THE EFFECT OF PATIENT WARMING ON PERIOPERATIVE CARDIOVASCULAR OUTCOMES IN INTERVENTIONAL CLINICAL TRIALS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

SUBMITTED TO THE UNIVERISTY OF CAPE TOWN IN

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DECLARATION

I, Sisalindele Mkhize, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 27/09/2021

FORMAT OF THE DISSERTATION

This dissertation is submitted in the 'publication ready format'. It consists of two sections:

Section A. The manuscript prepared in accordance with the author guidelines for the chosen journal (Anaesthesia – The official journal of the Association of Anaesthetists).

Section B. Appendices

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ABSTRACT

BACKGROUND: Perioperative cardiovascular events are a common contributor to perioperative morbidity and mortality. Patient warming affects the cardiovascular system in various ways and may protect against cardiovascular events. We aimed to estimate the effect of active patient warming on perioperative cardiovascular outcomes in clinical trials.

METHODS: A systematic review with meta-analyses was conducted. Six data bases were searched from inception until 5th July 2021 for studies that prospectively assigned participants to any physical warming strategy and reported on cardiovascular outcomes. Screening, data extraction and risk of bias assessment were conducted in duplicate. 8782 records were identified. After removing duplicates and screening titles and abstracts, fifty-two full-text articles were assessed for eligibility, fourteen studies with 1711 participants were included in the systematic review and meta-analyses.

RESULTS: The effect of physical warming was – risk ratio (95% confidence interval from random effects model) - 0.74 (0.11; 4.73) for major adverse cardiovascular events, 1.07 (0.09; 13.03) for myocardial infarction, 0.56 (0.17; 1.85) for myocardial ischaemia, 0.48 (0.19; 1.20) for arrhythmias and 0.77 (0.25; 2.37) for all-cause mortality. Statistical heterogeneity was not concerning in any of the meta-analyses. All of the meta-analyses carried serious risk of bias and represent low quality evidence.

CONCLUSION: We found little information on the treatment effect of active patient warming on cardiovascular outcomes. Inconsistent definitions and reporting of cardiovascular events in patient warming trials confound synthesis of the data. We recommend that prospective studies of patient warming routinely report on cardiovascular outcomes. The effect of active patient warming on perioperative cardiovascular outcomes remains an important unanswered question in perioperative medicine.

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LIST OF ABBREVIATIONS

MACE	Major adverse cardiovascular events
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	The international prospective register of systemic reviews (The Centre for Reviews and Dissemination at the University of York, UK)
ASA	American Society Anesthesiologists
BMI	Body mass index
RoB2	Risk of bias 2 – version 2 of the Cochrane risk-of-bias tool for randomized trials
GRADE	Grading of recommendations, assessment, development and evaluation
RCT	Randomised control trial
ECG	Electrocardiogram
PACU	Post anaesthetic care unit
SCIP Inf-10	Surgical Care Improvement Project for Body Temperature Management

SECTION A: PUBLICATION READY MANUSCRIPT

Title: The effect of patient warming on perioperative cardiovascular outcomes in interventional clinical trials: a systemic review and meta-analysis.

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Patient warming and perioperative cardiovascular outcomes

Keywords: Humans, Cardiovascular system, Hypothermia, Perioperative care

SUMMARY

Perioperative cardiovascular events are a common contributor to perioperative morbidity and mortality. Patient warming affects the cardiovascular system in various ways and may protect against cardiovascular events. We aimed to estimate the effect of active patient warming on perioperative cardiovascular outcomes in clinical trials.

A systematic review with meta-analyses was conducted. Six data bases were searched from inception until 5th July 2021 for studies that prospectively assigned participants to any physical warming strategy and reported on cardiovascular outcomes. Screening, data extraction and risk of bias assessment were conducted in duplicate. 8782 records were identified. After removing duplicates and screening titles and abstracts, fifty-two full-text articles were assessed for eligibility, fourteen studies with 1711 participants were included in the systematic review and meta-analyses. The effect of physical warming was – risk ratio (95% confidence interval from random effects model) - 0.74 (0.11; 4.73) for major adverse cardiac events, 1.07 (0.09; 13.03) for myocardial infarction, 0.56 (0.17; 1.85) for myocardial ischaemia, 0.48 (0.19; 1.20) for arrhythmias and 0.77 (0.25; 2.37) for all-cause mortality. Statistical heterogeneity was not concerning in any of the meta-analyses. All of the meta-analyses carried serious risk of bias and represent low quality evidence.

We found little information on the treatment effect of active patient warming on cardiovascular outcomes. Inconsistent definitions and reporting of cardiovascular events in patient warming trials confound synthesis of the data. We recommend that prospective studies of patient warming routinely report on cardiovascular outcomes. The effect of active patient warming on perioperative cardiovascular outcomes remains an important unanswered question in perioperative medicine.

INTRODUCTION

Each year, more than 300 million non-cardiac surgeries are performed worldwide [1]. Cardiovascular events (cardiac death, myocardial infarction and non-fatal cardiac arrest) are a significant source of perioperative morbidity and mortality [1]. A national inpatient sample of hospital admissions in the United States between 2004 and 2013 identified that one in every thirty-three hospitalizations for non-cardiac surgery experienced a major adverse cardiovascular or cerebrovascular event [1]. The consequences of cardiovascular complications are prolonged inpatient hospitalization, increase in medical costs, disability and death [1]. Patients experiencing myocardial infarcts after non-cardiac surgery have an in-hospital mortality rate of 15% to 25% and this is an independent risk factor for death six months following surgery [2]. Cardiac arrest after non-cardiac surgery has a hospital mortality rate of 65% and is a risk factor for cardiac death five years following surgery [2].

Temperature regulation and monitoring forms an important part of the perioperative management of patients undergoing non-cardiac surgery. Anaesthesia, type of surgery and exposure to the operating theatre environment can lead to hypothermia. Hypothermia leads to increase in blood catecholamine levels resulting in systemic vasoconstriction, shivering, increase in blood pressure and heart rate. This increase in oxygen consumption may cause myocardial ischaemia and has been associated with a threefold increase in morbid myocardial outcomes [1-3]. It has been suggested that keeping patients warm may decrease perioperative cardiovascular events [4]. Contrary to this, heart rate is linked to body temperature and a higher intraoperative core temperature is associated with higher intraoperative heart rate. Increased intraoperative heart rate may increase the risk of cardiovascular events. Indeed, hypothermia has long been known to offer protection to the myocardium and other organs [5, 6]. This suggests that the relationship between patient warming and cardiovascular events may not be simple and warming may not always offer cardiovascular protection. The evidence for cardiovascular benefit from patient warming is weak. The evidence supporting the three-fold increase in cardiovascular events refers only to 12 cardiovascular events (unstable angina, cardiac arrest and myocardial infarction) out of 300 participants in a randomized control trial [3,10]. The evidence supporting the National Institute for Health and Care Excellence guidelines on patient warming (CG65) found only 2 cardiovascular events in their review of the evidence [7]. It is not advisable to base practice on fewer than 200 events [8]. Moreover, our observation that hypothermia is associated with both cardiovascular harm and benefit leads us to hypothesize that there may be significant effect modifiers that will lead to heterogeneity in the effect of patient warming on perioperative cardiovascular effects. The primary objective of this review is to determine the effect of active perioperative patient warming on perioperative major adverse cardiovascular events (MACE) in adult surgical patients undergoing non-cardiac surgery. Other objectives are to determine the effect of warming on the individual components of MACE, other specified cardiovascular events and to explore sources of statistical heterogeneity in the observed effects.

METHODS

A systematic review with meta-analyses was conducted and reported in accordance with the PRISMA statement. The review protocol is publicly accessible on the International Prospective Register of Systemic Reviews (PROSPERO). The registration number is CRD42016045891.

We included randomised controlled trials and non-randomised experiments where participants were assigned to at least one perioperative warming strategy and a control group and prospectively followed up. We excluded case-control studies, case series and case reports. Only studies of adult non-cardiac surgical patients were considered; adults, because perioperative cardiovascular events in children have a different pathophysiology to adults; non-cardiac surgery, because patient cooling is intentional in many cardiac surgical procedures and perioperative cardiovascular events have different pathophysiology in this population. The primary outcome was the composite of MACE defined as any of, i) cardiac death, ii) non-fatal cardiac arrest, iii) myocardial infarction, iv) coronary revascularization, and or v) stroke, within 30 days of surgery. Our secondary outcomes were i) the individual components of the composite primary outcome, ii) all-cause mortality, iii) cardioversion, iv) arrhythmias, v) myocardial ischaemia and vi) pulmonary embolism. Only studies of physical warming strategies were included. Studies of warmed intravenous and irrigation fluid were included, but studies of pharmacological and nutritional strategies were excluded. We included only studies reported in English. No restrictions were placed on the year of publication.

The literature search strategy was developed in PubMed using medical subject headings (Mesh terms) and key words in conjunction with a health sciences librarian at the University of Cape Town. The search strategy was adapted to apply to the included databases; PubMed (Medline), Scopus (Embase), EBSCOhost (Africa-wide, CINAHL), Cochrane Library (Central), and ClinicalTrials.gov. These databases were searched from inception until 5th July 2021. ClincalTrials.gov was searched for ongoing or recently completed trials and PROSPERO was searched for ongoing or recently completed systematic reviews. We also searched the reference lists from related systematic reviews for additional relevant articles. Refer to the supplementary file for the full search strategy **(Supporting Information S1)**.

Search results were imported into EndNote (Clarivate Analytics, MA, USA) and duplicate records were removed before exporting the results to Microsoft Excel (Redmond, WA, USA). Title and abstract screening, risk of bias assessment and data extraction were done in Excel using prepared spreadsheets.

Two reviewers (Sisalindele Mkhize [SM] and Modjadji Maake[MM]) independently screened all titles and abstracts yielded by the search against the eligibility criteria. Full reports were obtained for all titles that appeared to meet the eligibility criteria. The same two reviewers assessed the full texts of these studies in duplicate and decided whether to include these in the review. Where there was uncertainty or disagreements about eligibility, a third reviewer (Leon du Toit [LDT]) was consulted.

Data extraction was done in duplicate by SM and LDT. Data extraction spreadsheets were prepared in Excel. The data extraction spreadsheets were piloted using the first three included full texts to ensure consistency. Thereafter data extraction was conducted independently. Only published data were used in this review.

The following information was extracted from included full texts; i) study population characteristics: number of participants in each study arm, type of surgery, age of participants, American Society Anesthesiologists (ASA) status, body mass index (BMI); ii) intervention characteristics: type of active warming intervention, pre-warming versus intra-operative warming; iii) comparison group as defined by the study (e.g. usual care or other warming interventions); iv) outcomes (events per arm): major adverse cardiovascular outcomes, cardiac death, non-fatal cardiac arrest, myocardial infarction, cardioversion, arrhythmia, coronary revascularization, stroke, myocardial ischaemia, pulmonary embolism, all-cause mortality and temperature differences between study arms; v) timing of assessment of MACE; vi) study design; vii) risk of bias elements.

Risk of bias assessment was done in duplicate by SM and LDT. We used the Cochrane risk of bias tool version 2 (RoB2) for randomised trials. Risk of bias was assessed for the outcome of interest to this review. Disagreements were resolved through discussion and where agreement could not be reached, LDT made the final decision.

All included studies were summarised narratively and in table format. A separate meta-analysis was conducted for every pre-specified outcome for which more than one study reported on the outcome event. Events were added across study groups of multi-arm trials so that for each study only one intervention and one control group was entered into meta-analysis. For example, where a three-arm study compared forced air warming to electric blankets to the combination of forced air warming plus electric blankets, the events and participants in the forced air only and electric blanket only arms were added together and treated as one control arm. For each study, the group(s) that received more warming than other group(s) was considered the intervention group.

The risk ratio (RR) was used as the measure of effect in all meta-analyses. All reported forest plots are weighted with Mantel-Haenszel method with a continuity correction of 0.5 in studies with zero cell frequencies as recommended by the Cochrane group. The Sidik-Jonkman method was used to estimate between study variance in random effects models. Both fixed and random effects are reported for comparison. I^2 of greater than 50% was considered unacceptable statistical heterogeneity. Throughout, the estimates from the random effects models are presented as the chosen summary method regardless of the level of quantitative heterogeneity (I^2), because of the observed qualitative variation in intervention and control strategies, the variation in quality of evidence and the small information size of each meta-analysis. The random effects models represent a more conservative estimate of the 95% confidence intervals.

The individual RoB2 assessments are summarised graphically across all studies included in meta-analyses weighted according to individual study sample size. Funnel plot and Egger's test were planned to assess publication bias if more than ten studies were included in a single meta-analysis.

Additional subgroup analyses and meta-regression were planned: by intervention type, type of surgery, ASA status, age, BMI, risk of bias, type of study and difference between temperatures in comparison groups. The strength of the body of evidence for each meta-analysis was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system [9] and summarised in table format.

RESULTS

The results of the literature research and study selection are outlined in the PRIMSA flow chart ***Figure 1***. We identified 8661 records through database searching and an additional 121 records were identified through reference lists from related systematic reviews. 167 duplicates were removed and 8615 titles and abstracts were screened. 8563 records were excluded for not meeting the eligibility criteria. 52 full-text articles were assessed for eligibility. 38 full-text articles were excluded for the following reasons: three articles were not prospective experimental studies; in three articles, patients were not exposed to active warming, cardiovascular outcomes were not reported in twenty-one articles, four articles were not in English, one study was withdrawn due to safety issues, one study was suspended and five full text articles could not be found. Fourteen studies were included in the qualitative synthesis and the quantitative meta-analyses. These studies report on 1711 participants.

Table 1 summarises the study; participant characteristics and cardiovascular outcomes of the fourteen studies included in this review. All included studies were randomised controlled trials. Trial size ranged from 19 to 443 participants. The methods of warming were warming of the operating theatre, forced air warming, circulating water systems, electric heating blankets and pads, radiant warmers, warmed irrigation solution, heated humidifiers, water blankets and heating mattress.

Meta-analysis was conducted for the following outcomes: MACE, myocardial infarction, myocardial ischaemia, arrhythmias and mortality. Meta-analysis was not possible for cardiac death, non-fatal cardiac arrest, coronary revascularization, stroke, cardioversion and pulmonary embolism because less than two studies reported these outcome events. One study reported a cardiac death but it was not mentioned in which arm the event occurred [10]. The same study reported on two events of non-fatal cardiac arrest in the control group. One study reported a single event of pulmonary embolism in the control group [11]. There were no studies reporting on emergency coronary revascularization, stroke, electrical or pharmacological cardioversion. The supplementary file reports detailed results of the analysis of heterogeneity (subgroup and meta-regression analyses) for each reported meta-analysis **(Supporting Information S2)**.

Major adverse cardiovascular events (MACE)

There were 302 participants randomised to a warming strategy; two events occurred in this group. 332 participants were randomised to a control strategy; five events occurred in this group. The control groups include both 'no warming' and 'less warming' strategies. MACE was not significantly decreased by active warming (RR=0.74 [95% CI 0.11-4.73]) with little heterogeneity (I^2= 6% [95% CI 0-86]) ***Figure 2***. RoB2 findings showed three studies at high risk of bias [12-14], two had some concerns [15, 16] and one study had low risk of bias [10]. Subgroup analysis by RoB2 explained the limited amount of statistical heterogeneity. Small studies with high risk of bias reported harm, while larger studies reported benefit. Residual I^2 = 0% after subgrouping.

Subgroup analyses by intervention category (environmental warming versus warmed blanket or mattress) and by type of surgery (extremity surgery versus major abdominal, thoracic or vascular surgery) did not explain the observed heterogeneity. In meta-regression, age did not modify the effect and lack of reporting precluded meta-regression against BMI and temperature differences between comparison groups. The GRADE strength of evidence for this meta-analysis was very low (Table 2).

Myocardial ischaemia

There were 277 participants randomised to a warming strategy; thirteen events occurred in this group. 292 participants were randomised to a control strategy; twenty-six events occurred in this group. The control groups include both 'no warming' and 'less warming' strategies. The risk of developing myocardial ischaemia was notably decreased by active warming but this effect was not statistically significant (RR= 0.56 [95% CI 0.17-1.85]). Twenty-five percent of the variation in this meta-analysis is attributable to heterogeneity (I^2=25% [95% CI 0-92]) ***Figure 3***. Using RoB2, two studies had high risk of bias [17, 18], one study had some concerns [11] and one study had low risk of bias [10]. Subgroup analysis by type of surgery and type of intervention similarly distinguished between studies with a protective estimate compared to the one with an estimate of harm. The information size is very small, with only one study with one event in the orthopaedic surgery and warm irrigation fluid subgroups [17]. In the meta-regression, age and BMI did not modify the effect. Lack of reporting precluded meta-regression against temperature differences between comparison groups. The GRADE strength of evidence was low for this meta-analysis (Table 2).

Myocardial infarction

There were 163 participants randomised to a warming strategy; one event occurred in this group. 179 participants were randomised to a control strategy; one event occurred in this group. The control groups include both 'no warming' and 'less warming' strategies. The risk of developing a myocardial infarct was not notably changed by active warming, but there is little confidence in the estimate due to the small information size (RR=1.07 [95% CI 0.09-13.03]). None of the variation in this meta-analysis is attributed to heterogeneity ($I^{\wedge 2}$ = 0%) ***Figure 4***. RoB2 findings showed one study with high risk of bias [12] and the other with low risk of bias [10]. Subgroup analysis and meta-regression was not conducted due to the small information size. The meta-analysis only contains two studies with one event in each study. The GRADE strength of evidence was very low (Table 2).

