Original Article

# Evidence for compromised data integrity in studies of liberal peri-operative inspired oxygen

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## Summary

In 2016 the World Health Organization recommended intra-operative ventilation with 80% inspired oxygen to reduce surgical site infection rates, based upon a meta-analysis of 15 randomised controlled trials, of which two were by Mario Schietroma's research group. Five trials by this group have been retracted for duplication, plagiarism, statistical error and lack of ethical approval. We analysed 40 papers by this group: 24 randomised controlled trials (5064 participants) and 16 observational studies (1847 patients). There was evidence that data integrity was compromised in 38 out of the 40 analysed papers. The distribution of baseline characteristics in randomised controlled trials was unlikely, $p = 1.5 \times 10^{-8}$: continuous variables within trials were heterogeneous, $p = 1.9 \times 10^{-9}$, and categorical variables were homogeneous, $p = 8.5 \times 10^{-20}$. Effects of interventions varied less than expected between studies: for categorical variables, for instance postoperative wound infection, $p < 1 \times 10^{-7}$, and for continuous variables, for instance HLA-DR concentration, $p = 0.00001$. Of 184 calculable p values, for baseline variables or results, 179 (98%) were incorrect, ranging from three orders of magnitude too small to 10 orders of magnitude too large. Twenty-one graphs occurred 81 times in 23 out of 40 papers. Liberal peri-operative oxygen did not reduce surgical site infection in a meta-analysis of 20 trials that excluded seven trials by Mario Schietroma and colleagues (odds ratio (95%CI) 0.89 (0.73-1.08); $p = 0.23$). An update by the World Health Organization has now excluded trials of liberal oxygen by Schietroma's group, four of which have not been retracted. We conclude that Mario Schietroma's work should not inform practice until investigated.

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## Introduction

Five papers authored by Schietroma et al. have been retracted [1–5]. Four of these papers were randomised controlled trials of liberal peri-operative oxygen (80% vs. 30%) [1, 3–5].

In 2016, the World Health Organization made a strong recommendation that *"adult patients undergoing general anaesthesia with endotracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen intra-operatively and, if feasible, in the immediate postoperative period for 2–6 h to reduce the risk of surgical site infection."* [6]

The merits of liberal peri-operative inspired oxygen have been disputed [7, 8]. Liberal oxygen administration increases mortality in acute illness [9]. Liberal peri-operative oxygen might also increase mortality or other harm, even if there were reliable evidence that it decreased surgical site

infection. Liberal peri-operative inspired oxygen did not reduce surgical site infection when three trials by Schietroma et al. were excluded in a recent meta-analysis [10].

We were concerned that the WHO recommendation to use 80% inspired peri-operative oxygen may harm patients and that the specific reduction of surgical site infection depended upon false evidence. The WHO has recently updated their guideline, and excluded trials by Schietroma et al. We remain concerned that data in unretracted papers by Dr Schietroma may be sufficiently compromised to warrant retraction.

## Methods

We searched Medline, Embase and CENTRAL databases for papers with Dr Mario Schietroma as an author (to November 2018). We included randomised controlled trials and observational series published in English. We searched trial websites for registration. We also searched the same databases for trials of peri-operative liberal supplemental oxygen vs. standard supplemental oxygen (80% vs. 30%, respectively). We excluded trials of other oxygen concentrations. We excluded case reports, letters, economic analyses and reviews. Details of the systematic review and search strategy are available in the supplementary material (see Supporting Information Appendix S1).

We extracted the numbers of participants and their categorical and continuous characteristics. We calculated the probabilities of distributions of baseline characteristics for participants in randomised controlled trials [11]. We derived p values, when not reported, for relative risks (RR) (95%CI) and odds ratios (OR) (95%CI) [12]. We checked the calculation of p values presented in any paper, whether for baseline characteristics or results, using the test stated in the methods of each paper. We estimated standard deviation (SD) as range/4 when necessary and estimated the p value with independent t-tests when the Mann–Whitney U-test had been used. We categorised the comparison of p values by: whether the p value was reported precisely or at a threshold (for instance "< 0.05") and whether we could generate a precise p value using mean (SD), rates, OR (95%CI) or RR (95%CI), using the same test as the paper's authors. We categorised a p value as incorrect if we calculated a different p value to the same precision or if we calculated a p value on the other side of the threshold. We calculated the probabilities for the variation in baseline characteristics within and between papers. We used simulation to calculate the probability for the variation in results between papers, separately for different outcomes [13]. We used random effects models with the restricted maximum-likelihood estimator or the Mantel–Haenszel method to pool trial results. We compared figures for duplication. We analysed the frequency of odd and even terminal digits for reported precise p values, with their expected frequencies determined by the number of numerals to the right of the last zero and Newcomb–Benford's law [14].

The meta-analysis of liberal oxygen trials was done using Cochrane Collaboration software (RevMan v5.3; The Nordic Cochrane Centre, Copenhagen, Denmark), to calculate a pooled OR using a random effects model. We used R (function, "package") for all other analyses: p values from mean (SD) for two groups tsum.test ("BSDA"); p values from mean (SD) for three or more groups (anovaSummarized, "CarletonStats"); p values from rates, with and without Yates' continuity correction (fisher.test or chisq.test, "stats"); uniform distribution (ad.test, "goftest" and ks.test, "stats"); and meta-analyses (escalc and rma, "metafor") [15].

