# 7.1 Combination Parenteral Nutrition and Enteral Nutrition May 2015

*There were no new randomized controlled trials since the 2013 update and hence there are no changes to the following summary of evidence.*

Recommendation 2013: *Based on one level 1 study and seven level 2 studies, for critically ill patients starting on enteral nutrition we recommend that parenteral nutrition not be started at the same time as enteral nutrition. In the patient who is not tolerating adequate enteral nutrition, there are insufficient data to put forward a recommendation about when parenteral nutrition should be initiated. Practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis. We recommend that PN not be started in critically ill patients until all strategies to maximize EN delivery (such as small bowel feeding tubes, motility agents) have been attempted.*

Discussion 2013: The committee noted that when the data from the three new trials (Abrishami 2010, Chen 2011 & Heidegger 2012) were added, combination EN + PN, in patients with an intact GI tract, had no effect on mortality even when the isocaloric trials were compared to non isocaloric trials. The lack of a treatment effect in infections was also noted. Combination enteral and parenteral nutrition was associated with a significant reduction in hospital LOS, a trend for a reduction in ICU LOS and no effect on days requiring mechanical ventilation. The committee noted the presence of clinical heterogeneity (Heidegger et al is the only one that used indirect calorimetry to determine energy requirements) and statistical heterogeneity. Given the lack of a clear benefit on clinical outcomes and potential harm with infectious risk and increased cost, the committee decided not to change the recommendation. However, the committee also noted that there was still a paucity of data from randomized trials of patients not tolerating adequate amounts of EN and when PN should be used in combination in this scenario.

Recommendation 2009: *Based on 5 level 2 studies, for critically ill patients starting on enteral nutrition we recommend that parenteral nutrition not be started at the same time as enteral nutrition. In the patient who is not tolerating adequate enteral nutrition, there are insufficient data to put forward a recommendation about when parenteral nutrition should be initiated. Practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis. We recommend that PN not be started in critically ill patients until all strategies to maximize EN delivery (such as small bowel feeding tubes, motility agents) have been attempted.*

Discussion 2009: The committee noted that these data pertain to patients with an intact GI tract, not to those who have an absolute indication for parenteral nutrition. The committee reviewed the results of 5 level 2 studies that initiated PN at the same time as starting EN. When aggregated statistically, these studies suggested no benefit. The committee noted that the study results were homogenous and that when the trials in which the combination EN + PN group received more calories than the EN group were compared to those trials that did not, there was no difference in mortality. Given the probability of harm from trials of PN vs. EN in critically ill patients (see section 1.0 En vs. PN) and excess costs associated with the addition of PN when initiating EN, a recommendation against its use was put forward. However, the committee noted the absence of data from randomized trials related to patients not tolerating adequate amounts of EN and when PN should be used in combination in this scenario.

# Semi Quantitative Scoring

| Values | Definition | 2009 Score (0,1,2,3) | 2013 Score (0,1,2,3) |
|---|---|---|---|
| Effect size | Magnitude of the absolute risk reduction attributable to the intervention listed--a higher score indicates a larger effect size | 2 | 0 (mortality)<br>0 (infection)<br>3 (hosp LOS) |
| Confidence interval | 95% confidence interval around the point estimate of the absolute risk reduction, or the pooled estimate (if more than one trial)--a higher score indicates a smaller confidence interval | 2 | 0 (mortality)<br>1 (infection) |
| Validity | Refers to internal validity of the study (or studies) as measured by the presence of concealed randomization, blinded outcome adjudication, an intention to treat analysis, and an explicit definition of outcomes--a higher score indicates presence of more of these features in the trials appraised | 2 | 2 |
| Homogeneity or Reproducibility | Similar direction of findings among trials--a higher score indicates greater similarity of direction of findings among trials | 3 | 1 (mortality)<br>3 (infection)<br>2 (LOS) |
| Adequacy of control group | Extent to which the control group presented standard of care (large dissimilarities=1, minor dissimilarities=2, usual care=3) | 2 | 1 |
| Biological Plausibility | Consistent with understanding of mechanistic and previous clinical work (large inconsistencies=1, minimal consistencies=2, very consistent=3) | 2 | 2 |
| Generalizability | Likelihood of trial findings being replicated in other settings (low likelihood i.e. single centre=1, moderate likelihood i.e. multicentre with limited patient population or practice setting=2, high likelihood i.e. multicentre, heterogenous patients, diverse practice settings=3) | 1 | 1 |
| Low cost | Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU | 1 | 1 |
| Feasible | Ease of implementing the intervention listed--a higher score indicates greater ease of implementing the intervention in an average ICU | 2 | 2 |
| Safety | Estimated probability of avoiding any significant harm that may be associated with the intervention listed--a higher score indicates a lower probability of harm | 1 | 1 |

