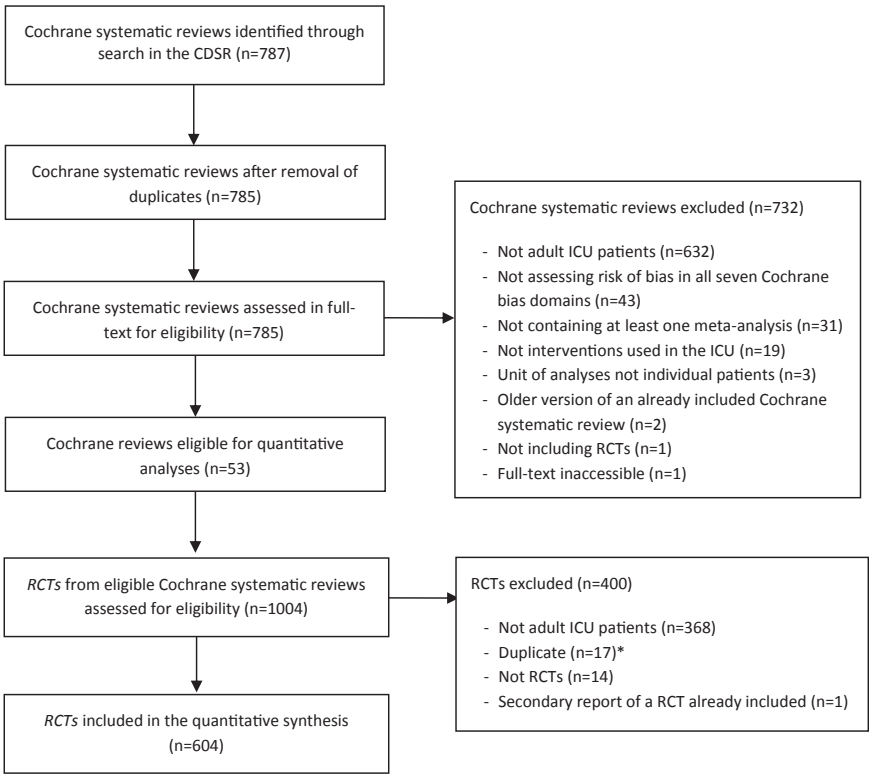

Fig. 1. Adapted PRISMA flowchart of the study selection.
Overview of the study selection process.
* RCTs included in multiple Cochrane systematic reviews were only included once, with the worst risk of bias ratings and the largest sample sizes used if discrepancies were present (see main text for details).
CDSR, Cochrane Database of Systematic Reviews; ICU, intensive care unit; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis; RCT, randomized clinical trial.

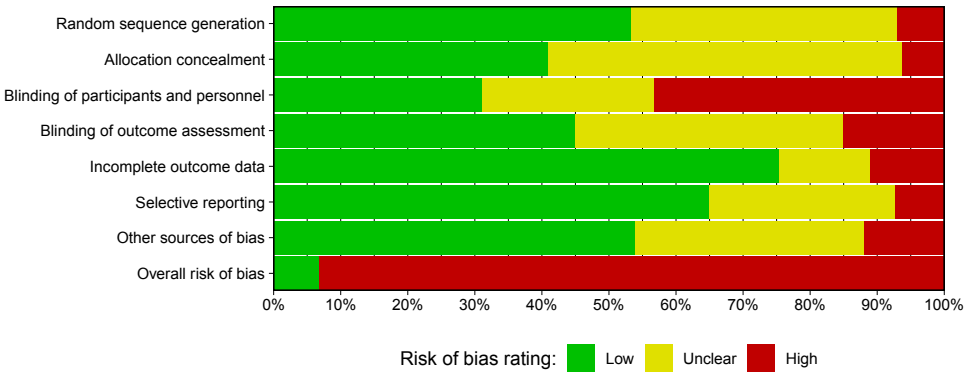

Fig. 2. Summarized risk of bias in all included randomized clinical trials.
Summarized distribution of risk of bias in 602 randomized clinical trials (RCTs) within each of the seven Cochrane bias domains. "Overall risk of bias" represents the proportion of RCTs with low risk of bias in all seven bias domains.

sequence generation" (53.3%), "incomplete outcome data" (75.4%), "selective reporting" (65.0%), and "other sources of bias" (54.0%). However, less than half of the RCTs had low risk of bias in "allocation concealment" (41.0%), "blinding of participants and personnel" (31.1%), and "blinding of outcome assessment" (45.0%).

