

City Research Online

City, University of London Institutional Repository

Citation: Aitken, L. M., Kydonaki, K., Blackwood, B., Trahair, L. G., Purssell, E., Sekhon, M. & Walsh, T. S. (2021). Inconsistent relationship between depth of sedation and intensive care outcome: systematic review and meta-analysis. Thorax, 76(11), pp. 1089-1098. doi: 10.1136/thoraxjnl-2020-216098

This is the accepted version of the paper.

This version of the publication may differ from the final published version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/26143/

Link to published version: https://doi.org/10.1136/thoraxjnl-2020-216098

Copyright: City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

Reuse: Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way. City Research Online: <u>http://openaccess.city.ac.uk/</u><u>publications@city.ac.uk</u>

Supplementary figure legends

Supplementary figure 1: Risk of bias summary – RCTs

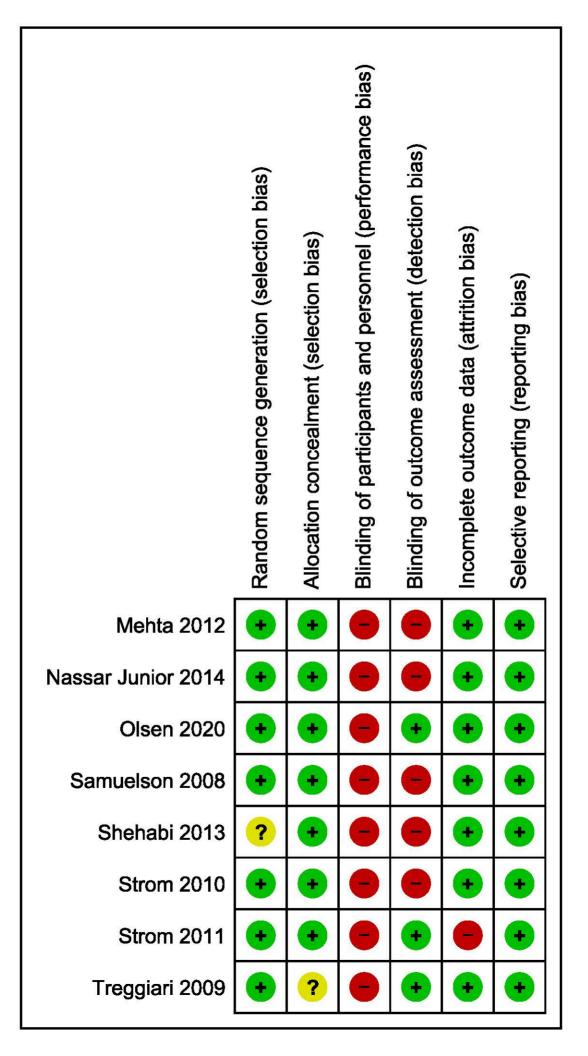
Supplementary figure 2: Risk of bias summary – cohort studies

Supplementary Figure 3: Forest plots for secondary outcomes – mortality domain: hospital mortality

Supplementary Figure 4: Forest plots for secondary outcomes – physiological domain: a) time to extubation; b) ventilator free days to day 28; c) delirium

Supplementary Figure 5: Forest plots – secondary outcomes – resource use domain: a) ICU LOS; b) hospital LOS; c) tracheostomies

Supplementary Figure 6: Forest plots – secondary outcomes – adverse events domain: a) selfextubation; b) re-intubation; c) Ventilator associated pneumonia



| | Meth | Mea | outio | dml | Len | othe |
|----|------|-----|-------|-----|-----|------|
| 07 | • | • | • | • | ? | • |
| 15 | • | • | • | ? | • | ? |
| 13 | ? | • | • | • | • | ٠ |
| 15 | ? | • | • | ٠ | • | • |
| 01 | • | • | • | ? | • | • |
| 4 | ٠ | | • | • | • | • |
| 4 | • | ٠ | | ٠ | • | ٠ |
| 16 | • | • | • | ? | • | • |
| 1 | • | • | • | ? | • | ? |
| 4 | • | • | • | ? | • | • |
| 08 | ? | • | • | • | • | • |
| 07 | • | • | • | ? | • | • |
| 17 | ? | • | • | • | • | • |
| 06 | • | • | • | ? | • | • |
| 07 | • | • | • | ? | • | ٠ |
| 17 | • | • | • | ? | • | • |
| 12 | ? | • | • | • | • | ? |
| 18 | ? | ? | • | ? | • | • |

