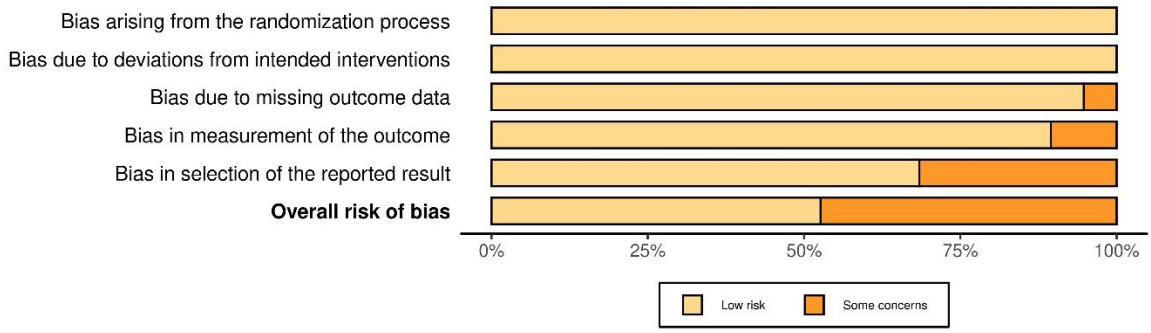
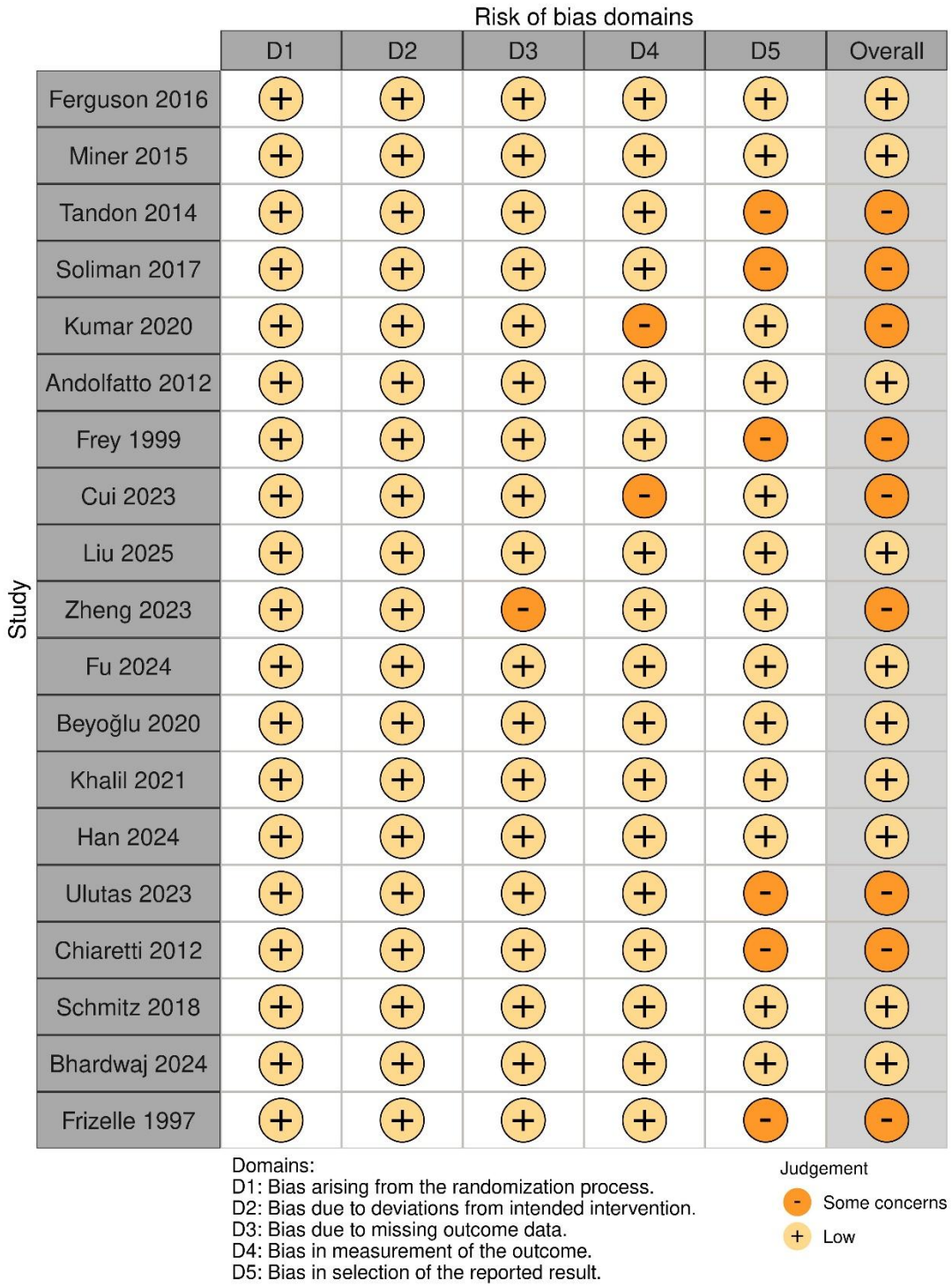
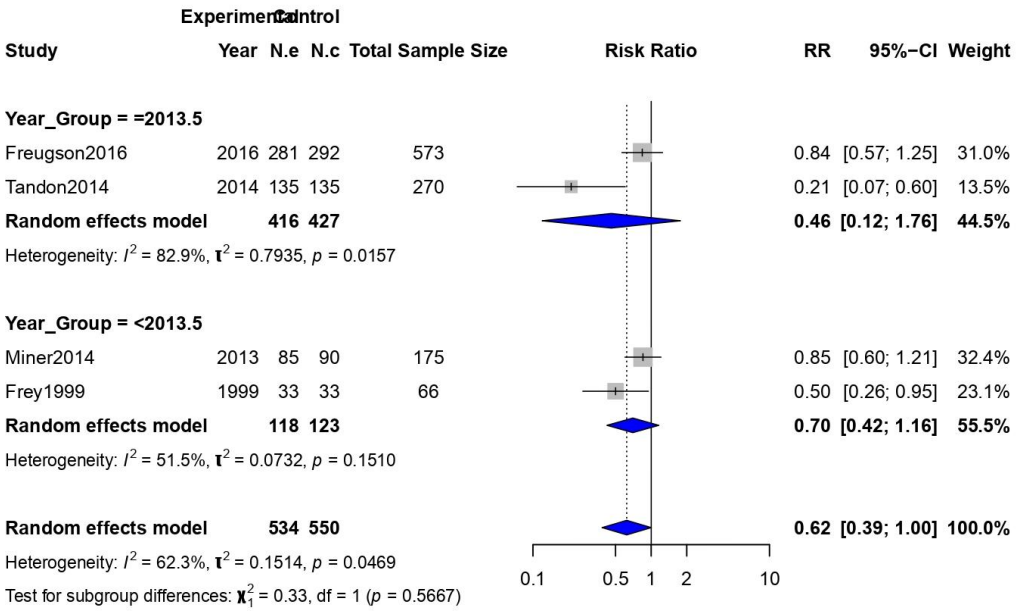
Supplementary Figure 1A. Risk of bias assessment using the Cochrane RoB2 tool: Summary Plot