3.3. Overall low risk of bias

We observed only random variation, suggesting lack of consistent increase in the annual proportion of RCTs with overall low risk of bias over time (Fig. 3).

3.4. Sample size

We observed only random variation in the annual median sample sizes suggesting lack of consistent increase over time (Fig. 4).

3.5. Individual risk of bias domains

We observed non-random variation over time in the bias domain "allocation concealment" with a larger annual proportion of RCTs with low risk of bias and a smaller annual proportion with unclear risk of bias (Fig. S6.2, ESM). In the domains "blinding of outcome assessment" and "other sources of bias," we observed non-random variation with a slightly increased annual proportion of RCTs at high and unclear risk of bias, respectively (Fig. S6.4 and S6.7 respectively, ESM). None of the remaining risk of bias domains showed non-random variation, suggesting lack of development over time (Fig. S6.1, S6.3, S6.5, and S6.6, ESM).

3.6. Sensitivity analyses

3.6.1. Sensitivity analysis 1: intervention categories

The sensitivity analyses based on intervention categories (drug, management, and medical device

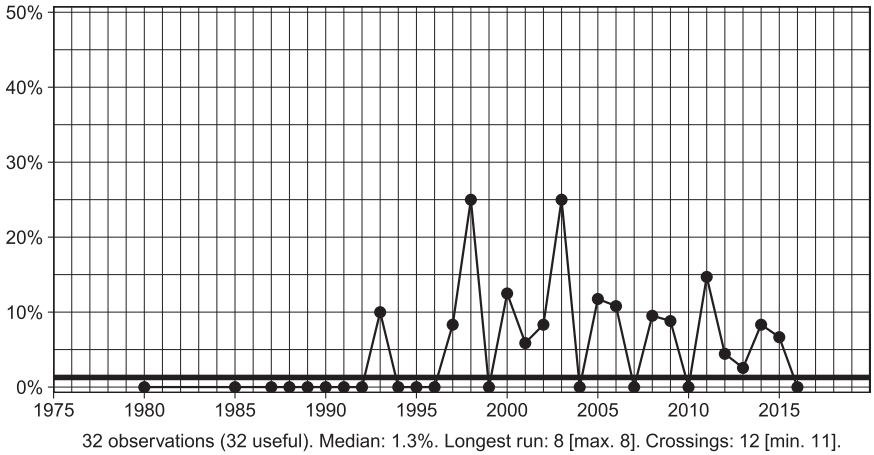

Fig. 3. Overall low risk of bias.
The annual proportion of low risk of bias trials in 578 RCTs.
Years without dots (10) represent years with less than five published RCTs (excluded from this analysis).
The predicted upper limit for longest run and the predicted lower limit for number of crossings are shown in the brackets.
RCT, randomized clinical trial.