Balzer 201 Bugedo 201 Burry 201 Capuzzo 200 Costa 201 Dale 201 Faust 201 Guttormson 201 Khan 201 Mendes 200 Quenot 200 Ren 201 Samuelson 200 Samuelson 200 Sen 201 Shehabi 201 Shehabi 201

Arabi 200

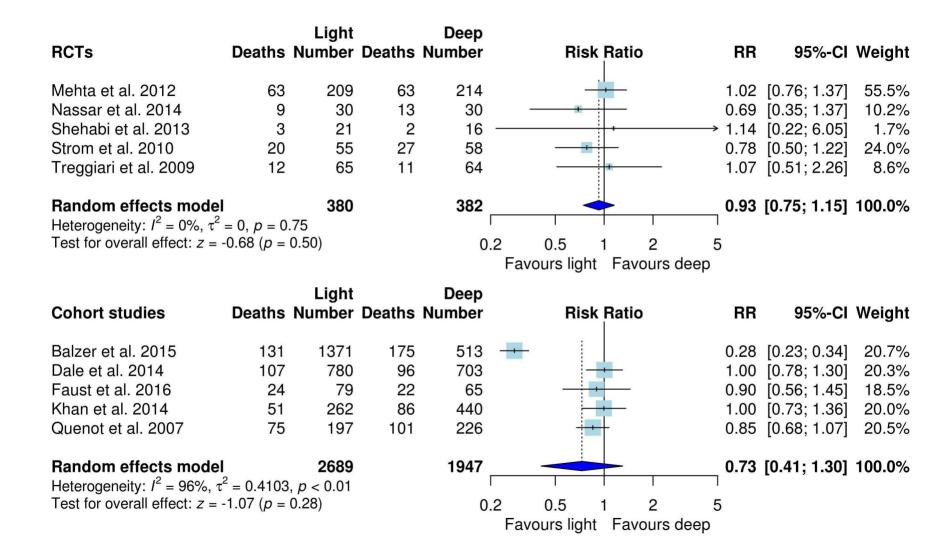
Method of recruitment (selection bias) Measurement of depth of sedation bias

Important confounding factors (bias)

(come assessment (detection bias)

Length & Completeness of follow-up (attrition bias)

er blas



| RCTs | Number | | ight SD I | Number | | eep SD | Mean Difference | MD | 95%-CI | |
|---|--------|-----------------|--------------|--------|------|-------------------|-----------------|--------------|----------------|--------|
| Mehta et al. 2012 Test for overall effect: 2 | | 7.33 = 0.31) | | 214 | 8.00 | 6.72 _Г | | 0.67 [| -1.95; 0.61] | |
| | | , | | | | -6 | -4 -2 0 | 2 | | |
| | | | | | | | Favours light | Favours deep | | |
| | | | | | | _ | | | | |
| Cohort studies | Number | | Light SD | Number | | Deep SD | Mean Difference | e MD | 95%-CI | Weight |
| Balzer et al. 2015 | 1371 | 0.80 | 0.78 | 513 | 3.72 | 3 68 | : 💻 | 2.02 | [-3.24; -2.60] | 51.1% |
| | | | | | | | | -2.92 | 0.24, 2.00 | |
| Shehabi et al. 2012 | 35 | 2.77 | 1.62 | | 7.43 | | | | [-5.26; -4.07] | 48.9% |

a)

