4.1a. EN Composition: Diets Supplemented with Arginine and Select Other Nutrients* March 2013

2013 Recommendation: *Based on 4 level 1 studies and 22 level 2 studies, we do not recommend diets supplemented with arginine and other select nutrients* be used for critically ill patients.*

2013 Discussion: The committee noted that with the addition of 2 new RCTs (Pearce 2006 and Kuhls 2007) there were no changes in the treatment effect on mortality or infections. The results of the subgroup analysis, which shows that in higher quality studies, diets supplemented with arginine and other nutrients had no effect on mortality whereas in lower quality studies there was a trend towards a reduction in mortality. As in 2009, in light of the potential harm (increased mortality) associated with the use of diets supplemented with arginine and other nutrients, the reduction in length of stay and mechanical ventilation is difficult to interpret. Given the possible harm in septic patients (Bower, Ross, Bertolini) and the increased costs, the committee decided to recommend against their use in critically ill patients.

2009 Recommendation: *Based on 4 level 1 studies and 20 level 2 studies, we recommend that diets supplemented with arginine and other select nutrients* not be used for critically ill patients.*

2009 Discussion: The committee noted the lack of a treatment effect with respect to mortality and infections. These results are similar to those in a recent meta-analysis of immunonutrition in ICU, trauma and burn patients[1] (Marik and Zaloga 2008).The committee noted the results of the subgroup analysis, which shows that in higher quality studies, diets supplemented with arginine and other nutrients had no effect on mortality whereas in lower quality studies there was a trend towards a reduction in mortality. In light of the potential harm (increased mortality) associated with the use of diets supplemented with arginine and other nutrients, the reduction in length of stay and mechanical ventilation is difficult to interpret. Given the possible harm in septic patients (Bower, Ross, Bertolini) and the increased costs, the committee decided to recommend against their use in critically ill patients.

[1] Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008 (11):1980-90.

Semi Quantitative Scoring

Value	Definition	2009 Score	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	0	0
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	1	1
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	2	2
Adequacy of control group	Extent to which the control group represented standard of care (large dissimilarities = 1, minor dissimilarities=2, usual care=3)	3	3
Biological plausibility	Consistent with understanding of mechanistic and previous clinical work (large inconsistencies =1, minimal inconsistencies =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.	2	2
Low cost	Estimated cost of implementing the intervention listed--a higher score indicates a lower cost to implement the intervention in an average ICU	2	2
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

The term “immune-enhancing diets” has been used to describe products that have immune-modulating properties such as arginine, glutamine, omega-3 fatty acids, and others. There are several commercially available enteral feeding products that contain varying amounts of arginine in combination with other immune modulating nutrients. Since arginine is the common ingredient across these various formulas, we elected to describe this section as “Diets supplemented with Arginine and other select Nutrients”.

* (refer to tables for specific nutrients)

4.1a. EN Composition: Diets Supplemented with Arginine and Select Other Nutrients* March 2013

Question: Compared to standard enteral feeds, do diets supplemented with arginine and other nutrients result in improved clinical outcomes in critically ill patients?

Summary of Evidence: There were 24 studies reviewed, 4 level 1 studies and 20 level 2 studies. The data from the Bertolini study was not included in the meta- analysis as the control feed was parenteral nutrition, not an enteral formulaThe Kuhls 2007 study had two interventions, one comparing enteral nutrition supplemented with arginine plus ß hydroxyl methyl butyrate & glutamine (Juven) to standard enteral nutrition alone, the data for which is included in this section. The data pertaining to the second intervention from this study comparing enteral nutrition supplemented with ß hydroxyl methyl to standard enteral nutrition alone is described in section 6.5 EN Other formulas.