Arrhythmias

642 participants were randomised to a warming strategy; forty-one events occurred in this group. 673 participants were randomised to a control group; eighty-seven events occurred in this group. The control groups include both 'no warming' and 'less warming' strategies. The risk of developing arrhythmias was notably decreased by active warming but the estimate was not statistically significant (RR = 0.48 [95% CI 0.19-1.20]). Thirty-five percent of the variation in the estimate is attributable to heterogeneity (I^2 = 35% [95% CI 0-74]) ***Figure 5***. RoB2 findings showed five studies with high risk of bias [17-21] one with some concerns [11] and one with low risk of bias [10].
Subgroup analysis by type of intervention explained some of the heterogeneity (residual I^2 = 24%). Subgroup analysis by type of surgery and by risk of bias did not explain the observed heterogeneity. In meta-regression, age and BMI did not modify the effect. Lack of reporting precluded meta-regression against temperature differences between comparison groups. The GRADE strength of evidence was low in this meta-analysis (Table 2).

Mortality

332 participants were randomised to a warming strategy; five events occurred in this group. 361 participants were randomised to a control strategy; seven events occurred. The control groups include both 'no warming' and 'less warming' strategies. The risk of mortality was not notably changed by active warming, but there is little confidence in the estimate due to the small information size (RR = 0.77 [95% CI 0.25-2.37]) ***Figure 6***. None of the variation in this meta-analysis is attributed to heterogeneity (I^2 = 0%). RoB2 findings showed four studies with high risk of bias [12, 13, 19, 22], three studies with some concern [23-25] and one study with low risk of bias [10].
Subgroup analysis and meta-regression was not conducted due to the small information size. Only three studies in the meta-analysis contributed information to the pooled estimate. The meta-analysis only contains twelve events in total. The GRADE strength of evidence was very low for this meta-analysis (Table 2).

All meta-analyses contain fewer than ten studies, which precluded evaluation of publication bias.

Figure 7 summarises the risk of bias across all included studies.

DISCUSSION

In this systematic review, we screened 8782 titles and included fourteen trials which reported on cardiovascular outcomes of participants randomised to a perioperative warming intervention or a control group. The mean age of participants ranged from 35 to 71 years. Compared to a younger surgical population, the elderly is at increased risk of developing cardiovascular complications because of the increased prevalence of chronic diseases and the physiological changes associated with advancing age. A total of 63 cardiovascular events occurred in the warming arms compared to 126 in the control groups. An additional three reported events could not be assigned to a specific study arm. Although the estimated risk reduction for MACE, myocardial ischaemia and arrhythmias were greater than 25%, none of the estimated effects reached statistical significance. These meta-analyses are all underpowered for the reported cardiovascular outcomes.

A retrospective observational study by Scott et al [26] showed that compliance with the Surgical Care Improvement Project for Body Temperature Management (SCIP Inf-10) was associated with reduced incidence of ischaemic cardiovascular events, mortality and reduced length of stay, which correlates with the reduced events in patients who were exposed to active warming in comparison to the control groups in this review. However, a higher intraoperative core temperature is associated with higher intraoperative heart rate and increased myocardial workload which may increase the risk of cardiovascular events. This suggests that the relationship between patient warming and cardiovascular events may not be simple and warming may not always offer cardiovascular protection. Outside the operating room, Young et al [36] demonstrated a U-shaped relationship between patient temperature and critical care outcomes; both too hot and too cold are associated with adverse outcomes. The true underlying relationship between patient warming and cardiovascular outcomes may well follow this goldilocks principle. We planned to use meta-regression to look for evidence of a dose-response relationship, but the available information was not sufficient to answer this question.

The confidence intervals of the effects assessed in our review are wide indicating that we have little evidence to support any effect (or absence of effect). Few studies reported on temperature differences 60 minutes into surgery and at the end of surgery. Lack of reporting precluded meta-regression against temperature differences between comparison groups. Demonstration of a dose-effect (linear or otherwise) would go a long way to support any claim of benefit (or harm) of perioperative warming practice. The most used warming intervention was forced-air warming (nine trials [10, 13-16, 18-21]). It is suggested that this is the most effective method of maintaining body temperature and it is one of the simplest and most cost-effective methods of improving perioperative care [28].

All meta-analyses had an I^2 less than 50%, but due to small information size contained in each meta-analysis, the confidence intervals for these estimates of heterogeneity were wide. We found evidence that difference in risk of bias and sample size between studies explained the heterogeneity in the effect of warming on MACE. We could not explain the source(s) of heterogeneity in the meta-analysis of myocardial ischaemia. The differences in warming methods explained some of the heterogeneity in the meta-analysis of arrhythmias. Where conducted, age and BMI did not modify the estimated effects in meta-regression, but the range of average ages and BMIs across included studies was restricted as were the number of studies available for meta-regression. Thirteen out of fourteen studies had high or some risk of bias. Subgroup analyses supported our hypothesis that type of surgery and type of warming intervention may modify the effect of patient warming (subgroup analysis of arrhythmias). We could not evaluate publication bias because all meta-analyses had fewer than ten studies.

The GRADE strength of evidence for each outcome was low (myocardial ischaemia, arrhythmias and mortality) or very low (MACE and myocardial infarction). The reasons for rating the strength of evidence as low was most studies had high risk of bias, all meta-analyses suffered from imprecision as the effect estimate came from only two to six small studies and we were not able to measure publication bias. Our findings couldn't support our hypotheses as there was insufficient data to make any conclusions.

We found five systematic reviews that set out to reported on the effects of temperature management on perioperative cardiovascular outcomes: Madrid et al [30] included 67 trials with 5438 participants assessing the effectiveness of preoperative and intra-operative active body warming systems in preventing unintended perioperative complications of hypothermia. This study reported that forced air warming has beneficial effects on major cardiovascular complications in people with substantial cardiovascular disease, although the evidence was limited to one study. Campbell et al [30] included 24 trials with 1250 participants estimating the effectiveness of preoperative and intra-operative warming of irrigation and intravenous fluids in preventing perioperative hypothermia and its complications. None of the included trials reported on cardiovascular outcomes. Warttig et al [31] included 11 trials with 699 participants estimating the effectiveness of treating inadvertent perioperative hypothermia through postoperative interventions. No data was available in relation to major cardiovascular complications. Alderson et al [29] included 22 trials. They assessed the effects of preoperative and intra-operative thermal insulation in preventing hypothermia and its complications. Major cardiovascular outcomes were not reported as there was no data. Balki et al published [32] included 54 trials with 3976 participants measuring the effect of perioperative active body warming systems on clinical outcomes. No significant differences were found in major cardiovascular events with very low quality of evidence. We excluded pharmacological and nutritional interventions as these may impact on cardiovascular outcomes through mechanisms unrelated to body temperature whereas three out of the five included these interventions [29-31]. Our review focused on perioperative cardiovascular outcomes whereas the other five reviews also reported on pain scores, shivering, patient satisfaction, wound infections, bleeding and its complications, blood transfusion, pressure ulcers and adverse effects. One of the five reviews reported very low [32] and another reported low [33] quality of evidence with cardiovascular outcomes. Articles from the five reviews were screened and 121 were considered for our review. Only two of these articles were included as they reported on cardiovascular outcomes. There are currently no ongoing studies on ClinicalTrials.gov that are trying to answer our research question.

Our review has limitations. These include limiting our search to English language publications and the inability to perform meta-analysis for all our stated outcomes, because we found insufficient evidence suitable for synthesis. There were small sample sizes for the studies and most studies did not investigate cardiovascular events as their primary outcome. The body of evidence was small for our primary outcomes. Some of the included trials were not fully powered for this. Each meta-analysis only contains so many participants and that there are few events recorded in each meta-analysis.

CONCLUSION

There is low certainty of association between patient warming and cardiovascular complications in clinical trials. The quality of evidence cannot support practice guidance regarding the effect of perioperative warming on cardiovascular outcomes. Inconsistent reporting and definitions of cardiovascular outcomes and potential effect modifiers hampers synthesis of evidence on this topic. We recommend that studies evaluating the effect of patient warming routinely report on patient important outcomes, specifically cardiovascular outcomes and not just differences in body temperature. Larger sample sizes for such trials are needed. It is concerning that after more than forty years of perioperative patient warming practice, we are not able to say whether or not this intervention poses cardiovascular benefit or harm.

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  Developing literature search strategy
  Reviewer
  Data extraction
  Drafting the manuscript and critical revision of the work
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REFERENCES

1. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. *Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery*. The Journal of the American Medical Association cardiology. 2017;**2**(2):181-7.
2. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. *Perioperative cardiac events in patients undergoing non-cardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk*. Canadian Medical Association Journal. 2005 **173**(6):627-34.
3. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. *Temperature regulation and monitoring*. 8th Edition ed: Elsevier Health Sciences; 2014.
4. Moola S, Lookwood C. *Effectiveness of strategies for the management and/or prevention of hypothermia within the adult perioperative environment.* The International Journal of Evidence-Based Healthcare 2011;**9**:337-45.
5. Kohlhauer M, Pell V, Burger N et al. *Protection against cardiac ischemia-reperfusion injury by hypothermia and by inhibition of succinate accumulation and oxidation is additive.* Basic Research in Cardiology. 2019;**114**(3):1-9.
6. Sun YJ, Zhang ZY, Bin F et al. *Neuroprotection by therapeutic hypothermia.* Frontiers in Neuroscience. 2019;**13**.
7. NICE guidelines. Inadvertent Perioperative Hypothermia. 2016 [cited 2019 21 November 2019]. Available from: http://www.nice.org.uk/guidance/cg65.
8. Flather MD, Farkouh ME, Pogue JM, Yusuf S. *Strengths and limitations of meta-analysis: larger studies may be more reliable. Controlled clinical trials.* 1997;**18**(6):568-79.
9. McMaster University (developed by Evidence Prime Inc). GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. 2020 [cited 5th August 2021]. Available from: https://gradepro.org/.
10. Frank SM, Fleisher LE, Breslow MJ, Hiaains MS, Ollson KF, Kelly S, Seattle C. *Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events: A randomized clinical trial. The Journal of the American Medical Association.* 1997;**277**(14):1124-27.
11. Zhang Z, Xu M, Wu D, Zhang X, Wu J. *Postoperative Myocardial Injury in Middle-Aged and Elderly Patients Following Curative Resection of Esophageal Cancer With Aggressive or Standard Body Temperature Management: a Randomized Controlled Trial.* Anesthesia & Analgesia. 2019 **129**(2):352-9.
12. Roizen MF, Sohn YJ, L'Hommedieu CS, Wylie EJ, Ota MK. *Operating room temperature prior to surgical draping: effect on patient temperature in recovery room.* Anesthesia and Analgesia. 1980 Nov;**59**(11):852-5.
13. University of Wisconsin, Madison. Prospective Trial of the Effect of Preoperative Forced-air Warming on Perioperative Body Temperature Following Neuraxial Anesthesia in Total Hip Arthroplasty Patients. [Internet]. 2016 [cited 12 November 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT01626690.
14. Yi J, Liang H, Song R, Xia H, Huang Y. *Maintaining intraoperative normothermia reduces blood loss in patients undergoing major operations: a pilot randomized controlled clinical trial.* BioMed Central Anesthesiology. 2018;**18**:126.
15. Krenzischek DA, Frank S, Kelly S. *Forced-air warming versus routine thermal care and core temperature measurement sites. Journal of Post Anesthesia Nursing.* 1995 **10**(2):69-78.
16. Wong PF, Kumar S, Bohra A, Whetter D, Leaper DJ. *Randomized clinical trial of perioperative systemic warming in major elective abdominal surgery.* British Journal of Surgery. 2007 April;**94**(4):421-6.
17. Oh JH, Kim JY, Chung SW, Park JS, Kim DH, Kim SH. *Warmed irrigation fluid does not decrease perioperative hypothermia during arthroscopic shoulder surgery.* Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2014;**30**(2):159-64.

18. Shu-Fen S, Hsiao-Chi N. *Efficacy of forced-air warming for preventing perioperative hypothermia and related complications in patients undergoing laparoscopic surgery: A randomized controlled trial* International Journal of Nursing Practice. 2018 **24**(5):e12660.
19. Grossman S, Bautista C, Sullivan L. *Using evidence-based practice to develop protocol for postoperative surgical intensive care unit patients.* Dimensions of Critical Care Nursing. 2002 **21**(5):206-14.
20. Huiying X, Guangjun R, Chunguang L et al. *Effect of forced-air warming system in prevention of postoperative hypothermia in elderly patients: A Prospective controlled trial.* Medicine. 2019;**98**(22):e15895.
21. Zhang R, Chen X, Xiao Y. *The effects of a forced-air warming system plus electric blanket for elderly patients undergoing transurethral resection of the prostate: A randomized controlled trial.* Medicine 2018;**97**(45):e13119.
22. Zhao R, Qiu J, Wu J et al. *Effect of heated humidified ventilation on intraoperative core temperature and prognosis in normothermic thoraco-abdominal aortic aneurysm repair.* Journal of Thoracic Disease. 2020;**12**(3):276-83.
23. Krenzischek DA, Frank S, Kelly S. *Forced-air warming versus routine thermal care and core temperature measurement sites.* J Post Anesth Nurs. 1995 April;**10**(2):69-78.
24. Zwakowski, M. Effect of a Warming Mattress on Perioperative Hypothermia Following Cesarean Delivery [Internet]. 2019 [cited 5th July 2021]. Available from: https://clinicaltrials.gov/ct2/show/NCT02837913.
25. Wong PF, Kumar S, Bohra A, Whetter D, Leaper DJ. *Randomized clinical trial of perioperative systemic warming in major elective abdominal surgery.* Br J Surg. 2007 April;**94**(4):421-6.
26. Scott AV, Frank SM. *Compliance with surgical care improvement project for body temperature management is associated with improved clinical outcomes.* Anesthesiology. 2015;**123**(1):116-25.
27. Devereaux PJ, Sessler D. *Cardiac complications in patients undergoing major non-cardiac surgery.* The New England Journal of Medicine. 2015;**373**:2258-69.
28. Hynson JM, Sessler D. *Intraoperative warming therapies: A comparison of three devices.*Journal of Clinical Anesthesia. 1992;**4**:194-9.
29. Alderson P, Campbell G, Smith AF, Warttig S, Nicholson A, Lewis SR. Thermal insulation for preventing inadvertent perioperative hypothermia. Cochrane Systematic Review 2014. [internet]. 2014 [cited 18 October 2019]. Available from: https://doi.org/10.1002/14651858.CD009908.pub2.
30. Campbell G, Alderson P, Smith AF, Warttig S. Warming of intravenous and irrigation fluids for preventing inadvertent perioperative hypothermia.Cochrane Systematic Review. [Internet]. 2015 [cited 16 October 2019]. Available from: https://doi.org/10.1002/14651858.CD009891.pub2.
31. Wartig S, Alderson P, Campbell G, Smith AF. Interventions for treating inadvertent postoperative hypothermia. Cochrane Systematic Review. [Internet]. 2014 [cited 16 October 2019]. Available from: https://doi.org/10.1002/14651858.CD00.
32. Balki I, Khan JS, Staibano P. *Effect of Perioperative Active Body Surface Warming Systems on Analgesic and Clinical Outcomes: A Systematic Review and Meta-analysis of Randomized Controlled Trials.* Anesthesia & Analgesia. 2020;**131**(5):1430-43.
33. Madrid E, Urrútia G, Roqué i Figuls M et al. Active body surface warming systems for preventing complications caused by inadvertentperioperative hypothermia in adults. Cochrane Systematic Review. [Internet]. 2016 [cited 16 December 2019]. Available from: https://doi.org/10.1002/14651858.CD009016.pub2.
34. Zhang R, Chen X, Xiao Y. *The effects of a forced-air warming system plus electric blanket for elderly patients undergoing transurethral resection of the prostate: a randomized controlled trial.* Medicine. 2018;**97**(45):e13119.

35. Xu H, Xu G, Ren C, Liu L, Wei L. *Effect of forced-air warming system in prevention of postoperative hypothermia in elderly patients: A Prospective controlled trial*. Medicine. 2019;**98**(22):e15895.

36. Young PJ, Saxena M, Beasley R, Bellomo R, Bailey M, Pilcher D, Finfer S, Harrison D, Myburgh J, Rowan K. Early peak temperature and mortality in critically ill patients with or without infection. Intensive care medicine. 2012 Mar; 38(3):437-44.