## Results

We identified 40 papers that fulfilled our criteria [1–5, 16–50]: 24 randomised controlled trials with 5064 participants [1–5, 20, 23–26, 28–32, 34, 36, 38, 41–43, 47–49]; and 16 observational studies with 1847 patients [16–19, 21, 22, 27, 33, 35, 37, 39, 40, 44–46, 50]. Surgical populations were studied from 1993 to 2016, with an annual maximum of 20 randomised controlled trials recruiting approximately 649 participants in 2011 (a year when seven observational studies recorded outcomes in approximately 136 participants in a single hospital (see Supporting Information Data S1)). Mario Schietroma was the first author in 29 papers [1–5, 17–19, 21–24, 26, 28, 31, 36–38, 41–50].

There was evidence that data integrity was compromised in 38 out of 40 analysed papers (Table 1 and Supporting Information Appendix S1). The distributions of baseline characteristics in randomised controlled trials were inconsistent with the expected distributions, $p = 2.85 \times 10^{-6}$ (Anderson–Darling test) and $p = 1.56 \times 10^{-11}$ (Kolmogorov–Smirnov test) (Fig. 1). The distribution of categorical variables was homogeneous between groups within and between studies (Table 1 and Fig. 2). The distribution of continuous variables was sometimes heterogeneous between groups within studies, but the distribution varied little between studies (Table 1 and Fig. 3). There was a similar pattern of little variation in differences for outcomes between papers, both randomised controlled trials and observational studies. The probabilities

**Table 1** Characteristics of 40 identified papers, authored by Mario Schietroma, five of which (red) have been retracted. Values are number or p value. Values in brackets were the number of p values calculated with standard deviation estimated as range/4 or the number of identical figures in papers lower in the list. The papers without baseline p values were observational studies.

| | Baseline p values | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Total | Continuous | Categorical | Incorrect p values | Identical means (SD or range) or rates | Similar means (SD or range) or rates | Identical figures | Similar figures | Incorrect RR or OR | Incorrect sums | Plagiarised |
| [1] | 0.16 | 0.008 | 0.001 | 7 (1) | – | 7 | – | – | 1 | – | 1 |
| [2] | 0.077 | 0.014 | 0.0013 | 6 (3) | 2 | 10 | – | – | – | – | – |
| [3] | 0.062 | 0.64 | 0.0019 | 6 (1) | 3 | 9 | 4 | – | – | – | – |
| [4] | 0.0066 | 0.13 | 0.00001 | 10 (2) | – | 28 | – | – | – | 2 | – |
| [5] | 0.44 | 0.005 | 0.0006 | 9 (8) | – | 8 | 4 | – | – | – | – |
| [16] | – | – | – | (2) | 2 | – | (2) | – | – | – | – |
| [17] | – | – | – | – | 3 | – | 2 | – | – | – | – |
| [18] | – | – | – | (1) | 6 | – | (2) | – | – | – | – |
| [19] | – | – | – | – | 3 | – | 1 (2) | – | – | – | – |
| [20] | 0.43 | 0.22 | 0.57 | 2[a] | – | – | – | – | – | – | – |
| [21] | – | – | – | – | 2 | – | (2) | – | – | – | – |
| [22] | – | – | – | 2 | 1 | 2 | 3 | – | – | – | – |
| [23] | 0.18 | 0.51 | 0.01 | (1) | 4 | – | – | – | – | – | – |
| [24] | 0.89 | 0.38 | 0.43 | 3 (1) | 2 | – | 2 (3) | – | – | – | – |
| [25] | 0.25 | 0.33 | 0.06 | 7 | – | 2 | – | – | – | 1 | – |
| [26] | 0.30 | 0.19 | 0.005 | 6 (2) | 22 | 3 | 2 (5) | – | – | 1 | – |
| [27] | – | – | – | (2) | 12 | – | 3 | – | – | 1 | – |
| [28] | 0.0032 | 0.0033 | 0.00001 | 2 (5) | – | – | – | – | 1 | 2 | – |
| [29] | 0.035 | 0.83 | 0.0025 | 5 (1) | – | – | – | – | – | – | – |
| [30] | 0.0053 | 0.60 | 0.0013 | – | – | 10 | (7) | – | – | 1 | – |
| [31] | 0.062 | 0.68 | 0.047 | – | – | – | 4 (1) | – | – | – | – |
| [32] | 0.018 | 0.87 | 0.0033 | 10 (2) | 2 | 2 | 4 | – | – | 1 | – |
| [33] | – | – | – | – | – | – | – | – | – | – | – |
| [34] | 0.17 | 0.83 | 0.064 | 1 | 22 | 2 | 6 | – | – | – | – |
| [35] | – | – | – | 2 | – | – | – | – | – | – | – |
| [36] | 0.017 | 0.10 | 0.00005 | 1 | 2 | 2 | 3 | – | – | – | – |
| [37] | – | – | – | 4 | – | – | – | 2 | – | – | – |
| [38] | 0.09 | 0.018 | 0.0002 | 4 (6) | – | 24 | – | – | – | 1 | – |
| [39] | – | – | – | 15 | – | – | – | – | – | – | – |
| [40] | – | – | – | 3 | – | – | – | – | – | – | – |
| [41] | 0.12 | 0.55 | 0.09 | – | – | 6 | 5 | – | – | – | – |
| [42] | 0.031 | 0.70 | 0.024 | – | – | 5 | 4 | – | – | – | – |
| [43] | 0.044 | 0.27 | 0.0003 | 5 (2) | 2 | 18 | – | – | – | – | – |
| [44] | – | – | – | 23 (7) | – | – | – | – | – | – | – |
| [45] | – | – | – | 32 (30) | – | 24 | 1 | – | 12 | – | – |
| [46] | – | – | – | 28 (26) | – | 24 | 1 | – | 12 | – | – |
| [47] | 0.10 | 0.00002 | 0.020 | 2 (1) | – | – | 4 | – | – | – | – |
| [48] | 0.60 | 0.0084 | 0.006 | 17 | – | – | – | – | – | – | – |
| [49] | 0.80 | 0.040 | 0.055 | 4 (1) | – | 6 | 3 | 1 | – | – | – |
| [50] | – | – | – | 23 (4) | – | – | – | – | – | – | – |
| Total | $1.5 \times 10^{-8}$ | $1.9 \times 10^{-9}$ | $8.5 \times 10^{-20}$ | 239 (109) | 90 | 192 | 80 | 3 | 26 | 10 | 1 |

