

Appendix

Supplementary Table 1 Details about the search strategies

Search strategy terms for PubMed, EMBASE, Cochrane Library and CNKI (China National Knowledge Infrastructure) databases.

The PubMed search terms were as follows:121

((dexmedetomidine[Title/Abstract])) AND (((POD[Title/Abstract])) OR (POCD[Title/Abstract])) OR
(((postoperative delirium[Title/Abstract])) OR (postoperative cognitive dysfunction[Title/Abstract]))

The Cochrane search terms were as follows:99

ID Search

#1 MeSH descriptor: [Dexmedetomidine] explode all trees

#2 MeSH descriptor: [Postoperative Delirium] explode all trees

#3 MeSH descriptor: [Postoperative Cognitive Dysfunction] explode all trees

#4 POD: ti,ab,kw

#5 POCD: ti,ab,kw

#6 #2 or #3or #4 or #5

#7 #1 and #6

The EMBASE search terms were as follows:169

#1 dexmedetomidine:ab,ti

#2 'postoperative delirium':ab,ti OR pod:ab,ti OR 'postoperative cognitive dysfunction':ab,ti OR
pocd:ab,ti

#3 #1 AND #2

The CNKI search terms were as follows:755

#1 dexmedetomidine:ab,ti

#2 'postoperative delirium':ab,ti OR 'postoperative cognitive dysfunction':ab,ti

#3 #1 AND #2

Supplementary Table 2 Characteristics of the included studies

| Study | Type of surgery | Number of participants (Male/Female) | Age(year) | Anesthesia technique | Use of dexmedetomidine | | POD/POCD measurement |
|------------|---|---|---|--|---|--|----------------------|
| | | | | | Loading dose | Maintenance rate | |
| Sun 2019 | Spinal, orthopedic, urologic, thoracic, general surgery | Dex:281(161/120) Con:276(154/122) | Dex: 68.0(66.0-73.0) Con: 69.0(65.0-74.0) | BIS-guided inhalational and intravenous general anesthesia. | NA | 0.1 μ g/kg/h for 48 hours after surgery | CAM/CAM-ICU |
| Zhang 2019 | Gastrointestinal surgery | Dex:80(51/29) Con:60(40/20) | Dex: 73.76 \pm 14.54 Con: 74.09 \pm 13.87 | BIS-guided total intravenous general anesthesia and all patients were intubated. | 1 μ g/kg for 15 minutes after induction | 0.2-0.7 μ g/kg/h until 30 minutes before the end of the surgery | MMSE |
| Xie 2018 | Hip fracture surgery | Dex:70(38/32) Con:70(36/34) | Dex: 68.2 \pm 5.6 Con: 69.7 \pm 5.3 | BIS-guided total intravenous general anesthesia. | 0.5 μ g/kg for 10 minutes before induction | 0.4 μ g/kg/h until 30 minutes before the end of the surgery | CAM |
| Ting 2019 | Lung cancer surgery | Dex:173(89/84) Con:173(94/79) | Dex:70 \pm 5 Con: 71 \pm 6 | BIS-guided total intravenous general anesthesia and all patients were intubated. | 0.5 μ g/kg for 20 minutes before beginning of the surgery | 0.1 μ g/kg/h until 30 minutes before the end of the surgery | ICDSC |
| Lee 2018 | Laparoscopic surgery | Dex1:95(44/51) Dex2:114(50/64) Con:109(47/62) | Group D1: 72.2 \pm 5.4 Group D2: 73.1 \pm 4.4 Con: 73.8 \pm 6.1 | BIS-guided inhalational and intravenous general anesthesia. | Group D1: 1 μ g/kg for 15 minutes since induction Group D2: NA | Group D1:0.2-0.7 μ g/kg/h until the end of the surgery. Group D2: 1 μ g/kg for 15 minutes before the end of the surgery | CAM |

