

7.1 Combination Parenteral Nutrition and Enteral Nutrition

Question: Does the use of parenteral nutrition in combination with enteral nutrition result in better outcomes in the critically ill adult patient?

Summary of evidence: There was one level 1 and nine level 2 studies that were reviewed and meta-analysed.

Mortality: All 10 studies reported on mortality. The meta-analysis shows that there was no effect on mortality with the use of combination EN + PN (RR 1.00, 95% CI 0.70, 1.41, $p=0.98$, heterogeneity $I^2=41\%$; figure 1). When a sub-group analysis was done comparing the trials where the groups differed in calories received (RR 0.92, 95% CI 0.60, 1.41, $p=0.71$, heterogeneity $I^2=52\%$; figure 1) to those that were fed isocalorically (RR 1.30, 95% CI 0.74, 2.29, $p=0.36$, heterogeneity $I^2=0\%$; figure 1), there was no difference in effect. A test for subgroup differences showed no significant differences between these two subgroups ($p=0.34$).

Infections: When the data from the 5 studies that reported infectious complications were aggregated, the use of combined EN + PN compared to EN had no effect on the overall incidence of infection (RR 1.02, 95% CI 0.89, 1.16, $p=0.82$, heterogeneity $I^2=0\%$; figure 2).

LOS & ventilator days: When the data from the 6 studies that reported hospital length of stay as a mean \pm standard deviation were aggregated, the use of combined EN + PN compared to EN alone was associated with a trend towards a reduction in hospital length of stay (WMD -3.14, 95% CI -6.46, 0.18, $p=0.06$, heterogeneity $I^2=38\%$; figure 3). When the data from the 5 studies that reported ICU length of stay as a mean \pm standard deviation were aggregated, the use of combined EN + PN compared to EN alone had no effect on ICU length of stay (WMD -0.76, 95% CI -2.52, 1.00, $p=0.39$, heterogeneity $I^2=51\%$; figure 4). When the data from the 4 studies that reported duration of ventilation as a mean \pm standard deviation were aggregated, the use of combined EN + PN compared to EN alone had no effect on duration of ventilation (WMD -0.62, 95% CI -1.93, 0.68, $p=0.35$, heterogeneity $I^2=64\%$; figure 5).

Blood sugars: Blood sugars were significantly higher in the EN + PN group when compared to the EN group but only on day 7 in one study (Bauer et al) ($p<0.05$). Chiarelli et al reported no difference in glycemia between the groups although no numbers were reported. None of the other studies reported on blood sugars.

Physical and Quality of Life Outcomes: Three studies (Chen 2011, Wischmeyer 2017, Ridley 2018) reported on physical outcomes. Within both groups, Chen found a significant improvement in respiratory muscle strength before and after nutrition support. Wischmeyer did not find a difference between groups with respects to handgrip strength at ICU discharge and 6 minute walk test at hospital discharge. However, there was trend towards greater hand grip strength in the EN+PN group vs the EN group at hospital discharge. In comparison, Ridley did not find a difference between groups in hand grip strength at hospital discharge. Ridley also found no difference between groups in the ICU mobility scale at hospital discharge.

Two studies (Wischmeyer 2017, Ridley 2018) reported on quality of life (QOL) outcomes. Wischmeyer looked at the Barthel Index at hospital discharge and the SF-36 at 3 and 6 months. There was a trend towards a greater Barthel Index score in the EN+PN group. For the SF-36 at 3 months, there was no difference in the components with the exception of *general health perceptions*, which showed a trend in improved scores in the EN group vs EN+PN group. At 6 months, there was a trend in improved scores in the *pain index, vitality, social functioning, role emotional, standardized physical component scale and standardized mental component scale*, all favouring the EN+PN group. Ridley did not find a difference between groups in the EQ-5D-3L at hospital discharge or at 90 days.

In summary, there are inconclusive data to make a conclusion on the effects of EN+PN vs EN on quality of life or physical outcomes.