TABLES AND FIGURES

TABLE 1: CHARACTERISTICS AND CARDIOVASCULAR FINDINGS OF INCLUDED STUDIES

First Author, year of publication	***Study population***	***Intervention and control***	***Cardiovascular findings***
Study design, sample size	***Primary outcome***	***Temperature difference between study groups***	***Risk of Bias***
Roizen et al, 1980[12]	Aorto-femoral bypass and aortic aneurysm resection. ASA not reported. Age not reported. BMI not reported.	Warm operating room (24 °C) compared to cold operating room (17 °C) before start of case. (Prewarming)	1/21 patients developed a myocardial infarct in the warm operating theatre group. All patients were discharged from hospital alive.
RCT, n=42	Difference in body temperature and incidence of shivering.	Temperature difference 0.2°C at 60 min into the surgery and 0.1°C at the end of surgery.	High risk of bias due to: too little information about randomisation, allocation concealment and baseline covariate balance; too little information provided to assume low risk on the effect of assignment to intervention; unknown whether outcome assessors where blinded; assessment subjective as not all got enzymes tested routinely and ECG abnormalities poorly defined; cardiovascular outcome not clearly defined and analysis plan not specified.
Zhang R et al, 2018[34]	TURP under spinal anaesthesia. 52% ASA I, 48% ASA II. Mean age 65, 66, 67 years. Mean BMI 26.	Intraoperative warming using electric blankets or forced-air warming compared to using both forced-air warming plus electric blankets.	10/160 patients developed arrhythmias in the aggressive warming group and 47/283 patients in the standard warming groups.
RCT, n=443, three arms	Difference in body temperature.	Temperature difference was not reported 60 min into the surgery or at the end of surgery.	High risk of bias due to: flow diagram, exclusion criteria and difference in group sizes suggest systematic exclusion of participants after randomisation; arrhythmia not specified outcome, no definition of arrhythmia provided, timing of assessment unknown, trial registry

			number refers to a different trial, can't find trial registry.
Oh et al, 2014[17]	Arthroscopic shoulder surgery. Participants were either ASA I or ASA II. Mean age 59 and 62 years. Mean BMI 25 and 26.	Warmed arthroscopic irrigation fluids compared to room-temperature irrigation fluid.	1/36 patient developed intraoperative ST elevation in the warm fluid group. It normalised following nitroglycerin infusion. 2/36 cases of bradyarrhythmia in the warm fluid group. Both resolved during warming in PACU.
RCT, n=72	Difference in body temperature.	Temperature difference was not reported 60 min into the surgery but it was 0.1°C at end of surgery.	High risk of bias due to: Only reporting on intraoperative ECG monitoring without routine postoperative monitoring and enzymes - inadequate for adjudicating perioperative ischaemia and arrhythmias; definition of cardiovascular events not pre-specified.
Zhang Z et al, 2019[11]	Elective curative resection of oesophageal cancer. 2.9% ASA I, 91.4% ASA II, 5.7% ASA III. Mean age 62 and 63 years. Mean BMI 22 and 23.	Active warming protocol using heating pads compared to no warming unless participant temperature decreased below 35.0°C.	3/35 myocardial ischaemia events in the intervention arm and 11/35 in the control arm. 1/35 participants in the control group developed a pulmonary embolism and none in the intervention arm. 1/35 participants in the intervention arm developed a ventricular premature contraction. In the control arm, 5/35 had atrial fibrillation, 2/35 had supraventricular tachycardia and 3/35 had ventricular premature contractions.
RCT, n=70	Incidence of post-operative myocardial injury assessed by Troponin levels.	Temperature difference was not reported 60 min into the surgery or at the end of surgery.	Some concerns in the risk of bias due to potential deviations from the intended intervention.
Frank et al, 1997[10]	Abdominal, Vascular and Thoracic surgery. ASA: 79.6 % ASA III, 8.7% ASA II and 11.7% ASA IV. Mean age 71 years. Mean BMI 26.	Active forced air warming intra-operatively and postoperatively compared to no active warming.	1 cardiac death occurred but it was not stated in which arm. 2/158 participant developed non-fatal cardiac arrest in the control arm and none in the intervention arm. 1/158 developed a myocardial infarct in the control arm and none in the intervention arm. 9/142 developed myocardial ischaemia in the intervention arm and 15/158 in the control arm. 3/142 patients developed arrhythmias in the intervention arm and 11/158 in the control arm. 2/142 in-hospital deaths occurred in the intervention arm and 2/158 in the control arm.

RCT, n=300	Cardiac morbidity (unstable angina, ischemia, cardiac arrest, myocardial infarct) for the first 24 hours postoperatively.	Temperature difference was not reported 60 min into the surgery and at the end of surgery.	Low risk of bias
Wong PF et al, 2007[16]	Major abdominal surgery requiring bowel resection with or without anastomosis. 28% ASA 1, 49% ASA 2, 23% ASA 3. Median age 61 and 63 years. Median BMI 23 and 25.	Use of a warming mattress pre-, intra-, and postoperatively in addition to standard care with intraoperative forced air warming and warmed intravenous fluids, compared to standards care alone.	There were 2/56 cardiovascular complications in the standard care group, none in the intensive warming group.
RCT, n=103	Postoperative morbidity	Temperature difference 60 min into the surgery was 0.2°C and not reported at the end of surgery.	Some concerns in the risk of bias due to limited information provided regarding MACE and no mention in the article how cardiac complications were measured.
Grossman et al, 2002[19]	Abdominal, vascular, arthroplasty, thoracic, gynaecologic surgeries. ASA not reported Mean age 71 years. BMI not reported.	Intraoperative forced air-warming or warm fluid circulating blanket compared to room temperature cotton blankets.	8/40 in the warming groups and 4/20 in the control group developed arrhythmias.
RCT, n=60, three arms	Difference in body temperature and postoperative rewarming time.	Temperature difference not reported 60 min into the surgery, but it was 0.8°C at the end of surgery.	High risk of bias due to picking index cards in a packet is unlikely to be random, concerns about deviation from intended intervention and measurement of the outcome.
Huiying Xu et al, 2019[35]	Knee & hip arthroplasty. 61% ASA I, 39% ASA II. Mean age 69 and 70 years. Mean BMI 24.	Intraoperative forced air warming at 38°C or 42°C compared to no warming.	17/165 in the warming groups developed arrhythmias. 15/78 in the control group developed arrhythmias.

RCT, n=243, three arms	Postoperative rewarming time	Temperature difference was not reported 60 min into the surgery and at the end of surgery.	High risk of bias due to no definition for outcome and no mention of blinded assessors
University of Wisconsin, 2012[13]	Total hip arthroplasty. ASA not reported Mean age 66 and 67. BMI not reported.	Patients warmed by forced air warming suit compared to regular forced air warming blanket.	1/47 in the intervention group developed a cardiovascular event. It was not specified whether the event was an arrhythmia or myocardial ischaemia.
RCT, n=100	Difference in body temperature	Temperature difference was not reported 60 min into surgery and at the end of surgery.	High risk of bias due to: study tells that there is randomisation but no info on allocation concealment, insufficient information on the effect of assignment to intervention; 2 patients, both in the intervention arm, lost to follow-up without explanation; no information on method of assessment of cardiovascular outcomes.
Su Shu-Fen et al, 2018[18]	Thoracoscopic pneumonectomy, laparoscopic prostatectomy, nephrectomy. 26% ASA I, 73% ASA II. Mean age 56 and 61. Mean BMI 24 and 25.	Forced air warming intra- and postoperatively compared to intraoperative blankets and postoperative radiant warming.	No patient experienced cardiac complications.
RCT, n=128	Difference in body temperature and perioperative morbidity.	Temperature difference was0.3°C 60 min into the surgery and 0.6°C at the end of surgery.	High risk of bias due to patient with intraoperative cardiovascular instability excluded after randomisation, cardiovascular outcomes not defined and timing not specified.
Jie Yi et al, 2016[14]	Hip arthroplasty and thoracic surgery. 26% ASA I, 69% ASA II, 5% ASA III. Mean age 58 and 59. Mean BMI 24 and 25.	Pre- and intraoperative forced air warming compared to cotton blankets.	No patient developed any cardiac events.
RCT, n=62	Blood loss	Temperature difference was not reported 60 min into the	High risk of bias due to: although deviations from the intended intervention seem balanced, no information is given about what happened; flow diagram

		surgery and at the end of surgery.	reports losses to follow-up not clarified in text, no information on methods of assessment of cardiovascular outcomes; cardiovascular outcomes not defined and timing not specified.
Krenzischek et al, 1995[15]	Thoracic, vascular, abdominal surgery. ASA not reported. Mean age 69 years. BMI not reported.	Forced air warming intra-and postoperatively compared to surgical drapes only.	No cardiovascular morbidity during first 24 hours after surgery.
RCT, n=29	Difference in body temperature	Temperature difference was 0.6°C 60 min into the surgery and 1.3°C at the end of the surgery.	Some concerns in the risk of bias as it was not specified how to ascertain that patients didn't develop cardiovascular complication eg. ECG, Troponin T
Zhao, 2020[22]	Open thoracoabdominal aortic aneurysm repair. ASA not reported. Mean age 47 and 40.7. Mean 24 and 25.	Heated humidified ventilation and water blanket compared to water blanket only.	2 patients died in the intervention group and 3 patients in the control group.
RCT, n=40	Difference in body temperature	Temperature difference was 0.06^{0}C 60 min into the surgery and 0.05^{0}C at the end of surgery.	High risk of bias
Karowski, 2019[24]	Caesarean section. ASA not reported. Mean age 34.6. Mean BMI 29.2.	Underbody warmer on and VitaHeat underbody heating mattress compared to underbody warmer off and VitaHeat underbody heating mattress.	No patients died.
RCT, N=19	Temperature at time of post anaesthesia care unit admission.	No temperatures recorded 60 min into the surgery and at the end of surgery.	Some concerns in the risk of bias.

ASA: American Society of Anesthesiology, RCT: Randomised control trial, BMI: body mass index, ECG: electrocardiogram, PACU: Post Anaesthetic Care Unit

TABLE 2: GRADE STRENGTH OF EVIDENCE TABLE

Certainty assessment							*Number of patients*		*Effect*		*Certainty*	*Impor-tance*
Number of studies	**Study design**	**Risk of bias**	**Incon-sistency**	**Indirect-ness**	**Impre-cision**	**Other consider-ations**	**Warming group**	**Standard care group**	**Relative (95% CI)**	**Absolute (95%CI)**		
Major adverse cardiovascular outcomes (MACE) (follow-up: median 30 days)												
6	RCT	Very serious	Not serious	Not serious	Serious	None	3/302 (1.0%)	5/332 (1.5%)	**RR 0.74** (0.11 to 4.73)	**4 fewer per 1,000**(from 13 fewer to 56 more)	Very low	Critical
Myocardial ischaemia (follow-up: median 30 days)												
4	RCT	Serious	Not serious	Not serious	Serious	None	13/227 (4.7%)	26/292 (8.9%)	**RR 0.56** (0.17 to 1.86)	**39 fewer per 1,000**(from 74 fewer to 77 more)	Low	Critical
Myocardial infarct (follow-up: median 30 days)												
2	RCT	Serious	Serious	Not serious	Serious	None	1/163 (0.6%)	1/169 (0.6%)	**RR 1.07** (0.09 to 13.03)	**0 fewer per 1,000**(from 5 fewer to 71 more)	Very low	Critical
Arrhythmias (follow-up: median 30 days)												
7	RCT	Very serious	Not serious	Not serious	Not serious	None	41/642 (6.4%)	87/673 (12.9%)	**RR 0.48** (0.19 to 1.20)	**67 fewer per 1,000**(from 105fewer to 26more)	Low	Critical
Mortality (follow-up: median 30 days)												
8	RCT	Very serious	Not serious	Not serious	Serious	None	5/332 (1.5%)	7/361 (1.9%)	**RR 0.77** (0.25 to 2.37)	**4 fewer per 1,000**(from 15 fewer to 27 more)	Very low	Critical

GRADE: Grading of recommendations assessment, development and evaluation; CI: Confidence interval; RR: Relative risk; RCT: Randomised control trial

TABLE 3: ROB-2 TABLE

	Risk of bias arising from the randomisation process	**Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**	**Missing outcome data**	**Risk of bias in measurement of the outcome**	**Risk of bias in selection of the reported result**	**Overall risk of bias judgment**
Riozen, M. 1980	Some concerns	High	Low	Some concerns	High	High
Zhang, R. 2018	High	High	Low	High	High	High
Oh, JH. 2014	Low	High	Low	Low	High	High
Zhang, Z. 2019	Low	Some concerns	Low	Low	Some concerns	Some concerns
Frank, S. 1997	Low	Low	Low	Low	Low	Low
Wong, PF. 2007	Low	Some concerns	Low	Low	Some concerns	Some concerns
Grossman, S. 2002	High	High	Low	Low	High	High
Shu-Fen, S. 2018	Low	High	High	High	High	High
Huiying, X. 2019	Low	Some concerns	Low	Low	High	High
Yi, J. 2018	Low	Some concerns	High	High	High	High
University of Wisconsin. 2016	Some concerns	Some concerns	Low	High	High	High
Krenzischek, DA. 1995	Low	Low	Low	Some concerns	Some concerns	Some concerns
Zhao, R. 2020	Low	Low	High	High	High	High
Zakowski, M. 2019	Low	Some concerns	Low	Low	Some concerns	Some concerns

Low	Some concerns	High

Figure Captions

Figure 1: PRIMSA flow diagram

Figure 2: Forest plot of the effect of patient warming on major adverse cardiovascular events. Figure

3: Forest plot of the effect of patient warming on myocardial ischaemia.

Figure 4: Forest plot of the effect of patient warming on myocardial infarction. Figure

5: Forest plot of the effect of patient warming on arrhythmias.

Figure 6: Forest plot of the effect of patient warming on mortality.

Figure 7: Risk of bias weighted by sample size.

FIGURE 1

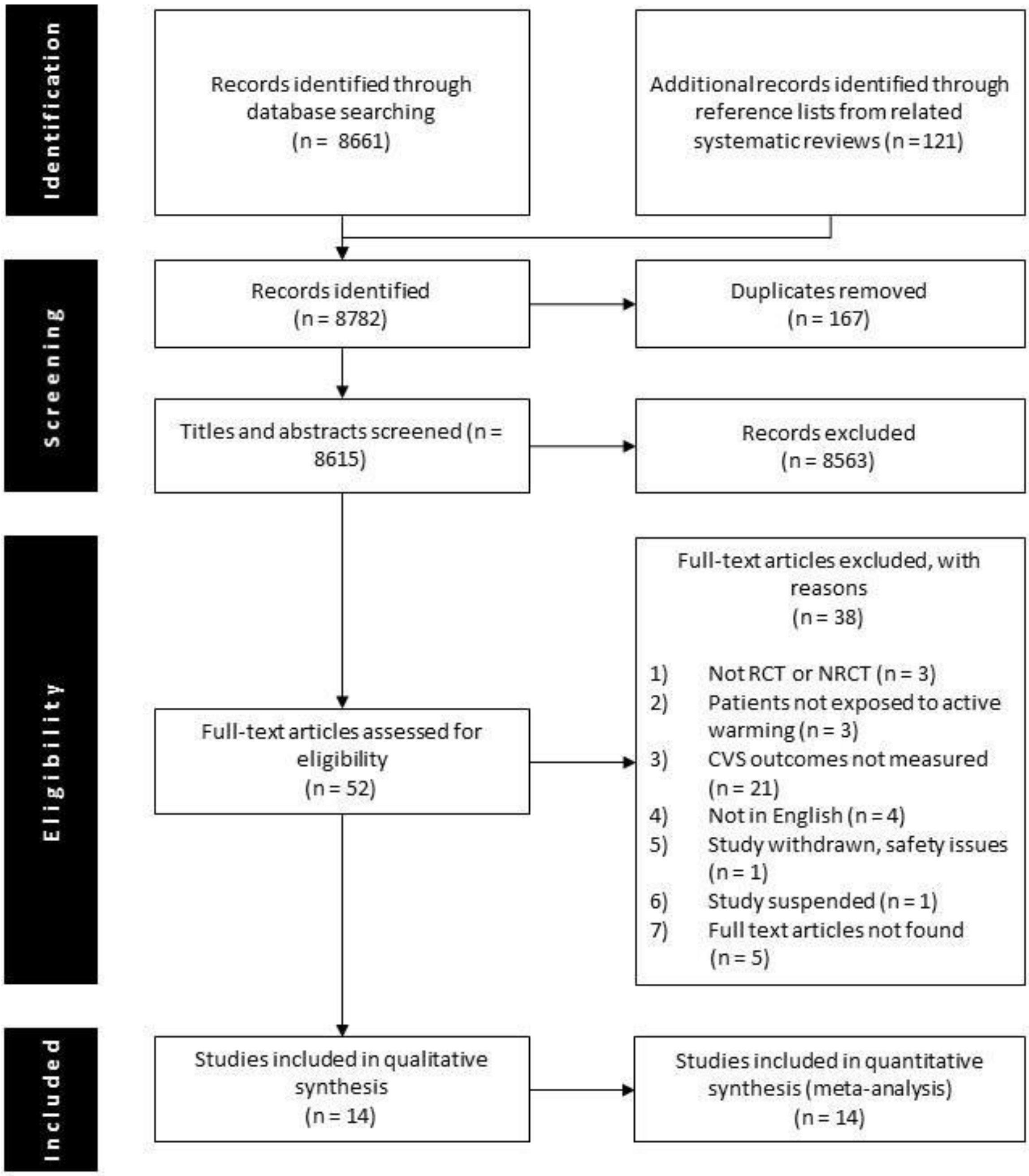
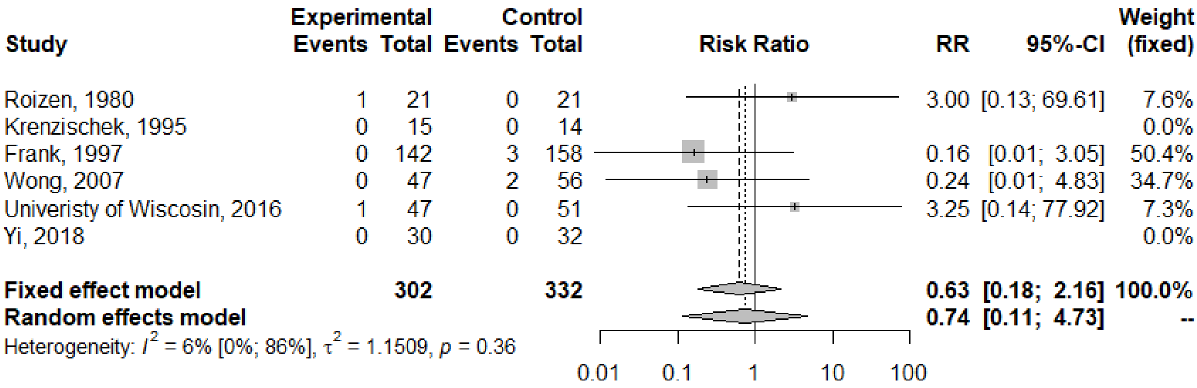
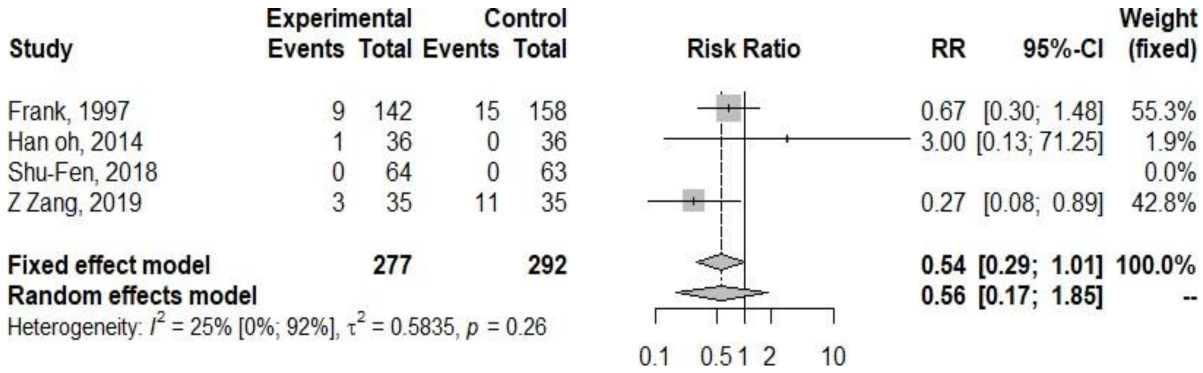