| | | | | | | | |
|----------------|---|--|--|--|---|---|-----------------|
| Li 2015 | laparoscopic cholecystectomy | Dex:50(28/22) Con:50(26/24) | Dex: 69±5 Con: 70±6 | BIS-guided total intravenous general anesthesia and all patients were intubated. | 1 μ g/kg for 10 minutes following induction | 0.4 μ g/kg/h until the end of the surgery | MMSE |
| Chen 2015 | Fracture, prostate removal, gallbladder surgery, radical resection of rectal carcinoma | Dex:87(56/31) Con:61(38/23) | Dex: 70.6±4.2 Con: 71.4±4.9 | Total intravenous general anesthesia. | 0.5 μ g/kg for 10 minutes after induction | 0.2 μ g/kg/h until 30 minutes before the end of the surgery | MMSE |
| Cheng 2019 | Laparotomy | Dex:269(194/75) Con:266(198/68) | Dex:71(67-75) Con:70(68-74) | BIS-guided total intravenous general anesthesia and all patients were intubated. | 0.5 μ g/kg for 15 minutes before induction | 0.4 μ g/kg/h until 30 minutes before the end of the surgery since induction | RCI |
| Deiner 2017 | Spinal, orthopedic, urologic, thoracic, general surgery | Dex:189(92/97) Con:201(98/103) | Dex:74.0(71.0-78.0) Con:74.0(71.0-78.0) | Total intravenous general anesthesia. | NA | 0.5 μ g/kg/h until 2 hours after surgery since start of the surgery | CAM/CAM- ICU |
| Liu 2015 | Joint replacement surgery | Dex- MCI:39(18/21) Con- MCI:40(23/17) Dex:60(26/34) Con:58(29/29) | Dex-MCI:72.84 ± 8.17 Con-MCI:75.25 ± 7.76 Dex:71.23 ±8.08 Con:72.81 ±9.22 | BIS-guided total intravenous general anesthesia and each patient was inserted a laryngeal mask. | NA | 0.2-0.4 μ g/kg/h during the surgery | CAM |
| Su 2016 | Intra- abdominal, Intra-thoracic, Spinal, Urologic surgery | Dex:350(NA) Con:350(NA) | Over 65 years old | Total intravenous anesthesia or combined epidural-general anesthesia. | NA | 0.1 μ g/kg/h for 24 hours after surgery | CAM-ICU |
| Wu 2016 | Intra- abdominal, Intra-thoracic, Spinal, Superficial surgery. | Dex:38(24/18) Con:38(20/18) | Dex:74±5 Con:76±6 | General anesthesia or combined epidural-general anesthesia. | NA | 0.1 μ g/kg/h for 15 hours after surgery | CAM-ICU |

| | | | | | | | |
|--------------|--------------------------------|-------------------------------------|------------------------------|---|---|--|-----------------|
| He 2018 | Vertebral osteotomy | Dex:30(16/14) Con:30(17/13) | Dex:82.5±5.4 Con:83.2±5.1 | BIS-guided inhalational and intravenous general anesthesia and all patients were intubated. | 0.5 μ g/kg for 10 minutes before induction | 0.4 μ g/kg/h until the end of the surgery | CAM |
| Xuan 2018 | Joint replacement | Dex:227(96/131) Con:226(101/125) | Dex:66.6±7.5 Con:66.9±5.1 | BIS-guided total intravenous general anesthesia and all patients were intubated. | NA | 0.1 μ g/kg/h for 3 days after surgery | CAM/CAM- ICU |
| Ma 2013 | Orthopedic surgery | Dex:30(10/20) Con:30(18/12) | Dex:69.1±7.0 Con:67.6±7.5 | Total intravenous general anesthesia and all patients were intubated. | 1 μ g/kg for 10 minutes before induction | 0.5 μ g/kg/h until 30 minutes before the end of the surgery | CAM |
| Guo 2015 | Oral cancer radical surgery | Dex:78(39/39) Con:78(41/37) | Dex:70.7±4.6 Con:71.9±5.1 | BIS-guided inhalational and intravenous general anesthesia. All patients were intubated. | NA | 0.2 μ g/kg/h for 12 hours since 2 hours after surgery | CAM-ICU |

30 Data are number, mean ± standard deviation or median(interquartile range).

31 DEX,dexmedetomidine; Con,control; BIS,bispectral index; POD,postoperative delirium; POCD,postoperative cognitive
32 dysfunction; MMSE, Mini-Mental State Examination; CAM,Confusion Assessment Method; CAM-ICU,Confusion Assessment
33 Method for Intensive Care Units; RCI,Robust Change Index; ICDSC,Intensive Care Delirium Screening Checklist; MCI,Mild
34 Cognitive Impairment; NA,not applicable.