Conclusions: When compared to EN alone,

- 1) PN in combination with EN has no effect on mortality in critically ill patients
- 2) PN in combination with EN has no effect on infectious complications in critically ill patients
- 3) PN in combination with EN may be associated with a reduction in hospital length of stay but has no effect on ICU LOS in critically ill patients.
- 4) PN in combination with EN has no effect on duration of ventilation in critically ill patients.
- 5) PN in combination with EN may be associated with some improvements in long-term physical function of surviving critically ill patients.
- 6) PN in combination with EN is associated with a higher cost compared to EN alone.

Level 1 study: if all of the following are fulfilled: concealed randomization, blinded outcome adjudication and an intention to treat analysis.

Level 2 study: If any one of the above characteristics are unfulfilled.

Table 1. Randomized studies evaluating combined EN + PN in critically ill patients

| Study | Population | Methods (score) | Intervention (both interventions started at same time) | Mortality # (%)† | | Infections # (%)‡ | |
|-------------------|--|---|---|---|---|-------------------|------------|
| | | | | EN + PN | EN | EN + PN | EN |
| 1) Herndon 1987 | Burns > 50 % TBSA N = 28 | C.Random: not sure ITT: yes Blinding: no (6) | EN + PN vs EN EN + PN group received significantly more calories than EN group | 8/13 (62) | 8/15 (53) | NR | NR |
| 2) Herndon 1989 | Burn patients N = 39 | C.Randomization: not sure ITT: yes Blinding: no (7) | EN+ PN vs EN EN + PN group received significantly more calories than EN group | > Day 14 10/16 (63) | > Day 14 6/23 (26) | NR | NR |
| 3) Dunham 1994* | Blunt trauma N = 37 | C.Random: not sure ITT: no Blinding: no (8) | EN+ PN vs EN EN + PN group given same calories as EN | 3/10 (30) | 1/12 (8.3) | NR | NR |
| 4) Chiarelli 1996 | ICU patients medical and surgical N = 24 | C.Random: not sure ITT: yes Blinding: no (8) | EN+ PN vs EN EN + PN were given 33 kcal/kg/day, EN were given 31 kcal/kg/day | 3/12 (25) | 4/12 (33) | 6/12 (50) | 3/12 (25) |
| 5) Bauer 2000 | Patients from 2 ICUs N =120 (all degrees of malnutrition) | C.Random: not sure ITT: yes Blinding: double (12) | EN+ PN vs EN + placebo. EN + PN received 24.6 ± 4.9 kcal/kg/day vs. EN group 14.2 ± 6.5 kcal/kg/day (p< 0.0001) | < Day 4 3/60 (5) 90-day 17/60 (28) | < Day 4 4/60 (6.7) 90-day 18/60 (30) | 39/60 (65) | 39/60 (65) |
| 6) Abrishami 2010 | SIRS patients with APACHE II > 10 N=20 | C.Random: not sure ITT: yes Blinding: no (7) | EN vs. EN + PN Metoclopramide if GRV >300mL Non isocaloric/isonitrogenous | 2/10 (20) | 1/10 (10) | NR | NR |

| | | | | | | | |
|--------------------|---|--|---|--|--|------------------------------|------------------------------|
| 7) Chen 2011* | Elderly Patients in respiratory intensive care unit N=147 | C.Random: yes ITT: yes Blinding: no (7) | EN + PN: EN as above + PN to make up kcal and nitrogen deficit vs EN: 100ml/hr=goal rate; metoclopramide if GRV >200mL, NJ if not tolerating NG Non-isocaloric/isonitrogenous | 20-day 3/49 (6) | 20-day 11/49 (22) | 6/49 (12) | 5/49 (10) |
| 8) Heidegger 2012 | ICU patients requiring at least 5 days of treatment with no contraindication to EN, not achieving 60% of energy target (equation based) by end of D3 N=305 | C.Random yes ITT: yes Blinding: single (13) | EN vs EN+PN to make up energy target verified by indirect calorimetry in 65% of patients. EN progression encouraged in both groups. Non-isocaloric/isonitrogenous | ICU 8/153 (5) 28-day 20/153 (13) | ICU 11/152 (7) 28-day 28/152 (18) | Day 4 to 28** 77/153 (50) | Day 4 to 28** 85/152 (56) |
| 9) Wischmeyer 2017 | Adult (≥18 years) mixed ICU patients with BMI <25 or >35. Multi-centre. N=125 | C.Random: yes ITT: yes Blinding: no (9) | sPN adjusted daily to reach 100% of goal calories in combination with EN vs standard EN. Non-isonitrogenous, non-isocaloric. | ICU 7/52 (13.5) Hospital 8/52 (15.4) | ICU 13/73 (17.8) Hospital 17/73 (23.3) | Newly acquired 38/52 | Newly acquired 46/73 |
| 10) Ridley 2018 | Adult (≥16 years), mixed ICU patients. Multi-centre N=99 | C.Random: yes ITT: yes Blinding: no (9) | sPN to provide 0, 40 or 80% of goal energy based on amount of EN received vs En as per usual care. Both groups dosed at 25 kcal/kg/d, or if on RRT or ECMO 30 kcal/kg/d. Isocaloric, non-isonitrogenous. | ICU 15/51 Hospital 16/51 90-day 19/51 180-day 19/51 | ICU 11/48 Hospital 11/48 90-day 13/48 180-day 13/48 | NR | NR |