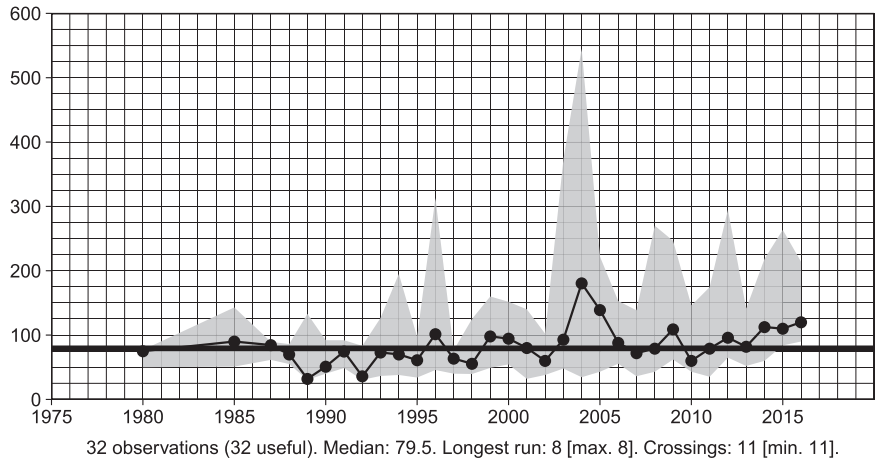

Fig. 4. Annual median sample sizes.
The annual median sample sizes in 578 RCTs.
Gray shaded area: annual interquartile ranges (IQRs).
Years without dots (10) represent years with less than five published RCTs (excluded from this analysis).
The predicted upper limit for longest run and the predicted lower limit for number of crossings are shown in the brackets.
RCT, randomized clinical trial.

interventions) largely confirmed our primary analyses (Fig. S7.1.1 - 7.3.10, ESM). However, regarding the individual bias domains, we only observed non-random variation in the annual proportion of drug RCTs with high and unclear risk of bias in the bias domains ''allocation concealment'' and ''blinding of participants and personnel,'' respectively (Fig. S7.1.5 and S7.1.6, ESM). We did not observe any signs of non-random variation in the annual proportion of RCTs with low, unclear, and high risk of bias within any other domains, regardless of intervention category (Fig. S7.1.4-5 and S7.2.4 – 7.3.10, ESM).

3.6.2. Sensitivity analyses 2: all years included

The sensitivity analyses in which we included all years irrespective of the number of trials also confirmed most findings from the primary analyses (Fig. S8.4.1-10, ESM). Contrary to the primary analyses, however, we observed non-random variation in the annual proportion of RCTs with overall low risk of bias, but in this analysis, the median was 0% making crossings and interruptions of runs impossible, which hampers the interpretation (Fig. S8.4.1, ESM). Regarding the individual bias domains, we also observed nonrandom variation in the domain ''random sequence generation'' with an increased annual

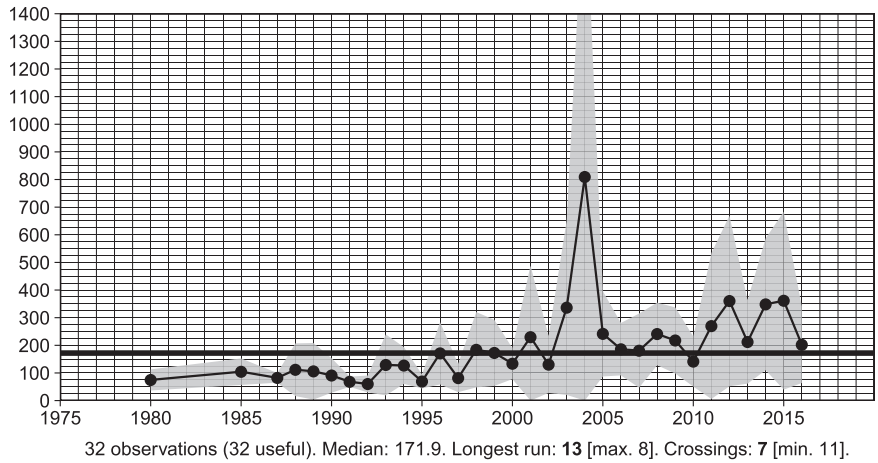

Fig. 5. Post hoc analysis; annual mean sample sizes.
The annual mean sample sizes in 578 RCTs.
Gray shaded area: annual 95% confidence intervals (CIs) of the mean.
Years without dots (10) represent years with less than five published RCTs (excluded from this analysis).
The predicted upper limit for longest run and the predicted lower limit for number of crossings are shown in the brackets.
Numbers in bold indicate nonrandom variation.
RCT, randomized clinical trial.

proportion of RCTs with low risk of bias adjudications (Fig. S8.4.4, ESM) and in "other sources of bias," with increased annual proportion with unclear and high risk of bias over time (Fig. S8.4.10, ESM).