Identification
Records identified through database searching (n = 8661)
Additional records identified through reference lists from related systematic reviews (n = 121)
Screening
Records identified (n = 8782)
Duplicates removed (n = 167)
Titles and abstracts screened (n = 8615)
Records excluded (n = 8563)
Eligibility
Full-text articles assessed for eligibility (n = 52)
Full-text articles excluded, with reasons (n = 38)
1) Not RCT or NRCT (n = 3)
2) Patients not exposed to active warming (n = 3)
3) CVS outcomes not measured (n = 21)
4) Not in English (n = 4)
5) Study withdrawn, safety issues (n = 1)
6) Study suspended (n = 1)
7) Full text articles not found (n = 5)
Included
Studies included in qualitative synthesis (n = 14)
Studies included in quantitative synthesis (meta-analysis) (n = 14)

FIGURE 2



Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI
Weight (fixed)
Roizen, 1980 1 21 0 21 3.00 [0.13; 69.61] 7.6%
Krenzischek, 1995 0 15 0 14 0.0%
Frank, 1997 0 142 3 158 0.16 [0.01; 3.05] 50.4%
Wong, 2007 0 47 2 56 0.24 [0.01; 4.83] 34.7%
Univeristy of Wiscosin, 2016 1 47 0 51 3.25 [0.14; 77.92] 7.3%
Yi, 2018 0 30 0 32 0.0%
Fixed effect model 302 332 0.63 [0.18; 2.16] 100.0%
Random effects model 0.74 [0.11; 4.73] --
Heterogeneity: I^2 = 6% [0%; 86%], τ^2 = 1.1509, p = 0.36
0.01 0.1 1 10 100

FIGURE 3



Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI
Weight (fixed)
Frank, 1997 9 142 15 158 0.67 [0.30; 1.48] 55.3%
Han oh, 2014 1 36 0 36 3.00 [0.13; 71.25] 1.9%
Shu-Fen, 2018 0 64 0 63 0.0%
Z Zang, 2019 3 35 11 35 0.27 [0.08; 0.89] 42.8%
Fixed effect model 277 292 0.54 [0.29; 1.01] 100.0%
Random effects model 0.56 [0.17; 1.85] --
Heterogeneity: I^2 = 25% [0%; 92%], τ^2 = 0.5835, p = 0.26
0.1 0.5 1 2 10

FIGURE 4

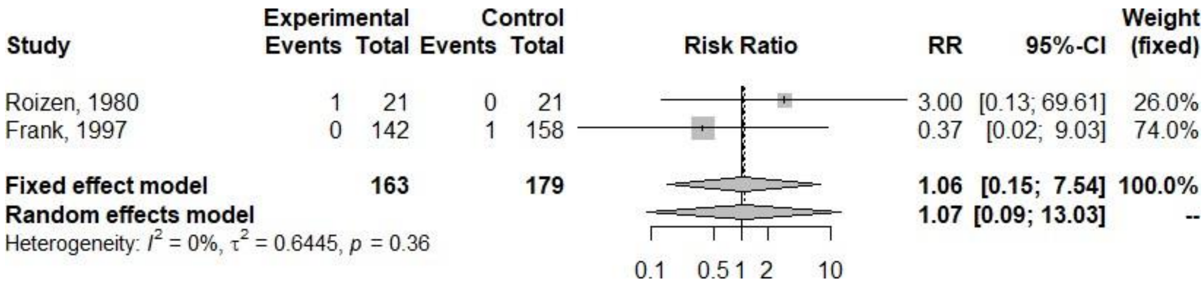

Study
Experimental
Events Total
Control
Events Total
Risk Ratio
RR
95%-CI
Weight
(fixed)
Roizen, 1980 1 21 0 21 3.00 [0.13; 69.61] 26.0%
Frank, 1997 0 142 1 158 0.37 [0.02; 9.03] 74.0%
Fixed effect model 163 179 1.06 [0.15; 7.54] 100.0%
Random effects model 1.07 [0.09; 13.03] --
Heterogeneity: I^2 = 0%, τ^2 = 0.6445, p = 0.36
0.1
0.5
1
2
10

FIGURE 5

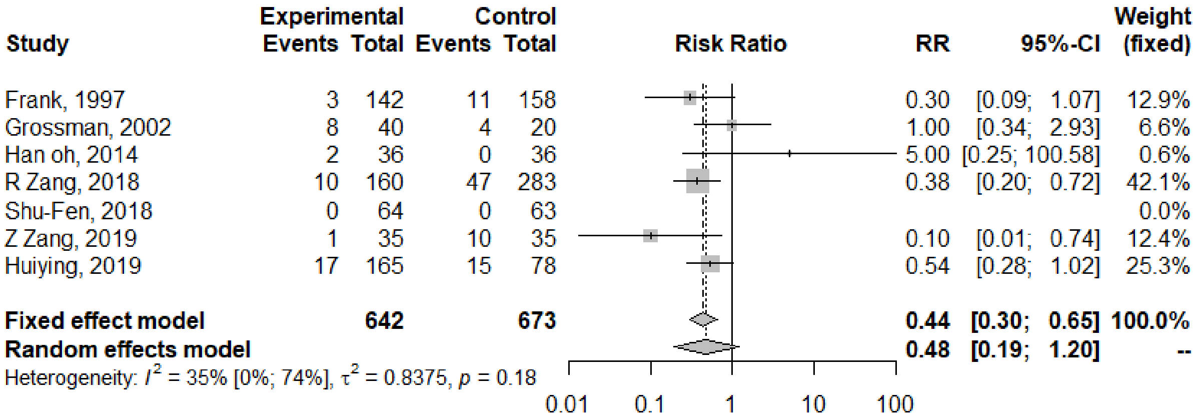

Experimental Control Weight
Study Events Total Events Total Risk Ratio RR 95%-CI (fixed)
Frank, 1997 3 142 11 158 0.30 [0.09; 1.07] 12.9%
Grossman, 2002 8 40 4 20 1.00 [0.34; 2.93] 6.6%
Han oh, 2014 2 36 0 36 5.00 [0.25; 100.58] 0.6%
R Zang, 2018 10 160 47 283 0.38 [0.20; 0.72] 42.1%
Shu-Fen, 2018 0 64 0 63 0.0%
Z Zang, 2019 1 35 10 35 0.10 [0.01; 0.74] 12.4%
Huiying, 2019 17 165 15 78 0.54 [0.28; 1.02] 25.3%
Fixed effect model 642 673 0.44 [0.30; 0.65] 100.0%
Random effects model 0.48 [0.19; 1.20] --
Heterogeneity: I^2 = 35% [0%; 74%], τ^2 = 0.8375, p = 0.18
0.01 0.1 1 10 100

FIGURE 6

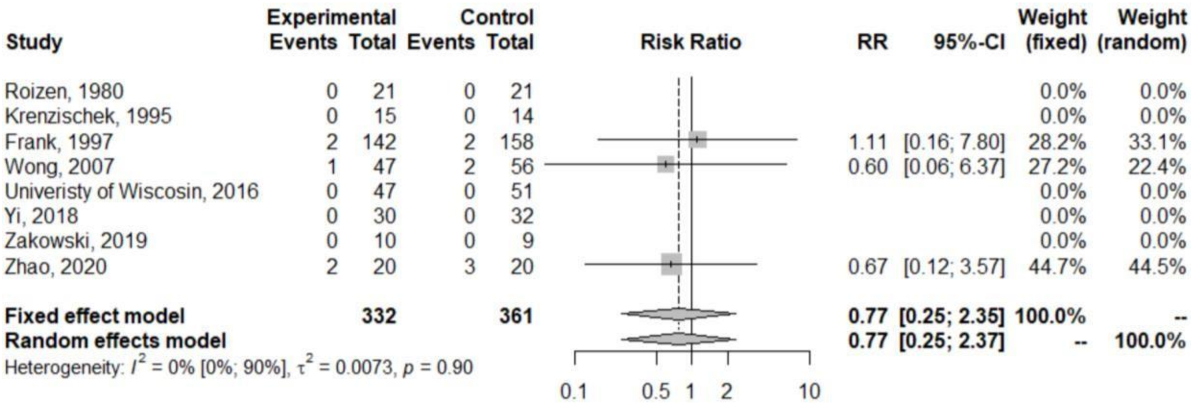
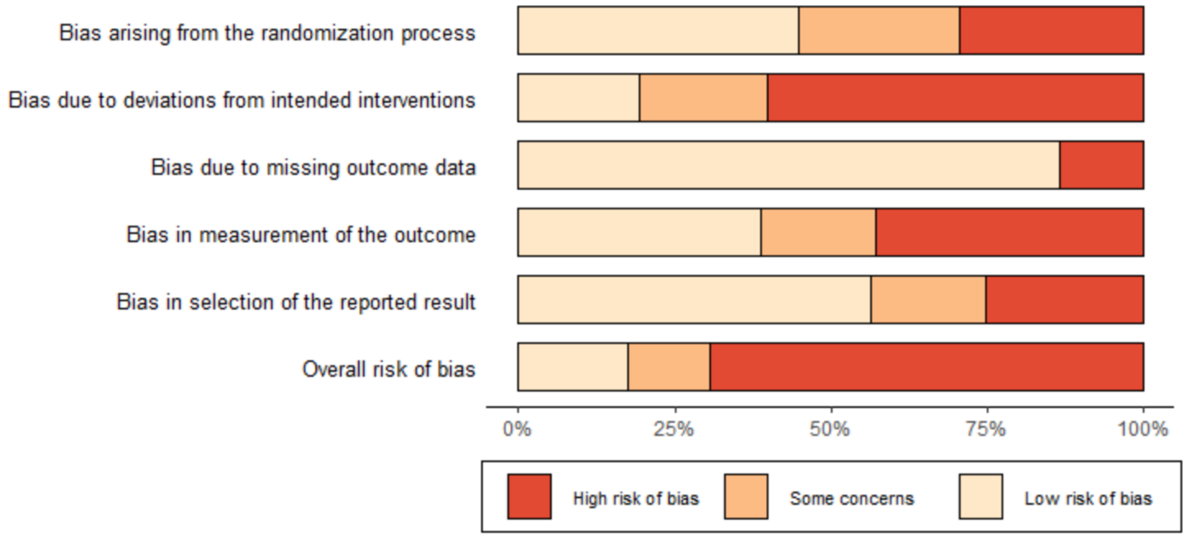

Study | Experimental Events Total | Control Events Total | Risk Ratio | RR | 95%-CI | Weight (fixed) | Weight (random)
Roizen, 1980 0 21 0 21 0.0% 0.0%
Krenzischek, 1995 0 15 0 14 0.0% 0.0%
Frank, 1997 2 142 2 158 1.11 [0.16; 7.80] 28.2% 33.1%
Wong, 2007 1 47 2 56 0.60 [0.06; 6.37] 27.2% 22.4%
Univeristy of Wiscosin, 2016 0 47 0 51 0.0% 0.0%
Yi, 2018 0 30 0 32 0.0% 0.0%
Zakowski, 2019 0 10 0 9 0.0% 0.0%
Zhao, 2020 2 20 3 20 0.67 [0.12; 3.57] 44.7% 44.5%
Fixed effect model 332 361 0.77 [0.25; 2.35] 100.0% --
Random effects model 0.77 [0.25; 2.37] -- 100.0%
Heterogeneity: I^2 = 0% [0%; 90%], τ^2 = 0.0073, p = 0.90
0.1 0.5 1 2 10

FIGURE 7


Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
High risk of bias
Some concerns
Low risk of bias

SUPPORTING INFORMATION S1:

LITERATURE SEARCH STRATEGY

Pubmed (MEDLINE):

	Concept	Mesh	Keywords
Population	Noncardiac surgery	"Surgical Procedures, Operative"[Mesh], NOT "Cardiac Surgical Procedures"[Mesh], NOT "Extracorporeal Circulation"[Mesh]	Perioperative OR peri operative OR peri-operative OR post-operative OR postoperative OR post operative OR intra-operative OR intraoperative OR intra operative OR surgery OR surgical
Intervention	Physical warming	"Hypothermia" [Mesh] OR "Body Temperature Regulation"[Mesh] OR "Rewarming"[Mesh] OR "Heating"[Mesh]	Hypothermia OR body temperature regulation OR heating OR rewarming OR thermoregulation OR warming
Comparators	Standard care	-	-
Outcome	**Primary**: cardiac death, non-fatal cardiac arrest, myocardial infarction. **Secondary**: electrical or pharmacological cardioversion, emergency coronary revascularization, stroke, myocardial ischaemia with Trop T > 0.03ng/nl, confirmed pulmonary embolism and arrhythmias.	**P:** "Cardiovascular System"[Mesh] OR Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Death, Sudden, Cardiac"[Mesh] **S: "Electric Countershock"** [Mesh] OR "Angioplasty"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Troponin" [Mesh]	**P:** stroke OR cardiovascular OR heart OR arrest OR OR asystole OR myocardial OR death OR cardiac **S:** electric countershock OR angioplasty OR pulmonary embolism OR arrhythmia OR Troponin OR defibrillation OR cardioversion
Timing		-	-

	Perioperative period and 30 day post-surgery		
Language	English	-	-
Study design	RCT, Non-Randomised Trials, Prospective and retrospective evaluations of interventions	-	-

Pubmed search string:
((((((("Heating"[MeSH]) OR "Rewarming"[MeSH]) OR "Body Temperature Regulation"[MeSH]) OR "Hypothermia"[MeSH])) AND ((((((((((("Troponin"[MeSH]) OR "Arrhythmias, Cardiac"[MeSH]) OR "Pulmonary Embolism"[MeSH]) OR "Angioplasty"[MeSH]) OR "Electric Countershock"[MeSH]) OR "Death, Sudden, Cardiac"[MeSH]) OR "Myocardial Ischemia"[MeSH]) OR "Stroke"[MeSH]) OR "Myocardial Infarction"[MeSH]) OR "Cardiovascular System"[MeSH])) OR (((((((((((((cardioversion) OR defibrillation) OR arrhythmia) OR pulmonary embolism) OR angioplasty) OR electric countershock) OR arrest) OR heart) OR asystole) OR myocardial) OR death) OR cardiac) OR cardiovascular) OR stroke))) AND (((((((((((intra operative) OR intra-operative) OR intraoperative) OR post operative) OR post-operative) OR postoperative) OR peri operative) OR peri-operative) OR perioperative) OR surgery) OR surgical)) OR "Surgical Procedures, Operative"[MeSH]))) NOT (("Cardiac Surgical Procedures"[MeSH]) OR "Extracorporeal Circulation"[MeSH])

Scopus(Embase; excluding Medline):

	Concept	**Keywords**
Population	Noncardiac surgery	Surgery OR surgical Perioperative OR “peri operative” OR peri-operative OR post-operative OR postoperative OR “post operative” OR intra-operative OR intraoperative OR “intra operative” NOT "cardiac surgery" NOT "cardiopulmonary bypass" NOT "coronary artery bypass"
Intervention	Physical warming	Hypothermia OR temperature OR heating OR rewarming OR thermoregulation OR warming
Comparators	Standard care	-

Outcome	**Primary**: cardiac death, non-fatal cardiac arrest, myocardial infarction. **Secondary**: electrical or pharmacological cardioversion, emergency coronary revascularization, stroke, myocardial ischaemia with Trop T > 0.03ng/nl, confirmed pulmonary embolism and arrhythmias.	**P:** stroke OR cardiovascular OR heart OR arrest OR asystole OR myocardial OR death OR cardiac **S:** countershock OR angioplasty OR "pulmonary embolism" OR arrhythmia OR troponin OR defibrillation OR cardioversion

Scopus search string:
TITLE-ABS-KEY (surgery OR surgical OR perioperative OR peri-operative OR "peri operative" OR intraoperative OR intra-operative OR "intra operative" OR postoperative OR post-operative OR "post operative") AND TITLE-ABS-KEY (hypothermia OR temperature OR heating OR rewarming OR thermoregulation OR warming) AND TITLE-ABS-KEY (stroke OR cardiovascular OR heart OR arrest OR asystole OR myocardial OR death OR cardiac OR countershock OR defibrillation OR angioplasty OR "pulmonary embolism" OR arrhythmia OR troponin OR cardioversion) AND NOT TITLE-ABS-KEY ("cardiac surgery" OR "cardiopulmonary bypass" OR "coronary artery bypass") AND NOT DBCOLL (medl)

EBSCOhost(Africa-wide, CINAHL):