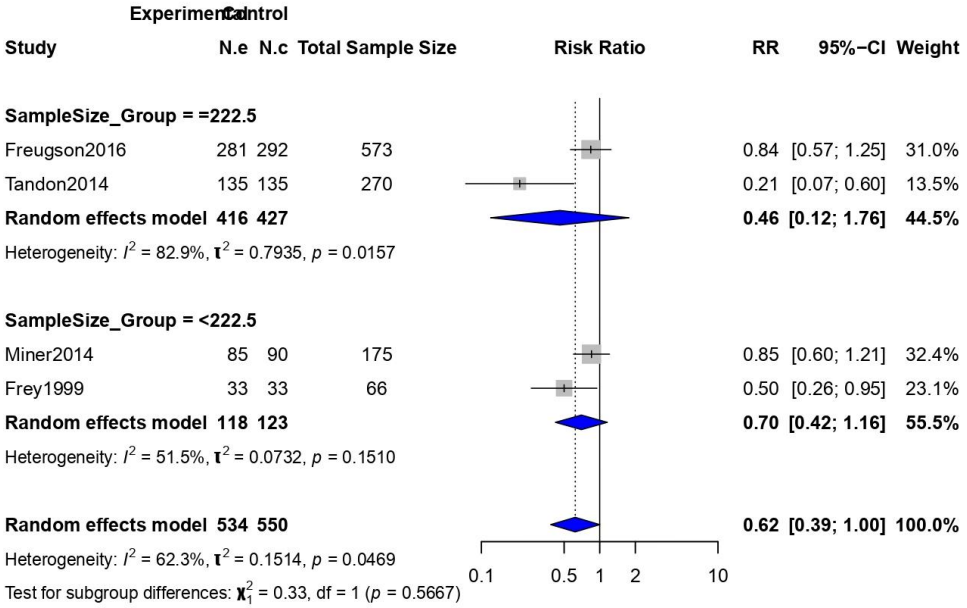
Supplementary Figure 1B. Risk of bias assessment using the Cochrane RoB2 tool: Traffic-light plot



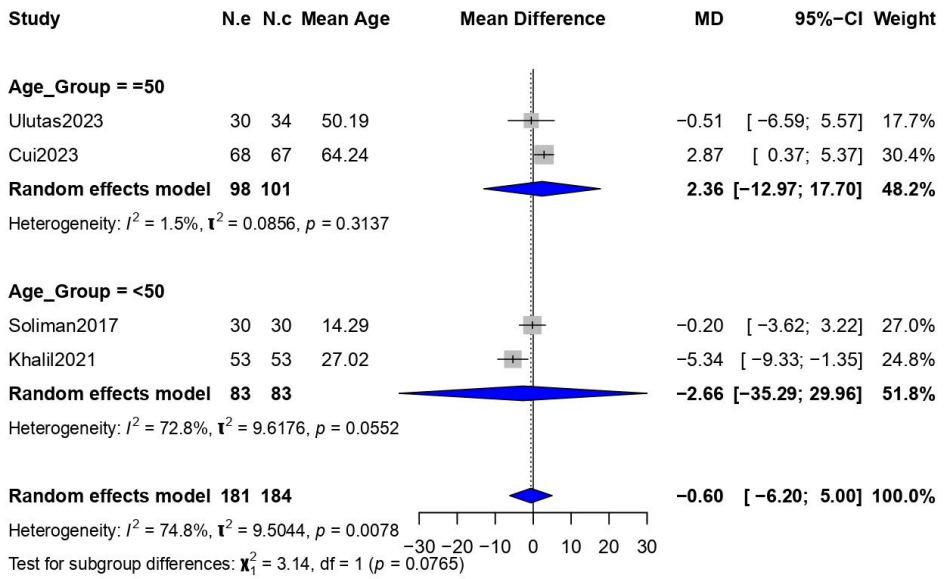
Supplementary Figure 2. Subgroup analysis of respiratory intervention, stratified by study year.



