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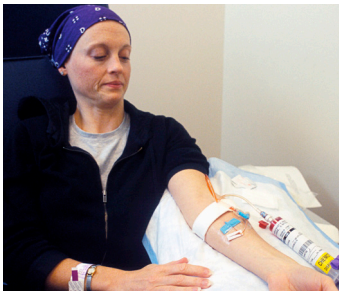

Neoadjuvant chemotherapy in nasopharyngeal cancer p77

Reporting of patient and public involvement in trials p 80

Hunting season and firearm incidents p 82

Induction chemotherapy for nasopharyngeal carcinoma

ORIGINAL RESEARCH Phase 3 multicentre randomised controlled trial

Four cycles of docetaxel plus cisplatin as neoadjuvant chemotherapy followed by concurrent chemoradiotherapy in stage N2-3 nasopharyngeal carcinoma

Xie WH, Xiao WW, Chang H, et al

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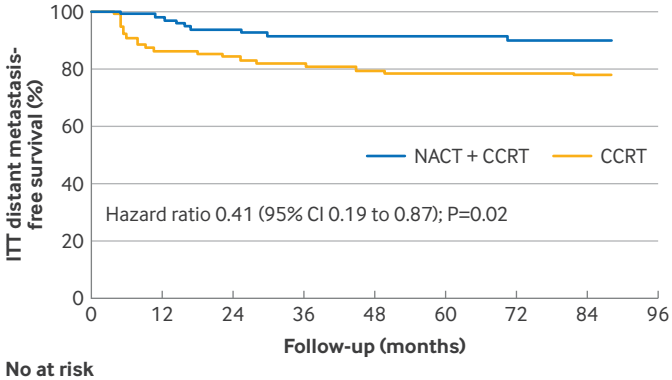
Find this at doi: 10.1136/bmj-2024-081557

Study question What is the curative effect of four cycles of docetaxel with cisplatin as a neoadjuvant chemotherapy followed by concurrent chemoradiotherapy for patients with stage N2-3 nasopharyngeal carcinoma?

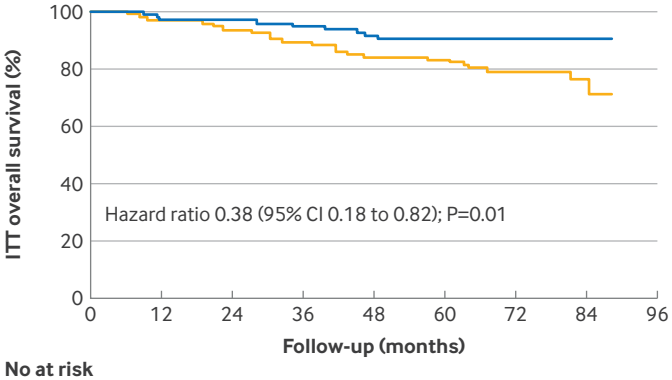
Methods This randomised controlled trial enrolled 186 patients aged ≤70 years with a diagnosis of untreated stage T1-4N2-3M0 nasopharyngeal carcinoma and randomly allocated them to two groups in a 1:1 ratio. The experimental group received four cycles of docetaxel (75 mg/m^2 on day 1) and cisplatin (37.5 mg/m^2 on days 2-3) followed by concurrent chemoradiotherapy (intensity modulated radiotherapy plus weekly cisplatin 40 mg/m^2), and the control group received concurrent chemoradiotherapy alone. The five year distant metastasis-free survival and overall survival were compared, and the acute and late toxicities were analysed.

Study answer and limitations After a median follow-up time of 76.9 months, the neoadjuvant chemotherapy plus concurrent chemoradiotherapy group had superior five year distant metastasis-free survival (91.3% (95% confidence interval (CI) 85.4% to 97.2%) *v* 78.2% (69.8% to 86.6%); hazard ratio 0.41 (95% CI 0.19 to 0.87); P=0.02) and five year overall survival (90.3% (84.2% to 96.4%) *v* 82.6% (75.0% to 90.2%); hazard ratio 0.38 (0.18 to 0.82); P=0.01). Grade 3/4 acute toxicities were observed in 60 (65%) patients in the neoadjuvant chemotherapy plus concurrent chemoradiotherapy group compared with 46 (51%) in the concurrent chemoradiotherapy only group (P=0.05). Whether this treatment modality is applicable in areas beyond the epidemic areas in China needs further validation.