	Concept	Keywords
Population	Non-cardiac surgery	surgery OR surgical OR perioperative OR "peri operative" OR peri-operative OR post-operative OR postoperative OR "post operative" OR intra-operative OR intraoperative OR "intra operative" NOT "cadiac surgery" NOT "cardiopulmonary bypass" NOT "coronary artery bypass"
Intervention	Physical warming	hypothermia OR temperature OR heating OR rewarming OR thermoregulation OR warming
Comparators	Standard care	-
Outcome	**Primary**: cardiac death, non-fatal cardiac arrest, myocardial infarction. **Secondary**: electrical or pharmacological cardioversion, emergency coronary revascularization, stroke, myocardial ischaemia with	**P:** stroke OR cardiovascular OR heart OR arrest OR OR asystole OR myocardial OR death OR cardiac **S:** countershock OR angioplasty OR "pulmonary embolism" OR arrhythmia OR

	Trop T > 0.03ng/nl, confirmed pulmonary embolism and arrhythmias.	troponin OR defibrillation OR cardioversion

EBSCOhost search string:
S1: perioperative OR peri-operative OR “peri operative” OR “post operative” OR postoperative OR post-operative OR intra-operative OR intraoperative OR “intra operative” OR surgery OR surgical
S2: “cadiac surgery” OR “cardiopulmonary bypass” OR “coronary artery bypass”
S3: S1 NOT S2
S4: hypothermia OR temperature OR heating OR rewarming OR thermoregulation OR warming S5: stroke OR cardiovascular OR heart OR arrest OR asystole OR myocardial OR death OR cardiac S6: countershock OR angioplasty OR “pulmonary embolism” OR arrhythmia OR troponin OR defibrillation OR cardioversion
S7: S5 OR S6
S8: S3 AND S4 AND S7

Cochrane Library(Central):

	Concept	**Keywords**
Population	Non-cardiac surgery	surgery OR surgical OR perioperative OR peri operative OR peri-operative OR post-operative OR postoperative OR post operative OR intra-operative OR intraoperative OR intra operative NOT "cardiac surgery" NOT "cardiopulmonary bypass" NOT "coronary artery bypass"
Intervention	Physical warming	hypothermia OR temperature OR heating OR rewarming OR thermoregulation OR warming
Comparators	Standard care	
Standard care	**Primary**: cardiac death, non-fatal cardiac arrest, myocardial infarction. **Secondary**: electrical or pharmacological cardioversion, emergency coronary revascularization, stroke, myocardial ischaemia with Trop T > 0.03ng/nl, confirmed pulmonary embolism and arrhythmias.	**P:** stroke OR cardiovascular OR heart OR arrest OR asystole OR myocardial OR death OR cardiac **S:** countershock OR angioplasty OR “pulmonary embolism” OR arrhythmia OR troponin OR defibrillation OR cardioversion

Cochrane search string:

#1 (perioperative):ti,ab,kw OR (peri-operative):ti,ab,kw OR ("peri operative"):ti,ab,kw OR (intraoperative):ti,ab,kw OR (intra-operative):ti,ab,kw (Word variations have been searched) #2 ("intra operative"):ti,ab,kw OR (post-operative):ti,ab,kw OR ("post operative"):ti,ab,kw OR (postoperative):ti,ab,kw OR (surgery):ti,ab,kw (Word variations have been searched)
#3 (surgical):ti,ab,kw (Word variations have been searched) #4
#1 OR #2 OR #3
#5 (hypothermia):ti,ab,kw OR (temperature):ti,ab,kw OR (heating):ti,ab,kw OR (warming):ti,ab,kw OR (thermoregulation):ti,ab,kw (Word variations have been searched)
#6 (rewarming):ti,ab,kw (Word variations have been searched) #7
#5 OR #6
#8 (stroke):ti,ab,kw OR (cardiovascular):ti,ab,kw OR (heart):ti,ab,kw OR (arrest):ti,ab,kw OR (asystole):ti,ab,kw (Word variations have been searched)
#9 (myocardial):ti,ab,kw OR (death):ti,ab,kw OR (cardiac):ti,ab,kw OR (countershock):ti,ab,kw OR (defibrillation):ti,ab,kw (Word variations have been searched)
#10 (angioplasty):ti,ab,kw OR ("pulmonary embolism"):ti,ab,kw OR (arrhythmia):ti,ab,kw OR (troponin):ti,ab,kw OR (cadioversion):ti,ab,kw (Word variations have been searched) #11 #8 OR #9 OR #10
#12 ("cardiac surgery"):ti,ab,kw OR ("cardiopulmonary bypass"):ti,ab,kw OR ("coronary artery bypass"):ti,ab,kw (Word variations have been searched)
#13 #4 NOT #12
#14 #13 AND #7 AND #11

ClinicalTrials.gov:

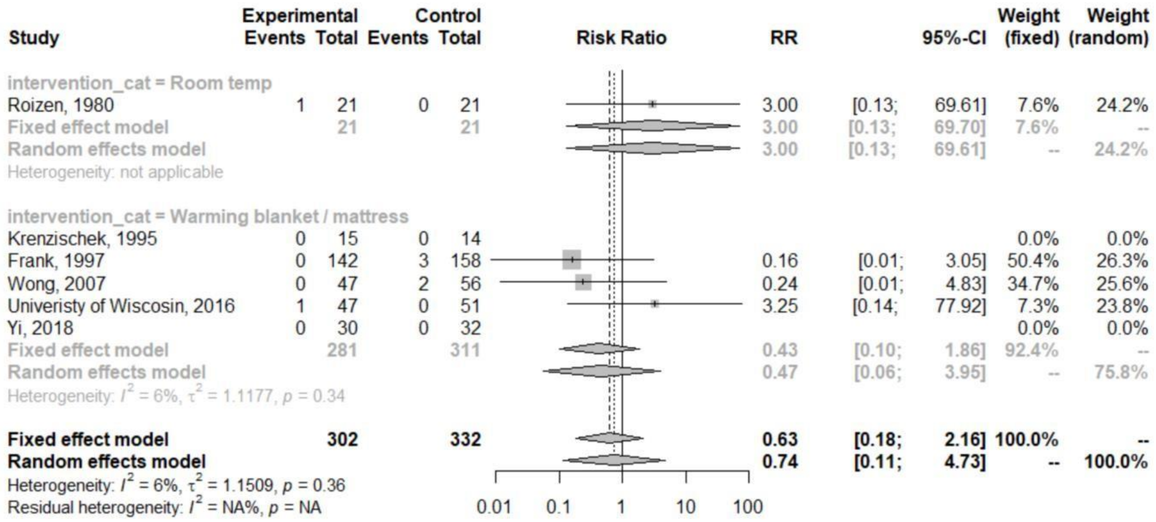
	Concept	**Keywords**
Population	Noncardiac surgery	perioperative OR perioperative OR surgery NOT "cardiac surgery" NOT "cardiopulmonary bypass" NOT "coronary artery bypass"
Intervention	Physical warming	Hypothermia OR temperature OR warming OR normothermia
Comparators	Standard care	
Outcome	**Primary**: cardiac death, non-fatal cardiac arrest, myocardial infarction.	**P:** cardiovascular OR heart OR myocardial OR death OR cardiac

Clinical Trials search string :
((peri-operative OR perioperative OR surgery) NOT ("cardiac surgery" OR "cardiopulmonary bypass" OR "coronary artery bypass")) AND (temperature OR hypothermia OR warming OR normothermia) AND (heart OR cardiac OR cardiovascular OR myocardial OR death)

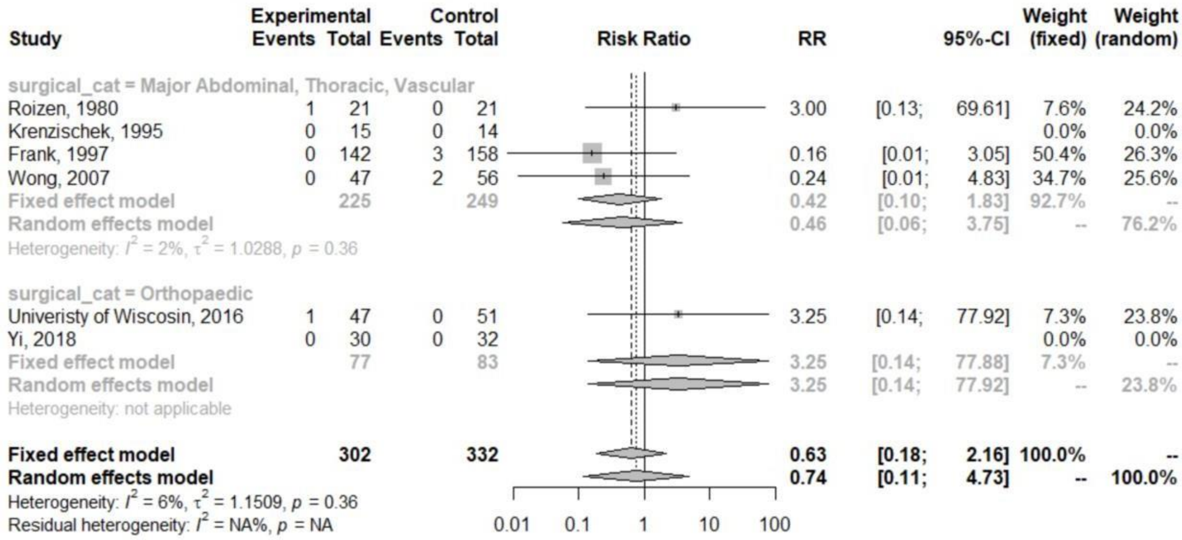
S2: Prespecified investigation of statistical heterogeneity major adverse cardiovascular events (MACE)

Insufficient data to conduct analyses for effect of ASA status, BMI and difference in temperature between comparison groups.

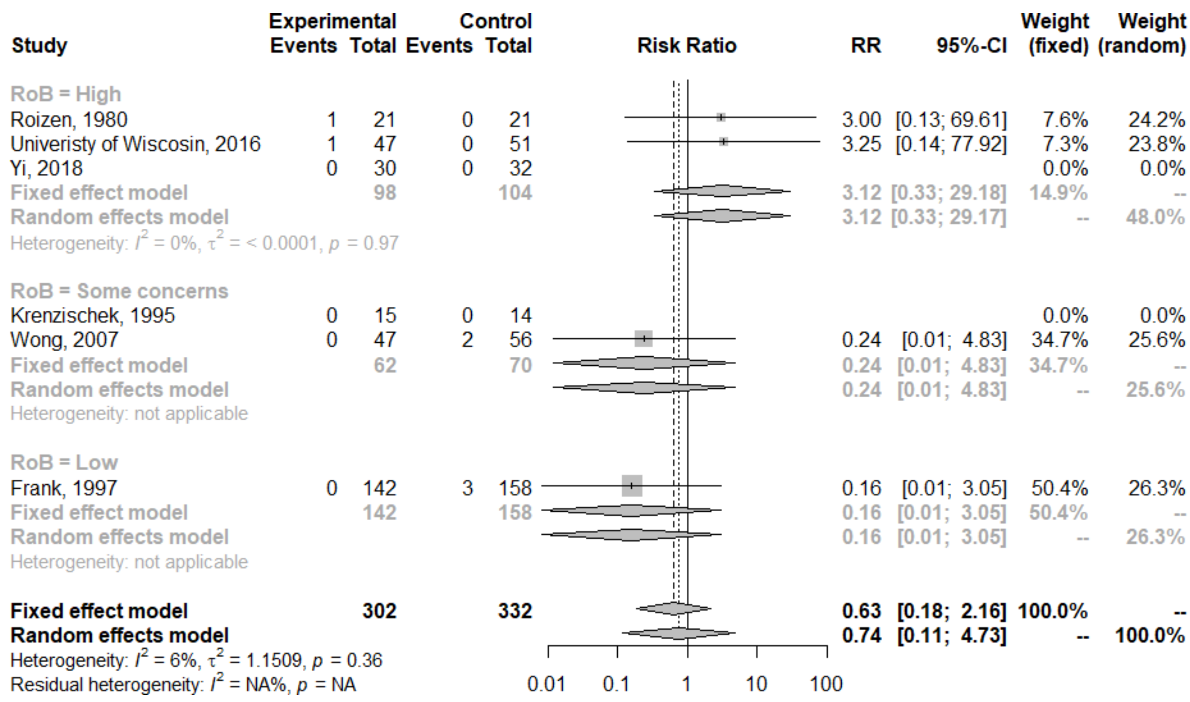
Subgroup by intervention category (i.e. warming method)



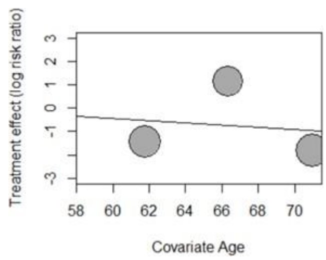
Subgroup by type of surgery



Subgroup by RoB2 assessment



Meta-regression against average age of study population



k = 3; tau^2 estimator: Sidik-Jonkman

R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:QE(df = 1) = 2.092, p-value = 0.148

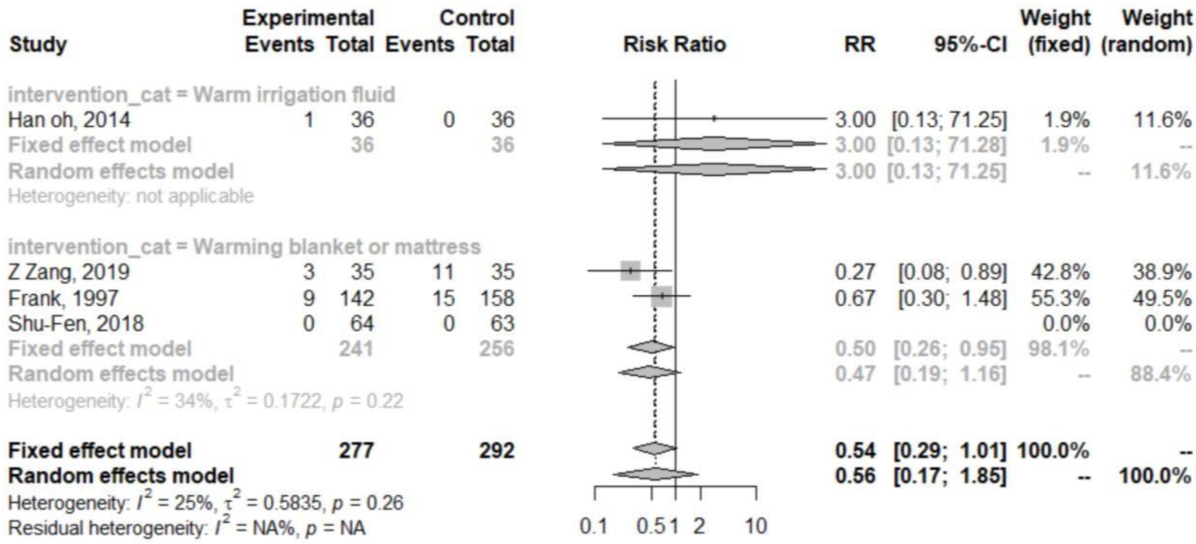
Test of Moderators (Age):QM(df = 1) = 0.0225, p-val = 0.881 Model Results (excluding intercept):

Covariate	Estimate	p-value	95% CI
Age	-0.049	0.881	-0.685; 0.588

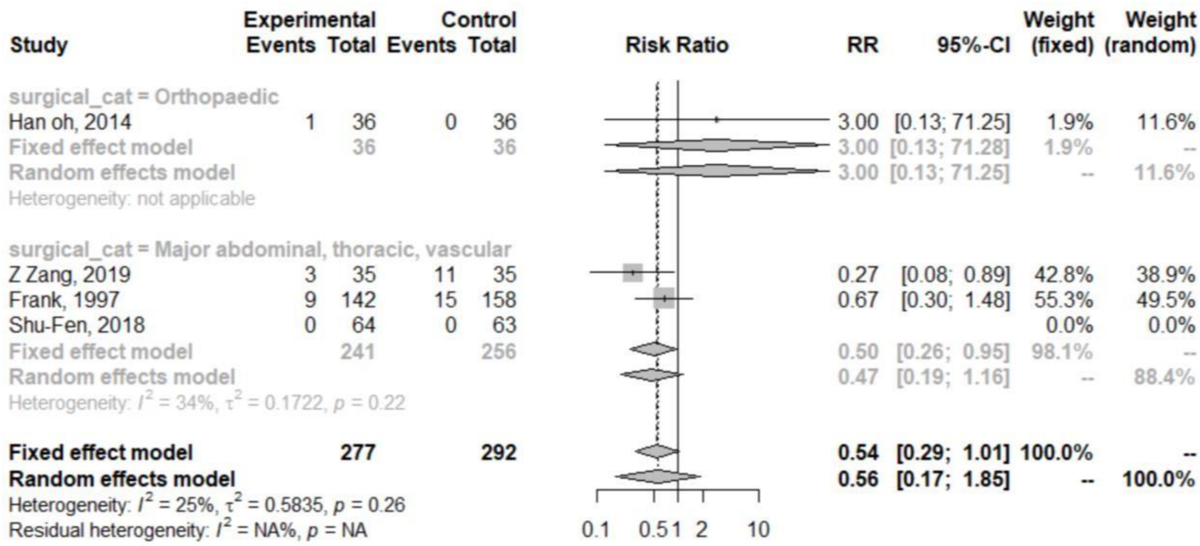
MYOCARDIAL ISCHAEMIA

Insufficient data to conduct analyses for effect of ASA status and difference in temperature between comparison groups