| | | ı | ight | | ſ | Deep | | | | | | | |
|--|------------------------|----------------------------------|-------------|--------|---------------------------------|------------------|---|----------------|-------------|----|--------------|---|----------------------------------|
| RCTs | Number | Days | SD | Number | Days | SD | | Mean Di | fferen | ce | MD | 95%-CI | Weight |
| Nassar et al. 2014 Olsen et al. 2020 Shehabi et al. 2013 Strom et al. 2010 | 349 21 | 24.33 15.33 21.30 13.80 | 19.4 9.2 | 351 | 16.67 14.67 20.10 9.60 | 18.6 10.1 | | | | _ | 0.67 1.20 | [0.23; 15.10] [-2.15; 3.48] [-5.12; 7.52] [0.32; 8.08] | 11.4% 43.2% 15.0% 30.4% |
| Random effects model Heterogeneity: $l^2 = 31\%$, τ Test for overall effect: $z = 1$ | ² = 2.3849, | p = 0.2 | 3 | 455 | Fa | l -: vours | - |) 5 Favours | 10 light | 15 | 2.62 | [-0.09; 5.34] | 100.0% |
| Cohort studies | Number | | _ight SD | Number | | Deep SD | | Mean Di | ifferen | ce | MD | 95%-CI | Weight |

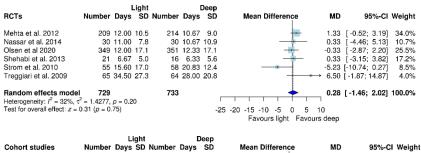
| Cohort studies | Number | Days | SD | Number | Days | SD | | Me | ean D | ifferen | се | MD | 95%-CI | Weight | |
|---------------------------------------|--------------|-------|-----|--------|-------|-------|-----|------------|-------|---------|----|------|---------------|--------|--|
| Bugedo et al. 2013 | | 12.33 | | | 10.33 | | | <u>+</u> • | | | | | [-2.09; 6.09] | | |
| Faust et al. 2016 | 79 | 24.10 | 3.1 | 65 | 23.60 | 4.9 | | | | | | 0.50 | [-0.87; 1.87] | 89.9% | |
| Random effects model | 211 | | | 220 | | | | + | | | | 0.65 | [-0.65; 1.95] | 100.0% | |
| Heterogeneity: $I^2 = 0\%$, τ^2 | = 0, p = 0.5 | 50 | | | | | | 1 | | 1 | | | | | |
| Test for overall effect: $z = 0$ | 0.98 (p = 0) | .33) | | | | | -5 | 0 | 5 | 10 | 15 | 20 | | | |
| | | | | | Fa | vours | dee | ep Fa | vours | light | | | | | |

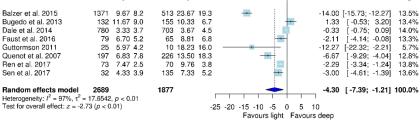
b)

