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# Halogenated Anesthetics vs Intravenous Hypnotics for short and long term Sedation in the Intensive Care Unit: A Meta-Analysis

## Supplemental Material


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**Supplemental Appendix 1**

[inhaled sedation in ICU NOT protocol NOT technic NOT technical NOT technology NOT pollution / volatile sedation in ICU NOT protocol NOT technic NOT technical NOT technology NOT pollution / Volatile sedation in adult in ICU NOT pharmacokinetics NOT bioavailable / inhaled sedation in adult in ICU NOT pharmacokinetics NOT bioavailable / Intravenous sedation acute respiratory distress syndrome / Volatile sedation acute respiratory distress syndrome, propofol sevoflurane sedation / long term sedation in ICU sevoflurane / sedation intensive care volatile versus propofol / volatile sedation versus propofol sedation in ICU / inhaled sedation versus intravenous sedation in ICU / ингаляционная седация в ОРИТ / сравнение внутривенной и ингаляционной седации]

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## Supplemental Table 1. Excluded studies with a cause of exclusion.

| Cause of exclusion | Study |
|---|---|
| **No data on primary/secondary outcome** | 1. Bisbal M, Arnal JM, Passelac A, Sallée M, Demory D, Donati SY, Granier I, Corno G, Durand-Gasselin J. Efficacité, tolérance et coût d'une sédation par sévoflurane en réanimation [Efficacy, safety and cost of sedation with sevoflurane in intensive care unit]. Ann Fr Anesth Reanim. 2011 Apr;30(4):335-41. French. doi: 10.1016/j.annfar.2011.01.019. Epub 2011 Mar 15. PMID: 21411266. |
| | 2. Grasselli G, Giani M, Scaravilli V, Fumagalli B, Mariani C, Redaelli S, Lucchini A, Zanella A, Patroniti N, Pesenti A, Foti G. Volatile Sedation for Acute Respiratory Distress Syndrome Patients on Venovenous Extracorporeal Membrane Oxygenation and Ultraprotective Ventilation. Crit Care Explor. 2021 Jan 8;3(1):e0310. doi: 10.1097/CCE.0000000000000310. PMID: 33458679; PMCID: PMC7803679. |
| | 3. Flinspach AN, Zacharowski K, Ioanna D, Adam EH. Volatile Isoflurane in Critically Ill Coronavirus Disease 2019 Patients-A Case Series and Systematic Review. Crit Care Explor. 2020 Oct 21;2(10):e0256. doi: 10.1097/CCE.0000000000000256. PMID: 33134946; PMCID: PMC7587445. |
| | 4. Türktan M, Güleç E, Hatipoğlu Z, Ilgınel MT, Özcengiz D. The Effect of Sevoflurane and Dexmedetomidine on Pulmonary Mechanics in ICU Patients. Turk J Anaesthesiol Reanim. 2019 Jun;47(3):206-212. doi: 10.5152/TJAR.2019.37108. Epub 2019 Jan 18. PMID: 31183467; PMCID: PMC6537958. |
| | 5. Steurer MP, Steurer MA, Baulig W, Piegeler T, Schläpfer M, Spahn DR, Falk V, Dreessen P, Theusinger OM, Schmid ER, Schwartz D, Neff TA, Beck-Schimmer B. Late pharmacologic conditioning with volatile anesthetics after cardiac surgery. Crit Care. 2012 Oct 14;16(5):R191. doi: 10.1186/cc11676. PMID: 23062276; PMCID: PMC3682293. |
| **Mixed sedation** | 6. Kermad A, Speltz J, Danziger G, Mertke T, Bals R, Volk T, Lepper PM, Meiser A. Comparison of isoflurane and propofol sedation in critically ill COVID-19 patients-a retrospective chart review. J Anesth. 2021 Oct;35(5):625-632. doi: 10.1007/s00540-021-02960-6. Epub 2021 Jun 25. PMID: 34169362; PMCID: PMC8225486. |
| | 7. Foudraine NA, Algargoush A, van Osch FH, Bos AT. A multimodal sevoflurane-based sedation regimen in combination with targeted temperature management in post-cardiac arrest patients reduces the incidence of delirium: An observational propensity score-matched study. Resuscitation. 2021 Feb;159:158-164. doi: 10.1016/j.resuscitation.2020.10.042. Epub 2020 Nov 12. PMID: 33189803. |
| | 8. Hanidziar D, Baldyga K, Ji CS, Lu J, Zheng H, Wiener-Kronish J, Xie Z. Standard Sedation and Sedation With Isoflurane in Mechanically Ventilated Patients With Coronavirus Disease 2019. Crit Care Explor. 2021 Mar 5;3(3):e0370. doi: 10.1097/CCE.0000000000000370. PMID: 33786446; PMCID: PMC7994032. |
| | 9. Scherer C, Kupka D, Stocker TJ, Joskowiak D, Scheuplein H, |