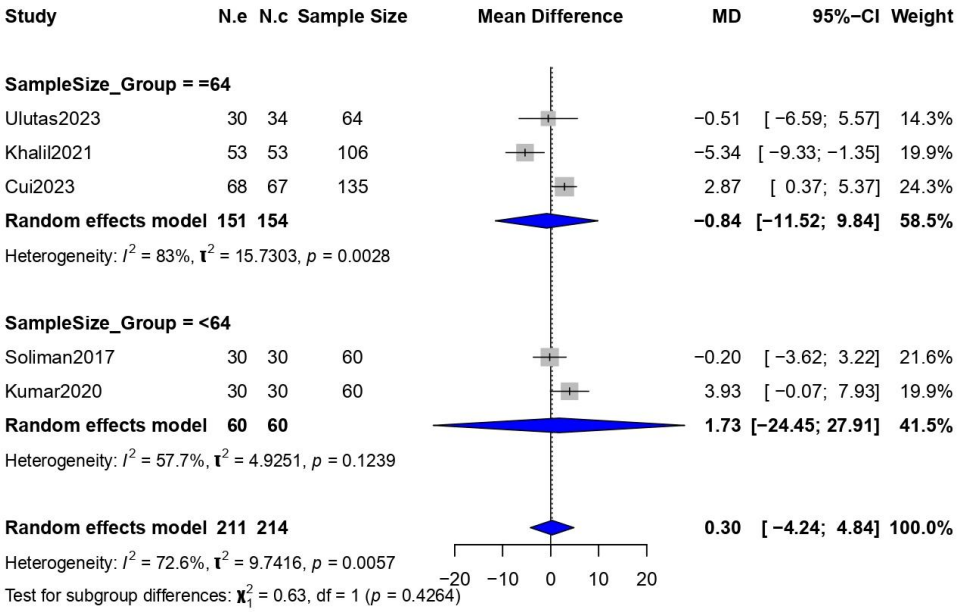
Supplementary Figure 3. Subgroup analysis of respiratory intervention, stratified by sample size.



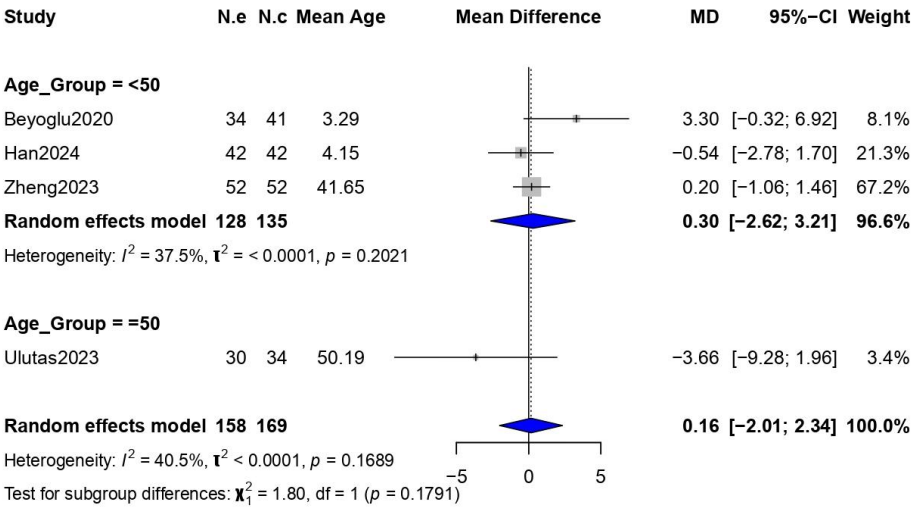
Supplementary Figure 4. Subgroup analysis of systolic blood pressure (SBP), stratified by age group.



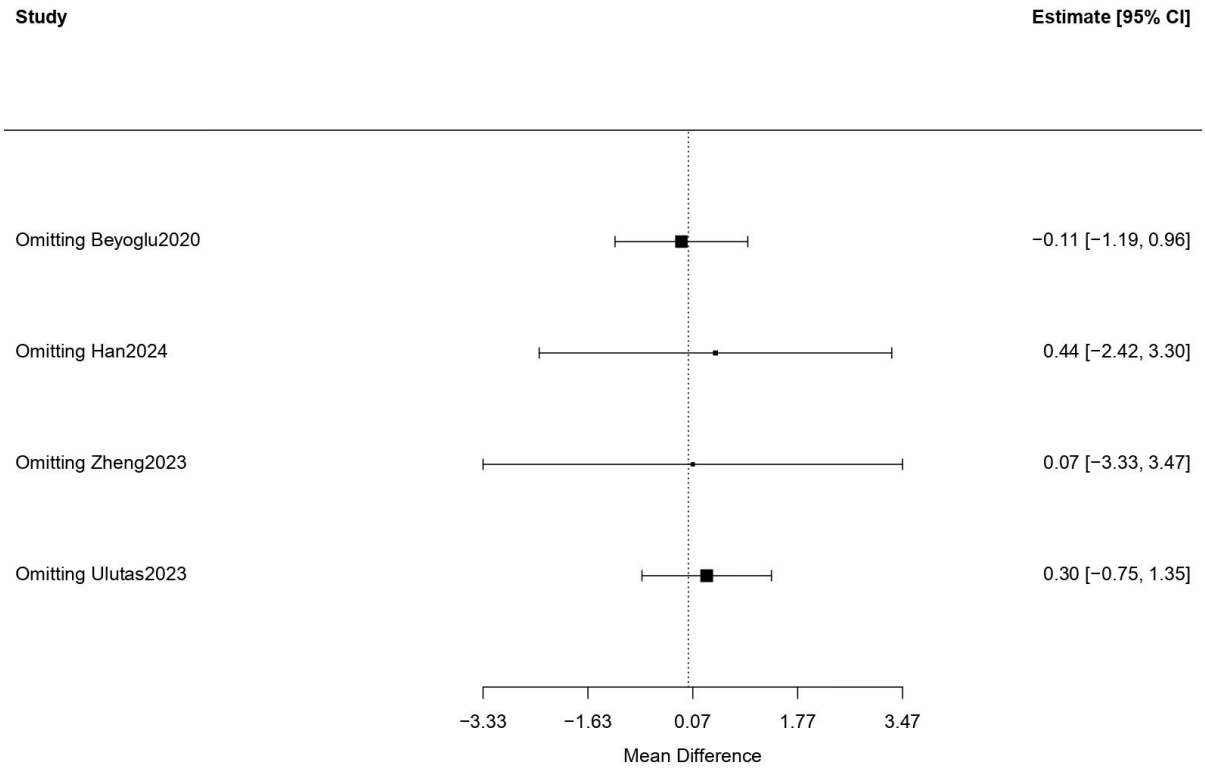
Supplementary Figure 5. Subgroup analysis of mean arterial pressure (MAP), stratified by sample size.



