BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2024.02.011
Advance Access Publication Date: xxx
Review Article

REVIEW ARTICLE

Influence of nitrous oxide added to general anaesthesia on postoperative mortality and morbidity: a systematic review and meta-analysis

Jasper M. Kampman[1,2,*], Kim Y. Q. Plasmans[3], Jeroen Hermanides[1], Markus W. Hollmann[1], Sjoerd Repping[4,5] and Nicolaas H. Sperna Weiland[1,2]

[1]Department of Anaesthesiology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, [2]Amsterdam UMC Centre for Sustainable Healthcare, Amsterdam UMC, Amsterdam, The Netherlands, [3]Department of Anaesthesiology, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands, [4]Healthcare Evaluation and Appropriate Use, National Healthcare Institute, Diemen, The Netherlands and [5]Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

*Corresponding author. E-mail: j.m.kampman@amsterdamumc.nl

Abstract

Background: Nitrous oxide (N_2O) is a common adjuvant to general anaesthesia. It is also a potent greenhouse gas and causes ozone depletion. We sought to quantify the influence of N_2O as an adjuvant to general anaesthesia on postoperative patient outcomes.
Methods: We searched Medline, EMBASE, and Cochrane Central for works published from inception to July 6, 2023. RCTs comparing general anaesthesia with or without N_2O were included. Risk ratios (RRs) and standardised mean differences (SMDs) were calculated, along with 95% confidence intervals (CIs), using a random-effects model. Outcomes were derived from the Standardised Endpoints for Perioperative Medicine (StEP) outcome set. Primary outcomes were mortality and organ-related morbidity, and secondary outcomes were anaesthetic and surgical morbidity.
Results: Of 3305 records, 179 full-text articles were assessed, and 71 RCTs, totalling 22 147 patients, were included in the meta-analysis. Addition of N_2O to general anaesthesia did not influence postoperative mortality or most morbidity outcomes. N_2O increased the incidence of atelectasis (RR 1.62, 95% CI 1.24 to 2.12) and postoperative nausea and vomiting (RR 1.27, 95% CI 1.15 to 1.40), and decreased intraoperative opioid consumption (SMD −0.19, 95% CI −0.35 to −0.04) and time to extubation (MD −2.17 min, 95% CI −3.32 to −1.03 min).
Conclusions: N_2O did not influence postoperative mortality or most morbidity outcomes. Considering the environmental effects of N_2O, these findings confirm that current policy recommendations to limit its use do not affect patient safety.
Systematic review protocol: PROSPERO CRD42023443287.

Keywords: environmental sustainability; greenhouse gas; morbidity; mortality; nitrous oxide; postoperative outcome

Editor's key points

- Nitrous oxide is a common adjuvant to general anaesthesia. It is also a potent greenhouse gas.
- The current meta-analysis included 71 RCTs, totalling 22 147 patients, and found that nitrous oxide did not influence postoperative mortality and major morbidity.
- Reduce use of nitrous oxide based on environmental considerations is not associated with effects on patient safety.

Received: 31 October 2023; **Accepted:** 19 February 2024

Climate change has been labelled as the biggest threat to global health by the World Health Organization.[1] Healthcare systems have responded to the burden of disease created by climate change, but simultaneously contribute 4–10% of worldwide greenhouse gas emissions.[2,3] In operating theatres, up to 63% of greenhouse gas emissions are from halogenated anaesthetics and nitrous oxide (N_2O).[4] These inhaled anaesthetics account for about 3% of the carbon footprint of the entire health sector.[5,6] Of the inhaled anaesthetics, N_2O has the longest atmospheric lifetime (109–123 yr) and causes global warming and ozone depletion.[6] Reducing N_2O emission is an important step in reaching the goal of carbon net-zero healthcare.[7] However, withholding N_2O from patients might affect the quality of care. Therefore, a thorough assessment of the influence of N_2O as an adjuvant to general anaesthesia on postoperative outcomes is needed.