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| | |
|---|---|
| | Schönegger CM, Born F, Stremmel C, Lüsebrink E, Stark K, Orban M, Petzold T, Peterss S, Hausleiter J, Hagl C, Massberg S, Orban M. Isoflurane Sedation in Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation Treatment for Cardiogenic Shock-An Observational Propensity-Matched Study. Crit Care Explor. 2020 Mar 24;2(3):e0086. doi: 10.1097/CCE.0000000000000086. PMID: 32259109; PMCID: PMC7098543. |
| **Data for only one of the groups** | 10. Hellström J, Öwall A, Martling CR, Sackey PV. Inhaled isoflurane sedation during therapeutic hypothermia after cardiac arrest: a case series. Crit Care Med. 2014 Feb;42(2):e161-6. doi: 10.1097/CCM.0b013e3182a643d7. PMID: 24145840. |
| | 11. Bösel J, Purrucker JC, Nowak F, Renzland J, Schiller P, Pérez EB, Poli S, Brunn B, Hacke W, Steiner T. Volatile isoflurane sedation in cerebrovascular intensive care patients using AnaConDa(®): effects on cerebral oxygenation, circulation, and pressure. Intensive Care Med. 2012 Dec;38(12):1955-64. doi: 10.1007/s00134-012-2708-8. Epub 2012 Oct 25. PMID: 23096426. |
| | 12. Villa F, Iacca C, Molinari AF, Giussani C, Aletti G, Pesenti A, Citerio G. Inhalation versus endovenous sedation in subarachnoid hemorrhage patients: effects on regional cerebral blood flow. Crit Care Med. 2012 Oct;40(10):2797-804. doi: 10.1097/CCM.0b013e31825b8bc6. PMID: 22824929. |
| | 13. L'Heudé M, Poignant S, Elaroussi D, Espitalier F, Ferrandière M, Laffon M. Nephrogenic diabetes insipidus associated with prolonged sedation with sevoflurane in the intensive care unit. Br J Anaesth. 2019 May;122(5):e73-e75. doi: 10.1016/j.bja.2019.02.009. Epub 2019 Mar 11. PMID: 30916031. |
| **Data on sedation outcomes presented, but patients were initially anesthetized** | 14. Landoni G, Lomivorotov VV, Nigro Neto C, Monaco F, Pasyuga VV, Bradic N, Lembo R, Gazivoda G, Likhvantsev VV, Lei C, Lozovskiy A, Di Tomasso N, Bukamal NAR, Silva FS, Bautin AE, Ma J, Crivellari M, Farag AMGA, Uvaliev NS, Carollo C, Pieri M, Kunstýř J, Wang CY, Belletti A, Hajjar LA, Grigoryev EV, Agrò FE, Riha H, El-Tahan MR, Scandroglio AM, Elnakera AM, Baiocchi M, Navalesi P, Shmyrev VA, Severi L, Hegazy MA, Crescenzi G, Ponomarev DN, Brazzi L, Arnoni R, Tarasov DG, Jovic M, Calabrò MG, Bove T, Bellomo R, Zangrillo A; MYRIAD Study Group. Volatile Anesthetics versus Total Intravenous Anesthesia for Cardiac Surgery. N Engl J Med. 2019 Mar 28;380(13):1214-1225. doi: 10.1056/NEJMoa1816476. Epub 2019 Mar 19. PMID: 30888743. |
| | 15. de la Gala F, Piñeiro P, Reyes A, Vara E, Olmedilla L, Cruz P, Garutti I. Postoperative pulmonary complications, pulmonary and systemic inflammatory responses after lung resection surgery with prolonged one-lung ventilation. Randomized controlled trial comparing intravenous and inhalational anaesthesia. Br J Anaesth. 2017 Oct 1;119(4):655-663. doi: 10.1093/bja/aex230. PMID: 29121283. |
| | 16. Likhvantsev VV, Landoni G, Levikov DI, Grebenchikov OA, Skripkin YV, Cherpakov RA. Sevoflurane Versus Total Intravenous Anesthesia for Isolated Coronary Artery Bypass Surgery With Cardiopulmonary Bypass: A Randomized Trial. J Cardiothorac Vasc Anesth. 2016 Oct;30(5):1221-7. doi: 10.1053/j.jvca.2016.02.030. Epub 2016 Mar 3. PMID: 27431595. |