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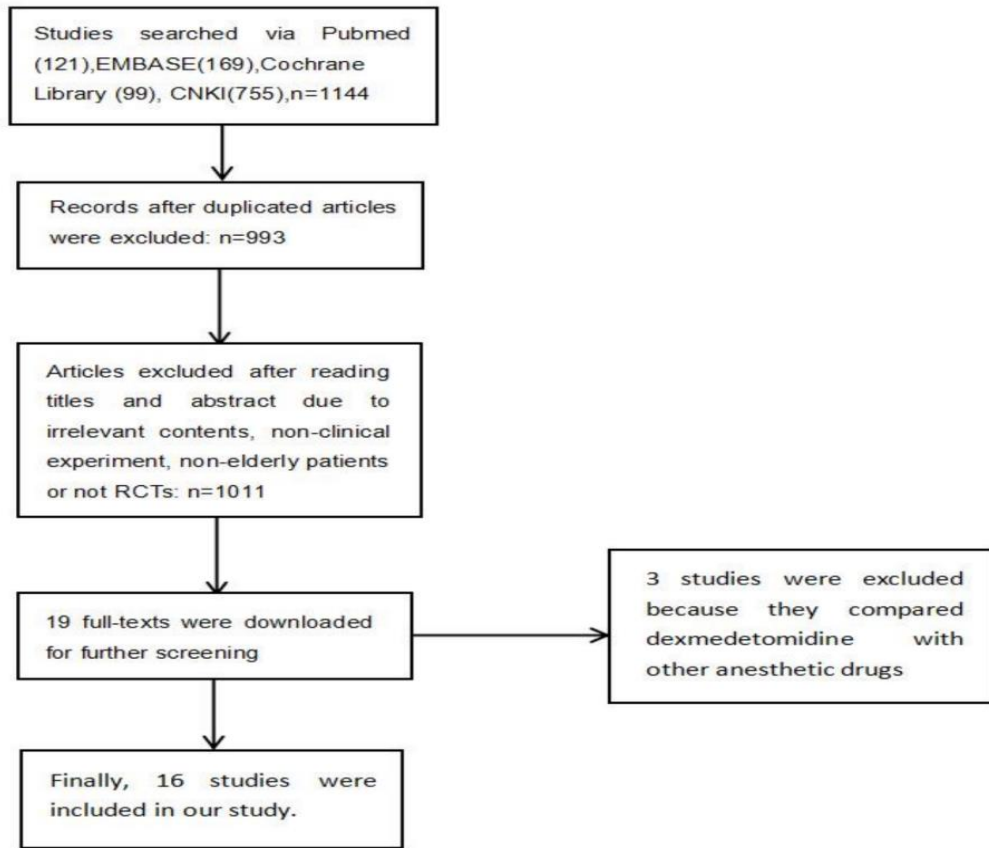
37 Supplementary Table 3 Descriptions of instruments used in the enrolled trials

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|--------------------------------------|---|
| MMSE (Mini-Mental State Examination) | The MMSE, compiled by Folstein et al.(1975), is one of the most influential standardized Mental State Examination tools. As a cognitive impairment Examination method, MMSE can be used for the screening of Alzheimer's disease, which is simple and easy to implement. |
| CAM (Confusion Assessment Method) | The CAM is a nine-item delirium diagnostic scale based on the DSM-III-R criteria for delirium. A unique and helpful feature of the CAM is that it has been simplified into a diagnostic algorithm that includes only four items of the CAM designed for rapid identification of delirium by nonpsychiatrists. The four-item algorithm requires the presence of: (a) acute onset and fluctuating course, (b) inattention, and either (c) disorganized thinking, or (d) altered level of consciousness. CAM has also been validated in palliative care. |