RR, relative risk; OR, odds ratio.
[a]Transposition of two correctly calculated p values.

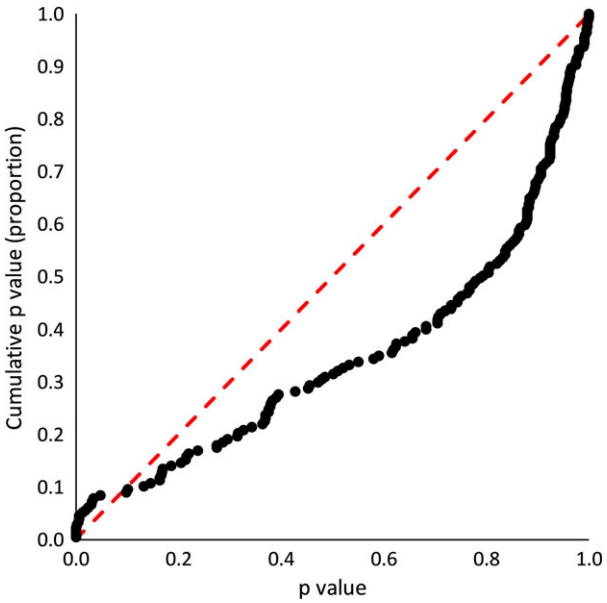


**Figure 1** The cumulative distribution of 210 p values calculated for baseline variables in 24 randomised controlled trials with Mario Schietroma as an author. The observed cumulative distribution (black circles) is inconsistent with the expected distribution (dashed red line), $p = 2.86 \times 10^{-6}$.

for variation between studies for some categorical outcomes were: anastomotic leak, p = 0.000006; ASEPSIS score < 19, p = 0.012; and wound infection, $p < 1 \times 10^{-7}$ (see Supporting Information Figures S1–S6). Notably, relative rates of wound infection, pivotal for the WHO guideline, were invariant even when the experimental intervention was not liberal inspired oxygen (Fig. 4). Similarly, there was little variation in the effects of different interventions on continuous outcomes, with low probabilities for: time to ambulate (p = 0.030); plasma elastase concentrations (p = 0.044, p = 0.00091 and p = 0.00067 for the first, third and fourth postoperative measurements, respectively); and human leukocyte antigen-DR expression (HLA-DR) p = 0.00001 for final postoperative measurement); (see also Supporting Information Figures S7–S16).

Out of 825 reported p values, 344 (42%) were incorrect, including 179/184 (97%) incorrect p values reported exactly ('=' rather than '>'or '<') (Fig. 5 and Supporting Information Data S1 and Fig. S11). For instance, in one paper the mean (SD) initial postoperative pain scores were 5.7 (1.26) and 4.38 (1.38) in 108 and 107 participants, respectively, for which $p = 5.07 \times 10^{-12}$, 10 orders of magnitude smaller than the reported p = 0.042 [48]. In another paper, five categories of hiatus hernia (none/large type 1/large type 2/small type 1/small type 2) in three groups were: 1/0/2/0/40; 3/1/8/1/76; and 5/1/5/2/56, respectively, for which p = 0.835, 835 times larger than the reported p = 0.001 [44]. The terminal (right-hand) digit was even (0, 2, 4, 6 or 8) for 149/184 (81%) p values, reported to one digit (83), for two digits (91) or three digits (10); this rate was different to the expected rate of 83/184, $p = 3.0 \times 10^{-12}$ and different to an equal number of odd and even terminal digits, 92/184, $p = 1.1 \times 10^{-9}$.