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**Supplemental figure 1 - Risk of bias evaluation of the included RCTs using the ROB 2 tool.**

| Study | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|
| Guinot PG et al. (2020) | + | + | + | + | + | + |
| Jabaudon M et al. (2017) | + | + | + | + | + | + |
| Mesnil M et al. (2011) | + | - | ! | ! | ! | - |
| Hellström J et al. (2012) | ! | + | + | - | + | - |
| Jerath A et al. (2015) | - | - | + | + | + | - |
| Soro M. et al. (2012) | + | + | + | + | + | + |
| Orriach JL et al. (2013) | ! | + | + | + | + | ! |
| Resepov NA et al. (2017) | + | + | + | ! | ! | ! |
| Plotnikov GP et al. (2014) | ! | - | + | - | ! | - |

D1 Randomisation process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

+ Low risk

! Some concerns

- High risk

In this color-coded ranking, green color represents low risk of bias, yellow some concerns (moderate risk), and red high risk of bias.

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**Supplemental figure 2 - Risk of bias evaluation of the non-randomized trials using the ROBINS-I tool.**

| Study | D1 | D2 | D3 | D4 | D5 | D6 | D7 | Overall |
|---|---|---|---|---|---|---|---|---|
| Krannich A et al. (2017) | ! | + | + | + | + | + | ! | ! |
| Meiser A et al. (2017) | !!! | + | + | + | + | + | + | !!! |
| Bellgardt M et al. (2016) | ! | !!! | + | ! | - | + | !!! | !!! |
| Staudacher DL et al. (2018) | ! | ! | + | + | + | + | + | ! |
| Jung S et al. (2020) | !!! | ! | + | + | + | + | - | !!! |
| Marcos-Vidal JM et al. (2014) | - | - | + | + | + | + | ! | - |

D1 Bias due to confounding

D2 Bias in selection of participants into the study

D3 Bias in classification of interventions

D4 Bias due to deviations from intended interventions

D5 Bias due to missing data

D6 Bias in measurement of outcomes

D7 Bias in selection of the reported result

| | |
|---|---|
| + | Low risk |
| ! | Some concerns |
| - | High risk |
| !!! | Critical risk |

In this color-coded ranking, green color represents low risk of bias, yellow some concerns (moderate risk), red high risk of bias and dark red critical risk of bias.