No at risk

NACT + CCRT	93	89	85	83	81	81	61	31
CCRT	93	80	75	72	70	68	49	27



No at risk

NACT + CCRT	93	90	90	88	85	84	65	32
CCRT	93	90	86	82	77	76	53	28

What this study adds Docetaxel plus cisplatin is an effective and safe neoadjuvant chemotherapy regimen for locoregionally advanced nasopharyngeal carcinoma. Four cycles of neoadjuvant chemotherapy reduced the risks of distant metastasis and prolonged survival for patients with stage N2-3 nasopharyngeal carcinoma.

Funding, competing interests, and data sharing The trial was supported by the Science and Technology Planning Project of Guangdong Province, China. The authors have no competing interests to declare. Data can be requested from the corresponding author.

Study registration ClinicalTrials.gov NCT02512315.

COMMENTARY A new treatment option for locally advanced disease

Nasopharyngeal carcinoma (NPC) is an epithelial malignancy that is associated with the Epstein-Barr virus and is characterised by distinct epidemiological patterns that are prevalent in China, Southeast Asia, and north Africa.[1] In early stage NPC, excellent outcomes have been achieved with radiotherapy alone. The application of intensity modulated radiotherapy has increased locoregional control and overall survival rates at five years to over 90% in these patients.[2 3] However, more than 70% of patients receive NPC diagnoses at a locally advanced stage.[4] Despite the technological advances in intensity modulated radiotherapy, the treatment of locally advanced NPC still relies on the combination of chemotherapy and radical radiotherapy.

Neoadjuvant chemotherapy, alternatively termed induction chemotherapy, involves the administration of chemotherapy for NPC before the initiation of radiotherapy. Concurrent chemoradiotherapy for NPC is a therapeutic approach that entails the simultaneous application of chemotherapy agents and radiotherapy.[5] In the era of intensity modulated radiotherapy, neoadjuvant chemotherapy combined with concurrent chemoradiotherapy (CCRT) has been identified as a strategic approach to enhance survival outcomes in patients with locally advanced NPC; however, previous clinical trials have generated conflicting evidence.[6-8] In a linked study (doi:10.1136/bmj-2024-081557), Xie and colleagues conducted a phase 3 multicentre trial to determine the optimal induction regimens and cycles, with a particular focus on assessing whether patients with stage N2-3 disease and an elevated risk of metastasis experience preferential benefits from this intensified therapeutic approach.[9]

The trial involved an inaugural direct comparison of four cycles of docetaxel with cisplatin as neoadjuvant chemotherapy (TP-NACT) followed by CCRT versus CCRT only in patients with locally advanced NPC. It was conducted between February 2016 and February 2019 and included 186 people with untreated locally advanced NPC across six tertiary care centres. Patients were randomised at a 1:1 ratio to either the intervention group (four cycles of TP-NACT induction followed by cisplatin based CCRT) or the control group (standard CCRT). Patients in both groups adhered to a weekly cisplatin dosing schedule during the radiotherapy phase.

What the findings mean

Patients in the intervention group presented significantly improved overall survival rates at five years (90.3% *v* 82.6%, hazard ratio 0.38 (95% confidence interval 0.18 to 0.82), P=0.01) and distant metastasis-free survival rates at five years (91.3% *v* 78.2%, 0.41 (0.19 to 0.87), P=0.02) compared with patients in the control group.

A subgroup analysis based on N stage revealed a marked survival benefit with TP-NACT combined with CCRT among patients with N2 disease, whereas a non-significant trend was observed among patients with N3 disease, indicating prognostic heterogeneity. Importantly, the intensified induction regimen did not result in an increase in acute or late adverse events relative to standard CCRT.

These data suggest that four cycles of TP-NACT before CCRT could be an effective strategy for reducing the risk of local recurrence and metastasis in patients with N2-3 NPC. This approach improves both overall survival and disease-free survival while maintaining toxicity levels comparable to those of standard treatment regimens. Consequently, TP-NACT has emerged as a clinically viable alternative to traditional induction protocols, such as docetaxel, cisplatin plus fluorouracil, or gemcitabine plus cisplatin regimens, for this anatomically complex malignancy.