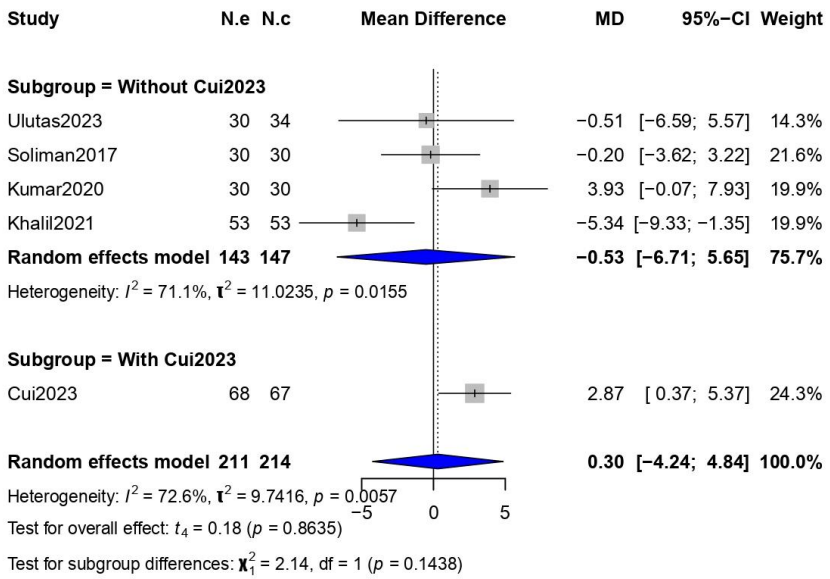
Supplementary Figure 6. Subgroup analysis of diastolic blood pressure (DBP), stratified by age group.



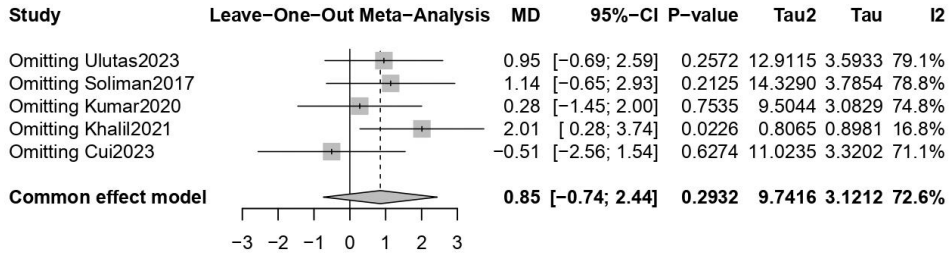
Supplementary Figure 7. Sensitivity analysis of diastolic blood pressure (DBP) using leave-one-out approach.



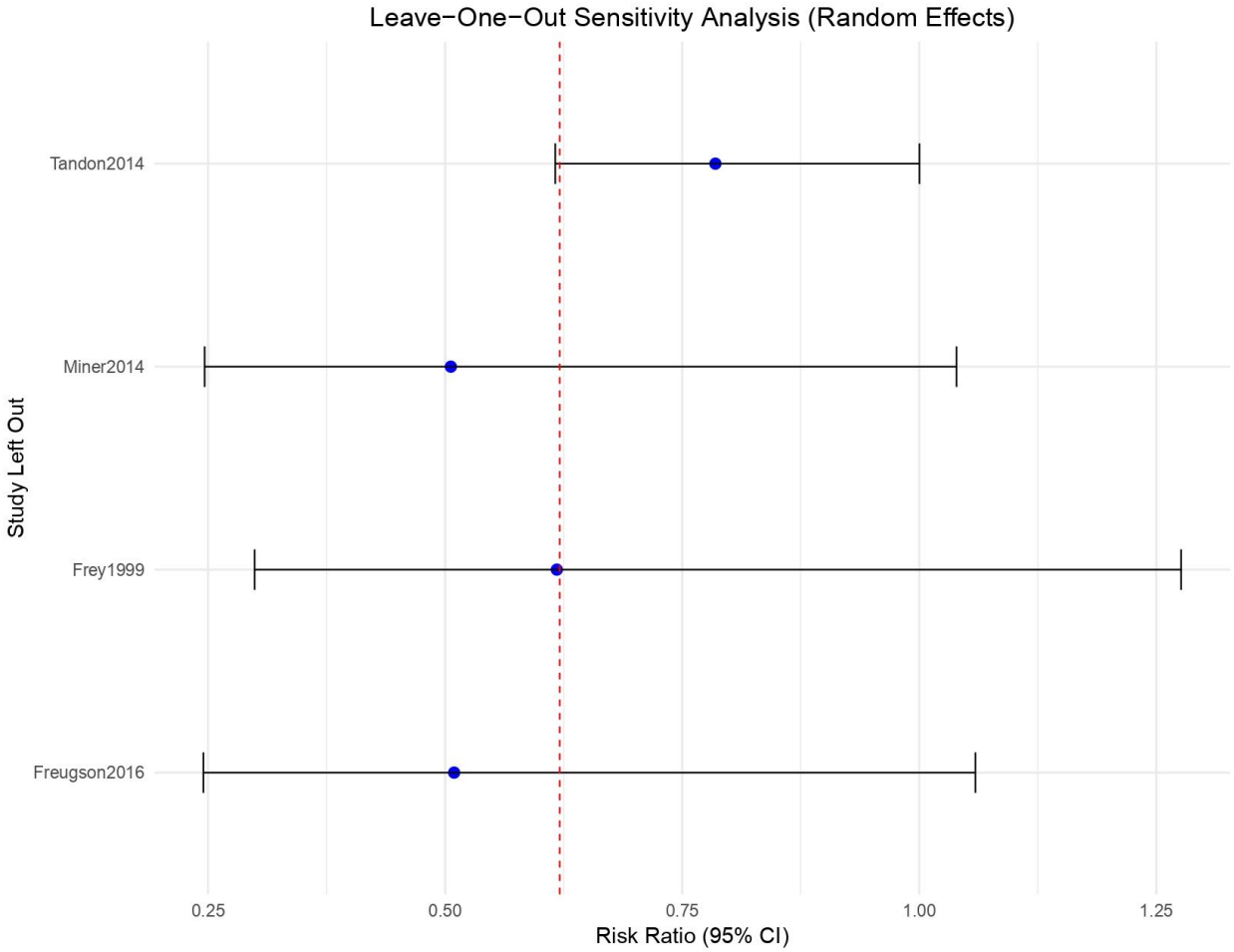
Supplementary Figure 8. Sensitivity analysis of mean arterial pressure (MAP) with and without the study by Cui (2023).