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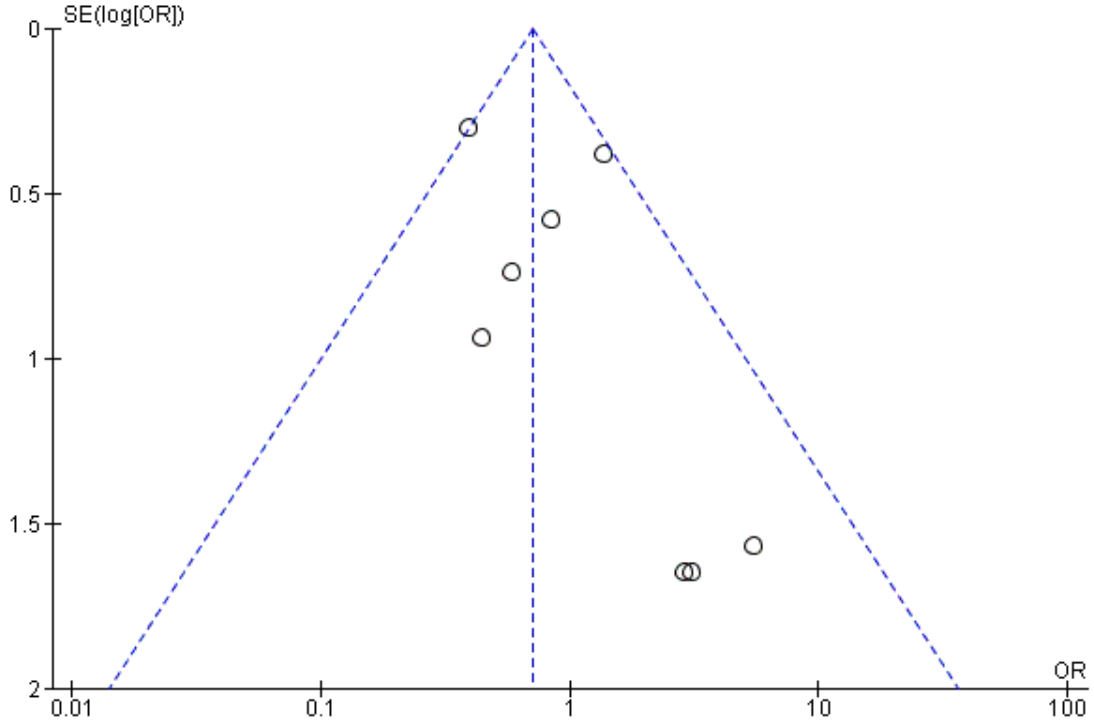
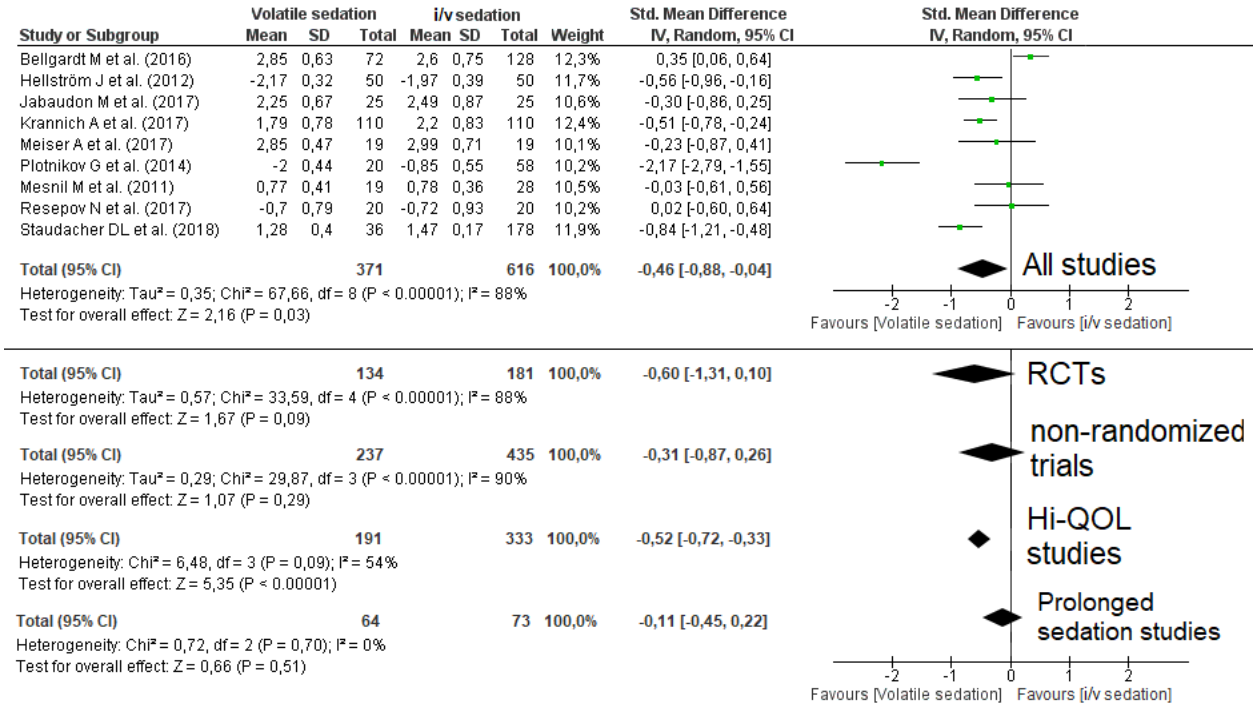
**Supplemental figure 3 - Funnel plot for hospital mortality. SMD - standardized mean difference.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI. Hi-QOL - studies with low-moderate risk of bias.