The largest RCT comparing general anaesthesia with or without N_2O is the ENIGMA II trial, which confirmed the safety of N_2O but did not show any clinical benefit of its use.[8] The most recent meta-analysis included trials up until 2014 and reported nine outcomes.[9] It reported that N_2O increased the incidence of pulmonary atelectasis, but it had no effect on in-hospital mortality, pneumonia, myocardial infarction, stroke, postoperative nausea and vomiting (PONV), venous thromboembolism, wound infection, or length of hospital stay. Since then, a series of consensus statements has been published by the Standardised Endpoints for Perioperative Medicine (StEP) working groups to establish a core and extended outcome set for perioperative trials.[10] This set includes major outcomes that have not been reviewed in relation to N_2O before, including 30-day and 1-yr mortality, atrial fibrillation, pulmonary embolism, aspiration, postoperative delirium, cognitive dysfunction, and acute kidney injury.

We conducted a systematic review and meta-analysis to summarise the available evidence from RCTs about postoperative outcomes, in order to inform decision-making on the use of N_2O as an adjuvant to general anaesthesia.

Methods

The protocol of this systematic review and meta-analysis was published in the PROSPERO registry (CRD42023443287). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in the design and reporting (checklist in Appendix 1 in the Supplementary material).[11]

Data sources and searches

We searched PubMed/Medline, EMBASE, and Cochrane Central Register of Controlled Trials for works published from inception to July 6, 2023 (full search in Appendix 2 in the Supplementary material). No language restrictions were applied. References of studies were screened for additional studies.

Study selection

We considered RCTs studying patients undergoing general anaesthesia for a surgical procedure and including two or more groups, of which at least one received N_2O and one did not. RCTs were considered if the anaesthetic agents other than N_2O were identical in both groups. RCTs in which the two groups received different concentrations of inspired oxygen were included, but these differences were noted and reported. Additional outcome data reported by prospectively designed follow-up publications of eligible RCTs were included in the meta-analysis.

The primary outcomes included mortality and organ-related morbidity derived from the recently published core outcome set established by the StEP working groups.[10] Secondary outcomes were derived from the StEP outcome set if possible and covered anaesthetic and surgical morbidity (e.g., awareness, surgical site infection, and PONV). Additional outcomes assessed efficiency, including intraoperative opioid consumption, time to tracheal extubation, length of hospital stay, and cost analyses. Table 1 lists the 20 primary, 16 secondary, and seven efficiency measures. Definitions of outcomes were based on the original RCT reporting them. Considering the large number of prespecified outcomes, and in order to preserve the readability of the results, only meta-analyses that included at least three RCTs are reported in the main text. Unabridged results are available in the Supplementary material.

Data extraction

Two reviewers (JK and KP) independently screened titles, abstracts, and full-text articles. Conflicts were settled by

Table 1 Prespecified outcome measures.

Category		Outcome measures
Primary outcomes	Mortality	Mortality 30 days, mortality 1 yr
	Cardiovascular	Myocardial infarction, myocardial injury, cardiovascular death, non-fatal cardiac arrest, coronary revascularisation, major adverse cardiac event, pulmonary embolism, deep vein thrombosis, atrial fibrillation
	Pulmonary	Atelectasis, pneumonia, acute respiratory distress syndrome, pulmonary aspiration
	Neurological	Cerebrovascular accident/stroke, postoperative delirium, postoperative cognitive dysfunction
	Renal	Acute kidney injury, initiation of new renal replacement therapy
Secondary outcomes	Anaesthetic	Postoperative nausea and vomiting, emergence delirium, postanaesthesia shivering, awareness, quality of recovery (QoR)-40 questionnaire, QoR-15 questionnaire, first pain <12 h after surgery, pain 12–24 h after surgery, persistent postsurgical pain
	Surgical	Clavien–Dindo classification grades $\geq$3, surgical site infection, re-operation, major bleeding, anastomotic leakage, cancer recurrence, World Health Organization Disability Assessment Schedule (WHODAS) questionnaire
Efficiency outcomes	Anaesthetic	Intraoperative opioid consumption, time to tracheal extubation, time in PACU
	General	Length of hospital stay, unplanned readmission or unplanned admission after day-case surgery, unplanned intensive care unit admission, cost analysis

discussion. The same reviewers assessed risk of bias and collected and analysed the data. Data were extracted on population, anaesthetic exposure, and outcomes.