Twenty-one graphs were used 81 times in 23 out of 40 papers (Table 2 and Supporitng Information Appendix S1). Relative risks, ORs and sums were incorrectly calculated 36 times (Table 1 and Supporting Information Appendix S1). Supplementary Information Data S1 details the numerical data analysed and the results.

We included 20 other randomised trials of liberal peri-operative inspired oxygen in 8357 participants [50–70]. Liberal inspired oxygen reduced the rate of postoperative wound infection if trials by Schietroma et al. were included (OR (95%CI) 0.77 (0.61–0.96); p = 0.02 (see also Supporting Information Figures S7–S17)). Pooled results without trials by Schietroma et al., both retracted [1, 4, 5] and not [28, 38, 43, 49], did not show an effect of liberal peri-operative inspired oxygen on wound infection (OR (95%CI) 0.89 (0.73–1.08); p = 0.23 (Fig. 6)).

## Discussion

We found extensive evidence to support an investigation into work by Mario Schietroma's group. The evidence challenges the veracity of much, if not all, of the published work from this group.

Our meta-analysis indicated that this group's trials of liberal inspired peri-operative oxygen to reduce surgical site infection were markedly different from the pooled results of all other published trials. In short, the Schietroma trials were more consistent in their results than one would expect, with each reporting more than a 50% reduction in outcome when using liberal inspired oxygen.

Should any of Schietroma's papers on liberal oxygen prove real we would question their ethics: despite reporting benefit from liberal oxygen, Schietroma and colleagues conducted further trials that assigned some participants to 30% oxygen. Each study claimed to have ethics committee approval from the University of L'Aquila, but this appears to be untrue [71, 72]. None of the trials had been pre-registered on a publicly available website.

Our updated meta-analysis provides similar information to that of others if the Schietroma trials are excluded in the analysis [9, 10]. The major strength of our investigation is that it is not only systematic (identifying