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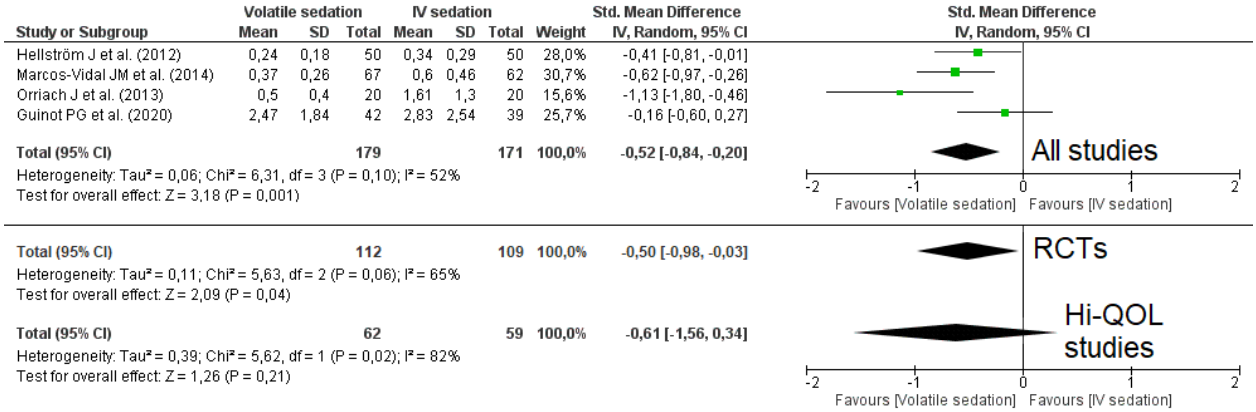
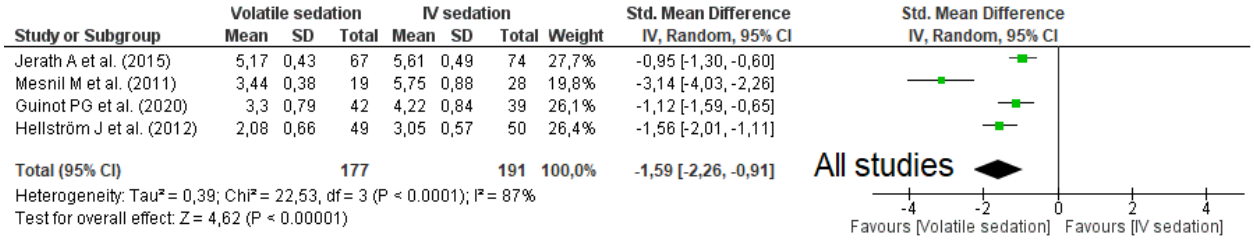
**Supplemental figure 5 - Forest plot for troponin level at 1 postoperative day. The plot displays the study, sample size, log-transformed standardized mean difference (SMD), confidence interval (CI), and p-value.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI. Hi-QOL - studies with low-moderate risk of bias.