*Pertains to EN+PN vs EN comparison; for the Chen EN+PN vs PN comparison see section 1.0

**Date obtained from authors

Table 1. Randomized studies evaluating combination parenteral nutrition and enteral nutrition in critically ill patients (continued)

| Study | LOS days | | Ventilator days | | Other | |
|-------------------|---|---|---|--|---|----|
| | EN + PN | EN | EN + PN | EN | EN + PN | EN |
| 1) Herndon 1987 | NR | NR | NR | NR | NR | |
| 2) Herndon 1989 | NR | NR | NR | NR | NR | |
| 3) Dunham 1994* | NR | NR | NR | NR | Nutrition related complications 5/10 (50) 3/12 (25) | |
| 4) Chiarelli 1996 | Hospital 37 ± 13 (12) | Hospital 41 ± 23 (12) | 19 ± 6 (12) | 19 ± 2 (12) | NR | |
| 5) Bauer 2000 | ICU 16.9 ± 11.8 (60) Hospital 31.2 ± 18.5 (60) | ICU 17.3 ± 12.8 (60) Hospital 33.7 ± 27.7 (60) | 11 ± 9 (60) | 10 ± 8 (60) | Glycemia on day 7 (g/L) 1.16 ± 0.36 1.31 ± 0.49 | |
| 6) Abrishami 2010 | ICU 25.7 Hospital 37.4 | ICU 27.7 Hospital 36.5 | NR | NR | NR | |
| 7) Chen 2011 | ICU 6.75 ± 1.75 (49) Hospital 17.3 ± 2.47 (49) | ICU 9.09 ± 2.75 (49) Hospital 23.32 ± 5.6 (49) | 5.76 ± 1.56 (49) | 7.95 ± 2.11 (49) | "Other complications" 8/49 (16) 10/49 (20) | |
| 8) Heidegger 2012 | ICU 13 ± 10 (153) Hospital 31 ± 23 (153) | ICU 13 ± 11 (152) Hospital 32 ± 23 (152) | 60 ± 111 hrs (153) 2.5 ± 4.625 (153) | 66 ± 101 hrs (152) 2.75 ± 4.21 days (152) | Similar glucose control in the EN+PN and EN groups Target < 8 mmol/l | |

