

# research



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## ORIGINAL RESEARCH Cross sectional analysis

### Retracted papers originating from paper mills

Candal-Pedreira C, Ross JS, Ruano-Ravina A, et al

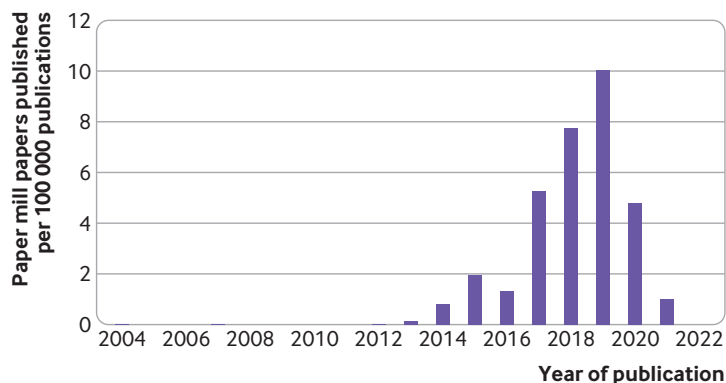
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**Study question** What are the characteristics, visibility, and impact of retracted papers originating from paper mills, and which journals were they published in?

**Methods** All paper mill papers retracted from 1 January 2004 to 26 June 2022 were identified from the Retraction Watch database. Papers bearing an expression of concern were excluded. Information about the characteristics of the journals involved and the papers retracted were taken from Journal Citation Reports. Web of Science was used for the total number of published papers. Descriptive statistics were used to characterise the sample and analyse the trend of retracted paper mill papers over time.

**Study answer and limitations** 1182 retracted paper mill papers were identified. The first paper mill paper was published in 2004 and the first retraction was in 2016; by 2021, paper mill retractions accounted for 772 (21.8%) of the 3544 total retractions. Almost all listed authors of 1143 (96.8%) paper



Proportion, per 100 000, of paper mill papers published and then retracted per year with respect to total publications

mill retractions came from Chinese institutions, and 909 (76.9%) listed a hospital as a primary affiliation. 15 journals accounted for 812 (68.7%) of 1182 paper mill retractions. The median number of citations received was 11 (interquartile range 5-22), with a range of 0-131. The main limitation of the study is that the investigation will need to be updated over time as the number of retracted paper mill papers increases. Also, the characteristics of detected paper mill papers might be substantially different from those not yet detected.

**What this study adds** This study suggests that paper mill paper retractions are increasing in frequency. Knowledge of the characteristics of identified paper mill papers is needed to help editors and reviewers detect this new type of scientific misconduct.

**Funding, competing interests, and data sharing** JSR receives research support through Yale University from different institutions and organisations and is an expert witness. DSE serves as an expert witness. No funding for this work was received. Restrictions apply to the availability of data from Retraction Watch.

# Optimising oxygen administration during surgery

## ORIGINAL RESEARCH Observational cohort study

### Oxygen administration during surgery and postoperative organ injury

McIlroy DR, Shotwell MS, Lopez MG, et al

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**Study question** Is supraphysiological oxygen administration during surgery associated with postoperative kidney, heart, and lung injury?

**Methods** Data from 42 medical centres across the United States participating in the Multicenter Perioperative Outcomes Group data registry were used to evaluate associations between increased supraphysiological oxygen administration during surgery and acute kidney injury, myocardial injury, and lung injury. The study cohort comprised adults who underwent inpatient surgical procedures of at least 120 minutes' duration with general anaesthesia and endotracheal intubation from January 2016 to November 2018. Using minute-by-minute fraction of inspired oxygen (FIO<sub>2</sub>) and haemoglobin oxygen saturation, supraphysiological oxygen administration was defined as the area under the curve of the FIO<sub>2</sub> above air (21%) during minutes when oxygen saturation was >92%. Primary endpoints were acute kidney injury, myocardial injury, and lung injury. Multivariable logistic regression used flexible splines to model the associations between oxygen administration and each primary endpoint, independent of baseline and perioperative factors.