**Supplemental figure 6 - Forest plot for time to extubation. The plot displays the study, sample size, log-transformed standardized mean difference (SMD), confidence interval (CI), and p-value.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI.

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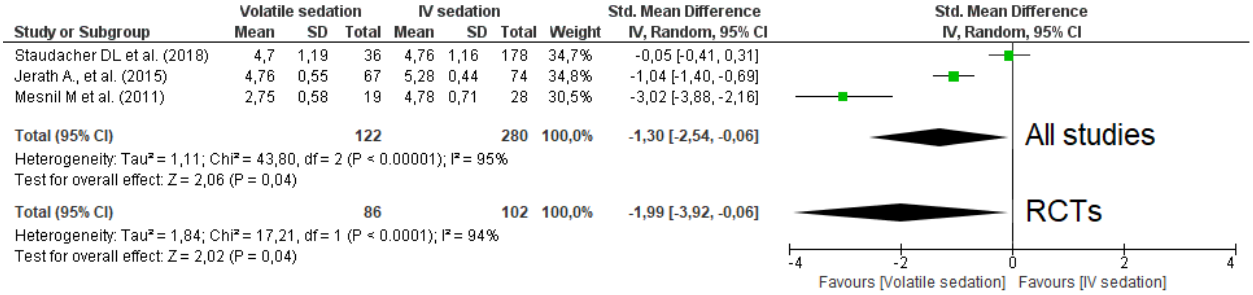
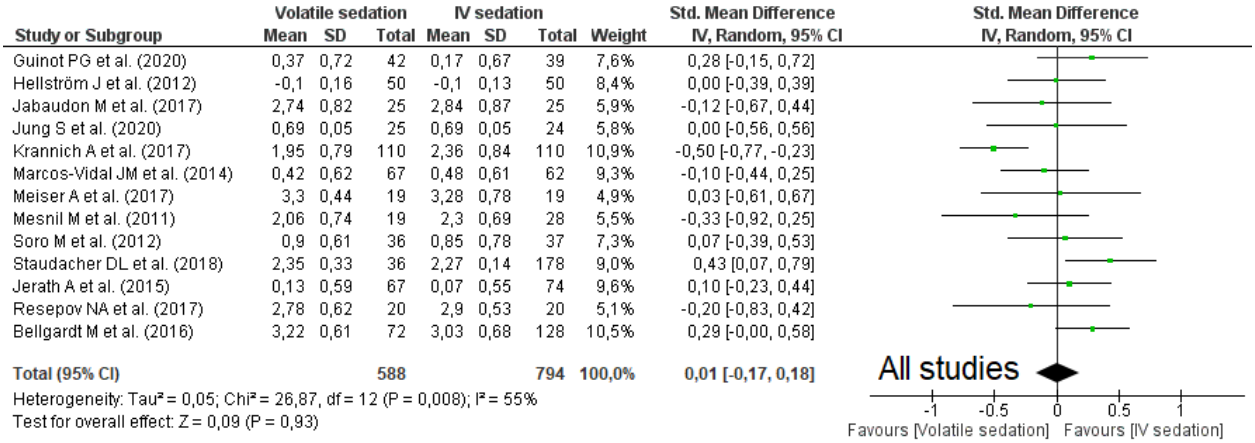
**Supplemental figure 7 - Forest plot for awakening time. The plot displays the study, sample size, log-transformed standardized mean difference (SMD), confidence interval (CI), and p-value.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI.