Risk of bias

Risk of bias was assessed for each RCT using the Cochrane Handbook for Systematic Reviews of Interventions.[12] The six domains were: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Blinding of the attending anaesthetist was not included in the assessment as this was considered impossible because of the way N_2O is provided. An RCT was considered at low risk if all other personnel were blinded to the group assignment. Funnel plots were visually assessed for evidence of publication bias.

Data analysis

A separate meta-analysis was performed for each outcome. Review Manager version 5.4 (The Cochrane Collaboration, 2020) was used for the analyses. Risk ratios (RRs), mean differences (MDs), and standardised mean differences (SMDs) were determined along with corresponding 95% confidence intervals (CIs). A random-effects model was applied for the meta-analysis of each outcome that included multiple RCTs, because of the prevailing clinical heterogeneity between RCTs. For binary incidence data, the Mantel–Haenszel approach was used to derive RRs, and for continuous data, we applied the inverse variance approach. When continuous data within one meta-analysis were reported in different forms (i.e., in means with standard deviation [SD] or medians with range or interquartile range [IQR]), data were transformed using the methods suggested by Wan and collegues.[13] A means-based method was preferred when the majority of data were means and SD, and a medians-based method when the majority of data were medians and ranges/IQRs.[14]

Three subgroups were prespecified: (1) inhalation *vs.* i.v. anaesthesia; (2) adults *vs.* children (<18 yr old); and (3) cardiac *vs.* noncardiac surgery. We conducted a *post hoc* sensitivity analysis in which only RCTs that were categorised as low risk of bias in every domain were included in the meta-analyses. No trial sequential analysis was performed to determine the usefulness of future trials, because evidence-based thresholds for clinical importance were not available for the included outcomes.

Results

Of 3305 records identified, 728 duplicates were excluded, 2577 titles and abstracts were screened, and 179 full-text articles were assessed. A total of 71 RCTs were included in the meta-analysis, comprising 22 147 patients (Fig. 1; Table 2). The included RCTs compared N_2O as an addition to volatile anaesthesia (52 RCTs, 73%), i.v. anaesthesia (17 RCTs, 24%), or a mix of the two (two RCTs, 3%). The majority of RCTs included adult patients (61 RCTs, 86%), and all except one RCT covered noncardiac surgery (70 RCTs, 99%). The oldest eligible RCT was published in 1985 and over half of the included trials were published since the year 2000 (36 RCTs, 51%). Most RCTs used identical concentrations of inspired oxygen for both groups (51 RCTs, 72%), but in 17 RCTs (24%) the non-N_2O group received a higher fraction of oxygen.

Of 43 prespecified outcome measures, 16 were reported by three or more RCTs (Fig. 2; Table 3). The results of the remaining 27 outcomes are provided in Supplementary Table S2 (Appendix 3 in the Supplementary material). Risk of bias was