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| CAM-ICU (Confusion Assessment Method for Intensive Care Units) | The CAM-ICU is an adapted version of the bedside assessment tool for non-psychiatrists, the Confusion Assessment Method(CAM), which was based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Re-vised (DSM-III-R). The CAM-ICU demonstrates good validity and reliability when administered by ICU nurses and physicians for both ventilated and non-ventilated ICU patients. Both CAM and CAM-ICU make the diagnosis according to four features of delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. The diagnosis of delirium was determined by the presence of features 1 and 2 plus either feature 3 or 4. |
| RCI (Reliable change index) | The RCI is a simple statistical computation which estimate if changes in two psychometric measures are probably due to measurement error or can be accounted by other factor, as a clinical intervention. Despite its clinical usefulness, the method is underutilized by psychiatrists and psychologists. |
| ICDSC (Intensive Care Delirium Screening Checklist) | According to ICDSC, we can define delirium as mild delirium (ICDSC score 4-5), moderate delirium (ICDSC score 6-7) and severe delirium (ICDSC score 8). |

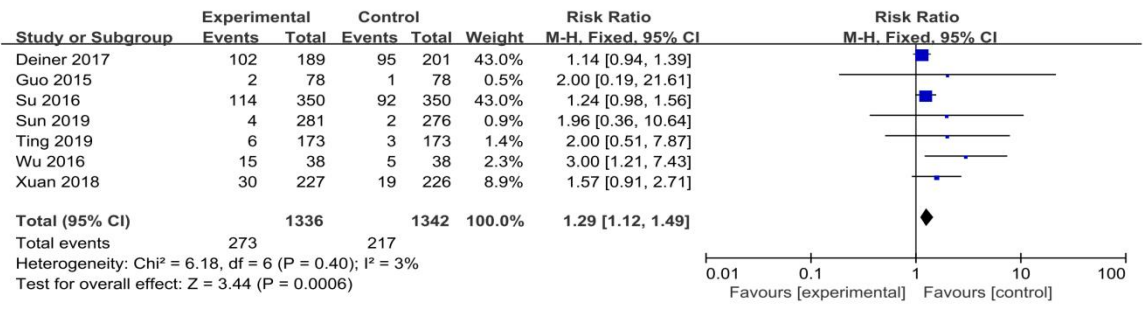
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Supplementary Figure 1 Flow diagram of the article-screening process



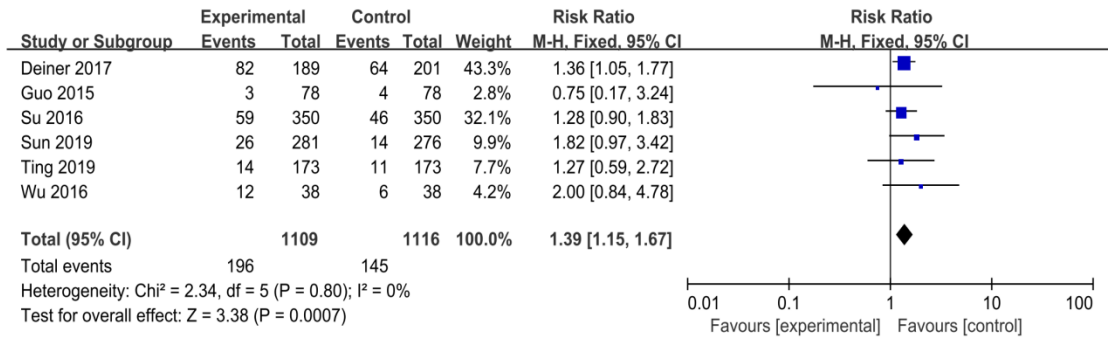
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Supplementary Figure 2 Meta-analysis for the incidence of hypotension



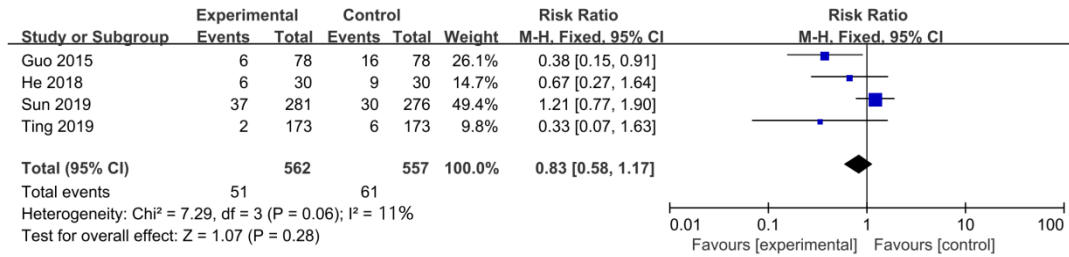
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Supplementary Figure 3 Meta-analysis for the incidence of bradycardia