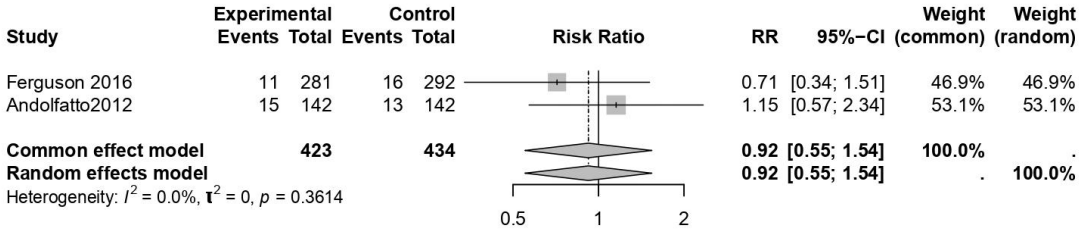
Supplementary Figure 9. Leave-one-out sensitivity analysis of mean arterial pressure (MAP).



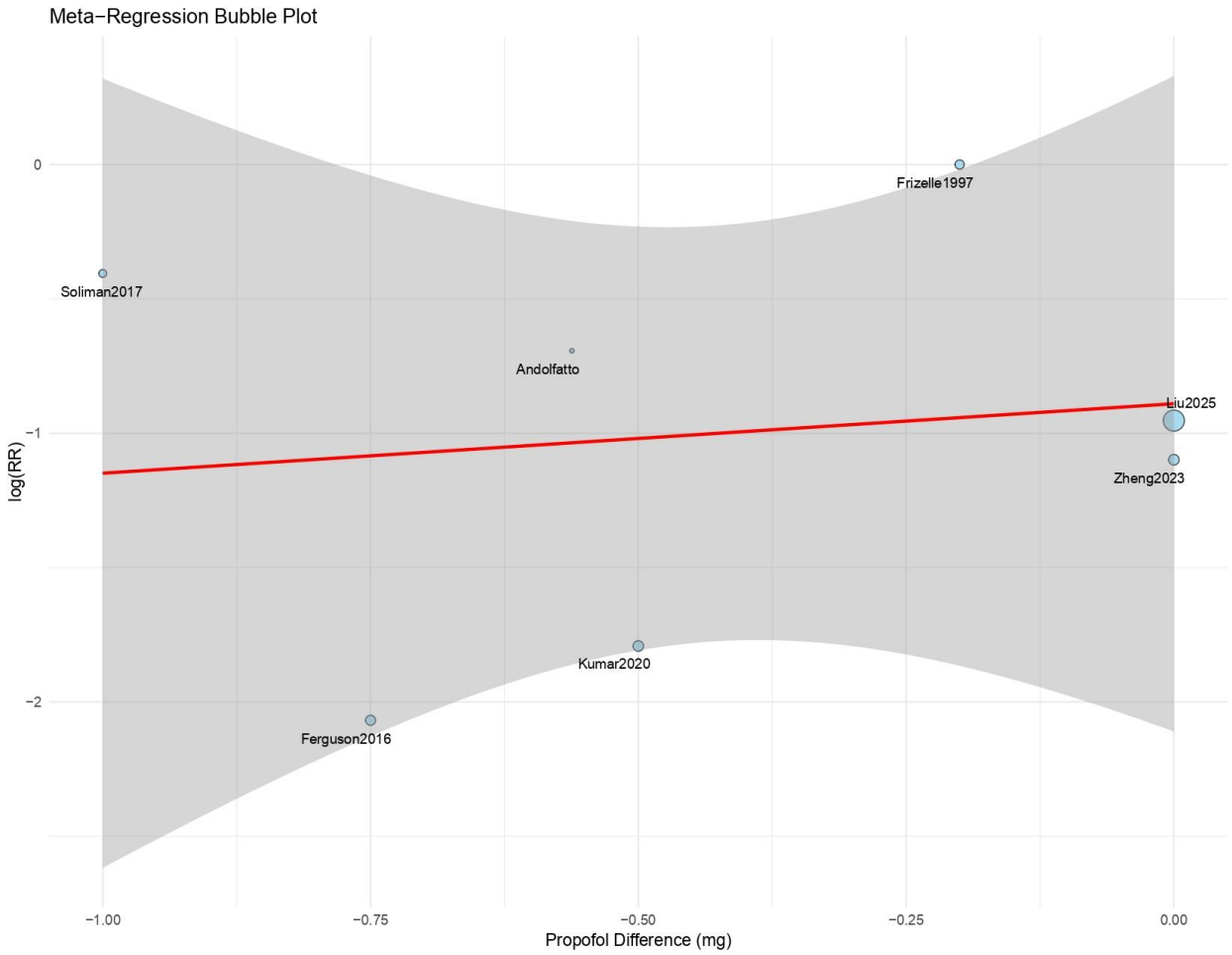
Supplementary Figure 10. Leave-one-out sensitivity analysis of respiratory intervention.