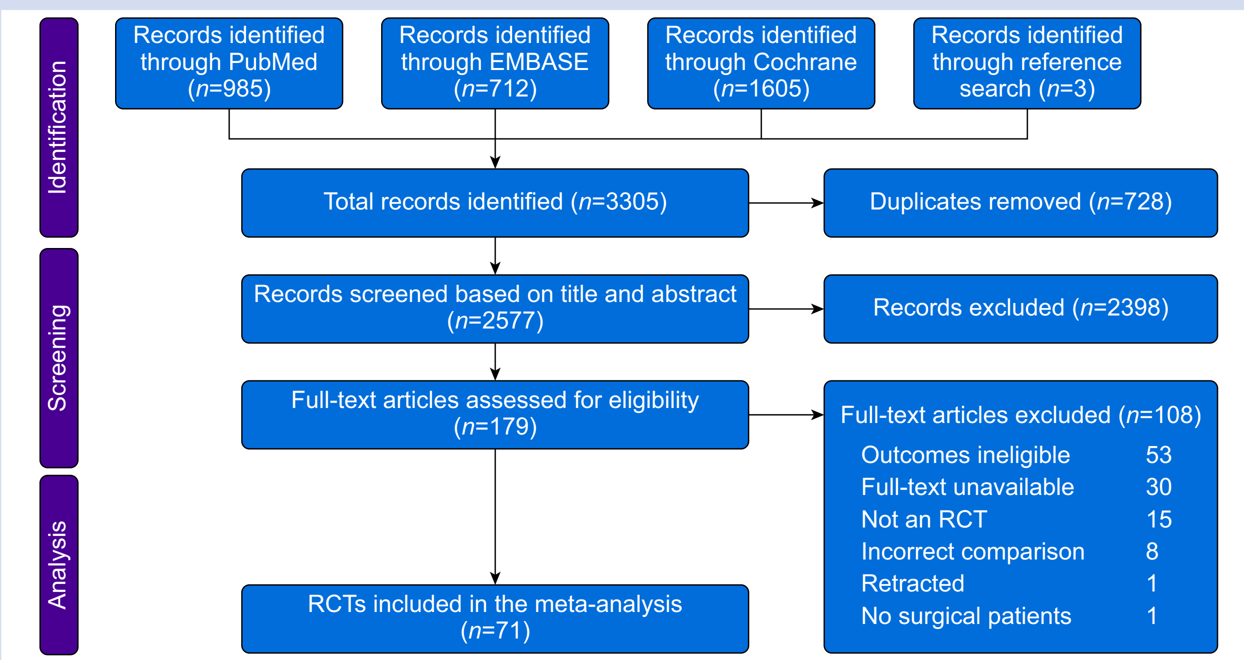

Fig 1. PRISMA flow chart of study inclusion.

Table 2 Characteristics of included RCTs. A full list of included trials is provided in Appendix 4 in the Supplementary material.

Characteristic	Number of RCTs	Number of patients
Total RCTs	71	22 147
Year of publication		
1980–9	5	1078
1990–9	30	2569
2000–9	20	9837
2010–9	14	8539
2020 to July 6, 2023	2	124
Population age		
Adults ≥18 yr	61	21 009
Children <18 yr	10	1138
Type of surgery		
Cardiac	1	32
Noncardiac	70	22 115
Type of anaesthesia		
Volatile	52	12 861
Total intravenous	17	2959
Unspecified/mixed	2	6327
FiO_2 between study groups		
Identical	51	14 273
Different	17	7705
Not disclosed	3	188

moderate overall, mainly as a result of uncertainty about blinding and allocation concealment. We provide a full list of included RCTs and study characteristics, including individual risk of bias assessment, in Supplementary Table S3 (Appendix 4 in the Supplementary material). All forest and funnel plots are provided in Appendix 5 in the Supplementary material.

Primary outcomes

The meta-analysis revealed no difference between general anaesthesia with or without N_2O with regard to 30-day mortality (with N_2O *vs.* without N_2O; RR 1.18, 95% CI 0.51 to 2.74, six RCTs, 9866 patients) and 1-yr mortality (RR 1.19, 95% CI 1.00 to 1.43, one RCT, 5841 patients). General anaesthesia with N_2O increased the incidence of pulmonary atelectasis (RR 1.62, 95% CI 1.24 to 2.12, five RCTs, 2418 patients). For the other organ-related morbidity outcomes, no difference between groups was found. Subgroup analyses did not reveal additional differences for volatile *vs.* i.v. anaesthesia, adults *vs.* children, or cardiac *vs.* noncardiac surgery (full subgroup analyses in Supplementary Table S4, Appendix 6 in the Supplementary material). Results were unchanged in the *post hoc* sensitivity analysis including only RCTs at low risk of bias (full results in Appendix 7 in the Supplementary material). The primary outcomes reported by fewer than three RCTs revealed no differences between groups and are listed in Supplementary Table S2 (Appendix 3 in the Supplementary material).