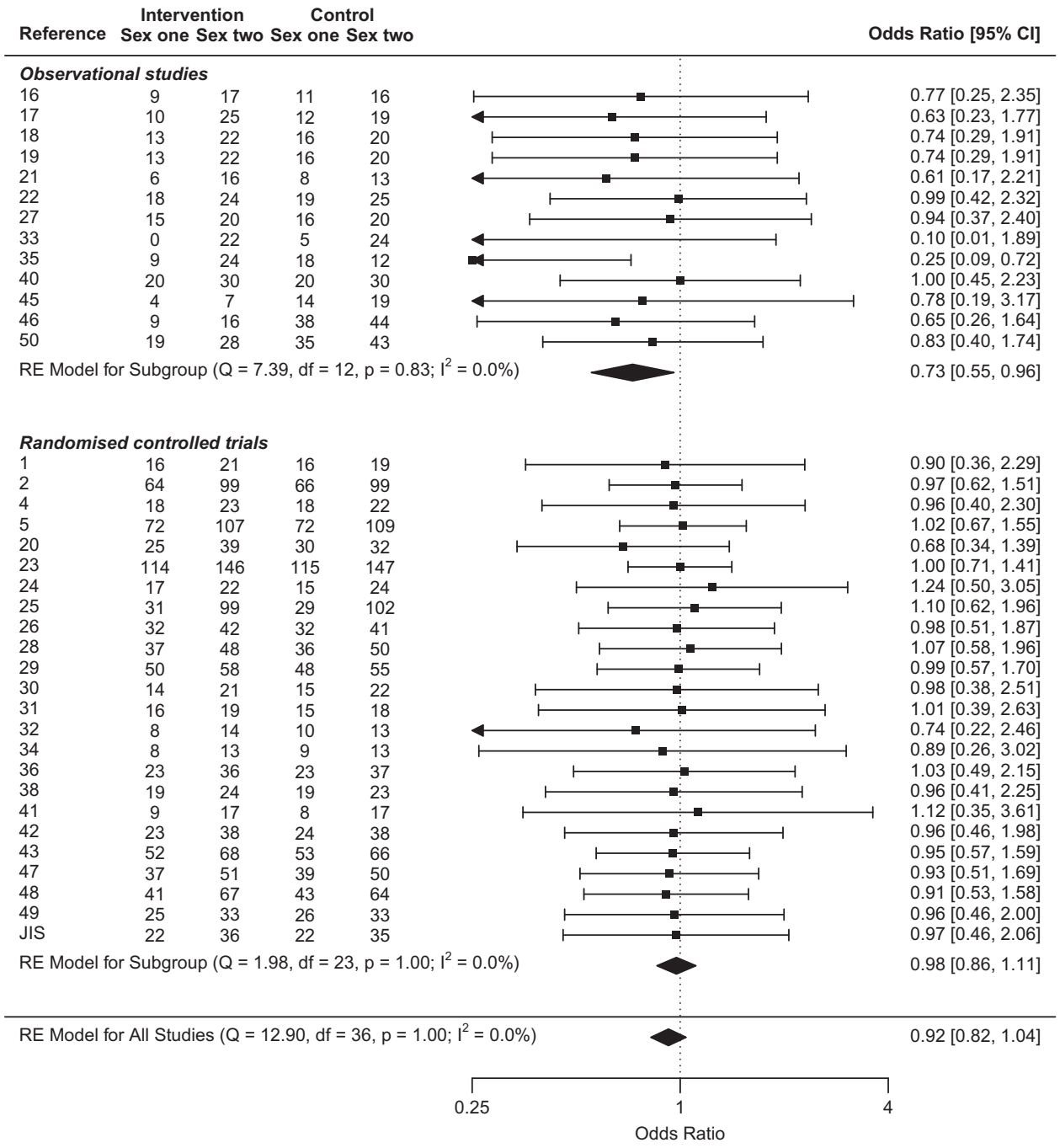


**Figure 2** A forest plot of the distribution of sex, as an example of a baseline categorical variable, in 13 observational studies and 24 randomised controlled trials with Mario Schietroma as an author. The probability that the distribution of sexes in randomised controlled trials was less varied than observed was $< 1 \times 10^{-6}$.

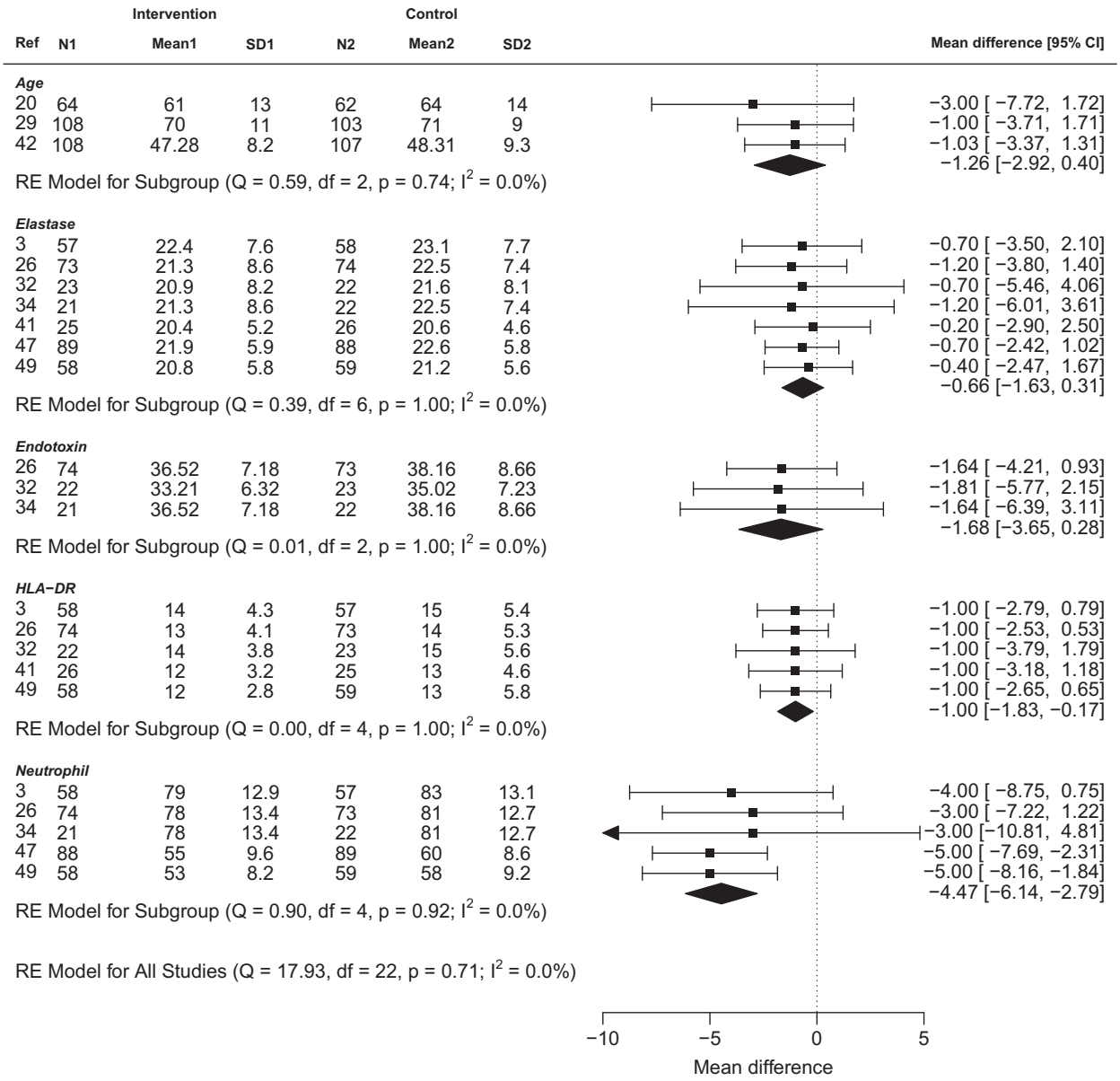


**Figure 3** A forest plot of mean (SD) for some baseline continuous variables from randomised controlled trials with Mario Schietroma as an author. The groups within trials were often imbalanced, particularly for neutrophil count, but their distribution was relatively homogeneous. For instance, the probabilities that the heterogeneous distribution of neutrophil count would be more extreme within separate trials were: p = 0.1684 [3]; p = 0.1018 [26]; p = 0.456 [34]; p = 0.00035 [47] and p = 0.0024 [49] (pooled p = $6.6 \times 10^{-5}$). Conversely, the probability that the distribution between trials would vary less is p = 0.020. HLA-DR, human leukocyte antigen-DR expression