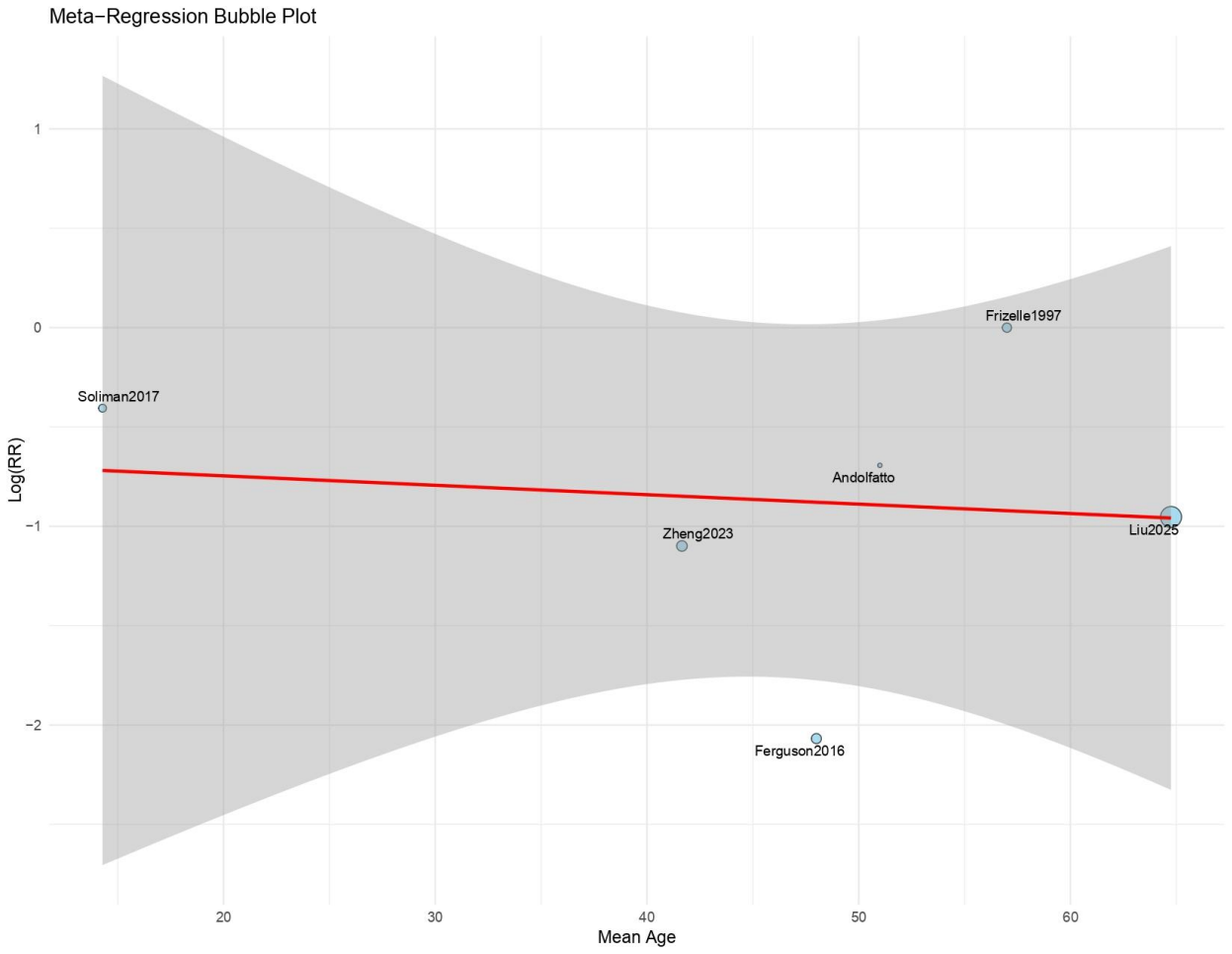
Supplementary Figure 11. Sensitivity analysis of apnea incidence using two included studies (Ferguson 2016 and Andolfatto 2012).