Secondary outcomes

Of the seven secondary outcomes reported by three or more RCTs, only the incidence of PONV differed between the two groups (Table 3). General anaesthesia with N_2O increased the risk of PONV (RR 1.27, 95% CI 1.15 to 1.40, 43 RCTs, 19 634 patients). The difference was more pronounced for the subgroup receiving i.v. anaesthesia (RR 1.79, 95% CI 1.20 to 2.69, 10 RCTs, 1956 patients) than the subgroup receiving inhalation anaesthesia (RR 1.19, 95% CI 1.10 to 1.29, 31 RCTs, 11 351 patients). No differences were observed in intraoperative awareness, postoperative pain scores, emergence delirium, surgical site infection, and re-operation rate. The meta-analysis results for the secondary outcomes reported by fewer than three RCTs, which similarly revealed no difference between groups, are listed in Supplementary Table S2 (Appendix 3 in the Supplementary material).

Efficiency outcomes

Four efficiency outcomes were reported by three or more RCTs (Table 3). Intraoperative opioid consumption was lower for the group receiving N_2O (SMD −0.19, 95% CI −0.35 to −0.04, 30 RCTs, 4930 patients). Similarly, the time to tracheal extubation was shorter in the group receiving N_2O (MD −2.17 min, 95% CI −3.32 to −1.03, 16 RCTs, 855 patients). No differences were seen in ICU admission rate, length of hospital stay, readmission rate, or cost.

Discussion

This systematic review and meta-analysis comparing general anaesthesia with or without N_2O found that N_2O did not influence mortality or most morbidity outcomes. N_2O increased the incidence of pulmonary atelectasis and PONV, whereas it decreased intraoperative opioid consumption and time to tracheal extubation. Because general anaesthesia with or without N_2O appears equally safe and effective, we believe that secondary considerations, including the environmental impact of N_2O, may be taken into account. These findings confirm that current policy recommendations to limit the use of N_2O do not affect perioperative patient safety.

Relation to previous work

The two largest RCTs on N_2O as an adjuvant to general anaesthesia were the ENIGMA and ENIGMA II trials.[8,15] The former, comprising 2050 patients, reported a higher incidence of several complications, including wound infections, pneumonia, atelectasis, fever, and PONV in the N_2O group. The trial has received substantial criticism, mainly concerning the different concentrations of inspired oxygen (30% in the N_2O group *vs.* 80% in the control group) and the fact that the anaesthesia regimen was not standardised. The subsequent and larger ENIGMA II trial (7112 patients) refuted all of the results of its predecessor except for atelectasis, which was not reported in the main paper.

Several systematic reviews studied N_2O as an adjuvant to general anaesthesia, but most focussed on specific outcomes. A meta-analysis of 13 RCTs focussing on cardiovascular outcomes found no differences between general anaesthesia with or without N_2O.[16] A meta-analysis of 30 RCTs focussing on PONV reported an odds ratio of 0.80 (95% CI 0.71 to 0.90) for general anaesthesia without N_2O.[17] The most recent systematic review, and the only one to include both ENIGMA trials, was published in 2015 by Sun and colleagues,[9] and included 24 RCTs in the meta-analysis. It examined in-hospital mortality and eight morbidity outcomes, concluding that N_2O should be avoided in patients with a history of poor pulmonary function based on an increased risk of atelectasis. We included 11 subsequently published RCTs (2014–23) and 36 RCTs reporting