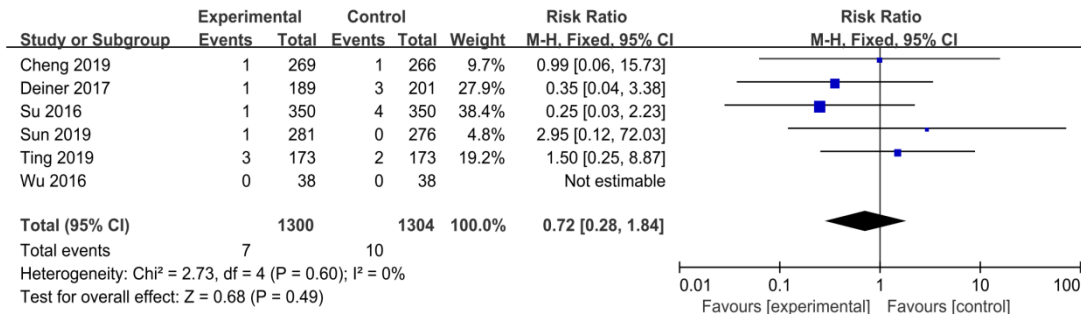


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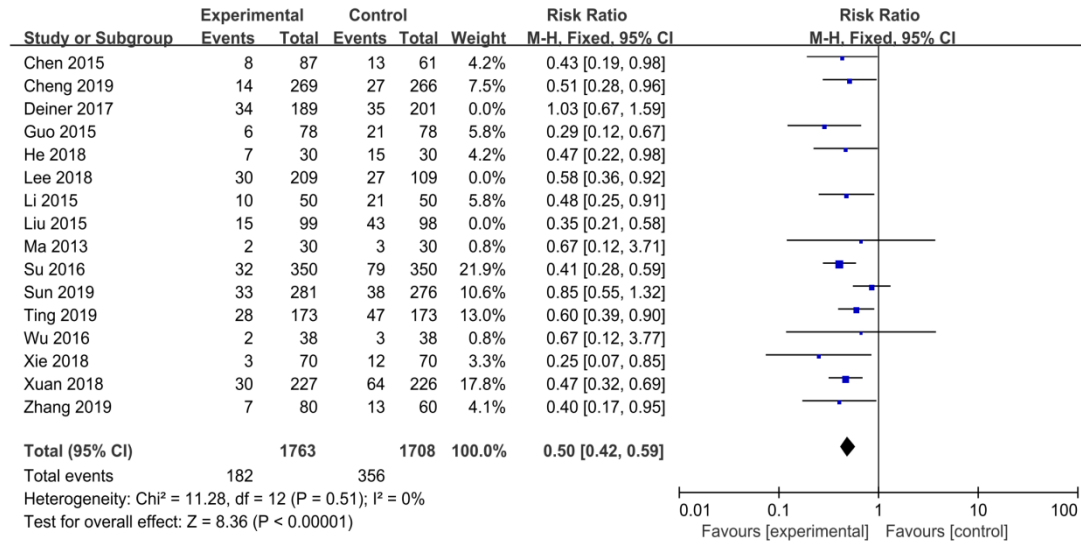
Supplementary Figure 4 Meta-analysis for the incidence of PONV