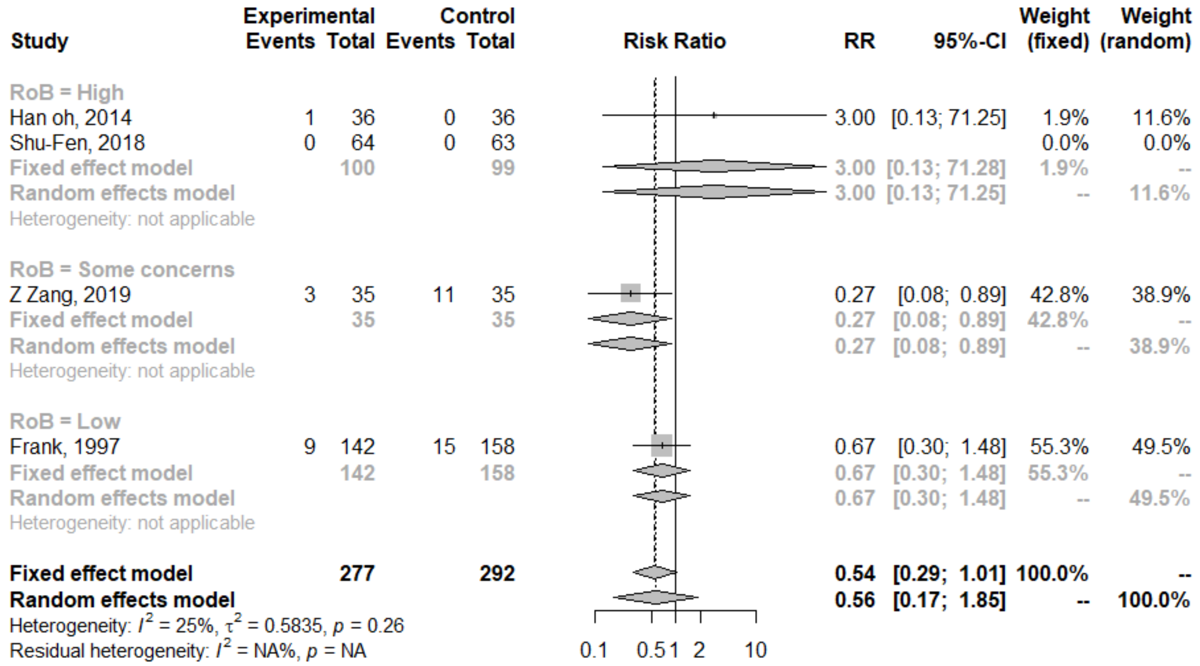
Subgroup by intervention category (i.e. warming method)



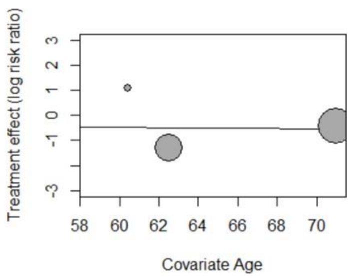
Subgroup by type of surgery



Subgroup by RoB2 assessment



Meta-regression against average age of study population



k = 3; tau^2 estimator: Sidik-Jonkman

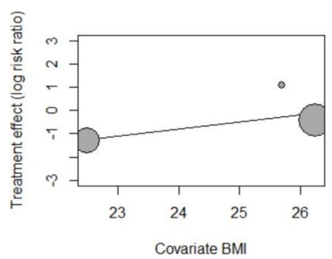
R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity: QE(df = 1) = 2.148, p-value = 0.143

Test of Moderators (Age): QM(df = 1) = 0.001, p-value = 0.975 Model Results (excluding intercept):

Covariate	Estimate	p-value	95% CI
Age	-0.005	0.975	-0.336; 0.326

Meta-regression against average BMI of study population



k = 3; tau^2 estimator: Sidik-Jonkman

R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity: QE(df = 1) = 0.975, p-value = 0.324

Test of Moderators (BMI): QM(df = 1) = 0.756, p-value = 0.385 Model Results (excluding intercept):

Covariate	Estimate	p-value	95% CI
BMI	0.297	0.385	-0.372; 0.966

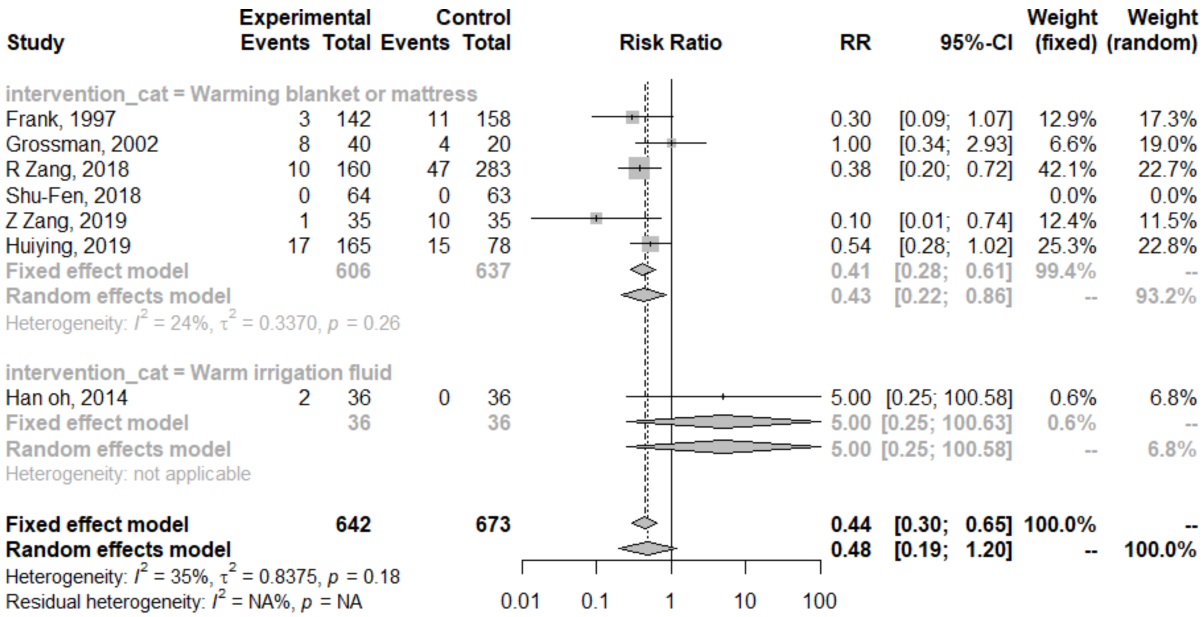
MYOCARDIAL INFARCTION

Insufficient data to analyse heterogeneity.

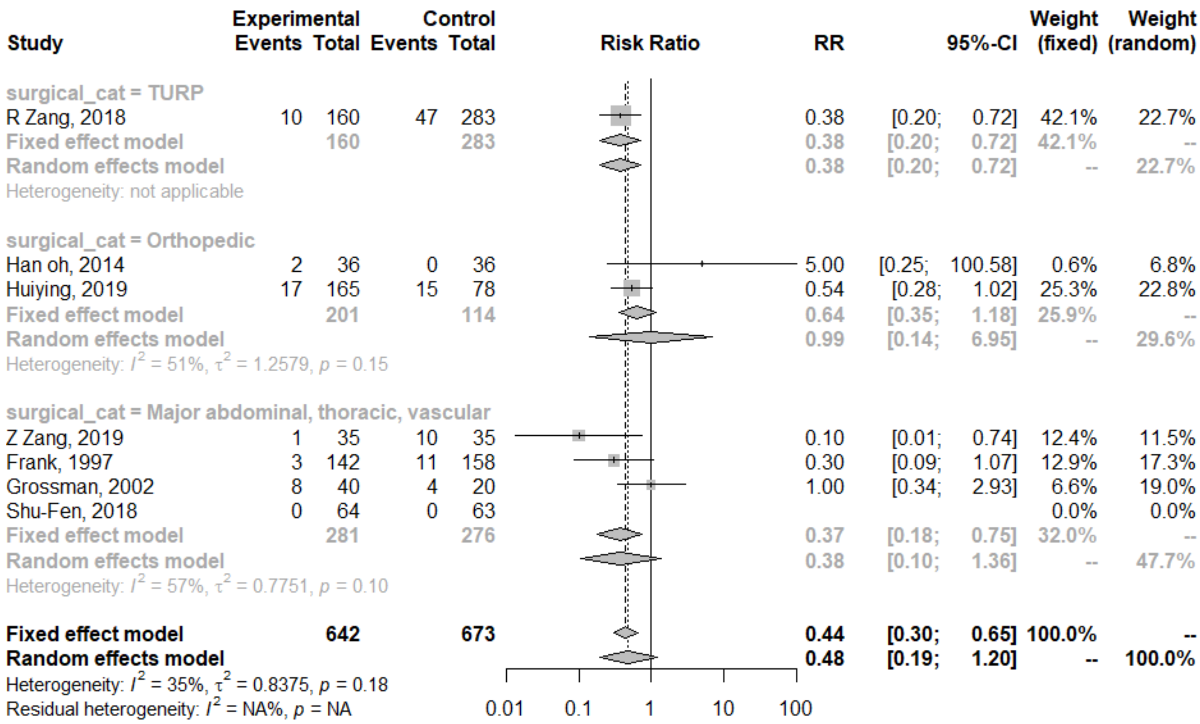
ARRHYTHMIAS

Insufficient data to conduct analyses for effect of ASA status and difference in temperature between comparison groups

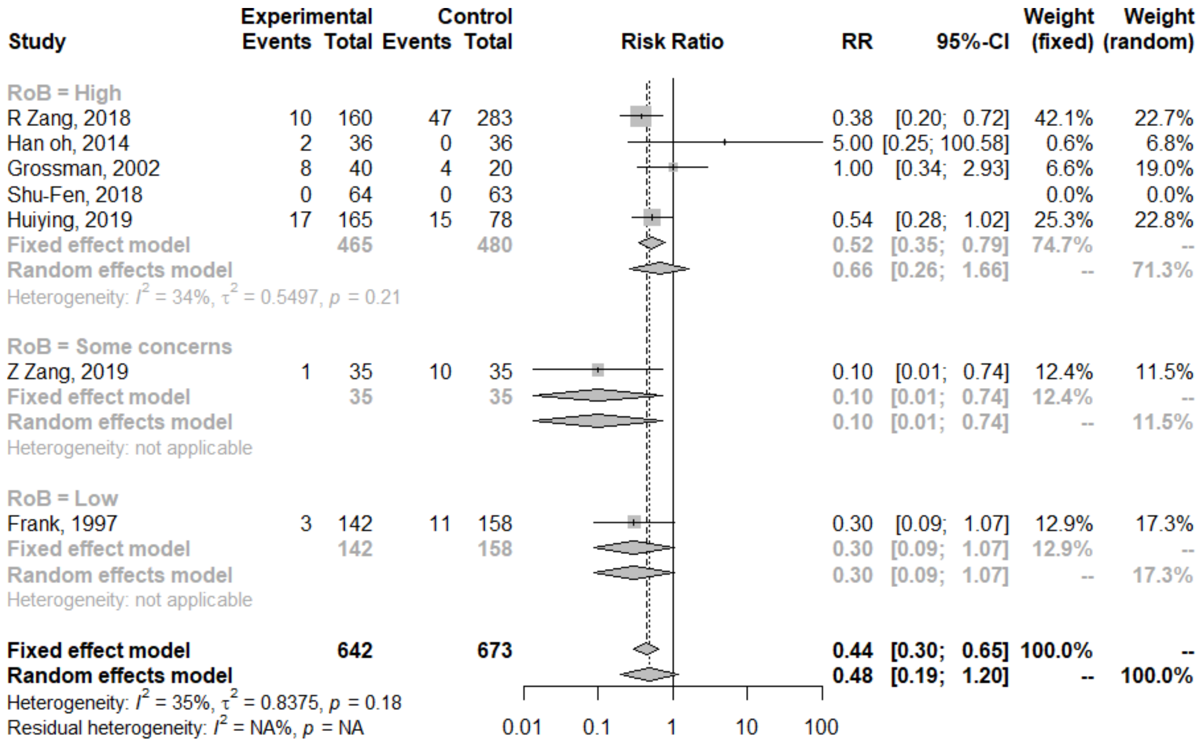
Subgroup by intervention category (i.e. warming method)



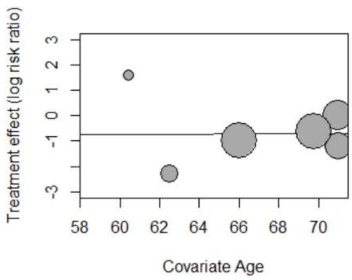
Subgroup by type of surgery



Subgroup by RoB2 assessment

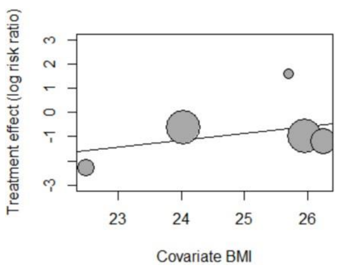


Meta-regression against average age of study population
k = 6; tau^2 estimator: Sidik-Jonkman
R^2 (amount of heterogeneity accounted for): 0.00%
Test for Residual Heterogeneity: QE(df = 4) = 6.937, p-value = 0.139
Test of Moderators (Age): QM(df = 1) = 0.001, p-value = 0.981 Model Results (excluding intercept):



Covariate	Estimate	p-value	95% CI
Age	0.003	0.981	-0.273; 0.280

Meta-regression against average BMI of study pop. k = 5; tau^2 estimator: Sidik-Jonkman
R^2 (amount of heterogeneity accounted for): 0.00%
Test for Residual Heterogeneity: QE(df = 3) = 5.510, p-value = 0.138
Test of Moderators (BMI):
QM(df = 1) = 0.473, p-value = 0.492
Model Results (excluding intercept):

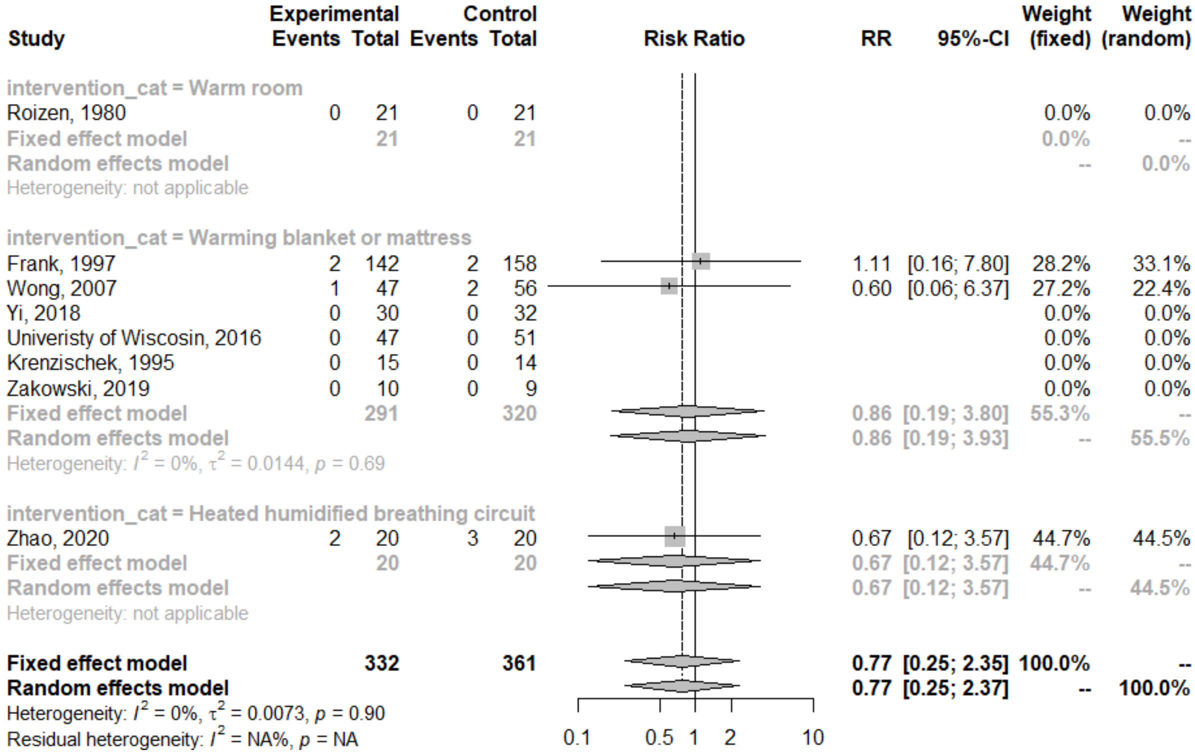


Covariate	Estimate	p-value	95% CI
BMI	0.288	0.492	-0.533; 1.109

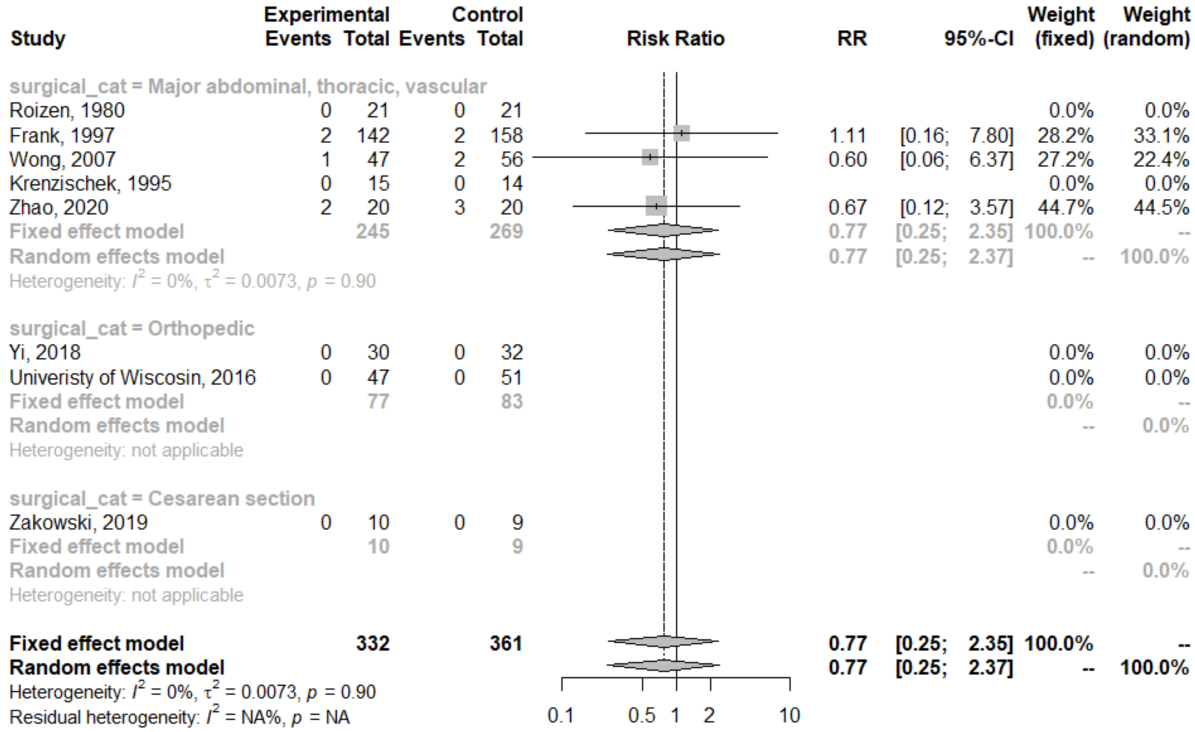
MORTALITY

Insufficient data to conduct analyses for effect of ASA status and difference in temperature between comparison groups.