Mortality: All 24 studies reported on mortality and when the results of the 23 studies (Bertolini excluded) were aggregated, there was no effect on mortality (RR 1.06, 95% CI 0.93, 1.20, p=0.40, heterogeneity I^2=0%; figure 1a). When a sensitivity analysis was done which excluded the Tsuei study, there also was no effect on mortality (RR 1.05, 95% CI 0.92, 1.21, p=0.46, heterogeneity I^2=4%; figure 1b). A subgroup analysis of high quality studies (score $\geq$ 8) vs. low quality studies (score < 8) showed that in higher quality studies, diets supplemented with arginine had no effect on mortality when including the Tsuei study (RR 1.09, 95% CI 0.95, 1.25, p=0.21, heterogeneity I^2=2%; figure 1a) and excluding the Tsuei study (RR 1.10, 95% CI 0.94, 1.28, p=0.24, heterogeneity I^2=6%; figure 1b); whereas in lower quality studies diets supplemented with arginine and other nutrients were associated with a trend towards a reduction in mortality (RR 0.75, 95% CI 0.49, 1.15, p=0.19, heterogeneity I^2=0%; figure 1a). The difference between these two subgroups was not statistically significant (p=0.10). When the studies of trauma including the Tsuei study (RR 1.04, 95% CI 0.56, 1.93, p=0.91, heterogeneity I^2=0%; figure 2a) and excluding the Tsuei study (RR 1.00, 95% CI 0.53, 1.88, p=1.00, heterogeneity I^2=0%; figure 2b) vs. non-trauma patients (RR 1.07, 95% CI 0.87, 1.30, p=0.52, heterogeneity I^2=29%; figure 2a) were compared, there were no differences in mortality. The difference between these two subgroups was not statistically significant (p=0.93). When the Tsuei study was considered by itself, there was no effect on mortality (RR 2.57, 95% CI 0.12, 57.44, p=0.55).

Infections: Based on the 14 studies that reported on the number of infectious complications, there was no difference in the rate of infectious complications in the analysis that included the Tsuei study (RR 0.99 95% CI, 0.85,1.15, p=0.88, heterogeneity I^2=48%; figure 3a) and the analysis that excluded the Tsuei study (RR 0.98, 95% CI 0.83, 1.15, p=0.81, heterogeneity I^2=52%; figure 3b). Subgroup analysis also showed no differences in infectious complications when high quality studies including the Tsuei study (RR 0.99, 95% CI 0.83, 1.17, p=0.87, heterogeneity I^2=52%; figure 3a) and excluding the Tsuei study (RR 0.98, 95% CI 0.81, 1.17, p=0.80, heterogeneity I^2=59%; figure 3b) were compared to lower quality studies (RR 0.97, 95% CI 0.65, 1.45, p=0.89, heterogeneity I^2=54%; figure 3a), and when studies of trauma patients including the Tsuei study (RR 0.86, 95% CI 0.52, 1.42, p=0.55, heterogeneity I^2=63%; figure 4a) and excluding the Tsuei study (RR 0.79, 95% CI 0.41, 1.50, p=0.46, heterogeneity I^2=71%;

figure 4b) were compared to studies of non-trauma patients (RR 1.00, 95% CI 0.86, 1.16, p=0.96, heterogeneity I^2=45%; figure 4a). When the Tsuei study was considered by itself, there was no effect on infectious complications (RR 1.13, 95% CI 0.57, 2.25, p=0.73).

Length of stay & duration of mechanical ventilation: Diets supplemented with arginine and other nutrients had no effect on hospital length of stay when the Tsuei study was included in the analysis (WMD -1.38, 95% CI -4.73, 1.97, p=0.42, heterogeneity I^2=84%; figure 5a) and when the Tsuei study was excluded from the analysis (WMD -0.89, 95% CI -4.53, 2.74, p=0.63, heterogeneity I^2=85%; figure 5b); or on ICU length of stay when the Tsuei study was included in the analysis (WMD -0.77, 95% CI -2.46, 0.92, p=0.37, heterogeneity I^2=68%; figure 6a) or when the Tsuei study was excluded from the analysis (WMD -0.44, 95% CI -2.31, 1.42, p=0.64, heterogeneity I^2=70%; figure 6b). When the Tsuei study was considered by itself, there was no effect on hospital length of stay (WMD -5.00, 95% CI -16.17, 6.17, p=0.38) or ICU length of stay (WMD -3.00, 95% CI -9.75, 3.75, p=0.38).