Induction chemotherapy enhances the eradication of subclinical metastases lesions and tumour debulking, improving locoregional control and reducing rates of distant metastases. Although two previous

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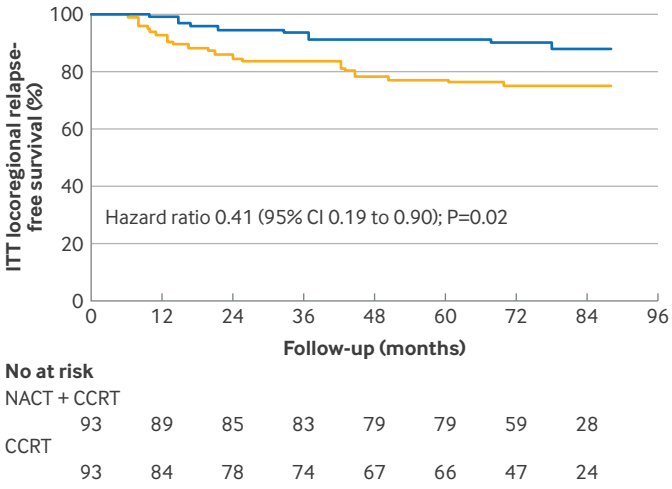

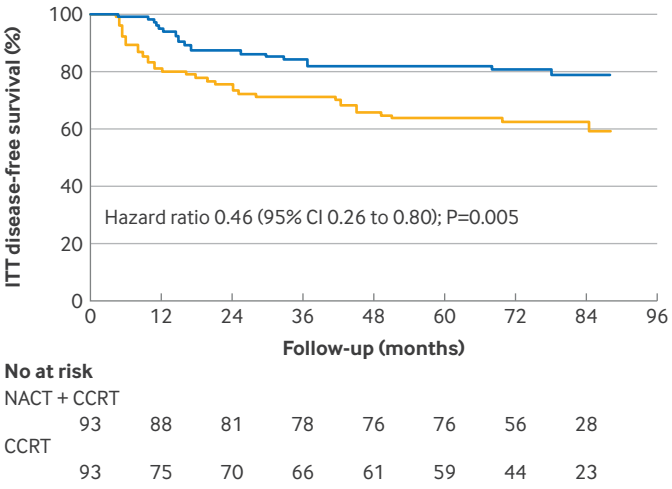

Kaplan-Meier survival curves in intention-to-treat (ITT) population. CCRT=concurrent chemoradiotherapy; CI=confidence interval; NACT=neoadjuvant chemotherapy

meta-analyses did not demonstrate a survival benefit with induction-CCRT strategies,[10 11] supporting evidence has emerged in recent years. A phase 3 trial revealed that cisplatin plus fluorouracil induction chemotherapy combined with CCRT resulted in superior five year control of distant metastases, along with significant improvements in disease-free survival and overall survival.[12 13] Concurrently, cisplatin plus fluorouracil induction followed by CCRT significantly increased disease-free survival at three years in another cohort.[14] These findings were corroborated by multinational trials showing improvements in the three year progression-free survival and overall survival of patients receiving docetaxel, cisplatin, and fluorouracil.[15] The MEPFL induction-CCRT regimen—consisting of mitomycin, epothilone, cisplatin, fluorouracil, and leucovorin—improved five year disease-free survival rates without increasing overall survival rates.[16] A meta-analysis of four randomised trials conducted in endemic regions indicated that radiotherapy enhanced by induction chemotherapy resulted in a 6% absolute increase in five year survival, primarily due to improved control of distant metastases.[17] These findings led to the 2018 revision of the National Comprehensive Cancer Network (NCCN) guidelines, which upgraded the induction CCRT from the guideline's category 3 consensus (ie, there is major NCCN disagreement that the intervention is appropriate) to category 2A consensus (ie, there is uniform NCCN consensus that the intervention is appropriate), aligning it with the evidence for adjuvant CCRT.[5]

SAM OGDEN/SPL

TP-NACT induction chemotherapy is associated with reduced toxicity and fewer side effects