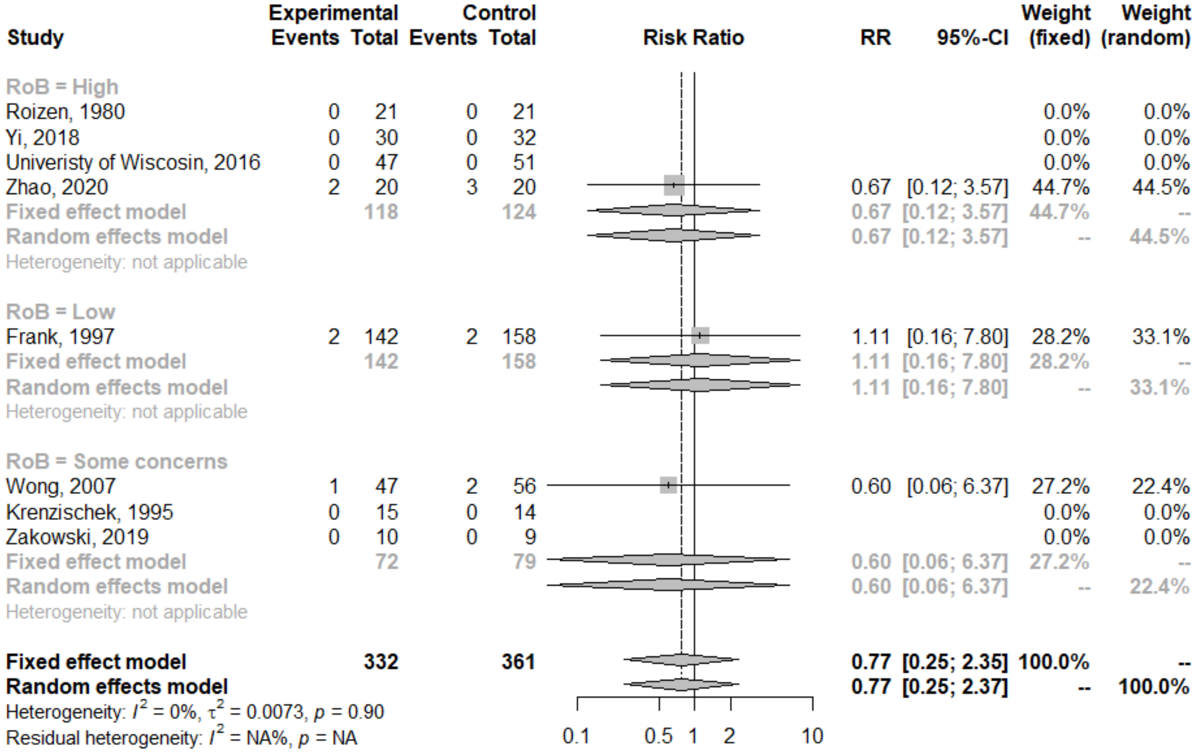
Subgroup by intervention category (i.e. warming method)



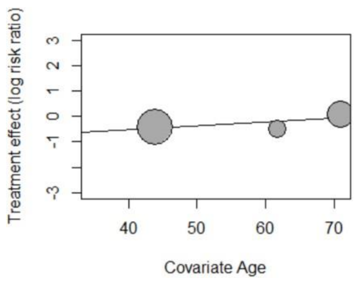
Subgroup by type of surgery



Subgroup by RoB2 assessment

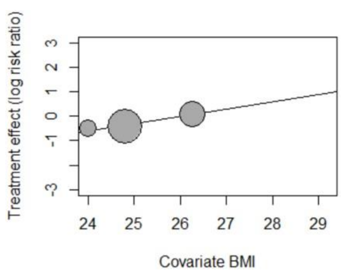


Meta-regression against average age of study population
k = 3; tau^2 estimator: Sidik-Jonkman
R^2 (amount of heterogeneity accounted for): 1.34%
Test for Residual Heterogeneity: QE(df = 1) = 0.103, p-value = 0.749
Test of Moderators (Age): QM(df = 1) = 0.107, p-value = 0.743 Model Results (excluding intercept):



Covariate	Estimate	p-value	95% CI
Age	0.016	0.743	-0.077; 0.109

Meta-regression against average BMI of study population
k = 3; tau^2 estimator: Sidik-Jonkman
$R^{\wedge 2}$ (amount of heterogeneity accounted for): 92.25%
Test for Residual Heterogeneity: QE(df = 1) = 0.008, p-value = 0.928
Test of Moderators (BMI): QM(df = 1) = 0.202, p-value = 0.653 Model Results (excluding intercept):



Covariate	Estimate	p-value	95% CI
Age	0.297	0.653	-0.998; 1.592

Section and Topic	Item#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 9-11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 9-11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supporting information 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9-11
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 9-11
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 9-11
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 9-11
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 9-11
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 9-11
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 9-11
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 9-11
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 9-11
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe themodel(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 9-11
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 9-11
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9-11
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 9-11
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9-11

Section and Topic	Item#	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	Page 11-13
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 11-13
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 11-13
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 11-13
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 11-13
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Supporting information 2
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supporting information 2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Table 3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 13-16
	23b	Discuss any limitations of the evidence included in the review.	Page 13-16
	23c	Discuss any limitations of the review processes used.	Page 13-16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13-16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 50
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 50
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 50
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 16
Competing interests	26	Declare any competing interests of review authors.	Page 3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supporting information 1&2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

SECTION B: APPENDICES

THE PROTOCOL

The effect of temperature management on perioperative cardiovascular outcomes in interventional studies: protocol for a systemic review and meta-analysis

In accordance with the guidelines, our systemic review protocol was registered with the International Prospective Register of Systemic Reviews (PROSPERO) on October 10, 2016 and was last updated on December 19, 2019 (**registration number CRD42016045891**).

Authors

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Main Road, Observatory, 7925

Contributions: Leon du Toit is the supervisor for this systemic review and Sisalindele Mkhize will be the first author doing a MMed project on the abovementioned topic. Bruce Biccard is a senior co-investigator and Modjadji Maake is a junior co-investigator.

Amendments

This is an update of a systematic review previous registered by Leon du Toit and Bruce Biccard. The systematic review was not completed due to insufficient evidence in the literature at the time (2016). We believe that the amount of evidence on the topic has increased over the past 3 years and we have broadened our inclusion criteria to incorporate evidence from non-randomised experiments in our review.

Support

The research is not funded and self-initiated by the senior investigator, Leon du Toit.

Introduction

Each year, more than 300 million non-cardiac surgeries are performed worldwide (1). Cardiovascular events (cardiac death, myocardial infarction and non-fatal cardiac arrest) are a significant source of perioperative morbidity and mortality (1). A national inpatient sample of hospital admissions in the United States between 2004 and 2013 identified that 1 in every 33 hospitalizations for non-cardiac surgery experienced a major adverse cardiovascular or cerebrovascular event (2). The consequences of cardiovascular complications are: prolonged inpatient hospitalization, increase in medical costs, disability and death (1). Patients experiencing myocardial infarcts after non-cardiac surgery have an in- hospital mortality rate of 15% - 25% and this is an independent risk factor for death 6 months following surgery (2). Cardiac arrest after non-cardiac surgery has a hospital mortality rate of 65% and is a risk factor for cardiac death 5 years following surgery (2).

Temperature regulation and monitoring forms an important part of the perioperative management of patients undergoing non-cardiac surgery. Anaesthesia, type of surgery and exposure to theatre environment can lead to hypothermia. Hypothermia leads to increase in blood catecholamine levels resulting in systemic vasoconstriction, shivering, increase in blood pressure and heart rate. This increases oxygen consumption, may cause myocardial ischaemia and is associated with a threefold increase in morbid myocardial outcomes (2, 3, 4, 5). Keeping patients warm is associated with fewer perioperative cardiovascular events. Contrary to this, heart rate is linked to body temperature and a higher intraoperative core temperature is associated with higher intraoperative heart rate. Increased intraoperative heart rate and myocardial workload may increase the risk of cardiovascular events. This suggests that the relationship between patient warming and cardiovascular events may not be simple and warming may not always offer cardiovascular protection. Indeed, hypothermia has long been known to offer protection to the myocardium and other organs (6,7). Since hypothermia is known to offer cardiovascular protection, we ask how strong is the evidence for cardiovascular benefit from patient warming. The evidence supporting the quoted three-fold increase in cardiovascular events (4) refers only to 11 of events. The evidence supporting the NICE guidelines on patient warming (CG65) found only 2 cardiovascular events in their review of the evidence (9). It is not advisable to base practice on fewer than 200 events (8). Moreover, our observation that hypothermia is associated with both cardiovascular harm and benefit leads us to hypothesise that there may be significant effect modifiers that will lead to heterogeneity in the effect of patient warming on perioperative cardiovascular effects.

We will be reviewing the effects of active perioperative temperature management on perioperative cardiovascular outcomes in interventional studies. Our population will be adult surgical patients undergoing non-cardiac surgery; adults because perioperative cardiovascular events in children have a different pathophysiology to adults; non-cardiac surgery because patient cooling is intentional in many cardiac surgical procedures and perioperative cardiovascular events have different pathophysiology in this population. Our primary outcome will be major adverse cardiovascular outcomes defined as: any of cardiac death, non-fatal cardiac arrest, myocardial infarction, , emergency coronary revascularization (percutaneous or CABG), and or stroke within 30 days of surgery. Our secondary outcomes will be: individual components of the composite primary outcome, all-cause mortality, electrical or pharmacological cardioversion or arrhythmias, myocardial ischaemia with Trop T of more than 0.03ng/nl (MINS), confirmed pulmonary embolism. We expect heterogeneity in the estimate of the effect. We hypothesise that the heterogeneity is due to the differing baseline risk between different surgical populations, different warming interventions (external warming versus warmed IV fluids) and the different study designs (randomised versus non-randomised experiments). Our hypothesis is there is an association between patient warming and cardiovascular outcomes. But there is much heterogeneity due to effect modification and biases. We hypothesize the sources of heterogeneity are true effect modification due to the complexity of association between warming and cardiovascular outcomes as well as differences in quality of evidence. We will explore the impact of different surgical populations (type of surgery, median ASA score), different warming interventions (warm IV fluids, external warming), the difference between temperature in interventions and control arm, differences in study design and risk of bias assessment. We will do sensitivity analyses for the differences in the definition of our outcome of interest.

Methods

Eligibility criteria

Studies will be selected according to the criteria outlined below.

1. Study design

We will include randomized controlled trials and non-randomised experiments. We will exclude case-control studies, case series and case reports. Titles that may be clinical trials with patients randomised to a perioperative normothermia management intervention will be selected.

2. Participants

We will include studies examining the adult human population (age 18 years or older) undergoing non-cardiac surgery.

3. Intervention

Patients that have been exposed to some active perioperative warming intervention with the goal of preventing hypothermia or maintaining normothermia. Excluding pharmacological and nutritional warming strategies as these may impact on cardiovascular outcomes through mechanisms unrelated to body temperature.

4. Comparators

Passive warming or standard care as defined by the primary study.

5. Outcomes

Primary outcomes: Major adverse cardiovascular outcomes defined as any of cardiac death, non-fatal cardiac arrest, myocardial infarction, emergency coronary revascularization (percutaneous or CABG), and or stroke within 30 days of surgery

Secondary outcomes: individual components of the composite primary outcome, all-cause mortality, electrical or pharmacological cardioversion or arrhythmias, myocardial ischaemia with Trop T of more than 0.03ng/nl (MINS), confirmed pulmonary embolism.

6. Setting

In-hospital, perioperative

7. Timing

We will include trials reporting on cardiovascular outcomes within 30 days post-surgery.

8. Language

We will include studies reported in English as our team only have English language expertise.

The year which the trial is published will be unrestricted. We will contact the authors to clarify any missing data in published articles.

Information sources

Literature search strategies will be developed using subject headings (Mesh). We will search PubMed (Medline), Scopus (Embase), EBSCOhost (Africa-wide, CINAHL), Cochrane Library (Central), and ClinicalTrials.gov.

Search strategy

PubMed, Scopus, EBSCOhost, Cochrane Library, and ClinicalTrials.gov will be searched. The specific search strategies will be created in conjunction with a Health Sciences Librarian (Dilshaad Brey, Gill Morgan) with the expertise in systemic review searching.

ClincalTrials.gov will be searched for ongoing or recently completed trials and PROSPERO will be searched for ongoing or recently completed systemic reviews. As relevant studies are identified, we will check for additional relevant cited and citing articles.

The search will be updated toward the end of the review.

Refer to accompanying search strategy document.

Study records

1. Data Management

We will use Endnote as our citation manager. Duplicate records will be removed in Endnote. This data will be exported from Endnote to Excel. Text and abstract screening, Risk of bias assessment and data extraction will be done in Excel using prepared spreadsheets.

2. Selection process

Two independent reviewers (SM and MM) will screen the titles and abstracts yielded by the search against the inclusion / exclusion criteria. We will obtain full reports for all titles that appear to meet the inclusion / exclusion criteria. The same two reviewers (SM and MM) will screen the full text of these studies and decide whether these meet the inclusion / exclusion criteria. We will contact study authors to seek more information where necessary to resolve questions about eligibility. Where there is uncertainty or disagreements about eligibility, the reviewers will contact the supervisor (LDT) who will decide whether the study will be included.

3. Data collection process

Data extraction will be done in Excel by SM and outcome data will be validated by MM. Data extraction spreadsheets will be prepared in Excel. We pilot the 1st 3 full texts in duplicate and thereafter independently. Where there is uncertainty or missing data, we will contact study authors via email. Risk of bias assessment will be done by two independent reviewers (SM and MM) in duplicate. We will use Cochrane RoB 2 for randomised trials and ROBINS-I for non-randomised studies. Disagreement will be resolved through discussion or decided on by senior investigator (LDT).

Data items

1. Population: number of participants in each arm, type of surgical population, age of patients, ASA status of patients (or other physiological status score as reported by study), BMI of patients.
2. Intervention: type of active warming intervention, prewarming versus intraoperative warming.
3. Comparison: as defined by the study (usual care, placebo, passive warming interventions).

4. Outcomes: events per arm: cardiac death, non-fatal cardiac arrest, myocardial infarction, electrical or pharmacological cardioversion, arrhythmia, emergency coronary revascularization, stroke, myocardial ischaemia with Troponin T of more than 0.03ng/nl (MINS), confirmed pulmonary embolism, all-cause mortality. Temperature differences between study arms.
5. Timing: Timing of assessment of primary outcome
6. Study: randomised/interventional studies, risk of bias elements

Data synthesis

Rstudio "meta" package will be used to combine point estimates of effect (Risk ratio; RR) in a meta-analysis assessing the dichotomous outcomes (presence or absence of adverse event). The primary outcome will be reported as a pooled estimate of composite outcomes and pooled estimates of the individual components of the composite outcome. Pooled estimates of the specified secondary outcomes will be presented. Additional subgroup analyses are planned: by intervention type, type of surgery, ASA status, age, BMI, risk of bias, type of study, and difference between temperatures in comparison groups (meta-regression). I-squared of >50% will be interpreted as unacceptable heterogeneity in which case pooled estimate(s) will be rejected. Forest Plot of Risk Ratios will be reported. Qualitative elements of included studies will be summarised in a study table.

Meta-bias(es)

Funnel plot and Egger's test will be used to assess publication if more than 10 studies are included.

Confidence in cumulative evidence

The strength of the body of evidence will be assessed using GRADE.

References:

1. Smilowitz NR, Gupta N, et al. Trends in perioperative major cardiovascular and cerebrovascular events associated with non-cardiac surgery. JAMA Cardiology. 2017 Feb 1; 2(2): 181-187.
2. Devereaux PJ, Goldman L, et al. Perioperative cardiac events in patients undergoing non-cardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ. 2005 Sep 13; 173(6): 627:634.
3. Berti M, Fanelli G, et al. Hypothermia prevention and treatment. Anaesthesia. 1998 May, 53 Suppl 2: 46-7.
4. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. Miller's Anesthesia E-Book. Elsevier Health Sciences; 2014 Oct 20. Chapter 54: Temperature regulation and monitoring. Pages: 1622-1646.e6.
5. Kurz A, Goll V, et al. Heat loss during major orthopaedic surgery. Anaesthesia. 1998 May, 53 Suppl 2: 43-45.
6. Ying-Jian Sun, Zi-Yuan Zhang, Bin Fan, Guang-Yu Li. Neuroprotection by therapeutic hypothermia. Front Neurosci. 2019; 13: 586. Published online 2019 Jun 11.