Duration of mechanical ventilation: Diets supplemented with arginine and other nutrients were associated with a trend towards a reduction in mechanical ventilation when the Tsuei study was included in the analysis (WMD -1.30, 95% CI -2.72, 0.12, p=0.07, heterogeneity I^2=73%; figure 7a) and when the Tsuei study was excluded from the analysis (WMD -1.02, 95% CI -2.53, 0.49, p=0.19, heterogeneity I^2=74%; figure 7b). When the Tsuei study was considered by itself, there was no effect on duration of mechanical ventilation (WMD -4.00, 95% CI -10.50, 2.50, p=0.23).

Conclusions:

1) Diets supplemented with arginine and other nutrients have no effect on overall mortality in critically ill patients.
2) Diets supplemented with arginine and other nutrients have no effect on rate of infectious complications in critically ill patients.
3) Diets supplemented with arginine and other nutrients have no effect on hospital length of stay, ICU length of stay and may possibly reduce duration of mechanical ventilation in critically ill patients.

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 diets supplemented with arginine and other nutrients in critically ill patients

Study	Population	Methods (score)	Intervention	Mortality # (%)‡		Infections # (%)	
				Arginine	Control	Arginine	Control
1) Cerra 1990	Surgical ICU N=20	C.Random: yes ITT: no Blinding: yes (8)	Impact *(see below)* vs. Osmolite HN non-isonitrogenous diets	1/11 (9)	1/9 (11)	NR	NR
2) Gottschlich 1990	Critically ill burn patients from 2 ICUs N=31	C.Random: not sure ITT: yes Blinding: yes (10)	Experimental formula (arginine, histidine, cysteine, ω 3 fatty acids) vs. Osmolite HN + protein isonitrogenous diets	2/17 (12)	1/14 (7)	NR	NR
3) Brown 1994	Trauma N=37	C. Random: not sure ITT: no Blinding: no (5)	Experimental formula (arginine, β carotene, lactalbumin, α linoleic acid) vs. Osmolite HN + protein isonitrogenous diets	0/19 (0)	0/18 (0)	3/19 (16)	10/18 (56)
4) Moore 1994	Trauma pts from 5 ICUs N=98	C.Random: not sure ITT: no Blinding: no (5)	Immun-Aid *(see below)* vs. Vivonex TEN non-isonitrogenous diets	1/51 (2)	2/47 (4)	9/51 (18)	10/47 (21)
5) Bower 1995	Mixed from 8 ICUs N=296	C.Random: yes ITT: no Blinding: yes (9)	Impact *(see below)* vs.Osmolite isonitrogenous diets	24/153 (16)	12/143 (8)	86/153 (56)	90/143 (63)
6) Kudsk 1996*	Trauma N=35	C.Random: yes ITT: yes Blinding: yes (10)	Immun-Aid *(see below)* vs. Promote + protein supplement isonitrogenous diets	1/17 (6)	1/18 (6)	5/16 (31)	11/17 (65)
7) Engel 1997	Trauma N=36	C.Random: not sure ITT: yes Blinding: no (6)	Impact (see below) vs. oligopeptide standard (Survimed OPD) non-isonitrogenous diets	ICU 7/18 (39)	ICU 5/18 (28)	6/18 (33)	5/18 (28)