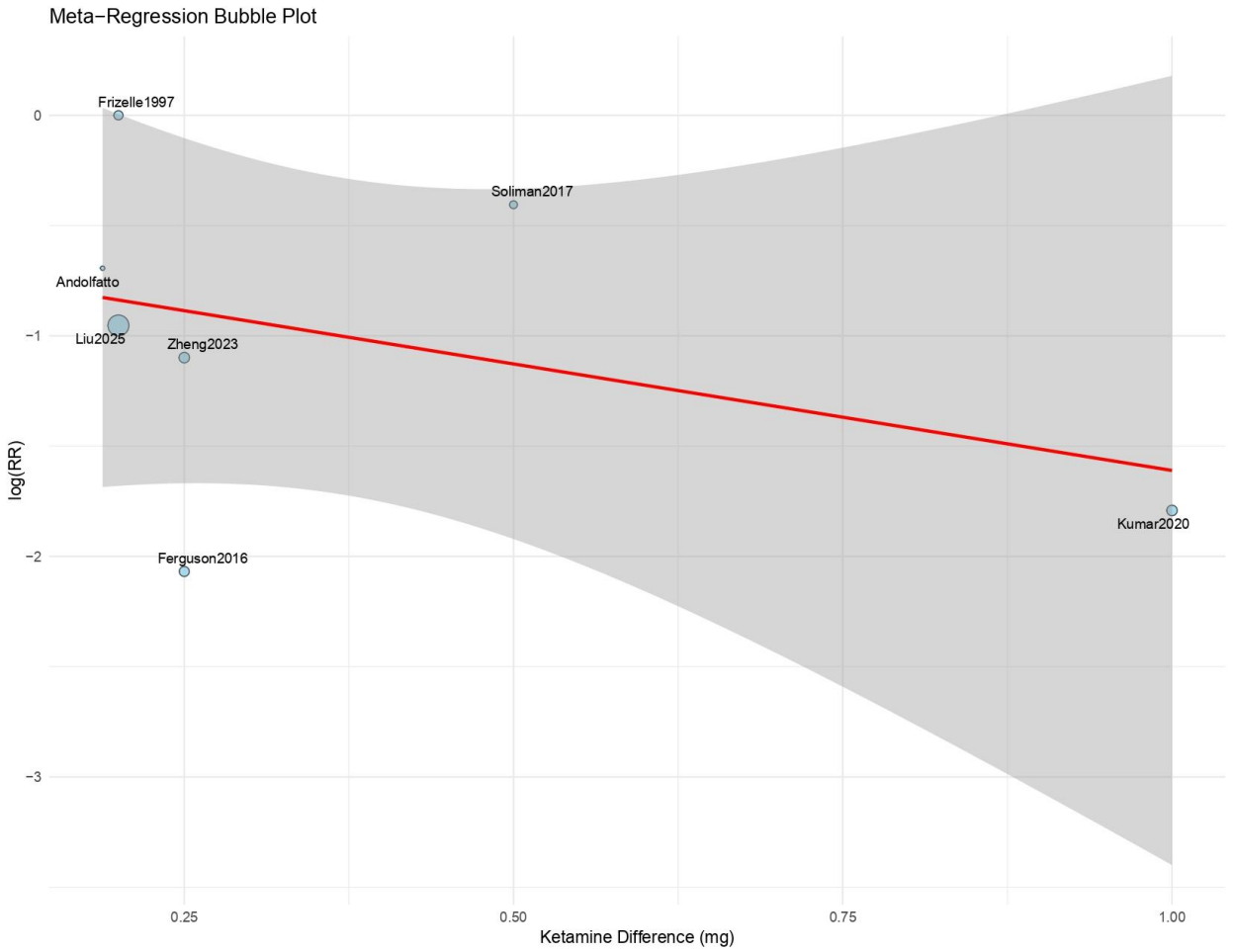
Supplementary Figure 12. Meta-regression of propofol dose difference (mg) and log risk ratio (LogRR) for hypotension.



Supplementary Figure 13. Meta-regression of mean age and log risk ratio (LogRR) for hypotension.



Supplementary Figure 14. Meta-regression of ketamine dose difference (mg) and log risk ratio (LogRR) for hypotension.



Supplemental Table 1. Search strategy and results

Database	Search Strategy	Results
PubMed	((procedural sedation OR conscious sedation OR deep sedation OR moderate sedation OR sedation OR PSA OR procedure-related sedation OR minimal sedation OR ambulatory sedation OR ("Deep Sedation/adverse effects"[Mesh] OR "Deep Sedation/methods"[Mesh] OR "Deep Sedation/mortality"[Mesh] OR "Deep Sedation/statistics and numerical data"[Mesh]) OR ("Conscious Sedation/adverse effects"[Mesh] OR "Conscious Sedation/classification"[Mesh] OR "Conscious Sedation/methods"[Mesh] OR "Conscious Sedation/mortality"[Mesh] OR "Conscious Sedation/standards"[Mesh] OR "Conscious Sedation/statistics and numerical data"[Mesh] OR "Conscious Sedation/trends"[Mesh])) OR (analgesia OR ("Analgesia/adverse effects"[Mesh] OR "Analgesia/methods"[Mesh] OR "Analgesia/mortality"[Mesh] OR "Analgesia/standards"[Mesh] OR "Analgesia/statistics and numerical data"[Mesh] OR "Analgesia/trends"[Mesh]))) AND ((Ketofol OR ketofol sedation OR ketamine plus propofol OR propofol-ketamine OR ketamine-propofol OR ketamine propofol combination OR ketamine-propofol mixture OR propofol-ketamine mixture) OR ((Ketamine OR ketamine hydrochloride OR ketamine HCl OR ketamine injection OR ketamine IV OR Ketalar OR Ketanest OR Ketaset OR esketamine OR S-ketamine OR Spravato OR "Esketamine" [Supplementary Concept] OR ("Ketamine/administration and dosage"[Mesh] OR "Ketamine/adverse effects"[Mesh] OR "Ketamine/therapeutic use"[Mesh])) AND (propofol OR propofol injection OR propofol IV OR Diprivan OR Disoprivan OR Propoven OR Fresofol OR Recofol OR ("Propofol/administration and dosage"[Mesh] OR "Propofol/adverse effects"[Mesh] OR "Propofol/therapeutic use"[Mesh]))))	1,082

Supplemental Table 2. Assessment of certainty in evidence using the GRADE approach