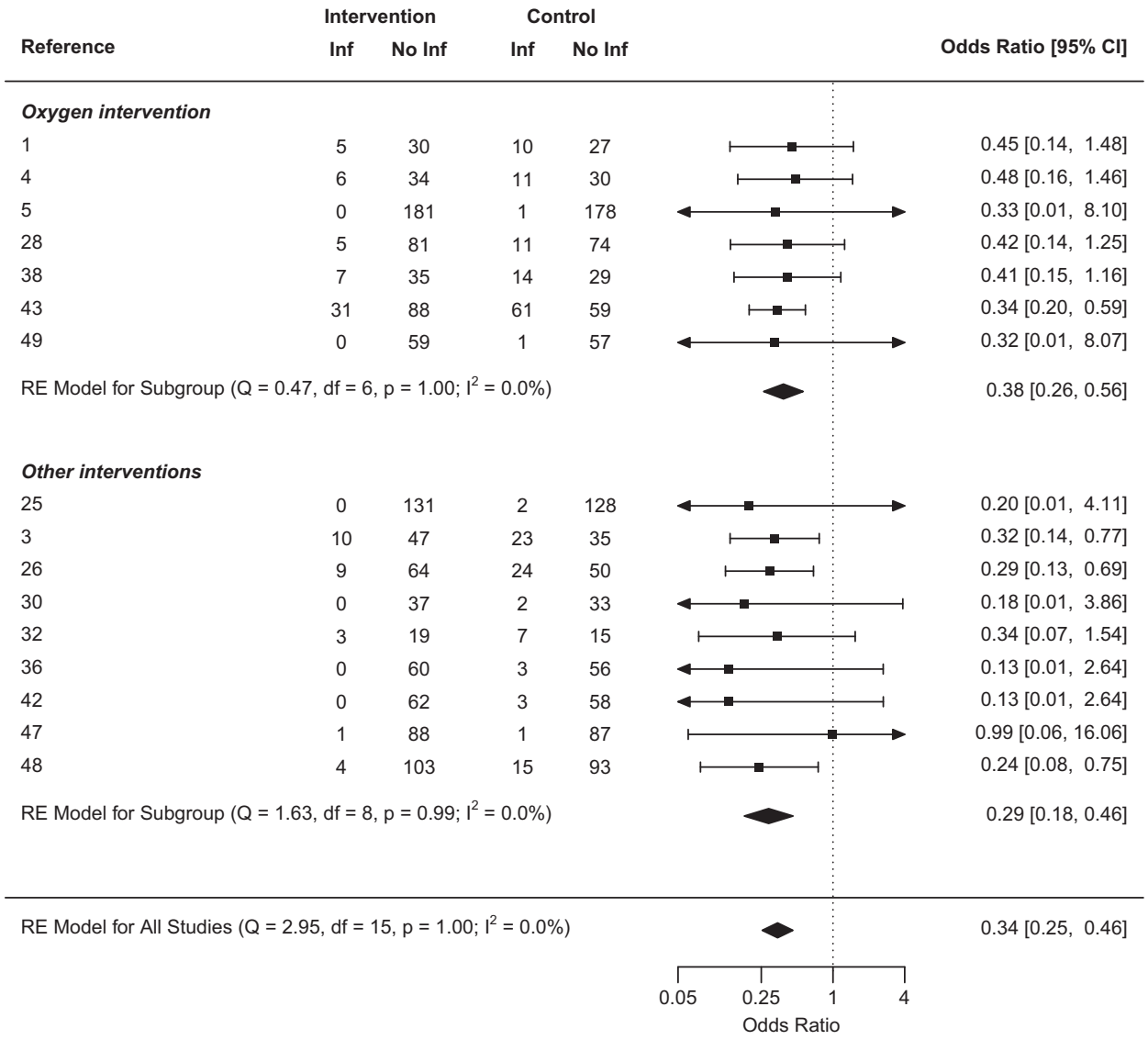


**Figure 4** A forest plot of wound infection rates in randomised controlled trials with Mario Schietroma as an author, categorised by whether the intervention was liberal oxygen, in seven trials, or something else, in nine trials. There was little variation in effect between studies across all interventions, $p < 1 \times 10^{-7}$. Inf, infection.

additional relevant trials) and based only on randomised trials but also fully checked the reported data in each of the relevant studies, resulting in the identification of numerous discrepancies. Limitations of our paper include those inherent in the Carlisle method and in meta-analysis. Our evaluation of disparate studies published in a wide variety of journals could be viewed as a limitation or a strength.