7. Kohlhauer M, Pell VR, Burger N, Spiroski M et al. Protection against cardiac ischemia-reperfusion injury by hypothermia and by inhibition of succinate accumulation and oxidation is additive. Basic Res Cardiol. 2019; 114(3):18. Published online Mar 2015.

8. Flather et al. Strengths and Limitations on meta-analysis. Controlled Clinical Trials 1997.

9. NICE guidelines (2016). Inadvertent Perioperative Hypothermia. Available from: http://www.nice.org.uk/guidance/cg65.

10. Shamseer L, Moher D, Clarke M et al. Research Methods and Reporting. Preferred reporting items for systemic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Available from: prisma-statement.org/Protocols/ProtocolGuidance. [cited 18 October 2019).

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Use 'survival' curves for outcomes that are time, e.g. 'time to extubation' or 'time to hospital discharge', particularly if it is the primary outcome
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Acknowledgments

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Tables

Include Tables in the same le as the text, but after the References. Each Table should be on a separate page. Number the Tables consecutively with Arabic numerals. Each Table should have a brief caption immediately above it; this should provide enough information for readers to follow the Table without having to look through the text (e.g. 'Baseline characteristics of patients receiving vecuronium or rocuronium for caesarean section' rather than just 'Patients' characteristics'). The caption should explain whether the values refer to mean (SD), number (proportion), etc. Abbreviations should not be mentioned in the caption without explanation. Abbreviations used in the body of the Table should be explained as footnotes in the order in which they are mentioned.

For adults: age, weight, height and BMI should be expressed as mean (SD). For children: age, weight, height and BMI should be expressed as median (IQR [range]). Study groups should form the columns rather than the rows. If statistical comparisons are being made, a separate column with exact p values should appear to the same number of decimal points which should normally be 3, e.g. p = 0.006 or p < 0.001 Example:

Table 2 Pre-operative laboratory parameters for anaemic (haemoglobin < 120 $g.l^{-1}$), borderline anaemic (haemoglobin 120–129 $g.l^{-1}$) and non-anaemic (haemoglobin ≥ 130 $g.l^{-1}$) women undergoing elective major abdominal surgery. Values are mean (SD) or median (IQR [range]).

Laboratory parameter	Anaemic n = 247	Borderline anaemic n = 339	Non-anaemic n = 968
Haemoglobin $g.l^{-1}$	108 (10)	125 (3)	140 (7)
MCV; fl	84 (9)	86 (6)	87 (5)
WCC; $10^9.l^{-1}$	7 (3)	7 (2)	8 (2)
Platelet count; $\times 10^9.l^{-1}$	311 (104)	282 (80)	274 (67)
Ferritin; $\mu g.l^{-1}$	89 (23–237 [5–9175])	64 (33–128 [7–1385])	99 (55–154 [11–1937])
TSAT; %	16 (15)	17 (8)	22 (9)
Albumin; $g.l^{-1}$	34 (5)	37 (4)	39 (3)
Creatinine; $\mu mol.l^{-1}$	79 (55)	71 (44)	66 (13)
CRP; $mg.l^{-1}$	8 (2–25 [0–164])	4 (2–11 [0–174])	4 (2–8 [0–132])

MCV, mean corpuscular volume; WCC, white cell count; TSAT, transferrin saturation; CRP, C-reactive protein.

Figures

Please supply each Figure as a separate le and not embedded within the Word document. We ask that Figures are supplied at a resolution of 300 pixels per inch for photographs and 600 pixels per inch for line art or a combination of photograph and labelling. Please do not send image les larger than 10MB. Further guidance can be found **here**.

Please ensure related graphs have the same format (fonts, use of symbols, etc.), and that the groups are presented in the same order in each graph (and in the same order as in the rest of the manuscript). The same requirements for abbreviations and units apply as for those in the text and Tables. There should be no titles, plot frames, gridlines or legend boxes within the graphs, and symbols and error bars should be explained in the caption. Avoid the use of 3-D unless absolutely necessary. Colour figures (e.g. photographs, complex diagrams, etc.) may be used without charge. Where possible, please use the font Avenir LT Pro.

For CONSORT diagrams, please use the templates provided on the **CONSORT website**.

Captions for Figures

Each Figure caption should include an explanation of the symbols used to provide enough information for readers to follow it without having to look through the text. Thus this:

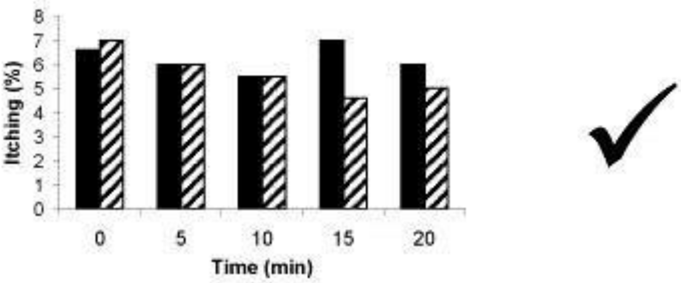

Figure 1 Itching after surgery in patients receiving saline ( ) or chlorphenamine ( ). No significant difference between groups.

Is preferable to this:

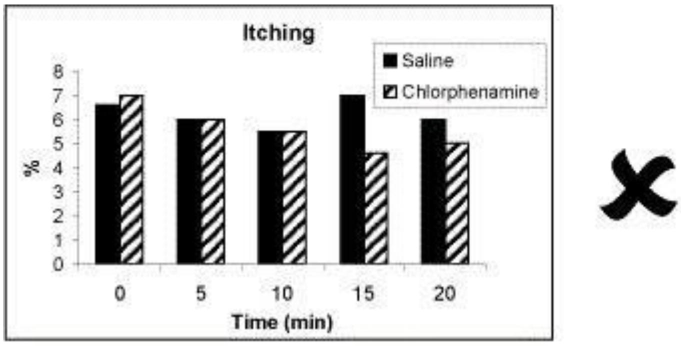

Figure 1 Itching after surgery.

See notes below for ethical considerations relating to photographs.

Supporting Information (online only)

Additional material such as video clips, lengthy Appendices (e.g. extensive reference lists, mathematical formulae/calculations, copies of questionnaires), which are relevant to a particular article but not suitable or essential for the print issue of the journal, may also be considered for publication. Please refer to all supporting information in the manuscript as online Supporting Information Table S1, online Supporting Information Figure S1, etc. and supply the les as separate to the main document. The captions for supporting information should be listed at the end of your submission. Authors must obtain permission from the copyright holders if the contents have been previously published. Further information on suitable le formats may be found **here**.

Language

Anaesthesia uses UK English spelling e.g. “ise” not “ize”, “anaesthesia” not “anesthesia”, etc. Please avoid long, complicated sentences and the passive voice when the active is more appropriate (e.g. ‘We chose epidural anaesthesia because...’ instead of ‘Epidural anaesthesia was chosen by the authors because...’). Focus on the actual message of each sentence; thus ‘Hypotension is important because...’ instead of ‘It would be remiss of us not to mention hypotension because...’. Remember that lungs are ventilated, not patients (nor are they intubated – their tracheas are).

Similarly, patients are not induced – anaesthesia is – or put on ventilators. Correct terms are tracheal (not **endo**tracheal) tube and neuromuscular blocking drugs (not muscle relaxants). Please refer to recent issues of the Journal for preferred wording/spelling.

Personal pronouns do not need to be used in the text when referencing works by single authors as the author’s name should be used. However, where pronouns are used, care should be taken to establish the correct pronoun for the cited author (e.g. ‘he’, ‘she’, ‘they’). Alternatively, it is acceptable to use non-gendered pronouns ‘they’ and ‘their’ when discussing prior works by single authors if their preferred pronoun cannot be established.

The abbreviation LMA is only to be used if referring to a specific device made by The Laryngeal Mask Company Ltd, and with the first mention in the Summary and in the main text highlighted by (R) and ‘LMA is a registered trademark of The Laryngeal Mask Company Ltd, an affiliate of Teleflex Incorporated’ as a footnote. If used, the correct format is ‘LMA® laryngeal mask’ for the first mention (n.b. not just ‘LMA®’) and ‘LMA laryngeal mask’ thereafter. The same to apply to LMA® Classic, LMA® Flexible, LMA® Fastrach (n.b.previously labelled ILMA®), LMA® ProSeal, LMA® Supreme, LMA® Unique (n.b. ‘cLMA’ not to be used). The generic term of ‘laryngeal mask’ should be used for describing in supraglottic airways in general.

Abbreviations

The Journal does not encourage the use of abbreviations, especially in the Summary, since their frequent use makes papers difficult to read. We will accept abbreviations in the following circumstances:

Universal abbreviations that do not need to be written out in full when first mentioned in the text, e.g. ASA, BMI, ECG, ICU, HDU, SD, SEM, 95% CI, IQR, ANOVA, S_pO_2, F_IO_2, pH.
Acceptable common abbreviations should be written out in full at their first mention, e.g. CNS, CSF, HME, PEEP, PCA, CTG, EEG, BIS, CVP, PAP, ECT – unless they are only mentioned a few times, in which case please spell them out throughout. Please do not use abbreviations that are clumsy or will be unfamiliar to the majority of readers, e.g. DI (difficult intubation), TTFB (time to first breath), etc.
Acceptable abbreviations whose use should be restricted to situations where space is limited, such as in formulae or in Tables and Figures, e.g. O_2, CO_2, N_2O, HCO^{3-}, Na^+, K^+, Mg^{2+}.

Numbers and units

Numbers should be spelled out in full when they start a sentence, and when they are less than 10 (unless they are followed by units of measurement). Thus: ‘Thirteen days later, patients each received 7 ml solution...' Commas are used to indicate thousands above 10,000: thus, 2000 and 20,000. Please give costs in sterling (£) with equivalent Euros and US dollars (€/$) in brackets.

Use the format $mg.kg^{-1}$ not mg/kg for all units. Use SI units throughout the text except for vascular pressure measurements (mmHg or cmH_2O) and haemoglobin concentration ($g.l^{-1}$). Litres are indicated by lower case 'l'. Use the 24-hour clock for times.

Ethical considerations

Manuscripts will only be considered for publication in *Anaesthesia* if they adhere to the highest ethical standards. These are detailed in two editorials published in the journal, that are available **here** and **here** and which potential authors are strongly advised to read.

The Editorial Board takes all cases of possible publication misconduct seriously and will investigate these according to the recommendations of the **Committee on Publication Ethics (COPE).**Further guidance can be found in our **Editorial Policies**.

All clinical trials that prospectively assign human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome should be registered before the time of first recruitment. There are several public registries now available which meet the requirements of the ICMJE and these are listed on the **WHO International Clinical Trials Registry Platform.** The registry, registration number and date of registration must be stated in the Acknowledgements section of the manuscript. This should have been done before patient recruitment commenced. Reports of original research that were not registered before the study was carried out should include separate submission of the original protocol for the study. If the submitted report differs from the protocol, an explanation of the reason for this should be provided. Authors should be willing and able to submit their raw study data to the journal, if requested, after submission.
Anaesthesia supports and encourages the use of the **EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network guidelines** to ensure the transparent and accurate reporting of research studies. The authors of clinical intervention studies are advised to review the **CONSORT statement** regarding the reporting of randomised trials prior to manuscript submission.

We strongly encourage authors to register systematic review protocols on a similar database (for instance, PROSPERO **http://www.crd.york.ac.uk/PROSPERO/**).

All clinical trails should be conducted in accordance with the ethical principles as set out in the Declaration of Helsinki. In brief, the minimum ethical standards for *Anaesthesia* include:

- Approval by a Research Ethics Committee (REC) or equivalent Institutional Review Board (IRB) must be obtained prospectively for all studies on human subjects, including studies in which participants' skills are tested using manikins. Some studies involving audit and epidemiological surveys, assessments of medical equipment or analysis of previously collected, non-identifiable information from a database may be exempt from this stricture if participants are appropriately protected against coercion and there is due regard to confidentiality. Publication of the results, however, would usually still require informed consent and assurances regarding confidentiality (including approval by the Caldicott Guardian or equivalent for patient data and the relevant Research and Development department), even if the REC/IRB has indicated that formal submission is unnecessary.

- While an essential preliminary step, REC/IRB approval does not guarantee the ethical standards of a study will meet the requirements of the Editorial Board of Anaesthesia. If authors have any concerns that ethical issues might compromise publication, they are invited to contact the Editor-in-Chief before embarking on the study.
- The Editorial Board supports the view of the ICH Harmonised Tripartite Guideline for Good Clinical Practice that full prospective written informed consent should be obtained from all subjects of clinical trials, including participants in manikin studies (see above). This would normally comprise provision of written information to potential research participants, allowance of adequate time for them to consider their involvement and ask questions, and the use of specific consent forms (for the study, not just for routine surgery/anaesthesia) that should be signed by the participants to indicate their consent and stored in case they require examination later.
- Studies of novel treatments, in particular drug studies where the agent used is given via unlicensed routes (especially neuraxial or perineural), may have received approval from the REC/IRB, but the Editorial Board is likely to reject such studies if it considers the risks posed outweigh the potential benefits. Such a conclusion is more likely to be reached if the drug in question is not widely used in routine practice (as evidenced by inclusion in standard textbooks), if the study participants are especially vulnerable (e.g. children, women in labour), if there are questions over consent, or if only modest improvements in outcome are expected where other, well established methods already exist.
- Animal studies will only be considered for publication if they have ethical and governmental approval, and have been conducted under appropriate standards of care. Researchers will be expected to follow the ARRIVE guidelines for experimentation in animal research.

Statistics

The following guidelines may help authors present their work in a better and more rigorous way that avoids common statistical errors that frequently lead to rejection. This is not an exhaustive list and, of course, the Editorial Board and reviewers of manuscripts may ask authors for revisions that are not detailed here. Authors are advised that it is a condition of submission that they be prepared to send individual patient data, or other data, to be checked.

Methods

Randomisation methods should be made explicit (e.g. coin toss, random numbers, etc.). Please describe if stratification of the allocation system in a randomised controlled trial is performed (e.g. by age or recruiting centre) or block (permuted sequence or otherwise). For instance, most anaesthetic randomised controlled trials have exactly the same number of patients in each group but do not mention any blocking method (which would include putting equal numbers of folded pieces of paper for each group in an urn). Blinding must be as good as possible within constraints of clinical practice.

Where there are several outcomes to be reported, the most important (primary) outcome should be clearly stated, along with any secondary outcomes. Beware of reporting as ‘significant’ or ‘important’ a positive result of a secondary outcome, when the study was in fact powered (sample sized) to a different primary outcome.

Power analysis

Some justification of sample size is always necessary for all observational studies, randomised or nonrandomised controlled trials, or other types of study. Justification may be quantitative or qualitative (e.g. a 'convenience sample'), although the latter may be regarded as weaker than the former. Details provided (for continuous variables) should include the power level; the significance level at which a result is sought; and the expected control and study group proportions or mean and pooled SD, in order to allow reviewers and readers to follow the calculation. The method used to justify power should be referenced and enough detail provided, so that the calculation can be repeated by readers. Conventionally, the power of study should be at least 80% but where different this should be stated and justified. The 'clinically important difference' that the study is designed to detect should indeed be clinically relevant. Beware of setting an unreasonably large 'clinically important difference' to justify small sample size, as reviewers will recognise this is done simply to facilitate a small study.

General rules:

Use mean (SD) unless data are discrete (e.g. Apgar scores, sedation scores) or grossly non-normally distributed: use median (IQR [range]) or you are interested in the 'true' value for the population (use SEM).
Visual analogue scores (VAS) for pain may be treated as continuous data and be subjected to parametric tests as long as the sample size is large (> 50) and the data appear normally distributed. VAS for other modalities (nausea, drowsiness) have not been so extensively validated and are best treated as ordinal data.
Scales of measurement can be problematic (e.g. Cormack-Lehane scale, VAS, etc.) because a value of say 2 on the scale does not imply something twice the value of 1, etc. So they cannot logically be regarded as linear, continuous scales. It is safer to regard them as ordinal scales. However, for some scales such as VAS for pain it appears established norm that this may be regarded as continuous, especially for large sample sizes (e.g. >50).

Inferential statistics

Avoid multiple comparisons, or correct for them if used.
Reference unusual tests; and assume that the more unusual the test, the more likely it is that a specialist statistical referee will review the paper.
Include details of any computer package/version used.

When looking for relationship between variables, use correlation to describe a simple descriptive association between two variables.
Use regression to describe a quantitative relationship between two or more variables, especially where one is predictive and other(s) dependent. Non-linear regression may be appropriate. Regression methods yield a formula to relate the variables being described.
Use the Bland-Altman method to describe the performance of two different methods used in measurement, analysis or diagnosis.

Conclusions

All conclusions should be warranted by the results and not extend beyond the confines of the study conditions. A negative result does not mean that there is definitely no difference (confidence in the conclusion is dependent upon the power of the study), and a positive result does not mean that there definitely is a difference (confidence in the conclusion is dependent upon the alpha error). The journal has a very useful **statistics section** containing articles which authors may find useful in preparing their manuscripts for statistical content.

HUMAN RESEARCH ETHICS WAIVER

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Faculty of Health Sciences
Human Research Ethics Committee

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Dear Dr du Toit

PROJECT TITLE: A SYSTEMATIC REVIEW OF THE EFFECT OF TEMPERATURE MANAGEMENT ON PERIOPERATIVE CARDIOVASCULAR OUTCOMES IN INTERVENTIONAL STUDIES (MMED Candidate DR SISLINDELE MKHIZE)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a systematic review.

As the systematic review involves published literature available through publicly accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: *"Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research."*

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledge that the MMED Candidate, Dr Sisalindele Mkhize, was also involved in this project.

Hrec.ref425/2020sa