## 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 seven level 2 studies that were reviewed and meta-analysed.

Mortality: All 8 studies reported on mortality. The meta-analysis shows that there was no effect on mortality with the use of combination EN + PN (RR 1.01, 95% CI 0.65, 1.56, p=0.98, heterogeneity $I^2$=47%; figure 1). When a sub-group analysis was done comparing the trials that overfed (RR 0.98, 95% CI 0.60, 1.60, p=0.93, heterogeneity $I^2$=57%; figure 1) to those that did not (RR 1.31, 95% CI 0.29, 5.82, p=0.72, heterogeneity $I^2$=38%; figure 1), there was no difference in effect. A test for subgroup differences showed no significant differences between these two subgroups (p=0.72).

Infections: When the data from the 4 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 0.96, 95% CI 0.81, 1.13, p=0.60, heterogeneity $I^2$=0%; figure 2).

LOS & ventilator days: When the data from the 4 studies that reported hospital length of stay as a mean ± standard deviation were aggregated, the use of combined EN + PN compared to EN alone was associated with a significant reduction in hospital length of stay ( WMD -4.59, 95% CI -7.27, -1.91, p=0.0008, heterogeneity $I^2$=21%; figure 3). When the data from the 3 studies that reported ICU length of stay as a mean ± standard deviation were aggregated, the use of combined EN + PN compared to EN alone was associated with a trend towards areduction in ICU length of stay ( WMD -1.39, 95% CI -3.13, 0.36, p=0.12, heterogeneity $I^2$=47%; figure 4). When the data from the 4 studies that reported duration of ventilation as a mean ± standard deviation were aggregated, the use of combined EN + PN compared to EN alone had no effect on duration of ventilation ( WMD -0.74, 95% CI -2.29, 0.82, p=0.35, heterogeneity $I^2$=76%; 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.

Conclusions:

1) PN in combination with EN, when compared to 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 is associated with a significant reduction in hospital length of stay and a trend towards a reduction in 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 enteral nutrition 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<br>N = 28 | C.Random: not sure<br>ITT: yes<br>Blinding: no<br>(6) | EN + PN vs EN<br>EN + PN group received significantly more calories than EN group | 8/13 (62) | 8/15 (53) | NR | NR |
| 2) Herndon 1989 | Burn patients<br>N = 39 | C.Randomization: not sure<br>ITT: yes<br>Blinding: no<br>(7) | EN+ PN vs EN<br>EN + PN group received significantly more calories than EN group | > Day 14<br>10/16 (63) | > Day 14<br>6/23 (26) | NR | NR |
| 3) Dunham 1994* | Blunt trauma<br>N = 37 | C.Random: not sure<br>ITT: no<br>Blinding: no<br>(8) | EN+ PN vs EN<br>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<br>N = 24 | C.Random: not sure<br>ITT: yes<br>Blinding: no<br>(8) | EN+ PN vs EN<br>EN + PN were given 33 kcal/kg/day,<br>EN were given 31 kcals/kg/day | 3/12 (25) | 4/12 (33) | 6/12 (50) | 3/12 (25) |
| 5) Bauer 2000 | Patients from 2 ICUs<br>N =120<br>(all degrees of malnutrition) | C.Random: not sure<br>ITT: yes<br>Blinding: double<br>(12) | EN+ PN vs EN + placebo.<br>EN + PN received 24.6 ± 4.9 kcal/kg/day vs. EN group 14.2 ± 6.5 kcal/kg/day<br>(p< 0.0001) | < Day 4<br>3/60 (5)<br>90-day<br>17/60 (28) | < Day 4<br>4/60 (6.7)<br>90-day<br>18/60 (30) | 39/60 (65) | 39/60 (65) |
| 6) Abrishami 2010 | SIRS patients with APACHE II > 10<br>N=20 | C.Random: not sure<br>ITT: yes<br>Blinding: no<br>(7) | EN vs.EN + PN<br>Metoclopramide if GRV >300mL<br>Non isocaloric/isonitrogenous | 2/10 (20) | 1/10 (10) | NR | NR |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 7) Chen 2011* | Elderly Patients in respiratory intensive care unit<br>N=147 | C.Random: yes<br>ITT: yes<br>Blinding: no<br>(7) | EN + PN: EN as above + PN to make up kcal and nitrogen deficit<br>vs<br>EN: 100ml/hr=goal rate; metoclopramide if GRV >200mL, NJ if not tolerating NG<br>Non-isocaloric/isonitrogenous | 20-day<br>3/49 (6) | 20-day<br>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<br>N=305 | C.Random yes<br>ITT: yes<br>Blinding: single<br>(13) | EN vs EN+PN to make up energy target verified by indirect calorimetry in 65% of patients. EN progression encouraged in both groups.<br>Non-isocaloric/isonitrogenous | ICU<br>8/153 (5)<br>28-day<br>20/153 (13) | ICU<br>11/152 (7)<br>28-day<br>28/152 (18) | Day 4 to 28**<br>77/153 (50) | Day 4 to 28**<br>85/152 (56) |

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

C.Random: concealed randomization
* Dunham:only looked at data pertaining to EN+PN vs EN (not EN +PN vs PN)
± ( ) : mean ± Standard deviation (number)

ITT: intent to treat; NA: not available
† presumed hospital mortality unless otherwise specified
‡ refers to the # of patients with infections unless specified