3.7. Post hoc analyses

3.7.1. Post hoc analysis 1: mean sample sizes

The analyses showed nonrandom variation with increasing annual mean sample sizes over time (Fig. 5), which was confirmed for drug RCTs (Fig. S7.1.3, ESM) but not for management or medical device RCTs (Fig. S7.2.3 and S7.3.3, respectively, ESM). Including all years (sensitivity analysis 2), mean sample sizes also increased over time (Fig. S7.4.3).

3.7.2. Post hoc analysis 2: annual numbers of RCTs according to overall risk of bias

From 1997 and onward, the absolute number of low risk of bias RCTs have almost consistently been around 1−5, whereas the absolute number of high risk of bias RCTs have increased (Fig. 9.1, ESM)

3.7.3. Post hoc analysis 3: annual numbers of small and large RCTs

The absolute numbers of small and large RCTs have both increased equally over time until 2012. From 2012 and onward, large RCTs equal or outnumber small RCTs (Fig 9.2, ESM).

4. Discussion

4.1. Principal findings

In this metaepidemiological study of 604 RCTs from 53 Cochrane systematic reviews, we observed that only 6.8% of the RCTs had overall low risk of bias. We observed no improvements over time in the annual proportion of overall low risk of bias RCTs and no increase in the annual median sample sizes. We found evidence of improved risk of bias ratings in the bias domain "allocation concealment" over time.

4.2. Strengths and weaknesses

The strengths of our study include the rigorous methodology used, including a prepublished protocol and statistical analyses plan [17]; duplicate and independent literature search, study selection process and data extraction, and public availability of the final dataset and analysis code (http://dx.doi.org/10.17632/mb7wt2wghs.1), ensuring full transparency [74,75]. In addition, we followed the recommendations of the Cochrane Collaboration [2] where applicable, and we prepared the manuscript according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement (checklist is available in the ESM) [18].

The study also holds important limitations. First, our sample of RCTs is a convenience sample because far from all RCTs are included in Cochrane systematic reviews. However, as Cochrane systematic reviews perform extensive, regularly updated systematic searches, we are convinced that most RCTs of the included interventions are represented in our sample of RCTs. However, some of the analyses (especially the sensitivity analyses restricted to management and medical device interventions) contained few RCTs/year and are most likely underpowered. The results of these analyses should be interpreted with caution. Second, we used preaggregated data and did not consult original trial reports. Although Cochrane systematic reviews generally are regarded as high-quality systematic reviews [76], inconsistencies in the risk of bias adjudications and incoherence with the Cochrane handbook are still present and are an inherent limitation of this study [77−79]. Third, although run charts represent a simple and easy way to detect non-random variation over time, the direction of the change (increase or decline) is dependent on visual examination and is not always clear. Fourth, no method to account for multiple testing using run charts exists and due to the number of analyses performed, some findings may merely represent chance findings. Finally, changes in risk of bias is not necessarily an indicator for improved methodological quality, as well-conducted RCTs, especially older RCTs, may have been reported poorly and hence receive unclear risk of bias adjudications [80]. Improvements within any domain may therefore reflect better reporting rather than improvements in design, conduct, or analysis of the RCTs.

4.3. Interpretation

4.3.1. Overall low risk of bias

In total, 6.8% of the included RCTs had overall low risk of bias, and we observed no improvement in the annual proportion of RCTs with overall low risk of bias. This finding was confirmed in the sensitivity analysis of drug, management, and medical device intervention RCTs. Although we observed signs of improvement in the sensitivity analysis in which we included all years, this finding is fragile; first, the low number of RCTs with overall low risk of bias resulted in a median of 0%, effectively making crossings and interruptions of runs impossible, and second because years with few trials may influence the result disproportionately. Taken together, our results suggest that any improvement in the annual proportion of low risk of bias RCTs is probably small if present at all.

4.3.2. Sample size

Contradictive to our a priori hypothesis, we did not observe any evidence of an increase in the annual median sample sizes over time in any of our analyses. However, we found consistent indications that the mean sample sizes have increased over time. Together, these results suggest

that although most RCTs include a low number of patients, there seems to be an increase in the size and number of the largest RCTs, especially in recent years.