Author(s):
Question: Ketofol compared to Propofol for patients undergoing procedural sedation
Setting: in emergency departments or procedural settings
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketofol	Propofol	Relative (95% CI)	Absolute (95% CI)		
Occurrence of Respiratory Intervention (assessed with: Risk Ratio (RR))												
4	Randomized trials	serious [a]	serious [b]	serious [c]	serious [d]		1166/2358 (49.4%)	1192/2358 (50.6%)	**RR 0.62** (0.39 to 1.00)	**192 fewer per 1,000** (from 308 fewer to 0 fewer)	Very Low	CRITICAL
Desaturation (assessed with: Risk Ratio)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketofol	Propofol	Relative (95% CI)	Absolute (95% CI)		
4	Randomised trials	not serious	serious[e]	not serious	not serious		507/1028 (49.3%)	521/1028 (50.7%)	**RR 0.93** (0.67 to 1.29)	**35 fewer per 1,000** (from 167 fewer to 147 more)	Moderate	CRITICAL

Apnea (assessed with: Risk Ratio)

3	Randomized trials	Not serious	not serious	not serious	serious[f]		443/897 (49.4%)	454/897 (50.6%)	**RR 0.95** (0.57 to 1.58)	**25 fewer per 1,000** (from 218 fewer to 294 more)	Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketofol	Propofol	Relative (95% CI)	Absolute (95% CI)		
Hypotension												
9	Randomised trials	serious[g]	not serious	not serious	not serious		884/1778 (49.7%)	894/1778 (50.3%)	**RR 0.40** (0.26 to 0.60)	**302 fewer per 1,000** (from 372 fewer to 201 fewer)	Moderate	IMPORTANT
Patient Satisfaction (assessed with: Risk Ratio)												
3	Randomised trials	not serious	not serious	not serious	not serious		374/757 (49.4%)	383/757 (50.6%)	not estimable		High	IMPORTANT
Recovery Time (assessed with: Standardized mean difference)												
8	Randomised trials	not serious	serious[h]	not serious	not serious		679	684	-	**0** (0 to 0)	Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

[a] Two studies were at low risk of bias, while 2 had some concerns in the reporting domain D5. Overall judged as a serious risk of bias.

b. Downgraded by 1 level due to substantial heterogeneity across the studies

c. Some inconsistency in study results downgraded 1 level

d. Evidence indirect as study populations/interventions were not fully representative of the review question.

e. The confidence interval crosses the line of no effect and includes both appreciable benefit and harm, suggesting uncertainty in the true effect.

f. The common effect model has a risk ratio (RR) of 0.95 with a 95% confidence interval (CI) of [0.57, 1.58]. Since this interval crosses the line of no effect (RR = 1), we cannot be confident that there is a true effect, which indicates imprecision. The sample size is also small, which contributes to this uncertainty.

g. Six of the nine included studies had some concerns in risk of bias domains, which may have influenced the overall certainty of evidence.

h. I2 value is 97.5%, which is very high and indicates a significant amount of variability between the study results. The p-value for heterogeneity is <0.0001, which is very significant.

Supplemental Table 3. Assessment of certainty in evidence using the GRADE approach

Author(s):
Question: Ketofol compared to Propofol for patients undergoing procedural sedation
Setting: in emergency departments or procedural settings
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketofol	Propofol	Relative (95 % CI)	Absolute (95 % CI)		
Systolic blood pressure (assessed with: Mean difference)												
4	randomised trials	serious [a]	not serious	not serious	not serious		158	169	-	**0** (0 to 0)	Moderate	IMPORTANT
Mean arterial blood pressure (assessed with: Mean Difference)												
5	randomised trials	serious [b]	serious [c]	not serious	serious [d]		211	214	-	**0** (0 to 0)	Very Low	IMPORTANT
Diastolic blood pressure (assessed with: Mean difference)												
4	randomised trials	serious [e]	not serious	not serious	not serious		158	169	-	**0** (0 to 0)	Moderate	IMPORTANT
Vomiting (assessed with: Risk Ratio)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketofol	Propofol	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	not serious	not serious	not serious	not serious		497/1008 (49.3%)	511/1008 (50.7%)	**RR 1.29** (0.61 to 2.76)	**147 more per 1,000** (from 198 fewer to 892 more)	High	IMPORTANT

Hallucinations (assessed with: Risk Ratio)

3	randomised trials	not serious	not serious	not serious	not serious		475/960 (49.5%)	485/960 (50.5%)	**RR 2.24** (1.65 to 3.03)	**626 more per 1,000** (from 328 more to 1,000 more)	High	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketofol	Propofol	Relative (95% CI)	Absolute (95% CI)		
Airway Events (assessed with: Risk Ratio)												
3	randomised trials	not serious	not serious	not serious	not serious		508/1032 (49.2%)	524/1032 (50.8%)	**RR 0.63** (0.41 to 0.99)	**188 fewer per 1,000** (from 300 fewer to 5 fewer)	High	CRITICAL
Heart Rate (assessed with: Mean difference)												
5	randomised trials	serious[f]	not serious	not serious	not serious		184	188	-	**0** (0 to 0)	Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Two of the four studies had some concerns in risk of bias, including one study that contributed 78% of the weight, which reduces confidence in the pooled estimate

b. Four of five studies had some concerns for selective reporting (D5), which may bias the pooled estimate — downgraded one level.

c. The heterogeneity test shows a high I 2 value of 72.6%. The p-value for heterogeneity is 0.0057, which is statistically significant. This suggests that the results of the individual studies are highly variable and inconsistent.

d. The pooled mean difference for the random effects model is 0.30 with a 95% confidence interval of [-4.24, 4.84]. This confidence interval is very wide and crosses the line of no effect (zero), indicating a lack of precision in the overall estimate.
e. Two studies had some concerns in risk of bias, including one that contributed 67% of the total weight, which reduces confidence in the pooled effect
f. Four studies had some concerns in risk of bias, including one that contributed 55% of the total weight, which reduces confidence in the pooled effect.