Supplementary Figure 5 Meta-analysis for the incidence of mortality



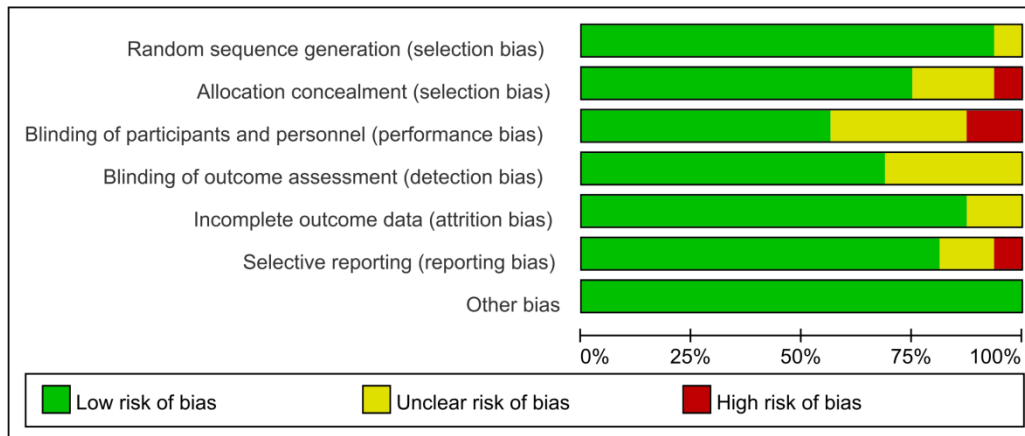
Supplementary Figure 6 Sensitivity analysis by excluding certain studies



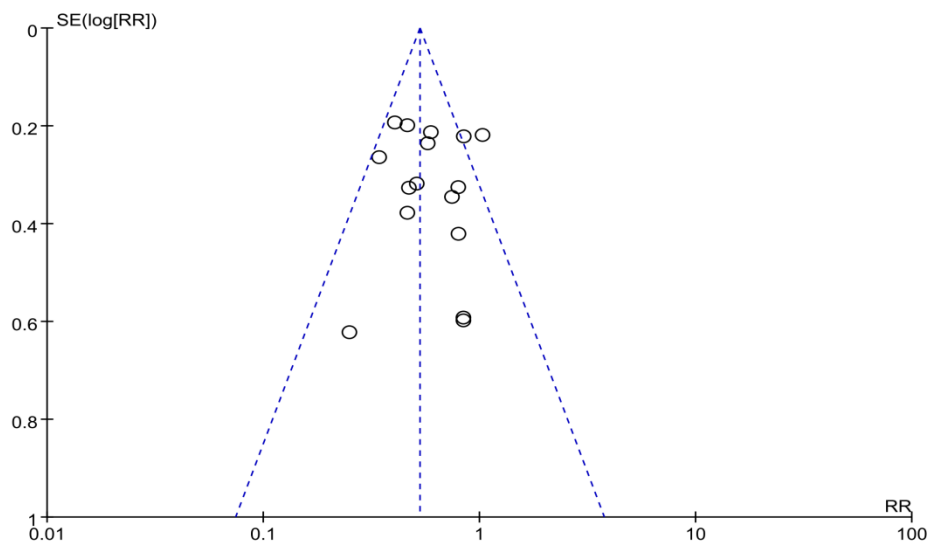
Supplementary Figure 7 Risk of bias summary

| | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------------|---|---|---|---|--|--------------------------------------|------------|
| Chen 2015 | + | + | ⊖ | + | + | + | + |
| Cheng 2019 | + | + | ? | + | ? | + | + |
| Deiner 2017 | + | + | + | + | + | + | + |
| Guo 2015 | ? | ? | ? | ? | + | + | + |
| He 2018 | + | ? | ? | ? | + | + | + |
| Lee 2018 | + | ? | ⊖ | + | + | + | + |
| Li 2015 | + | + | + | + | + | + | + |
| Liu 2015 | + | + | + | + | + | + | + |
| Ma 2013 | + | + | + | + | + | + | + |
| Su 2016 | + | + | + | + | + | + | + |
| Sun 2019 | + | + | + | ? | ? | ? | + |
| Ting 2019 | + | + | ? | ? | + | + | + |
| Wu 2016 | + | + | + | + | + | + | + |
| Xie 2018 | + | + | ? | ? | + | + | + |
| Xuan 2018 | + | + | + | + | + | ⊖ | + |
| Zhang 2019 | + | ⊖ | + | + | + | ? | + |