4.3.3. Risk of bias domains

We found consistent evidence of improved risk of bias ratings in the bias domain ''allocation concealment'' over time. As the annual proportion of RCTs with high risk of bias within this domain seemed stable, the finding suggests improvement in the reporting of the RCTs rather than improvement in the actual methodology used. In the sensitivity analysis including all years, we also observed nonrandom variation in ''random sequence generation'' with an increase in the annual proportion of RCTs with low risk of bias over time. However, we observed no reciprocal changes in RCTs with unclear or high risk of bias in that domain, why this finding should be interpreted with cation.

4.4. Relations to other meta-epidemiological studies and implications

Generally, risk of bias in individual bias domains has improved over time [12,13]. Recent large meta-epidemiological studies of all RCTs included in Cochrane reviews regardless of medical subspecialty and intervention found evidence of improvements within ''random sequence generation,'' ''allocation concealment,'' ''incomplete outcome data,'' and ''selective outcome reporting'' [12,13]. Within the ICU setting, we found evidence of improvement only in ''allocation concealment.'' Direct comparisons are difficult, as the studies differ considerably with respect to the time periods included and the statistical methods used. Furthermore, these studies are considerably larger than the present study and differences in statistical power may partly explain the differences. Worryingly, a study evaluating risk of bias adjudications for ''allocation concealment'' in Cochrane systematic reviews found that 29% of risk of bias adjudications within this specific domain were discrepant from the Cochrane Handbook, and most of the discrepancies were present when risk of bias was adjudicated as low [79]. Hence, there is risk that the improvement seen in ''allocation concealment'' in our study may be due to incorrect risk of bias adjudications in the included Cochrane systematic reviews. Another recent study revealed that adjudications for ''selective reporting'' in Cochrane systematic reviews did not comply with the Cochrane Handbook in most reviews [81].

No former meta-epidemiological study has assessed time trends in risk of bias and sample sizes in RCTs within the ICU setting. In contrast to former metaepidemiological studies, we evaluated time trends in the annual proportion of overall low risk of bias RCTs, as these represent the most trustworthy assessment of benefits and harms of healthcare interventions and therefore should be prioritized in systematic reviews and contribute the most to clinical practice recommendations [82,83]. Our findings raise concern that the general methodological quality of RCTs within the ICU setting is poor and has not improved substantially over time. In previous work, we found no firm evidence that lack of blinding affected mortality estimates in RCTs of ICU interventions, but we did observe that RCTs with higher risk of bias produced significantly higher effect estimates on all-cause mortality at the longest follow-up [84]. Together, our findings indicate that much of the current knowledge about interventions in the ICU is based on evidence from high risk of bias RCTs and that the validity of the evidence behind many recommendations in clinical practice guidelines may be questioned. In agreement, Zhang et al. recently found that less than 10% of recommendations in critical care guidelines are based on high-quality evidence [85]. Therefore, clinicians, guideline committee members, and policymakers must be cautious not to recommend or implement interventions that may be futile or even harmful and that may not be cost-effective. In addition, substantial efforts are necessary to increase the methodological quality of RCTs conducted in the ICU setting.

5. Conclusion

In this meta-epidemiological study of 604 RCTs from 53 Cochrane systematic reviews in adult ICU patients, we observed that only 6.8% of the RCTs had overall low risk of bias, and we found no evidence of improvement in the annual proportion of RCTs with overall low risk of bias or an increase in the median sample sizes over time. We observed evidence of improved risk of bias ratings in the domain ''allocation concealment'' over time.

CRediT authorship contribution statement

Carl Thomas Anthon: Conceptualization, Investigation, Methodology, Project administration, Data curation, Validation, Visualization, Writing - original draft, Writing - review & editing. **Anders Granholm:** Conceptualization, Formal analysis, Investigation, Methodology, Data curation, Validation, Visualization, Writing - review & editing. **Anders Perner:** Conceptualization, Methodology, Writing - review & editing. **Jon Henrik Laake:** Conceptualization, Methodology, Writing - review & editing. **Morten Hylander Møller:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.05.021.

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