The conduct of studies published by Schietroma et al. should be critically examined by their employers. Until such investigations are concluded their data should not be used to inform practice and guidelines. Pooled data from all trials by authors other than Schietroma et al. do not support the use of liberal inspired oxygen to reduce surgical site infection rates.

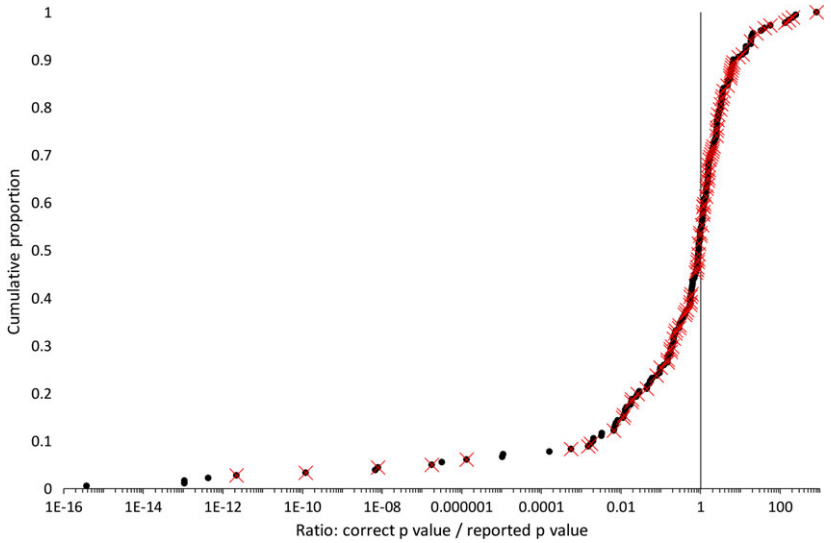


**Figure 5** The cumulative distribution of 184 p values, calculated for 40 papers with Mario Schietroma as an author, presented as their ratio to the reported precise p value (black circles). Five ratios equalled one, that is, 5/184 (3%) p values were correct. One of the 96 reported p values that we could also calculate precisely were correct (red crosses).

**Table 2** The replication of figures within 40 papers published by the same author group.

| First instance [reference] | Figure | Times used | Subsequent instances |
|---|---|---|---|
| [16] | Fig. 1 | 5 | [17] Fig. 1<br>[19] Fig. 1<br>[22] Fig. 1<br>[27] Fig. 1 |
| [16] | Fig. 2 | 7 | [17] Fig. 4<br>[26] Fig. 2<br>[31] Fig. 1<br>[32] Fig. 3<br>[34] Fig. 2<br>[41] Fig. 1 |
| [17] | Fig. 2 | 3 | [31] Fig. 2<br>[41] Fig. 2 |
| [18] | Fig. 9 and Fig. 10 (equivalent) | 7 | [2] Fig. 2b<br>[5] Fig. 5<br>[24] Fig. 5<br>[41] Fig. 4<br>[47] Fig. 3 |
| [19] | Fig. 3 | 7 | [3] Fig. 6<br>[22] Fig. 2<br>[26] Fig. 6<br>[31] Fig. 5<br>[34] Fig. 6<br>[41] Fig. 5 |
| [21] | Fig. 2 | 4 | [3] Fig. 7<br>[26] Fig. 7<br>[34] Fig. 7 |
| [22] | Fig. 3 | 6 | [3] Fig. 3<br>[26] Fig. 3<br>[27] Fig. 2<br>[32] Fig. 4<br>[34] Fig. 3 |
| [24] | Fig. 1 | 3 | [2] Fig. 1<br>[5] Fig. 2 (partial) |

(continued)

**Table 2** (*continued*)

| First instance [reference] | Figure | Times used | Subsequent instances |
|---|---|---|---|
| [24] | Fig. 2 | 3 | [2] Fig. 2<br>[5] Fig. 3 (partial) |
| [24] | Fig. 3 | 6 | [2] Fig. 1c<br>[5] Fig. 4<br>[27] Fig. 4<br>[47] Fig. 4<br>[49] Fig. 3 |
| [26] | Fig. 1 | 4 | [3] Fig. 1<br>[32] Fig. 2<br>[34] Fig. 1 |
| [26] | Fig. 5 | 6 | [3] Fig. 5<br>[31] Fig. 4<br>[32] Fig. 5b<br>[34] Fig. 5<br>[49] Fig. 2 |
| [30] | Fig. 1 | 2 | [42] Fig. 1 |
| [30] | Fig. 2 | 2 | [42] Fig. 2 |
| [30] | Fig. 3 | 4 | [42] Fig. 3a<br>[45] Fig. 1<br>[46] Fig. 1 |
| [30] | Fig. 4 | 2 | [42] Fig. 3b |
| [30] | Fig. 5 | 2 | [36] Fig. 1 |
| [30] | Fig. 6 | 2 | [36] Fig. 2 |
| [30] | Fig. 7 | 2 | [36] Fig. 3 |
| [47] | Fig. 1 | 2 | [49] Fig. 5 |
| [47] | Fig. 2 | 2 | [49] Fig. 7 |