| | | Light | | Deep | | | | |
|--|--|---|------------------|--|---------------------------|--|--|---------------------------------|
| RCTs | Delirium | Number | Delirium | Number | Risk Ratio | RR | 95%-CI W | eight |
| | | | | | | | | |
| Mehta et al. 2012 | 113 | 209 | 113 | 214 | | 1.02 | [0.86; 1.22] 9 | 0.1% |
| Nassar et al. 2014 | 12 | 30 | 9 | 30 | | 1.33 | [0.66; 2.69] | 5.8% |
| Samuelson 2008 | 0 | 18 | 0 | 18 | | | | 0.0% |
| Shehabi et al. 2013 | 8 | 21 | 6 | 16 | | 1.02 | [0.44; 2.34] | 4.1% |
| | | | | | | | | |
| Random effects mode | | 278 | | 278 | + | 1.04 | [0.88; 1.23] 10 | 0.0% |
| Heterogeneity: $l^2 = 0\%$, τ^2 | $p^2 = 0, p = 0.7$ | 7 | | | | | | |
| Test for overall effect: z = | 0.45 (p = 0.6) | 65) | | 0. | 2 0.5 1 2 | 5 | | |
| | | | | | Favours light Favours dee | ae | | |
| | | | | | 8 | | | |
| | | | | | | | | |
| | | Light | | Deep | | | | |
| Cohort studies | Delirium | | Delirium | | Risk Ratio | RR | 95%-CI W | eight |
| | | Number | | Number | | | | 5 |
| Cohort studies Balzer et al. 2015 | Delirium 445 | | Delirium 213 | | Risk Ratio → | | | eight ?7.3% |
| | | Number | | Number | | 0.78 | [0.69; 0.89] 2 | 5 |
| Balzer et al. 2015 | 445 | Number 1371 | 213 | Number 513 | | 0.78 2.12 | [0.69; 0.89] 2 [1.65; 2.72] 2 | 27.3% |
| Balzer et al. 2015 Dale et al. 2014 | 445 176 | Number 1371 780 | 213 75 | Number 513 703 | | 0.78 2.12 1.21 | [0.69; 0.89] 2 [1.65; 2.72] 2 [1.03; 1.41] 2 | 27.3% 25.8% |
| Balzer et al. 2015 Dale et al. 2014 Khan et al. 2014 | 445 176 94 | Number 1371 780 141 | 213 75 167 | Number 513 703 302 | | 0.78 2.12 1.21 | [0.69; 0.89] 2 [1.65; 2.72] 2 [1.03; 1.41] 2 | 27.3% 25.8% 27.0% |
| Balzer et al. 2015 Dale et al. 2014 Khan et al. 2014 Ren et al. 2017 Random effects mode | 445 176 94 13 | Number 1371 780 141 73 2365 | 213 75 167 | Number 513 703 302 | | 0.78 2.12 1.21 0.43 | [0.69; 0.89] 2 [1.65; 2.72] 2 [1.03; 1.41] 2 | 27.3% 25.8% 27.0% 9.9% |
| Balzer et al. 2015 Dale et al. 2014 Khan et al. 2014 Ren et al. 2017 | 445 176 94 13 | Number 1371 780 141 73 2365 | 213 75 167 | Number 513 703 302 70 | | 0.78 2.12 1.21 0.43 | [0.69; 0.89] 2 [1.65; 2.72] 2 [1.03; 1.41] 2 [0.24; 0.76] 1 | 27.3% 25.8% 27.0% 9.9% |
| Balzer et al. 2015 Dale et al. 2014 Khan et al. 2014 Ren et al. 2017 Random effects mode | 445 176 94 13 τ ² = 0.2088, μ | Number 1371 780 141 73 2365 0 < 0.01 | 213 75 167 | Number 513 703 302 70 | | 0.78 2.12 1.21 0.43 | [0.69; 0.89] 2 [1.65; 2.72] 2 [1.03; 1.41] 2 [0.24; 0.76] 1 | 27.3% 25.8% 27.0% 9.9% |
| Balzer et al. 2015 Dale et al. 2014 Khan et al. 2014 Ren et al. 2017 Random effects mode Heterogeneity: <i>I</i> ² = 95%, | 445 176 94 13 τ ² = 0.2088, μ | Number 1371 780 141 73 2365 0 < 0.01 | 213 75 167 | Number 513 703 302 70 1588 | | 0.78 2.12 1.21 0.43 1.01 5 | [0.69; 0.89] 2 [1.65; 2.72] 2 [1.03; 1.41] 2 [0.24; 0.76] 1 | 27.3% 25.8% 27.0% 9.9% |

Supplementary Figure 4: Forest plots for secondary outcomes – physiological domain: a) time to extubation; b) ventilator free days to day 28 (VFD28); c) delirium

Note: data converted from median/IRQ to mean/SD¹² – time to extubation in the following studies: Balzer et al 2015; Mehta et al 2012; Shehabi et al 2012; VFD28 in the following studies: Bugedo et al 2013; Nassar Jr et al 2014.