Lower toxicity

Nevertheless, the optimal induction chemotherapy regimen has yet to be determined. A phase 3 trial conducted in 2019 in southern China, which compared gemcitabine plus cisplatin followed by CCRT with CCRT alone, demonstrated significant improvements in three year recurrence-free survival rates and overall survival rates, and no considerable differences in late toxicities.[18] The publication of this study provides robust evidence supporting the selection of induction chemotherapy regimens for locally advanced NPC. Consequently, this regimen has been endorsed as having category 1A consensus in the 2022 revision of NCCN guidelines for nasopharyngeal carcinoma. Nevertheless, the experimental design of this study did not include a direct comparison with the gemcitabine plus cisplatin regimen for induction chemotherapy; instead, the researchers opted for a four cycle TP-NACT regimen.[19] This choice could have been informed by a meta-analysis in 2024, which identified the TP-NACT regimen combined with CCRT as the preferred strategy for patients with locally advanced NPC, based on cost efficacy analyses.[20]

This four cycle regimen of induction chemotherapy potentially reduces mucosal toxicity by omitting fluorouracil, thereby broadening the therapeutic window for subsequent CCRT. The enhanced efficacy of induction chemotherapy when combined with CCRT might be attributable to the increased number of induction chemotherapy cycles.

The four cycle TP-NACT regimen presents itself as a novel clinically viable alternative for patients with locally advanced NPC who are unable to tolerate gemcitabine plus cisplatin regimens. Compared with immunotherapy based induction strategies, TP-NACT induction chemotherapy is associated with reduced toxicity and fewer side effects.[21] We expect that additional clinical advantages will emerge, based on the outcomes of future real world studies.

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Patient and public involvement in research reporting

ORIGINAL RESEARCH Meta-epidemiological evaluation

Evolution of reported patient and public involvement over time in randomised controlled trials in major medical journals and in their protocols

Vanneste A, Wens I, Sinnaeve P, et al

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Study question How has the reporting of patient and public involvement (PPI) in randomised controlled trials evolved over time in major medical journals and their respective trial protocols?

Methods This meta-epidemiological evaluation assessed the reporting of PPI in randomised controlled trials published since 2015 in four major medical journals. PubMed was searched for a comprehensive sample of 360 articles reporting randomised controlled trials and 299 respective peer reviewed protocols. Data extraction focused on the involved stakeholders, the description and extent of PPI activities and processes, and the recognition of PPI contributions. The published articles and their protocols were evaluated to assess the consistency of the reported PPI in both.

COMMENTARY More focus needed to improve PPI reporting in research

Patient and public involvement (PPI) has become a key part of health and social care research in many countries with a focus on working with or by patients rather than to, about, or for them, aiming to coproduce knowledge that is relevant, appropriate, and acceptable for patients.[1 2] Patient and public contributors can and should be included at all stages of research, including identifying key questions, designing, recruiting, selecting outcomes, and implementing findings.[1]

Patient involvement in a study should be reported within a paper to ensure that this knowledge contributes to building the PPI evidence base for practice. While reporting PPI might seem obvious, the reporting of PPI in research remains more elusive than we might expect. Past studies have identified poor and inconsistent reporting,[3 4] which resulted in development of the GRIPP2 reporting guidance specifically for PPI.[5 6] GRIPP2 is supported by journals that request authors to report PPI, including *The BMJ* and *BMC Research Involvement and Engagement*.[7 8]

Despite highlighting the problem of poor PPI reporting and the availability of reporting guidance, a linked study by Vanneste and colleagues (doi:10.1136/bmj-2024-082697) has identified poor progress in reporting PPI in randomised controlled trials.[9] They used a meta-epidemiological evaluation to systematically review PPI reporting in highly influential randomised controlled trials, drawing on four major medical journals since 2015. With the focus on PPI encouraged by many funders, we might assume that some of these trials included patients collaborating with research teams to coproduce the studies.

Poor PPI reporting

The authors[9] extracted data on a range of parameters, including the involvement of patients/communities, description and extent of PPI activities/processes, and recognition of PPI contributions. The findings provide a disappointing assessment of PPI reporting. Of 360 articles, PPI was reported in 64 (18%) articles and 56 (19%) protocols. Overall, 84 (23%) of 360 trials reported PPI in the article or protocol. The narrative analysis provides a gloomier picture about the depth of reporting. Most articles (n=15, 23%) and protocols (n=16, 35%) described one single study activity/process involving PPI. Compared to the protocols, the PPI information provided in the articles was often vague or moderately detailed. The most common study activity was participation in trial committees, with generally broad descriptions of the specific roles and contributions but without detailed information on specific outcomes and the impact on decision making.