8) Mendez 1997	Trauma N=43	C.Random: no ITT: no Blinding: yes (6)	Experimental (arginine, selenium, carnitine, taurine) vs. Osmolite HN + protein isonitrogenous diets	ICU 1/22 (4.5)	ICU 1/21 (5)	19/22 (86)	12/21 (57)
9) Rodrigo 1997	Mixed ICU N=30	C. Random :no ITT: yes Blinding: no (5)	Impact *(see below)* vs. standard (Precitene high protein) isonitrogenous diets	ICU 2/16 (13)	ICU 1/14 (7)	5/16 (31)	3/14 (21)
10) Saffle 1997	Burns N=50	C. Random: no ITT: no Blinding: double (8)	Impact *(see below)* vs. Replete (high protein, ω 3 fatty acids, glutamine) isonitrogenous diets	5/25 (21)	3/24 (13)	2.36 per patient	1.71 per patient
11) Weimann 1998	Trauma N=29	C.Random: no ITT: no Blinding: yes (9)	Impact *(see below)* vs. standard formula (Sandoz) isonitrogenous diets	2/16 (13)	4/13 (31)	NR	NR
12) Atkinson 1998	Mixed ICU N=390	C.Random: no ITT: yes Blinding: yes (11)	Impact *(see below)* vs. specially prepared isocaloric isonitrogenous diets	95/197 (48)	85/193 (44)	NR	NR
13) Galban 2000	Critically ill septic patients from 6 ICUs N=176	C.Random:yes ITT: no Blinding: no (6)	Impact *(see below)* vs standard (Precitene high protein) isonitrogenous diets	17/89 (19)	28/87 (32)	39/89 (44)	44/87 (51)
14) Capparos 2001	Mixed ICU patients from 15 ICUs N=235	C.Random:yes ITT: yes Blinding: yes (10)	Experimental formula (glutamine, arginine,75gpro/L, vit A,C E, MCT & fibre) vs control 62.5 g pro/L non-isonitrogenous diets]	27/130 (21)	30/105 (29)	64/130 (49)	37/105 (35)
15) Conejero 2002	SIRS patients from 11 ICUs N=84	C.Random: yes ITT: no Blinding: yes (8)	Experimental formula 8.5 g/L arginine, 27 g/L glutamine,52.5 g pro/L) vs. control 66.2 g pro/L	28-day 14/43 (33)	28-day 9/33 (27)	11/43 (26)	17/33 (52)

16) Dent 2003	Mixed from 14 ICUs N=170	C.Random: yes ITT: yes Blinding: Yes (11)	Optimental (arginine, Vit E, β carotene structured lipids, MCT) vs. Osmolite HN isonitrogenous diets]	20/87 (23)	8/83 (10)	57/87 (66)	52/83 (63)
17) Bertolini 2003**	Patients with severe sepsis from 33 ICUs N=39	C.Random:yes ITT: yes Blinding: no (10)	Perative *(see below)* vs. parenteral nutrition non-isocaloric diets	ICU 8/18(44) 28-day 8/18 (44)	ICU 3/21(14) 28-day 5/21 (24)	NR	NR
18) Chuntrasakul 2003	Trauma, burns N=36	C.Random: no ITT: yes Blinding: single (6)	Neommune (12.5 g/L arginine, 62.5 g pro/L) vs. Traumacal (83 g pro/L, 6.25 g/L glutamine and fish oils) non-isocaloric, non-isonitrogenous diets	1/18 (5)	1/18 (5)	NR	NR
19) Tsuei 2004***	Trauma with ISS>20 N=25	C.Random: no ITT: yes* Blinding: single (9)	EN (Deliver 2.0) plus 30 gms arginine vs. EN (Deliver 2.0) plus 28 gms Casec isocaloric, isonitrogenous diets	1/13 (8) RR 2.57, 95% CI 0.12, 57.44, p=0.55	0/11 (0)	8/13 (61) RR 1.13, 95% CI 0.57, 2.25, p=0.73	6/11 (55)
20) Kieft 2005	Mixed ICU patients from 2 ICUs N=597	C.Random:yes ITT: yes Blinding: double (10)	Stresson (Nutricia) *(see below)* vs. standard control 50 g pro/L isocaloric, non-isonitrogenous diets	ICU 84/302 (28) Hospital 114/302 (38) 28-day 93/302 (34)	ICU 78/295 (26) Hospital 106/295 (36) 28-day 82/295 (30)	130/302 (43)	123/295 (42)
21) Pearce 2006	Acute pancreatitis patients N=31	C.Random: yes ITT: no Blinding: double (9)	Complete prototype formula with feed with feed with glutamine, arginine, omega 3 fatty acids and antioxidants vs. control prototype feed isonitrogenous, isocaloric diets	0/15 (0)	3/16 (19)	NR	NR
22) Wibbenmeyer 2006	Burns with >20% TSBA N=23	C.Random: no ITT: yes Blinding: double (10)	Crucial (19 g/L arginine, 63 g pro/L, 2.9 gms fish oils) vs. control (67 g pro/L) isonitrogenous, isocaloric diets	2/12 (17)	0/11	9/12 (75)	7/11 (64)