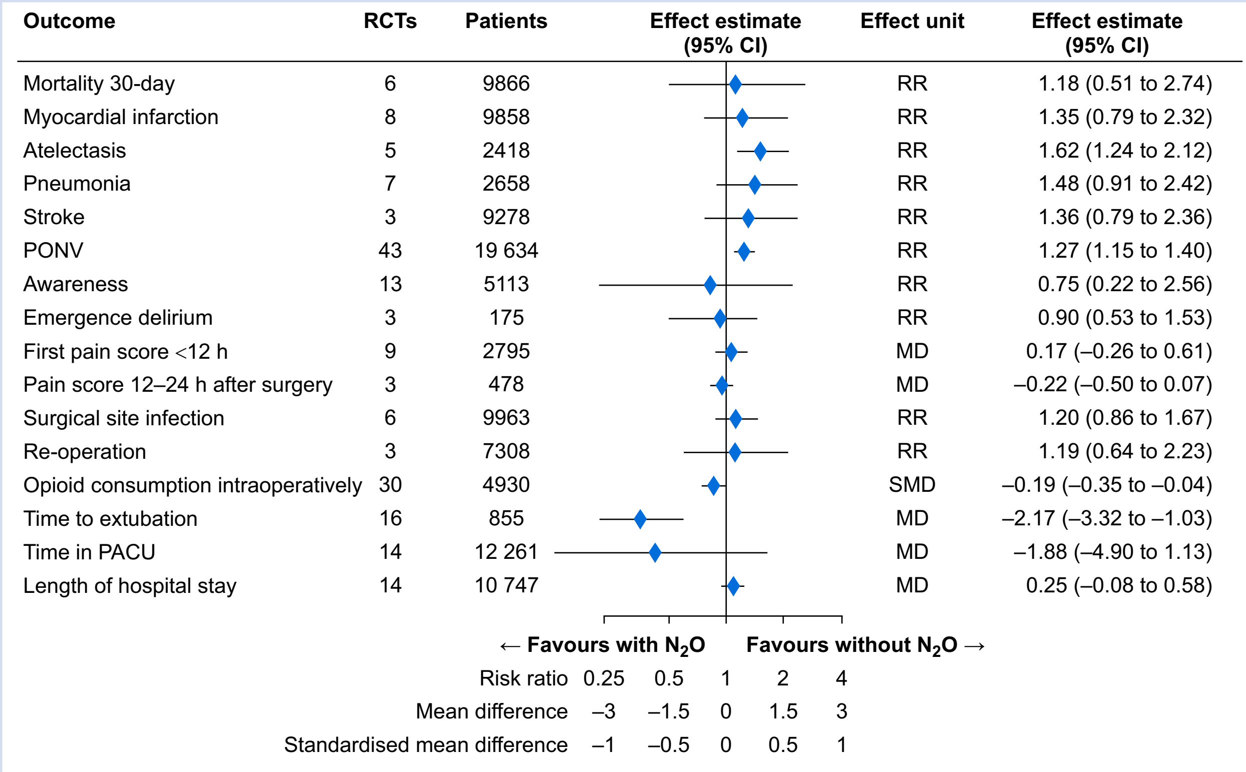

Fig 2. Results of the meta-analysis for general anaesthesia with N_2O or without N_2O. CI, confidence interval; MD, mean difference; PONV, postoperative nausea and vomiting; RR, risk ratio; SMD, standardised mean difference.

Table 3 Results of the meta-analysis for general anaesthesia with N_2O *vs* without N_2O. All calculations are performed using a random-effects model. Outcomes that include at least three RCTs are reported, all other outcomes are listed in Appendix 3 in the Supplementary material. Forest plots are provided in Appendix 5 in the Supplementary material. CI, confidence interval; MD, mean difference; RR, risk ratio; SMD standardised mean difference.