We might ask ourselves why poor PPI reporting continues, despite the obvious commitment to PPI expressed internationally by patients, funders, and the research community. One possibility is that PPI is still not fully embedded as a core part of research practice.[10] Perhaps PPI is not planned for in as much detail as other parts of a research study, which can make reporting difficult as activity can feel vague, or it might not be captured or evaluated in ways that can lead to high quality reporting. Or word length restrictions in journals affect what teams can report.

Whatever the reason for poor PPI reporting, we should consider several

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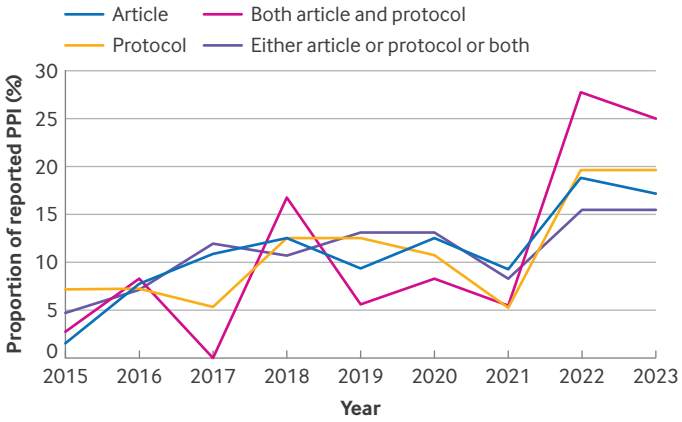
Study answer PPI was reported in only 18% (64/360) of articles and 19% (56/299) of protocols. When reported, PPI mainly involved patients and their representatives, with the most common PPI activity being participation in trial committees (44/64 PPI reporting articles; 39/56 protocols). PPI primarily occurred during the trial development phase, including feedback on study design, review of study materials, and assessment of feasibility. Protocols occasionally had more detailed information than did the published articles, but most PPI contributions were vague without detailed information on specific outcomes and the effect on decision making within the trial. Recognition of PPI contributions was more frequent in published articles (37/64; 58%) than in protocols (18/56; 32%), mainly in the acknowledgment section. Limitations include the possibility of inaccurate, misclassified, overestimated, or understated PPI reporting, especially if journals do not mandate PPI statements.

What this study adds This study found limited PPI reported in randomised controlled trials published in major medical journals and their protocols. The findings underscore the need for standardised PPI reporting practices to ensure consistent, detailed, and structured descriptions, ultimately enhancing the transparency and impact of PPI in clinical research.



Evolution over time of reported patient and public involvement in articles (total n=64), protocols (total n=56), both article and protocol (36/64 articles and 36/56 protocols), and either article or protocol or both (total n=84). Forty articles were sampled for each year from 2015 to 2023. Trends were modelled in R using logistic regression with year as continuous variable, resulting in P values of 0.003 for articles, 0.009 for protocols, P<0.001 for both article and protocol, and 0.02 for either article or protocol or both. Protocols were classified according to publication data of corresponding published article

Funding, competing interests, and data sharing No specific funding was received for this study. The authors have no competing interests to declare. All data, including the full dataset, are available from the corresponding author.

Study registration https://doi.org/10.17605/OSF.IO/4EQG2.

implications. From the patient's perspective, poor PPI reporting means that their contributions to a study are not publicly acknowledged, remaining only within the team. It might also mean that other patients view the study as being less credible or trustworthy. For clinicians who draw on an evidence base, it might be unclear to what extent patients have shaped the evidence; for example, they might not know if the outcomes measured in a study are important to patients. For researchers attempting to identify good practice, attempts to synthesise studies can be severely limited, leading to a fragmented evidence base that does not inform practice. From the funder and policy perspective, poor PPI reporting represents a form of research waste, when activity is undertaken but lost.[11]

JIM WEST/SPL

The highest levels of PPI reporting were observed in the past two years

Promising future

While providing a disappointing picture of PPI reporting, the study offers some promise: the highest levels of PPI reporting were observed in the past two years, which might suggest the beginning of an upward trend. Key reporting guideline updates, such as CHEERS 2022 for health economic evaluation,[12] now include PPI items. For randomised controlled trials, the forthcoming updated CONSORT 2025 checklist for trials and SPIRIT 2025 checklist for trial protocols will include one item on PPI,[13 14] addressing one of the recommendations made by Vanneste and colleagues.[9] We hope that this new focus on PPI reporting sends a new powerful signal to the international research community: plan well funded PPI in your protocol; do it using evidence to inform your practice; capture/evaluate it; and then report it in your paper, ideally with patients as coauthors. With this approach, we will grow the international PPI evidence base, support excellence in PPI reporting and practice, and contribute to more efficient and relevant randomised controlled trials that address patient needs and preferences.