23) Kuhls 2007***	Trauma patients in ICU Injury Severity Score >18 N=100	C.Random: not sure ITT: no Blinding: double (10)	Standard EN + 3 gms ß hydroxyl methyl butyrate (HMB) + 14 gm arginine + 14 gms glutamine (Juven) vs. standard EN + isonitrogenous placebo supplement 25kcal/kg/day, 1.5g pro/kg/day isonitrogenous, isocaloric diets	3/22 (14)	2/22 (9)	4.0 ± 2.81 (per patient)	4.6 ± 2.81 (per patient)
24) Beale 2008	SIRS patients N=55	C.Random: no ITT: yes Blinding: double (9)	Intestamin (30 g glutamine) +Reconvan (10 g glutamine/L, 6.7 gm arginine/L), 98 g pro/L vs. control supplement +Fresubin 38 g pro/L. Both received 20% IV glucose nonisonitrogenous, isocaloric diets	ICU 6/27 (21) Hospital 7/27 (25) 28-day 5/27 (18) 6-month 10/27 (36)	ICU 4/27 (15) Hospital 7/28 (25) 28-day 3/28 (11) 6-month 8/27 (30)	NR	NR

Table 1. Randomized studies evaluating diets supplemented with arginine and other nutrients in critically ill patients (continued)

Study	Length of Stay (days)		Duration of Ventilation (days)	
	Arginine	Control	Arginine	Control
1) Cerra 1990	36.7 ± 8.5	54.7 ± 10.5	NR	NR
2) Gottschlich 1990	NR	NR	9 ± 4.5	10 ± 2.5
3) Brown 1994	NR	NR	NR	NR
4) Moore 1994	ICU 5.3 ± 0.8 Hospital 14.6 ± 1.3	ICU 8.6 ± 3.1 Hospital 17.2 ± 2.8	1.9 ± 0.9	5.3 ± 3.1
5) Bower 1995	Hospital 27.6 ± 23	Hospital 30.9 ± 26	NR	NR

6) Kudsk 1996*	ICU 5.8 ± 1.8 Hospital 18.3 ± 2.8	ICU 9.5 ± 2.3 Hospital 32.6 ± 7	2.4 ± 1.3	5.4 ± 2.0
7) Engel 1997	ICU 19 ± 7.4 Hospital NR	ICU 20.5 ± 5.3 Hospital NR	14.8 ± 5.6	16 ± 5.6
8) Mendez 1997	ICU 18.9 ± 20.7 Hospital 34 ± 21.2	ICU 11.1 ± 6.7 Hospital 21.9 ± 11	16.5 ± 19.4	9.3 ± 6
9) Rodrigo 1997	ICU 8 ± 7.3 Hospital NR	ICU 10 ± 2.7 Hospital NR	NR	NR
10) Saffle 1997	Hospital 37 ± 4	Hospital 38 ± 4	22 ± 3	21 ± 2
11) Weimann 1998	ICU 31.4 ± 23.1 Hospital 70.2 ± 53	ICU 47.4 ± 32.8 Hospital 58.1 ± 30	21.4 ± 10.8	27.8 ± 14.6
12) Atkinson 1998	ICU 10.5 ± 13.1 Hospital 20.6 ± 26	ICU 12.2 ± 23.2 Hospital 23.2 ± 32	8 ± 11.1	9.4 ± 17.7
13) Galban 2000	ICU 18.2 ± 12.6 Hospital NR	ICU 16.6 ± 12.9 Hospital NR	12.4 ± 10.4	12.2 ± 10.3