**Study answer and limitations** The cohort comprised 350 647 patients with median age 59 years (interquartile range 46-69 years). Acute kidney injury was diagnosed in 19 207 of 297 554 patients (6.5%),

myocardial injury in 8972 of 320 527 (2.8%), and lung injury in 13 789 of 312 161 (4.4%). The median fraction of inspired oxygen was 54.0% (interquartile range 47.5%-60.0%), and the area under the curve of supraphysiological inspired oxygen was 7951% min (5870-11 107% min), equivalent to an 80% fraction of inspired oxygen throughout a 135 minute procedure, for example. After accounting for baseline covariates and other potential confounding variables, increased oxygen exposure was associated with a higher risk of acute kidney injury, myocardial injury, and lung injury. Patients at the 75th centile for the area under the curve of the fraction of inspired oxygen had 26% greater odds of acute kidney injury (95% confidence interval 22% to 30%), 12% greater odds of myocardial injury (7% to 17%), and 14% greater odds of lung injury (12% to 16%) compared with patients at the 25th centile. Unmeasured residual confounding cannot be excluded.

**What this study adds** Increased supraphysiological oxygen administration during surgery does not appear to limit perioperative organ injury and could increase the risk of kidney, heart, and lung injury.

**Funding, competing interests, and data sharing** Several authors received funding from the US National Institutes of Health and Association of University Anesthesiologists. See full paper on [bmj.com](https://bmj.com) for competing interests. Cohort data and analytical code may be available on reasonable request.

**Trial registration** Open Science Framework [osf.io/cfd2m](https://osf.io/cfd2m).

## COMMENTARY Oxygen can be a double edged sword

Oxygen is routinely administered to almost all patients undergoing general anaesthesia,<sup>1</sup> to ensure adequate oxygenation from intubation until awakening.<sup>2</sup>

Currently, the optimal target for oxygen administration is not yet clear and varies from normal arterial oxygen saturation to hyperoxaemia (usually defined as >97-98% arterial oxygen saturation). The hyperoxaemia strategy has been widely used since a seminal study highlighted the benefits of liberal (80%) compared with restrictive (30-35%) inspired oxygen to reduce the risk of postoperative infection.<sup>3</sup> Accordingly, the

### It is time to reconsider the liberal use of oxygen during general anaesthesia

2016 World Health Organization guidelines recommend that patients receive a liberal fraction of inspired oxygen during general anaesthesia and in the immediate postoperative period.<sup>4 5</sup>

Basic research, however, shows that oxygen can be a double edged sword.<sup>6</sup> It is a fundamental substrate for the oxidative phosphorylation that feeds biological energy to every aerobic cell. But in certain circumstances, oxygen may give rise to highly reactive compounds that cause damage and functional impairment to vital tissues such as the brain, disrupting the redox balance,

weakening the antioxidant barrier, and increasing the vulnerability of tissues to oxidative injury during periods of both hypoxaemia and hyperoxaemia.<sup>7</sup>

### Mixed evidence

In a clinical context, one large cross sectional study performed during general anaesthesia in Japan reported that 83% of the participants had a "preventable hyperoxaemia," defined as >98% arterial oxygen saturation.<sup>8</sup> Subsequent studies showed no substantial benefit associated with 80% inspired oxygen (compared with 30%) in reducing the risk of infection,<sup>9-11</sup> and others showed that supraphysiological oxygen administration may be