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Firearm availability and firearm incidents

Worsham CM, Bray CF, Jena AB

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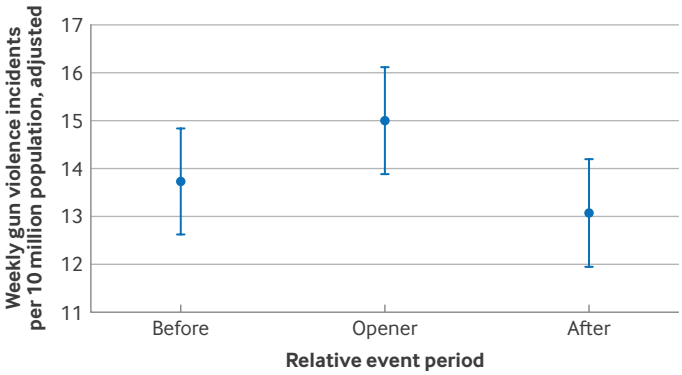
Study question Is the start of the hunting season in the United States associated with increased risk of adverse firearm incidents, both hunting and non-hunting related?

Methods The study took advantage of the arbitrarily timed increase in firearm and ammunition availability brought on by the start of deer hunting seasons to study the impact on hunting and non-hunting related firearm incidents. A retrospective ecological event study analysis was conducted of the populations of 10 US states for deer hunting seasons from 2016 to 2019. Data from the Gun Violence Archive were used to calculate average per capita weekly rates of firearm incidents overall and among specified categories in the periods before, during, and after the opening of deer hunting seasons combined into a single analysis across four years and 10 states, adjusting for state fixed effects.

Study answer and limitations Compared with control periods before and after the opening period, the start of the hunting season was associated with a 12.3% increase in the rate of firearm incidents overall (absolute change 1.34-1.50 incidents per 10 million population, 95% confidence interval for relative change 3.0% to 21.6%, P<0.01). Relative increases were observed for incidents categorised as hunting incidents (absolute change <0.01-0.05 per 10 million; relative change 566%), suicide (0.70-0.77; 11.1%), incidents involving alcohol or other substances (0.07-0.13; 87.5%), domestic violence (0.13-0.16; 27.4%), defensive use (0.08-0.10; 27.8%), home invasion or robbery (0.13-0.17; 30.4%), and incidents related to firearm carry licences (0.40-0.48; 19.4%). No differences were observed for incidents involving children or police officers. The study was observational and despite its quasi-experimental design, residual confounding is possible.



Total firearm incident rates before, during, and after opening of deer hunting season in 10 states. Adjusted firearm incident rates were calculated at weekly level and estimated from linear regression model that adjusted for fixed effects for state and fixed effects for period relative to hunting season opener. Opener was defined as three week period starting seven days before and ending 14 days after first day of firearm deer hunting season. This definition was chosen because increases in firearm availability might be greatest in the days before and shortly after opening day. Periods before and after opener were defined as three weeks before and three weeks after opening period, allowing for comparison of three mutually exclusive three week periods. Error bars represent point estimates' 95% confidence intervals. Incident types are not mutually exclusive except for hunting incidents. Included states are Alabama, Indiana, Michigan, Minnesota, Missouri, New York, Ohio, Pennsylvania, Texas, and Wisconsin

What this study adds The start of hunting season in the US was associated with increased rates of hunting and non-hunting related firearm incidents, most plausibly because of the increased availability of firearms and ammunition.

Funding, competing interests, and data sharing No funding. No competing interests declared. Data are publicly available.

CORRECTION

Sonolysis during carotid endarterectomy: randomised controlled trial

In the print abstract for this research paper by Školoudík and colleagues (*BMJ* 2025;388:e082750, published in the print issue of 22 March 2025), the study question should have stated 2 MHz rather than 2 Hz.