Figure 1. Overall Mortality

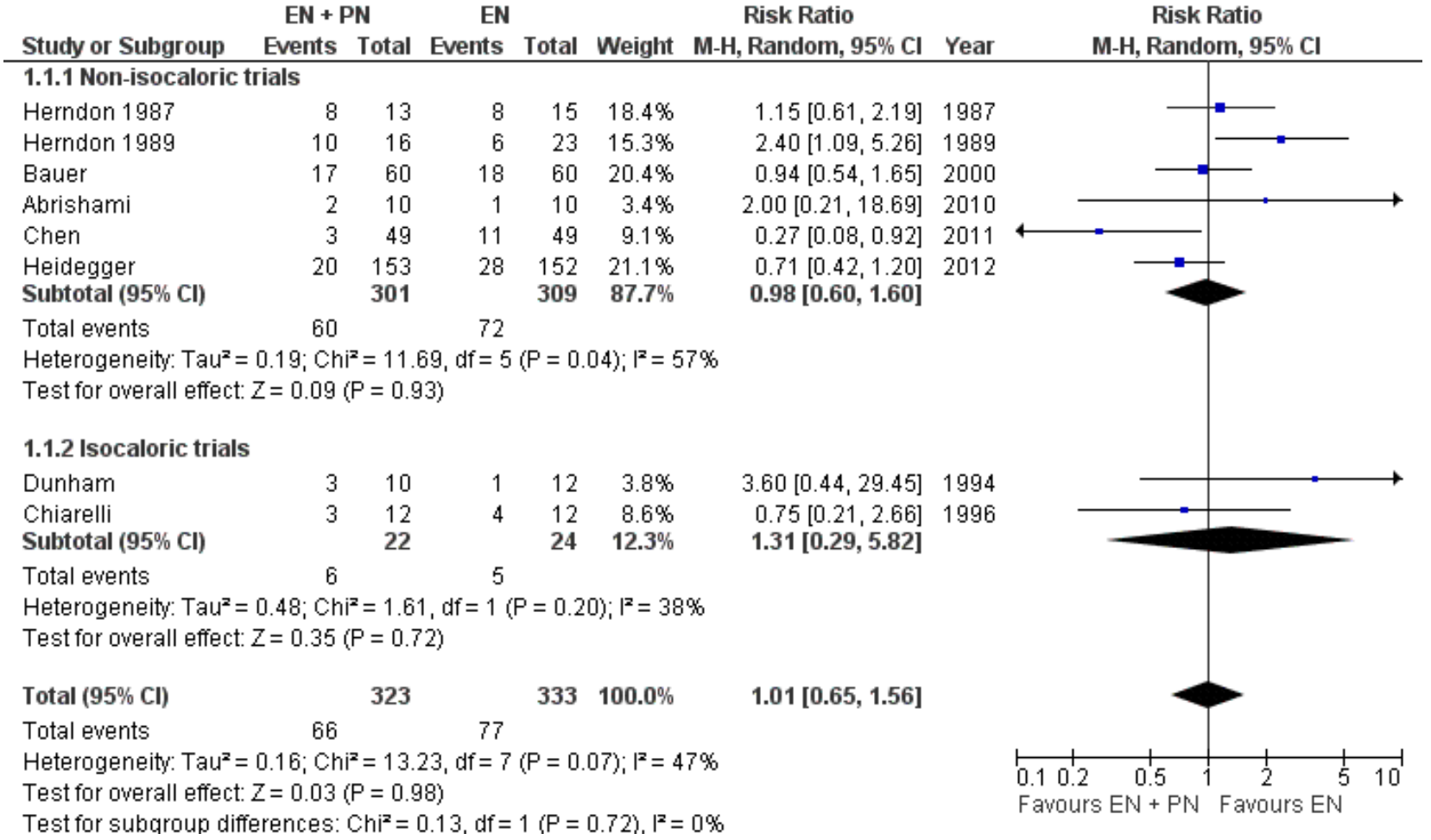

Figure 2. Infectious complications

| Study or Subgroup | EN +PN Events | Total | EN Events | Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Chiarelli | 6 | 12 | 3 | 12 | 2.0% | 2.00 [0.65, 6.20] | 1996 |
| Bauer | 39 | 60 | 39 | 60 | 37.7% | 1.00 [0.77, 1.30] | 2000 |
| Chen | 6 | 49 | 5 | 49 | 2.1% | 1.20 [0.39, 3.67] | 2011 |
| Heidegger | 77 | 153 | 85 | 152 | 58.2% | 0.90 [0.73, 1.11] | 2012 |
| **Total (95% CI)** | | **274** | | **273** | **100.0%** | **0.96 [0.81, 1.13]** | |
| Total events | 128 | | 132 | | | | |

Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 3 (P = 0.53); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)