| | | |
|--|--|--|
| | | <p>49.5 ± 24.3 (24, 63%) 61.2 ± <u>18.3</u> (27, 50%) P=0.14</p> <p>SF-36 3 Months: Vitality 51.0 ± 21.7 (24, 63%) 52.8 ± <u>21.4</u> (28, 52%) P=0.72</p> <p>SF-36 3 Months: Social Functioning 56.5 ± 28.2 (25, 66%) 60.4 ± <u>31.8</u> (30, 55%) P=0.56</p> <p>SF-36 3 Months: Role emotional 65.3 ± 34.4 (25, 63%) 63.2 ± <u>34.6</u> (29, 54%) P=0.88</p> <p>SF-36 3 Months: Mental health index 76.1 ± 18.5 (23, 61%) 72.9 ± <u>18.7</u> (28, 52%) P=0.39</p> <p>SF-36 3 Months: Standardized physical component scale 33.3 ± 10.1 (22, 58%) 35.3 ± <u>10.8</u> (27, 50%) P=0.38</p> <p>SF-36 3 Months: Standardized mental component scale 51.5 ± 10.0 (22, 58%) 50.0 ± <u>10.5</u> (27, 50%) P=0.38</p> <p>SF-36 6 Months: Physical Functioning 50.8 ± 36.5 (20, 53%) 39.3 ± <u>34.0</u> (31, 57%) P=0.21</p> <p>SF-36 6 Months: Role-physical 47.5 ± 33.4 (20, 53%) 40.2 ± <u>33.1</u> (32, 59%) P=0.43</p> <p>SF-36 6 Months: Pain Index 68.6 ± 28.2 (20, 53%) 52.5 ± <u>31.0</u> (31, 57%) P=0.08</p> <p>SF-36 6 Months: General health perceptions 56.8 ± 26.2 (20, 53%) 50.9 ± <u>20.6</u> (31, 57%) P=0.46</p> <p>SF-36 6 Months: Vitality 59.1 ± 21.7 (20, 53%) 47.8 ± <u>21.2</u> (31, 57%) P=0.06</p> <p>SF-36 6 Months: Social Functioning 68.8 ± 32.6 (20, 53%) 50.4 ± <u>32.2</u> (31, 57%) P=0.06</p> <p>SF-36 6 Months: Role emotional</p> |
|--|--|--|

| | | |
|-----------------|--|---|
| | | <p>72.13 ± 30.3 (20, 53%) 52.2 + <u>41.0</u> (32, 59%) P=0.10</p> <p>SF-36 6 Months: Mental health index 70.5 ± 24.9 (20, 53%) 66.1 + <u>22.5</u> (31, 57%) P=0.36</p> <p>SF-36 6 Months: Standardized physical component scale 39.3 ± 10.2 (20, 53%) 35.8 + <u>11.2</u> (30, 55%) P=0.17</p> <p>SF-36 6 Months: Standardized mental component scale 49.0 ± 13.5 (20, 53%) 43.2 + <u>14.8</u> (30, 55%) P=0.11</p> |
| 10) Ridley 2018 | <p>Hand grip at hospital d/c, kg, mean (SD) 19 (13.5), n=19 20 (8), n=24 P=0.71</p> <p>ICU mobility scale at hospital d/c, median (IQR) 9 [5-10], n=25 8 [4-10], n=33 P=0.58</p> | <p>EQ-5D-3L hospital d/c mean (SD) 0.25 (0.34), n=27 0.32 (0.36), n=17 P=0.54</p> <p>90 days median (IQR) 0.69 (0.24), n=35 0.76 (0.23), n=29 P=0.29</p> <p>180 days, mean (SD) 0.75 (0.26), n=35 0.77 (0.24), n=29 P=0.76</p> |

Note: Only studies reporting on these outcomes are shown in this table.