14) Capparos 2001	ICU 15 (9.8-25) Hospital 29 (16.8-51)	ICU 13 (8.8-20.3) Hospital 26 (17.8-42)	10 (5-18)	9 (5-14)
15) Conejero 2002	14 (4-63)	15(4-102)	14 (5-25)	14 (5-29)
16) Dent 2003	ICU 14.8 ± 19.6 Hospital 25.4 ± 26	ICU 12 ± 10.9 Hospital 20.9 ± 17	14.3 ± 22.4	10.8 ± 12.8
17) Bertolini 2003**	13.5 (9-26)	15 (11-29)	NR	NR
18) Chuntrasakul 2003	ICU 3.4 ± 5.8 Hospital 44.9 ± 30.2	ICU 7.8 ± 13.6 Hospital 28.8 ± 25.7	2.7 ± 5.2	7.4 ± 1.3
19) Tsuei 2004***	ICU 13 ± 6 (13) WMD -3.00, 95% CI -9.75, 3.75, p=0.38 Hospital 22 ± 9 (13) WMD -5.00, 95% CI -16.17, 6.17, p=0.38	ICU 16 ± 10 (11) Hospital 27 ± 17 (11)	10 ± 5 (13) WMD -4.00, 95% CI -10.50, 2.50, p=0.23	14 ± 10 (11)
20) Kieft 2005	ICU 7 (4-14) Hospital 20 (10-35)	ICU 8 (5-16) Hospital 20 (10-34)	6 (3-12)	6 (3-12)
21) Pearce 2006	ICU 11.0 ± 9.5 Hospital 19.1 ± 14.4	ICU 4.0 ± 3.6 Hospital 13.4 ± 11.1	NR	NR

22) Wibbenmeyer 2006	NR	NR	Longer in experimental group; specific numeric data not reported	
23) Kuhls 2007	ICU 27.8 ± 17.82 (22) Hospital 40.0 ± 23.45 (22)	ICU 22.4 ± 17.35 (22) Hospital 30.3 ± 22.98 (22)	23.1 ± 12.66 (22)	20.9 ± 12.66 (22)
24) Beale 2008	ICU 16.6 ± 14.8 Hospital 43.8 ± 36.6	ICU 13.4 ± 11.5 Hospital 31.3 ± 27.2	NR	NR

**Mortality data was ITT, data on infections was non ITT*
***Bertolini data not included in meta-analysis as control formula was Parenteral Nutrition, not an enteral formula.*
****Kuhls 2007: data pertaining to* ß hydroxyl methyl butyrate (HMB) supplement vs none not shown here, refer to section 6.5 Other EN Formulas for more details

C.Random: Concealed randomization NR: Not Reported ITT: intent to treat
‡ Hospital mortality reported or presumed unless specified

Impact: 12.5 g/L arginine, ω 3 fatty acids, ribonucleic acid and 55.8 gm protein/litre
Immun-Aid: 14 g/L arginine, glutamine, BCAA, ω 3 fatty acids, nucleic acids, Vit E, selenium, zinc and 80gms protein/litre
Perative: 6.8 g/L arginine, ω 3 fatty acids, Vit E, beta Carotene, zinc and selenium and 66 gms protein/litre
Optimental: 5.5 g/L arginine, ω 3 fatty acids, VitC, E, beta-carotene and 51 gms protein/litre
Stresson: 9g/L arginine, 13 g/L glutamine, ω 3 fatty acids, Vitamin E, C, beta-carotene, 75g protein/litre
Crucial: 10 g/L arginine, ω 3 fatty acids, VitC, E, 67 g protein/litre.