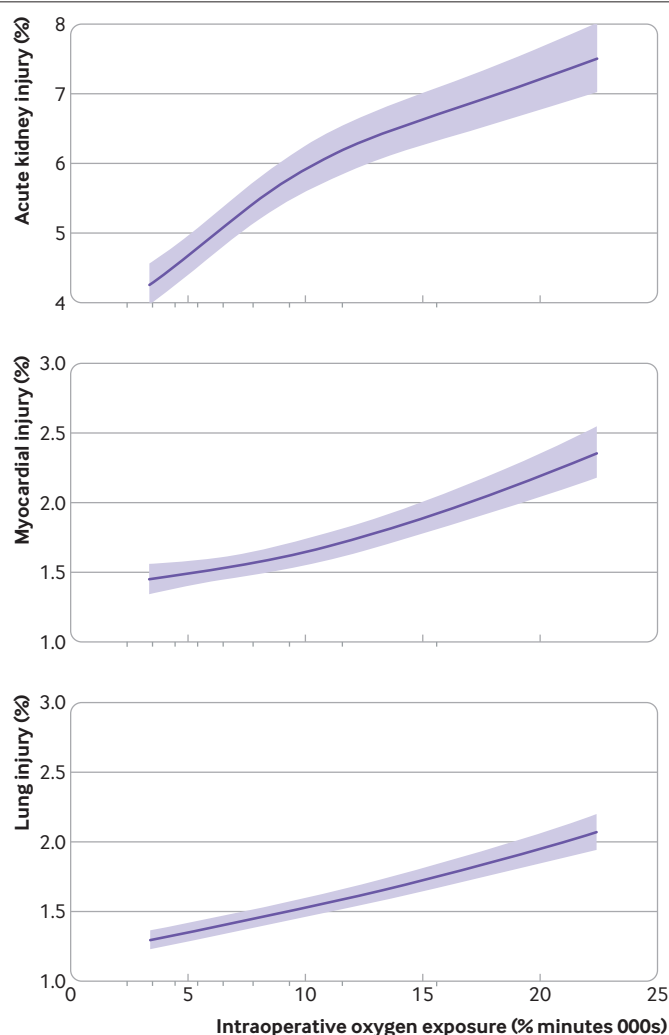
associated with worse outcomes than restrictive strategies.<sup>1-15</sup> Accordingly, the current British Thoracic Society guidelines recommend keeping arterial oxygen saturation in the 94-98% range to avoid harm from both hypoxaemia and hyperoxaemia.<sup>16</sup>

In their paper, McIlroy and colleagues add to this evidence the results of a retrospective multicentre cohort study evaluating the association between high fractional oxygen administration during general anaesthesia and postoperative organ injury (primary endpoint), and 30 day mortality (secondary endpoint).<sup>17</sup> To quantify the participants' exposure to supraphysiological oxygen, the authors used an algorithm to calculate the area under the

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Association between intraoperative oxygen exposure and acute kidney injury, myocardial injury, and lung injury, adjusted for factors included as covariates (age, sex, race, body mass index, American Society of Anesthesiologists status, Agency for Healthcare Research and Quality Elixhauser comorbidity index, chronic pulmonary disease, emergency surgery, preoperative serum creatinine, haemoglobin, troponin, and lactate concentrations, nitrous oxide exposure, median tidal volume, median intraoperative positive end expiratory pressure, volumes of intraoperative intravenous crystalloid and packed red blood cells administrations, and intraoperative hypotension). Tick marks on x axes identify each decile of patients



curve plotting administered oxygen >21% against the time spent with oxygen saturation >92%.

Their study included 350 647 adults from 42 centres in the United States and documented postoperative organ injury in 6.5% (kidneys), 2.8% (myocardium), and 4.4% (lungs) of participants.

Supraphysiological oxygen administration was associated with a higher risk of organ injury: Patients at the 75th centile of area under the curve had 26% greater odds of acute kidney injury (95% confidence interval 22% to 30%), 12% greater odds of myocardial injury (7% to 17%), and 14% greater odds of lung injury (12% to 16%) than those at the 25th

centile. In addition, it was also associated with 30 day mortality (odds ratio 1.06, 0.98 to 1.15).

Unlike previous studies, this new investigation leaves little room for uncertainty: supraphysiological oxygen administration and saturation are associated with a higher risk of organ damage, although the absolute risk remains low.

Future research on this topic could deal with some of the study's acknowledged limitations. Firstly, not all participants were screened for kidney and heart injury after their surgery. Secondly, it is unclear how the findings would change if the threshold definition for supraphysiological oxygen was increased. Thirdly, the

authors were unable to consider confounders such as diet, lifestyle, and drug use, which can influence the strength of the antioxidant barrier and hence susceptibility to organ injury.

Future researchers could also consider the oxygen carrying capacity of blood (haematocrit, haemoglobin concentration) and include an outcome measuring cognitive impairment because experimental evidence suggests that brain tissue is particularly vulnerable to redox imbalance.<sup>18</sup> Finally, observational analyses such as this cannot be used to infer a causal link between supraphysiological oxygen and organ injury. Experimental studies may be more suitable

to help establish cause and effect.