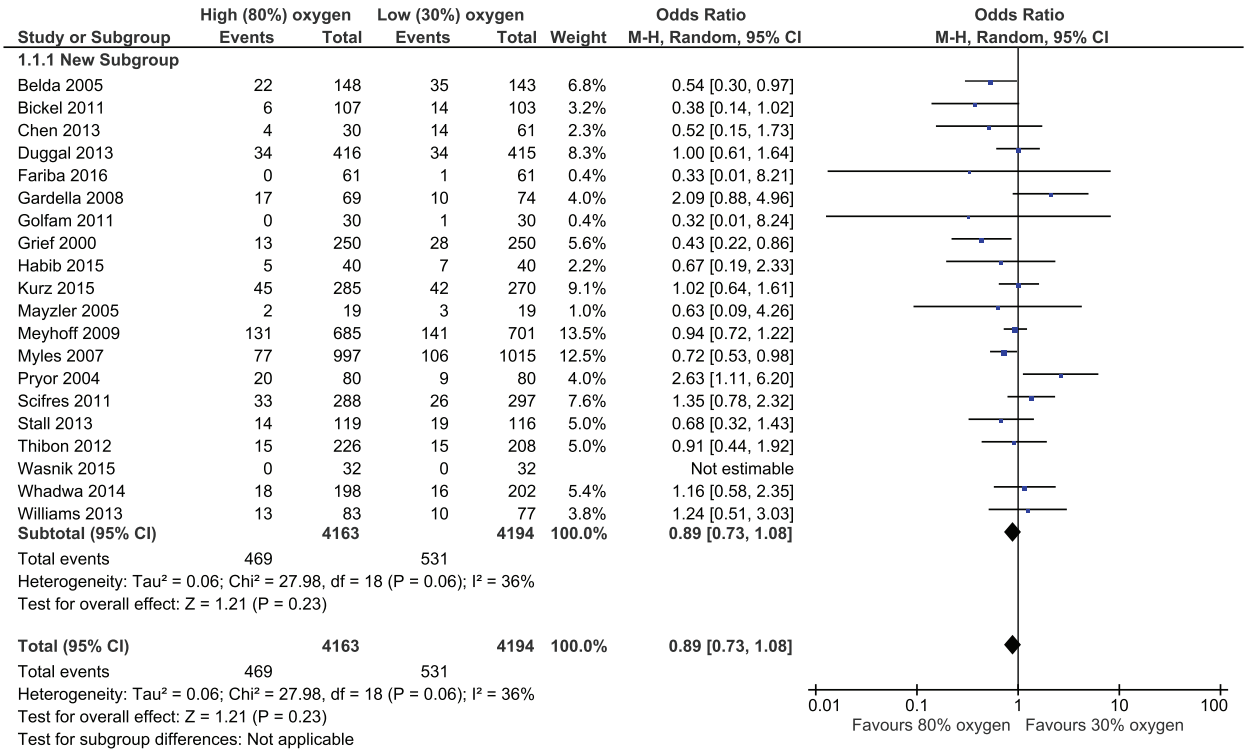


**Figure 6** Updated systematic review and meta-analysis: forest plot of supplemental oxygen-surgical site infection trials.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1**. Forest plot of anastomotic leak relative risks.

**Figure S2**. Cumulative probability of heterogeneity (variation) in anastomotic leak rates.

**Figure S3**. Forest plot of ASEPSIS relative risks.

**Figure S4**. Cumulative probability of heterogeneity (variation) in ASEPSIS scores.

**Figure S5**. Forest plot of surgical site infection relative risks.

**Figure S6**. Cumulative probability of heterogeneity (variation) in surgical site infection rates.

**Figure S7**. Forest plot of standardised mean differences in times to ambulation.

**Figure S8**. Cumulative probability of heterogeneity (variation) in times to ambulation.

**Figure S9**. Forest plot of standardised mean differences in plasma elastase (1$^{st}$ measurement).

**Figure S10**. Cumulative probability of heterogeneity (variation) in differences in plasma elastase (1$^{st}$ measurement).

**Figure S11**. Forest plot of standardised mean differences in plasma elastase (3$^{rd}$ measurement).

**Figure S12**. Cumulative probability of heterogeneity (variation) in differences in plasma elastase (3$^{rd}$ measurement).

**Figure S13**. Forest plot of standardised mean differences in plasma elastase (4$^{th}$ measurement).

**Figure S14**. Cumulative probability of heterogeneity (variation) in differences in plasma elastase (4$^{th}$ measurement).

**Figure S15**. Forest plot of standardised mean differences in plasma HLA-DR levels.

**Figure S16**. Cumulative probability of heterogeneity (variation) in differences in plasma HLA-DR levels.

**Appendix S1**Tabulation of Schietroma et al. studies analysed in this review.

**Data S1**. Details of suspected duplication in Schietroma et al. studies.