Figure 1a. Mortality (with quality sub-analyses)

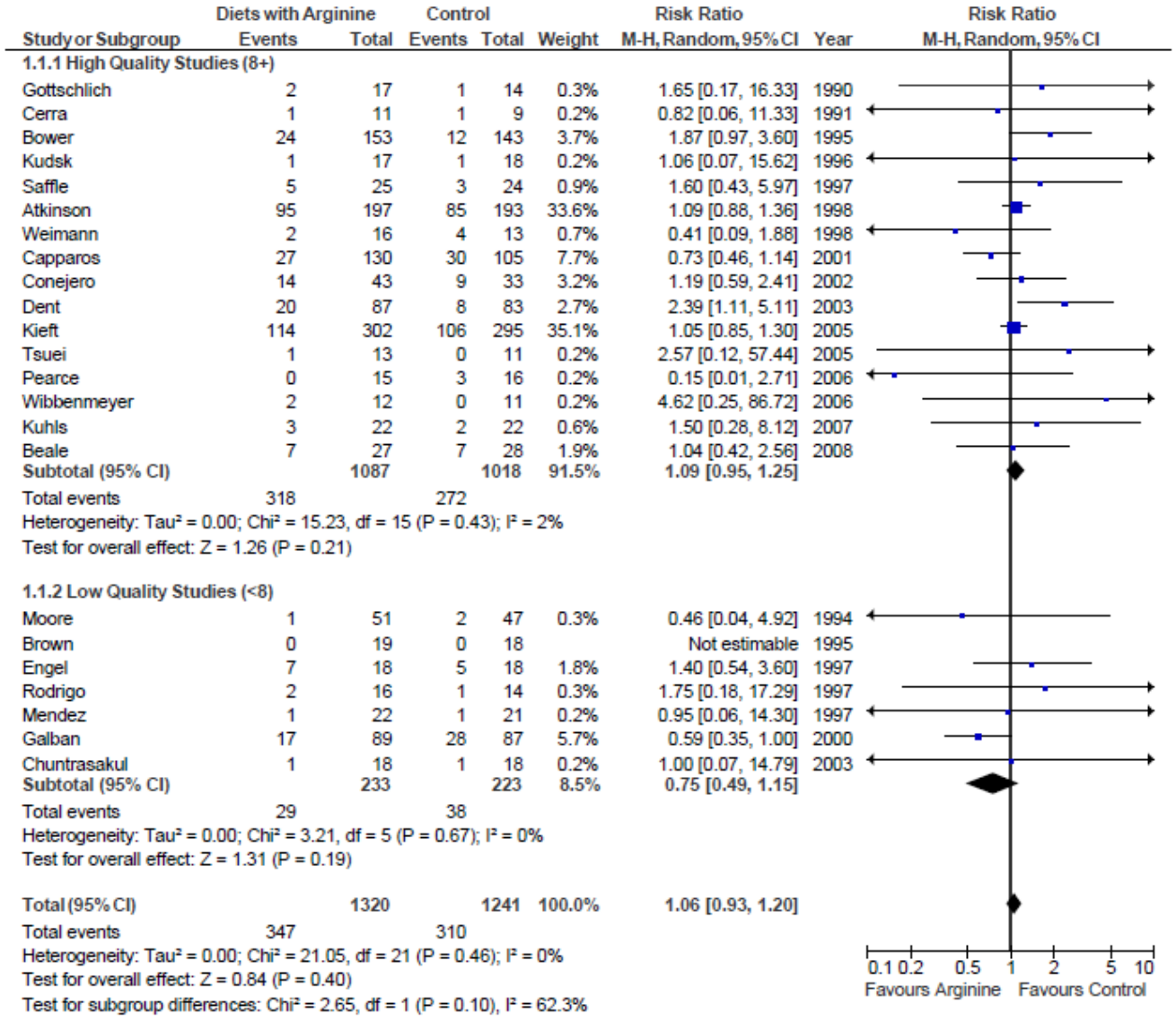


Figure 1b. Mortality (with quality sub-analyses; excluding Tsuei)