a)

| RCTs | Number Days | Light SD | Number | Days | Deep SD | Mean Difference | MD | 95%-CI Weight |
|---|---|-------------------------------|----------------|----------------|--|---|-----------------------|--|
| Mehta et al 2012 Nassar et al. 2014 Shehabi et al. 2013 Strom et al. 2010 Treggiari et al. 2009 | 209 26.00 30 24.33 21 19.55 55 38.61 65 19.25 | 3 19.46 7 19.08 7 36.54 | 30 16 58 | 16.67 58.67 | 19.41 14.79 20.32 39.53 5.35 | | 7.00 2.90 20.00 | [-0.64; 8.64] 26.0% [-1.75; 15.75] 19.1% [-9.97; 15.77] 13.3% [-34.03; -5.97] 12.0% [-5.17; -1.83] 29.6% |
| Random effects mode Heterogeneity: $t^2 = 80\%$, τ Test for overall effect: $z =$ | ² = 33.7865, <i>p</i> < 9 | 0.01 Light | 382 | | -2 Deep | 25 -20 -15 -10 -5 0 5 10 Favours light Favours d | | [-6.96; 5.58] 100.0% |

| Cohort studies | Number | Days | SD | Number | Days | SD | Mean Difference | MD | 95%-CI | Weight |
|--|--------------|----------|-------|--------|-------|-------|--|----------------|---------------|--------|
| Balzer et al. 2015 | 1371 | 21.00 | 15.58 | 513 | 30.67 | 23.79 | | -9.67 [- | 11.88; -7.45] | 18.6% |
| Bugedo et al. 2013 | | | 15.74 | | | 17.21 | | | -4.48; 3.15] | 15.5% |
| Dale et al. 2014 | 780 | 10.67 | 10.40 | 703 | 12.33 | 11.89 | | -1.67 [| -2.81; -0.52] | 20.1% |
| Khan et al. 2014 | 440 | 19.23 | 20.46 | 262 | 22.95 | 52.12 | | -3.72 [- | 10.31; 2.87] | 10.4% |
| Quenot et al. 2007 | 197 | 14.67 | 12.70 | 226 | 19.67 | 20.89 | | -5.00 [| -8.25; -1.75] | 16.7% |
| Sen et al. 2017 | 32 | 9.33 | 5.43 | 135 | 13.33 | 6.74 | ÷- | -4.00 [| -6.20; -1.80] | 18.6% |
| Random effects model Heterogeneity: $l^2 = 88\%$, τ^2 | | . p < 0. | .01 | 1994 | | | | -4.21 [| -7.22; -1.19] | 100.0% |
| Test for overall effect: $z = -$ | -2.74 (p < 0 | 0.01) | | | | -2 | 25 -20 -15 -10 -5 0 5 Favours light Favou | 10 Jrs deep | | |

b)

| RCTs | Tracheostomy | Light Number | Tracheostomy | Deep Number | Risk Ratio | RR | 95%-CI | Weight |
|---|----------------------|-------------------------------------|--------------------|---------------------------------------|--|------------------------|---|--|
| Mehta et al. 2012 Nassar et al. 2014 Strom et al. 2010 Treggiari et al. 2009 Random effects mode Heterogeneity: $f^2 = 0\%$, t^2 Test for overall effect: $z =$ | = 0, <i>p</i> = 0.94 | 209 30 55 65 359 | 49 1 17 4 | 214 30 * 58 64 366 | | → 1.00 0.99 0.74 | [0.81; 1.58] [0.07; 15.26] [0.56; 1.76] [0.17; 3.17] [0.81; 1.43] | 70.8% 1.1% 24.3% 3.8% 100.0% |
| Cohort studies | . , | Light Number | Tracheostomy | 0. Deep Number | 1 0.2 0.5 1 2 5 Favours light Favours de Risk Ratio | | 95%-CI | Weight |
| Bugedo et al. 2013 Faust et al. 2016 | 6 8 | | 12 11 | 155 65 | | | [0.23; 1.52] [0.26; 1.40] | 44.3% 55.7% |
| Random effects mode Heterogeneity: $l^2 = 0\%$, τ^2 Test for overall effect: $z =$ | = 0, <i>p</i> = 0.98 | 211 | | 220 _г 0. | 1 0.2 0.5 1 2 5 Favours light Favours de | 10 | [0.31; 1.12] | 100.0% |

c)

Supplementary Figure 5: Forest plots – secondary outcomes – resource use domain: a) ICU LOS; b) hospital LOS; c) tracheostomies

Note: data converted from median/IRQ to mean/SD¹² – ICU LOS& hospital LOS in the following studies: Balzer et al 2015; Bugedo et al 2013; Dale et al 2014; Guttormson et al 2011 (ICU LOS only); Mehta et al 2012; Nassar Jr et al 2014; Quenot et al 2007; Sen et al 2017; Shehabi et al 2013; Strom et al 2010; Treggiari et al 2009.