Despite such limitations, McIlroy and colleagues' study suggests it is time to reconsider the liberal use of oxygen during general anaesthesia.<sup>17</sup> The study also highlights the role of basic research in paving the road to clinical research, following the paradigm "from bench to bedside—and back." Research collaborations between biochemists and anaesthesiologists should be encouraged, especially to identify cause-effect relationships between supraphysiological oxygen administration and organ injury.

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## ORIGINAL RESEARCH Test negative, case-control study

# Effectiveness of mRNA-1273, BNT162b2, and BBIBP-CorV vaccines against infection and mortality in children in Argentina, during predominance of delta and omicron covid-19 variants

Castelli JM, Rearte A, Olszevicki S, et al

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**Study question** Are primary vaccine schedules effective in preventing SARS-CoV-2 infection and covid-19 related death in children and adolescents?

**Methods** This test negative, matched case-control study in children (3-11 years) and adolescents (12-17 years) used secondary data from the National Surveillance System and the Nominalized Federal Vaccination Registry of Argentina. 844 460 children and adolescents without previous SARS-CoV-2 infection and eligible to receive a primary vaccination schedule who were tested for SARS-CoV-2 by polymerase chain reaction or rapid antigen test from September 2021 to April 2022 were evaluated. After matching, 139 321 cases remained for analysis.

**Study answer and limitations** Estimated vaccine effectiveness against SARS-CoV-2 infection was 61.2% (95% confidence interval 56.4% to 65.5%) in children and 66.8% (63.9% to 69.5%) in adolescents during the delta dominant period, and



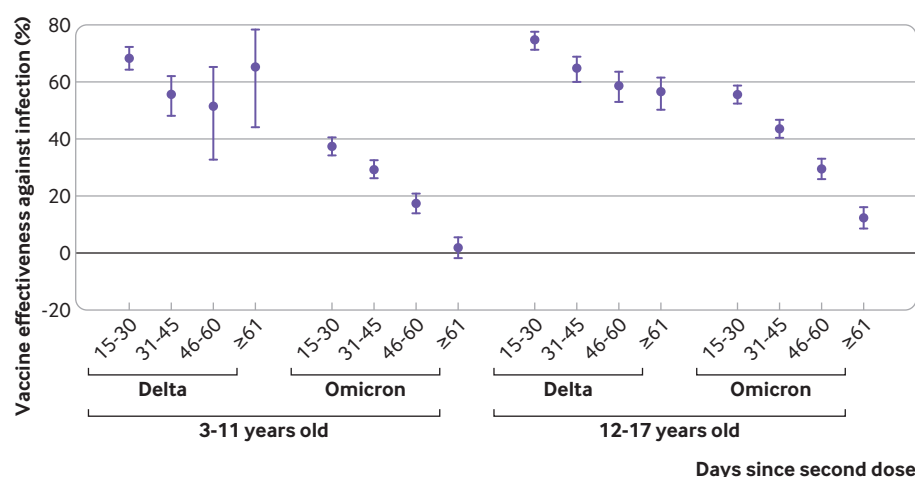
AGUSTIN MARCARIAN/ALAMY

15.9% (13.2% to 18.6%) and 26.0% (23.2% to 28.8%), respectively, when omicron was dominant. Vaccine effectiveness declined over time, especially during the omicron period. Nevertheless, vaccine effectiveness in preventing death remained

high (97.6% for adolescents and 66.9% for children). Some information, such as symptoms and hospital admissions, was incomplete and was consequently not included in any analysis. Persistent potential confounders, misclassification, or selection bias might have been present but were minimised by matching with strict criteria on all the available confounders.

**What this study adds** This study suggests that vaccine effectiveness remained high for prevention of mortality in children and adolescents regardless of the predominant circulating variant. Waning of effectiveness for infection was described for both types of vaccines, especially for the omicron variant.

**Funding, competing interests, and data sharing** No external funding received. Authors JMC and CV were involved in the decision making process of the vaccination campaign in Argentina. The data that support the findings of this study will be available for researchers who provide a methodologically sound proposal after it is approved, on request from the corresponding author.



Vaccine effectiveness of two dose schemes against SARS-CoV-2 infection, by age group, study period, and days since second dose

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