Figure 1. Overall Mortality

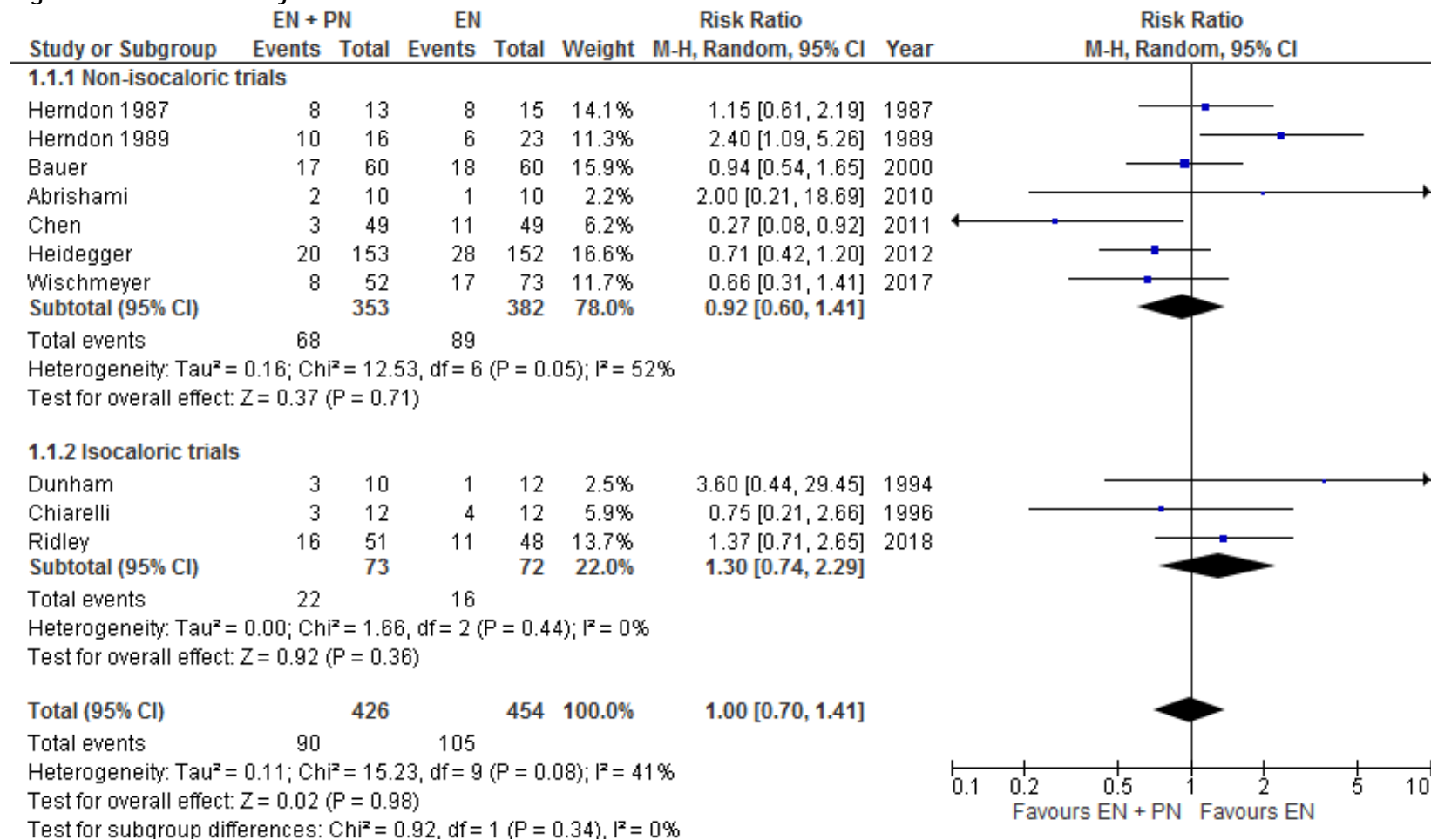


Figure 2. Infectious complications

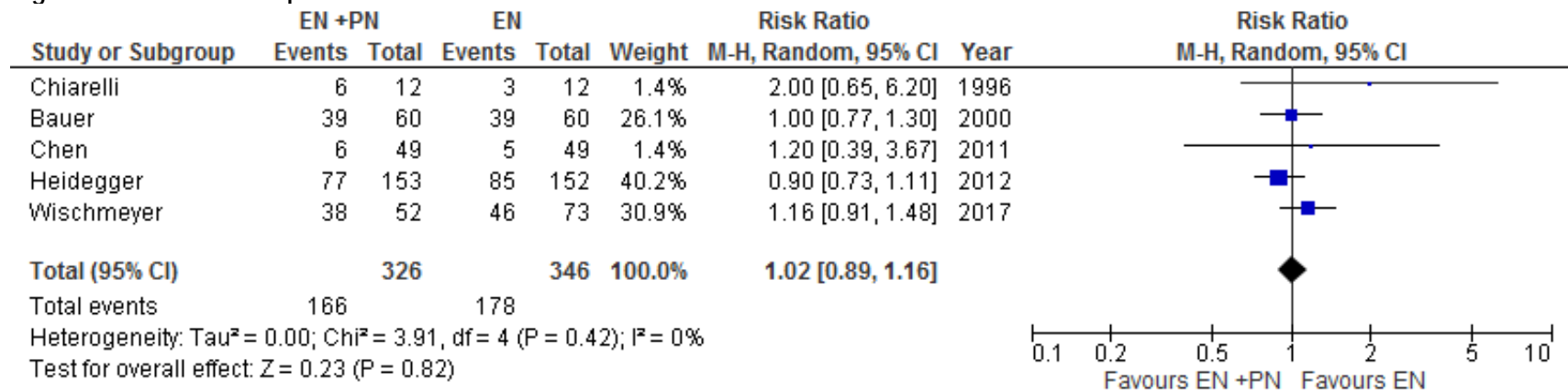