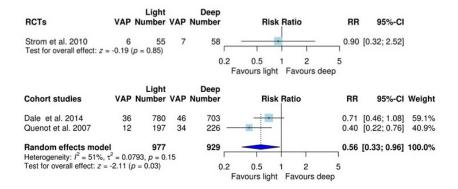
| RCTs | Extubated Nu | Light | Extubated | Deep Number | Risk | Ratio | RR | 95%-CI Weight |
|---|----------------------|------------------|---------------|--------------------|----------------------------|---------------------|----------|---|
| Nassar et al. 2014 Treggiari et al. 2009 | 2 2 | 30 65 | 1 2 | 30 64 | | | | 0.19; 20.90] 40.3% [0.14; 6.78] 59.7% |
| Random effects model Heterogeneity: $I^2 = 0\%$, τ^2 Test for overall effect: $z =$ | = 0, <i>p</i> = 0.65 | 95 | | 94 r 0. | 1 0.2 0.5 Favours light | 1 2 5 Favours de | 10 | [0.30; 5.82] 100.0% |
| Cohort studies | Extubated Nu | Light | Extubated | Deep Number | Risk | Ratio | RR | 95%-CI Weight |
| Bugedo et al. 2013 Faust et al. 2016 Quenot et al. 2007 | 12 5 21 | 132 79 197 | 14 2 16 | 155 65 226 | | | → 2.06 [| [0.48; 2.10] 38.3% 0.41; 10.26] 8.0% [0.81; 2.80] 53.6% |
| Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 Test for overall effect: $z =$ | = 0, <i>p</i> = 0.61 | 408 | | 446 r 0. | I 0.2 0.5 Favours light | 1 2 5 Favours de | 10 | [0.84; 2.09] 100.0% |

a)

| RCTs | Reintubated | Light Number | Reintubated | Deep Number | Risk Ratio | RR | 95%-CI We | eight |
|---|-----------------------------------|------------------------------|--------------------|------------------------------|---|----------------------|---|--------------------------------------|
| Mehta et al. 2012 Nassar et al. 2014 Olsen et al. 2020 Samuelson 2008 Treogiari et al. 2009 | 16 1 35 1 2 | 209 30 349 18 65 | 12 4 15 2 | 214 30 351 18 64 | | 0.25 2.35 0.50 | [0.03; 2.11] 7 [1.31; 4.22] 43 [0.05; 5.04] 6 | 6.1% 7.6% 3.5% 6.6% 6.2% |
| Random effects mode Heterogeneity: $l^2 = 30\%$, τ Test for overall effect: $z =$ | l ² = 0.1419, p = 0 | 671 | | 677 0. | 1 0.2 0.5 1 2 5 Favours light Favours de | 1.45 | [0.78; 2.71] 100 | |
| Cohort studies | Reintubated | Light Number | Reintubated | Deep Number | Risk Ratio | RR | 95%-CI We | eight |

| Cohort studies | Reintubated | Number | Reintubated | Number | Risk | Ratio | RR | 95%-CI W | /eight |
|---|----------------------|-----------|-------------|-----------------|-----------------------------|-------|------|---------------|----------------|
| Bugedo et al. 2013 Faust et al. 2016 | 7 2 | 102 79 | 8 1 | 116 65 | | | | | 85.5% 14.5% |
| Random effects model Heterogeneity: $l^2 = 0\%$, τ^2 Test for overall effect: $z = l^2$ | = 0, <i>p</i> = 0.70 | 181 | | 181 0 | .1 0.2 0.5 Favours light | | 5 10 | 0.43; 2.65] 1 | 00.0% |

b)



c)

Supplementary Figure 6: Forest plots – secondary outcomes – adverse events domain: a) selfextubation; b) re-intubation; c) Ventilator associated pneumonia