**Supplemental figure 8 - Forest plot for ICU length of stay. The plot displays the study, sample size, log-transformed standardized mean difference (SMD), confidence interval (CI), and p-value.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI. Hi-QOL - studies with low-moderate risk of bias.

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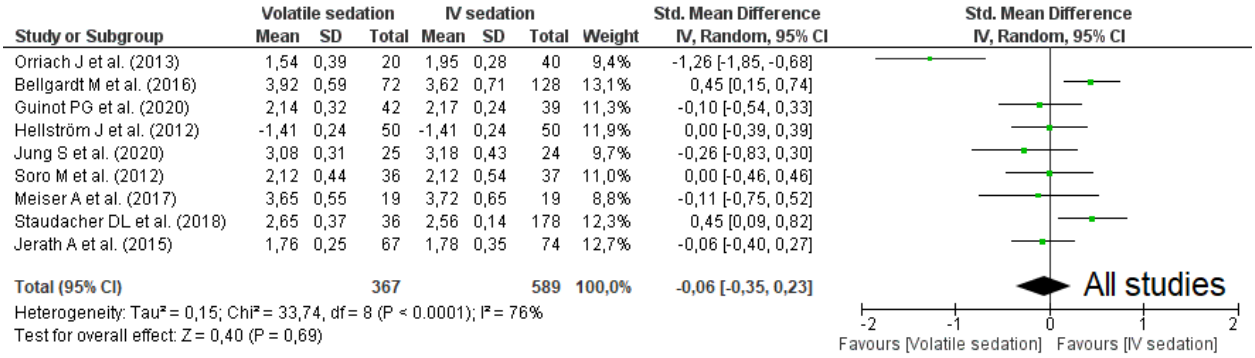
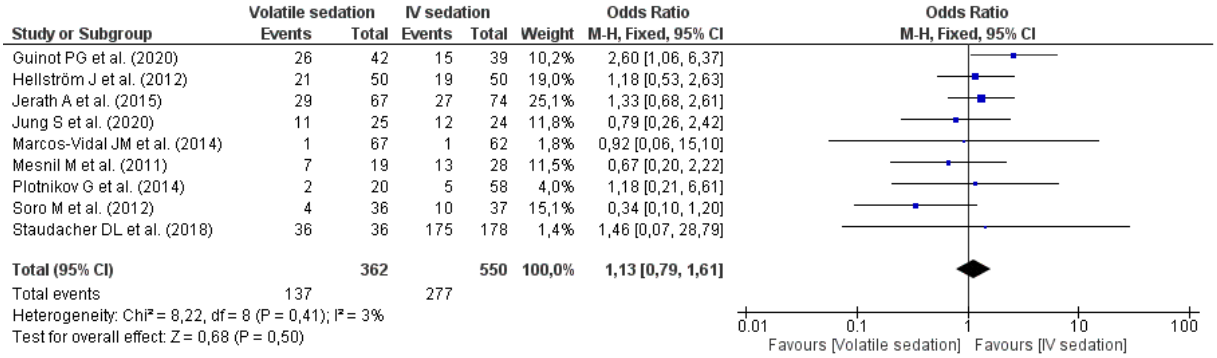
**Supplemental figure 9 - Forest plot for hospital length of stay. The plot displays the study, sample size, log-transformed standardized mean difference (SMD), confidence interval (CI), and p-value.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled SMD with CI. Hi-QOL - studies with low-moderate risk of bias.

**Supplemental figure 10 - Forest plot for catecholamine requirements. The plot displays the study, sample size, odds ratio (OR), confidence interval (CI), and p-value.**




The size of the squares indicates the weight of the studies (taking into account sample size and standard deviations); the diamond represents the pooled OR with CI. Hi-QOL - studies with low-moderate risk of bias.