Outcome measures	With N_2O	Without N_2O	Unit	Effect estimate (95% CI)	Preference
Primary outcomes					
30-day mortality	54/4994	64/4992	RR	1.18 (0.51–2.74)	None
Myocardial infarction	245/4925	239/4933	RR	1.35 (0.79–2.32)	None
Atelectasis	129/1206	79/1212	RR	1.62 (1.24–2.12)	Without N_2O
Pneumonia	40/1330	25/1328	RR	1.48 (0.91–2.42)	None
Cerebrovascular accident/stroke	30/4655	22/4623	RR	1.36 (0.79–2.36)	None
Secondary outcomes					
Postoperative nausea and vomiting	2300/9836	1808/9798	RR	1.27 (1.15–1.40)	Without N_2O
Awareness	5/2560	8/2553	RR	0.75 (0.22–2.56)	None
Emergence delirium	25/86	30/89	RR	0.90 (0.53–1.53)	None
First pain score <12 h after surgery	2795 patients	9 RCTs	MD	0.17 (−0.26 to 0.61)	None
Pain score 12–24 h after surgery	478 patients	3 RCTs	MD	−0.22 (−0.50 to 0.07)	None
Surgical site infection	471/4984	434/4979	RR	1.20 (0.86–1.67)	None
Re-operation	21/3715	18/3693	RR	1.19 (0.64–2.23)	None
Efficiency outcomes					
Intraoperative opioid consumption	4930 patients	30 RCTs	SMD	−0.19 (−0.35 to −0.04)	With N_2O
Time to extubation (min)	855 patients	16 RCTs	MD	−2.17 (−3.32 to −1.03)	With N_2O
Time in PACU (min)	12261 patients	14 RCTs	MD	−1.88 (−4.90 to 1.13)	None
Length of hospital stay (days)	10747 patients	14 RCTs	MD	0.25 (−0.08 to 0.58)	None

on StEP outcomes that were not included in this previous review.

Meaning of the results

The results of the present meta-analysis were derived from over 22 000 randomised patients in 71 RCTs and examined a large number of clinically relevant outcomes. The main finding is that N_2O as an adjuvant to general anaesthesia did not lead to improvements in postoperative patient outcomes.

Our meta-analysis found an increased incidence of pulmonary atelectasis in the N_2O group. This outcome was not based on clinical symptoms, but on the presence of atelectasis on X-ray or computed tomography, which means its relevance is uncertain. Occurrence of atelectasis may be easily prevented by using positive end-expiratory pressure intraoperatively.[18] Also, although five RCTs were included in this analysis, the ENIGMA trial carried 97% of the weight. It is unfortunate that atelectasis was not an outcome in the subsequent ENIGMA II trial. However, a recent *post hoc* analysis in one-third of the ENIGMA II cohort found that the incidence of atelectasis was lower in the N_2O group than in the N_2O-free group.[19] Although this *post hoc* analysis did not meet the criteria for inclusion in the current meta-analysis, the combined results would likely nullify significance of atelectasis incidence (with N_2O 300/2375 [12.6%] *vs*. without N_2O 289/2371 [12.2%]).

The most frequently reported outcome was PONV. The 43 RCTs all but unanimously reported a higher incidence of PONV in the N_2O group, and the emetogenic effects of N_2O have been reported by previous reviews.[17] Interestingly, the emetogenic effects persist despite decreased intraoperative opioid consumption in the N_2O groups. Administration of antiemetic prophylaxis is a common part of perioperative care. Several large RCTs have suggested that this may adequately control the emetogenic effects of N_2O.[8,20] The subgroup of RCTs using i.v. anaesthesia showed a much larger difference in PONV (RR 1.79, 95% CI 1.20 to 2.69), suggesting that the equally well-known emetogenic effects of volatile anaesthetics partly mask the emetogenic effects of N_2O. This is relevant to the growing number of anaesthetists using i.v. anaesthesia, a trend that may be similarly driven by environmental concerns.

The present meta-analysis revealed a reduction in intraoperative opioid consumption when N_2O was used as an adjuvant to general anaesthesia. The pooled SMD of −0.19 (95% CI −0.35 to −0.04) is considered a rather small effect.[21] Similar to other non-opioid analgesics, N_2O could contribute to opioid-free anaesthesia techniques. Reducing opioid use is a prominent ambition of modern medical practice. The difference in intraoperative opioid consumption in our meta-analysis did not translate into a difference in postoperative pain scores, suggesting that analgesic effects may not persist after N_2O administration is ceased.

The time to tracheal extubation was lower for patients receiving N_2O, reflecting that its low blood solubility leads to a rapid emergence from anaesthesia.[22] However, we believe that the MD of only 2 min is of minimal relevance to perioperative patients. It did not translate into a faster discharge from the PACU.