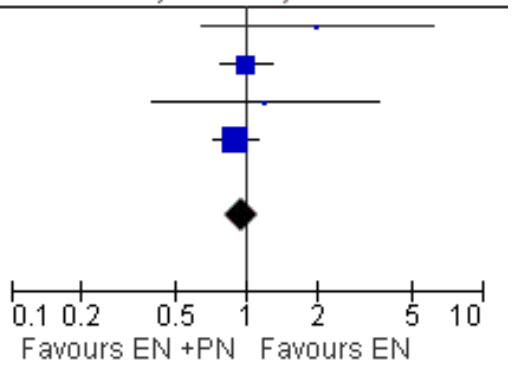


Figure 3. Hospital LOS

| Study or Subgroup | EN + PN Mean | SD | Total | EN Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Chiarelli | 37 | 13 | 12 | 41 | 23 | 12 | 3.1% | -4.00 [-18.95, 10.95] | 1996 |
| Bauer | 31.2 | 18.5 | 60 | 33.7 | 27.7 | 60 | 9.1% | -2.50 [-10.93, 5.93] | 2000 |
| Chen | 17.3 | 2.47 | 49 | 23.32 | 5.6 | 49 | 66.9% | -6.02 [-7.73, -4.31] | 2011 |
| Heidegger | 31 | 23 | 153 | 32 | 23 | 152 | 20.9% | -1.00 [-6.16, 4.16] | 2012 |
| **Total (95% CI)** | | | **274** | | | **273** | **100.0%** | **-4.59 [-7.27, -1.91]** | |

Heterogeneity: Tau² = 2.03; Chi² = 3.78, df = 3 (P = 0.29); I² = 21%
Test for overall effect: Z = 3.35 (P = 0.0008)

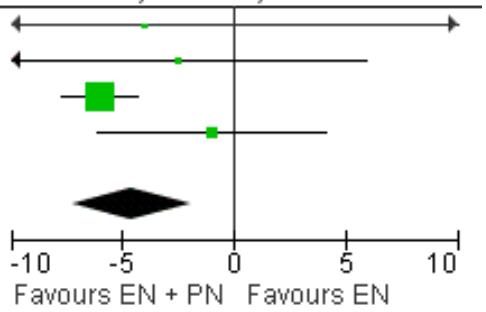

Figure 4. ICU LOS

| Study or Subgroup | EN + PN Mean | SD | Total | EN Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Bauer | 16.9 | 11.8 | 60 | 17.3 | 12.8 | 60 | 12.7% | -0.40 [-4.81, 4.01] | 2000 |
| Chen | 6.75 | 1.75 | 49 | 9.09 | 2.75 | 49 | 57.1% | -2.34 [-3.25, -1.43] | 2011 |
| Heidegger | 13 | 10 | 153 | 13 | 11 | 152 | 30.2% | 0.00 [-2.36, 2.36] | 2012 |
| **Total (95% CI)** | | | **262** | | | **261** | **100.0%** | **-1.39 [-3.13, 0.36]** | |

Heterogeneity: Tau² = 1.17; Chi² = 3.80, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 1.56 (P = 0.12)

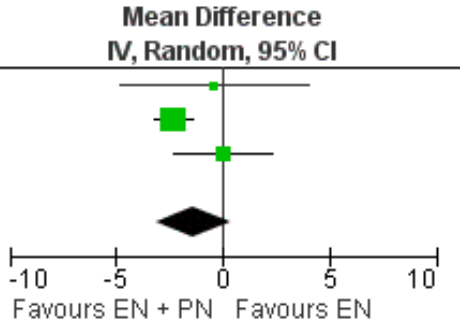


Figure 5. Ventilator days

| Study or Subgroup | EN + PN Mean | SD | Total | EN Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Chiarelli | 19 | 6 | 12 | 19 | 2 | 12 | 12.8% | 0.00 [-3.58, 3.58] | 1996 |
| Bauer | 11 | 9 | 60 | 10 | 8 | 60 | 15.8% | 1.00 [-2.05, 4.05] | 2000 |
| Chen | 5.76 | 1.56 | 49 | 7.95 | 2.11 | 49 | 36.8% | -2.19 [-2.92, -1.46] | 2011 |
| Heidegger | 2.5 | 4.625 | 153 | 2.75 | 4.21 | 152 | 34.5% | -0.25 [-1.24, 0.74] | 2012 |
| **Total (95% CI)** | | | **274** | | | **273** | **100.0%** | **-0.74 [-2.29, 0.82]** | |

Heterogeneity: Tau² = 1.57; Chi² = 12.56, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 0.93 (P = 0.35)