Figure 3. Hospital LOS

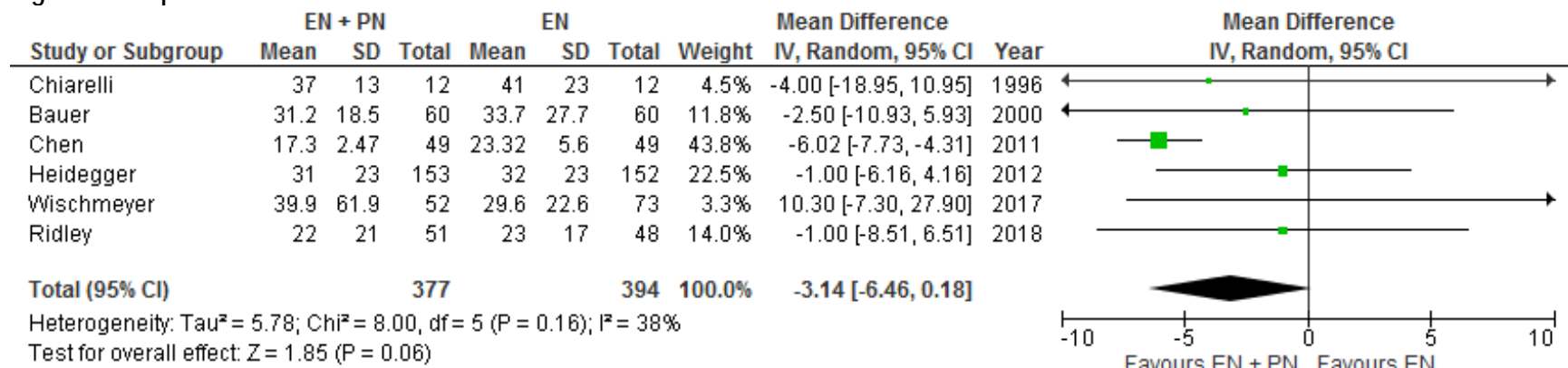


Figure 4. ICU LOS

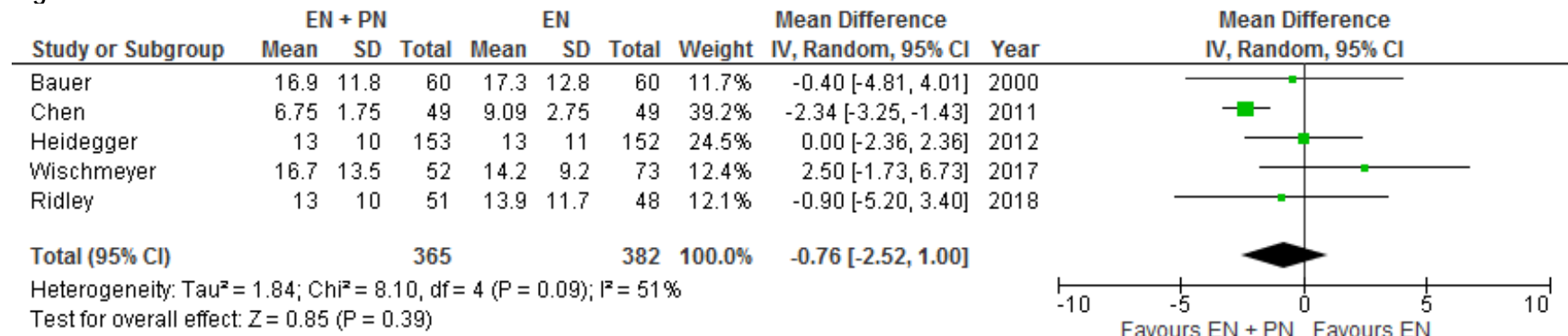


Figure 5. Ventilator days