Nitrous oxide in future clinical practice

In 2019, the N_2O Task Force of the European Society of Anaesthesiology and Intensive Care concluded that perceived drawbacks of N_2O have been exaggerated or misplaced, and recommended that hospitals should maintain N_2O supplies.[23] Presently, some members of the Task Force advocate increased environmental awareness.[24] In a recent Europe-wide consensus paper, 36 experts from 24 different countries agreed unanimously to stop the use of N_2O 'unless no other alternative were available'.[25] This indicates a paradigm shift over the last 5 yr with respect to how N_2O is viewed by anaesthetists.

The use of N_2O has decreased since the start of the century, but surveys conducted in the last 10 yr show that it is still regularly used by 5−30% of anaesthetists.[26−28] N_2O accounts for up to 80% of greenhouse gas emissions from anaesthetic gases in the UK.[29] This high percentage may partly result from N_2O leaking from manifolds and associated piped infrastructure. Chakera and colleagues[30] performed a series of case studies in various hospitals and found that roughly 90% of N_2O was wasted when comparing the total N_2O volume consumed with the volume that was clinically utilised. This led the aforementioned consensus paper to unanimously advise hospitals to decommission their N_2O central delivery system and remove it from future hospital plans.[25] Bottled N_2O can be provided when its use is strictly indicated.

Strengths and limitations

Outcomes in this systematic review were based on the StEP consensus statements for perioperative trials[10] and reduce the likelihood that relevant outcomes were missed. However, the large number of outcomes also increased the risk of false-positive findings. It is important to note that identified differences between general anaesthesia with or without N_2O should ideally be large, clinically relevant, and based on a sound pathophysiological rationale.

A limitation of this meta-analysis is the prevailing heterogeneity of the included RCTs. Firstly, the included RCTs were performed over an extensive period and covered many different surgical disciplines. This clinical heterogeneity may decrease the certainty of our overall results. Secondly, some of the outcomes might be correlated when derived from the same RCT. A multivariable meta-analysis would be needed to address this correlation; however, because the number of RCTs differed for each outcome, this was not possible and a separate univariate meta-analysis was performed for each outcome. Thirdly, reported methodology was insufficient to perform the risk of bias assessment at the level of the outcome. Therefore, risk of bias was assessed at the trial level only, although it might have differed between outcomes (e.g., no blinding for intraoperative opioid use, but appropriate blinding for the 30-day mortality assessment).

Conclusions

In this systematic review and meta-analysis, use of N_2O as an adjuvant to general anaesthesia did not influence postoperative mortality and major morbidity. Use of N_2O led to an increased incidence of pulmonary atelectasis and PONV, whereas it decreased intraoperative opioid consumption and time to tracheal extubation. The overall findings imply that general anaesthesia with and without N_2O is both safe and effective. We believe this means that secondary considerations can be taken into account, including the environmental impact of N_2O. These findings confirm that current policy recommendations to limit the use of N_2O will not influence general perioperative patient safety.

Authors' contributions

Study design: all authors
Conceived the idea: JK, JH, NHSW
Screening of records: JK, KP
Data extraction and analysis: JK, KP
Assessment of risk of bias: JK, KP
Drafting of the initial manuscript: JK
Critical revisions of the manuscript: NHSW, JH, KP, MWH, SR
Project supervision: NHSW
Guarantors: JK and NHSW
The corresponding author attests that all authors meet authorship criteria and that no others have been omitted.

Declarations of interest

NHSW and SR are both frequent speakers at public and private events concerning sustainability in healthcare, for which they have received travel reimbursements, but never any other financial payment. NHSW chairs the Sustainability Taskforce of the Dutch Society for Anaesthesiology (NVA) and is a member of the Sustainability Committee of the European Society for Anaesthesiology and Intensive Care (ESAIC). SR is a member of the advisory committee about sustainability at the University of Amsterdam. MWH is section editor for *Anesthesia & Analgesia, Journal of Clinical Medicine*, and *Frontiers of Physiology*. The other authors declare that they have no conflicts of interest.

Funding

Dutch Society for Anaesthesiology (NVA) (unrestricted grant to JK).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.02.011.

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Handling Editor: Kate Leslie