Supplementary Figure 8 Risk of bias graph



Supplementary Figure 9 The funnel plot for assessment of the publication bias



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Raw data
Primary outcome: POD/POCD
Intraoperative use of dexmedetomidine

| Study | Dexmedetomidine | | Control | |
|------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| He 2018 | 7 | 30 | 15 | 30 |
| Ma 2013 | 2 | 30 | 3 | 30 |
| Lee 2018 | 30 | 209 | 27 | 109 |
| Liu 2015 | 15 | 99 | 43 | 98 |
| Cheng 2019 | 14 | 269 | 27 | 266 |
| Zhang 2019 | 7 | 80 | 13 | 60 |
| Xie 2018 | 3 | 70 | 12 | 70 |
| Li 2015 | 10 | 50 | 21 | 50 |
| Chen 2015 | 8 | 87 | 13 | 61 |

Perioperative use of dexmedetomidine

| Study | Dexmedetomidine | | Control | |
|-------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| Deiner 2017 | 34 | 189 | 35 | 201 |
| Guo 2015 | 6 | 78 | 21 | 78 |
| Su 2016 | 32 | 350 | 79 | 350 |
| Xuan 2018 | 30 | 227 | 64 | 226 |
| Wu 2016 | 2 | 38 | 3 | 38 |
| Sun 2019 | 33 | 281 | 38 | 276 |
| Ting 2019 | 28 | 173 | 47 | 173 |

With a loading dose

| Study | Dexmedetomidine | | Control | |
|------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| He 2018 | 7 | 30 | 15 | 30 |
| Ma 2013 | 2 | 30 | 3 | 30 |
| Lee 2018 | 30 | 209 | 27 | 109 |
| Zhang 2019 | 7 | 80 | 13 | 60 |
| Xie 2018 | 3 | 70 | 12 | 70 |
| Ting 2019 | 28 | 173 | 47 | 173 |
| Li 2015 | 10 | 50 | 21 | 50 |
| Chen 2015 | 8 | 87 | 13 | 61 |
| Cheng 2019 | 14 | 269 | 27 | 266 |

Without a loading dose

| Study | Dexmedetomidine | | Control | |
|-------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| Deiner 2017 | 34 | 189 | 35 | 201 |
| Guo 2015 | 6 | 78 | 21 | 78 |
| Su 2016 | 32 | 350 | 79 | 350 |
| Xuan 2018 | 30 | 227 | 64 | 226 |
| Liu 2015 | 15 | 99 | 43 | 98 |
| Sun 2019 | 33 | 281 | 38 | 276 |
| Wu 2016 | 2 | 38 | 3 | 38 |

Bradycardia

| Study | Dexmedetomidine | | Control | |
|-------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| Deiner 2017 | 82 | 189 | 64 | 201 |
| Su 2016 | 59 | 350 | 46 | 350 |
| Wu 2016 | 12 | 38 | 6 | 38 |
| Ting 2019 | 14 | 173 | 11 | 173 |
| Sun 2019 | 26 | 281 | 14 | 276 |
| Guo 2015 | 3 | 78 | 4 | 78 |

Hypotension

| Study | Dexmedetomidine | | Control | |
|-------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| Deiner 2017 | 102 | 189 | 95 | 201 |
| Su 2016 | 114 | 350 | 92 | 350 |
| Wu 2016 | 15 | 38 | 5 | 38 |
| Guo 2015 | 2 | 78 | 1 | 78 |
| Xuan 2018 | 30 | 227 | 19 | 226 |
| Ting 2019 | 6 | 173 | 3 | 173 |
| Sun 2019 | 4 | 281 | 2 | 276 |

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All-cause mortality

| Study | Dexmedetomidine | | Control | |
|-------------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| Deiner 2017 | 1 | 189 | 3 | 201 |
| Cheng 2019 | 1 | 269 | 1 | 266 |
| Su 2016 | 1 | 350 | 4 | 350 |
| Wu 2016 | 0 | 38 | 0 | 38 |
| Ting 2019 | 3 | 173 | 2 | 173 |
| Sun 2019 | 1 | 281 | 0 | 276 |

Nausea and vomiting

| Study | Dexmedetomidine | | Control | |
|-----------|-----------------|-------|---------|-------|
| | Events | Total | Events | Total |
| He 2018 | 6 | 30 | 9 | 30 |
| Guo 2015 | 6 | 78 | 16 | 78 |
| Ting 2019 | 2 | 173 | 6 | 173 |
| Sun 2019 | 37 | 281 | 30 | 276 |