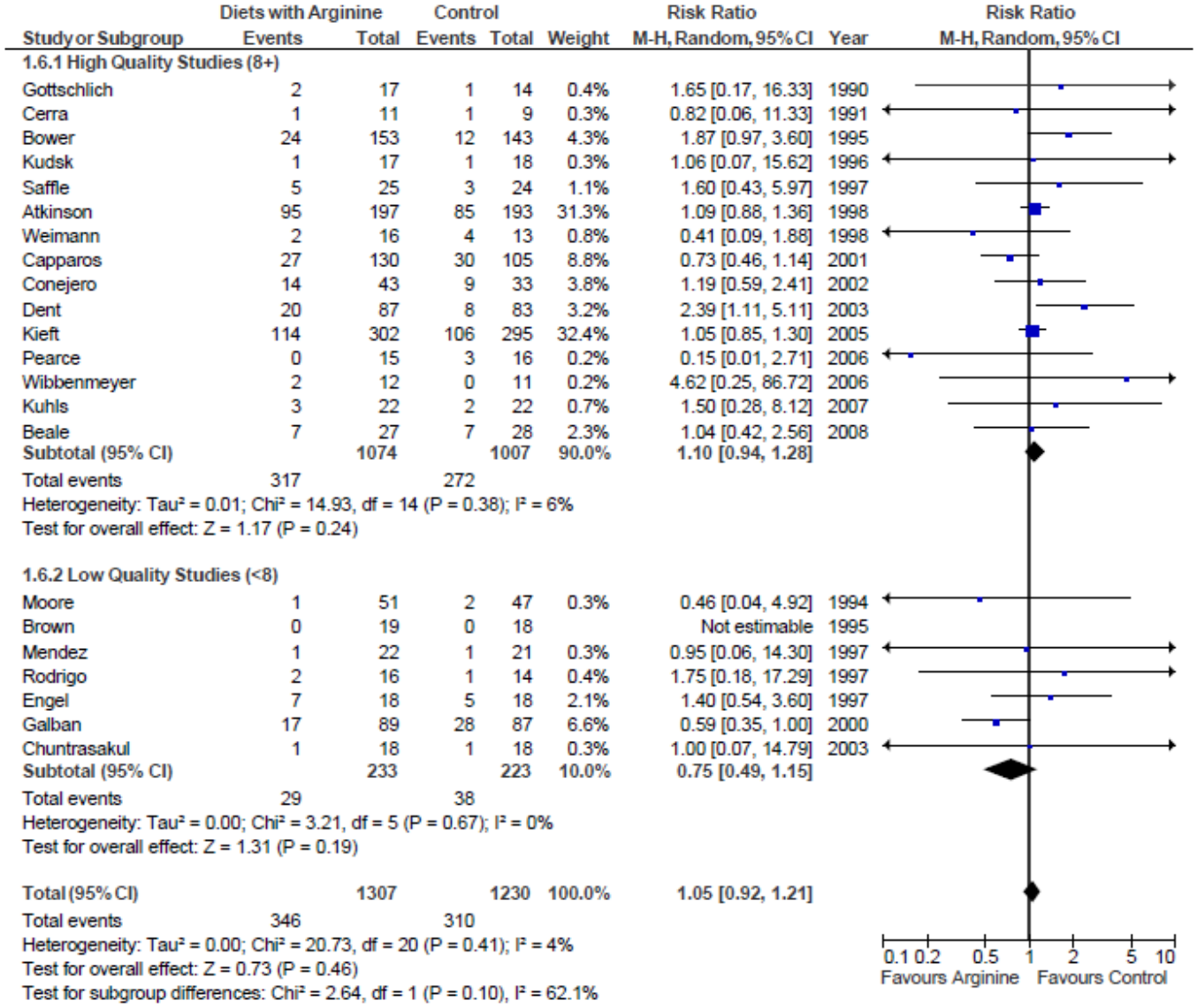


Figure 2a. Mortality (with trauma/non-trauma sub-analyses)

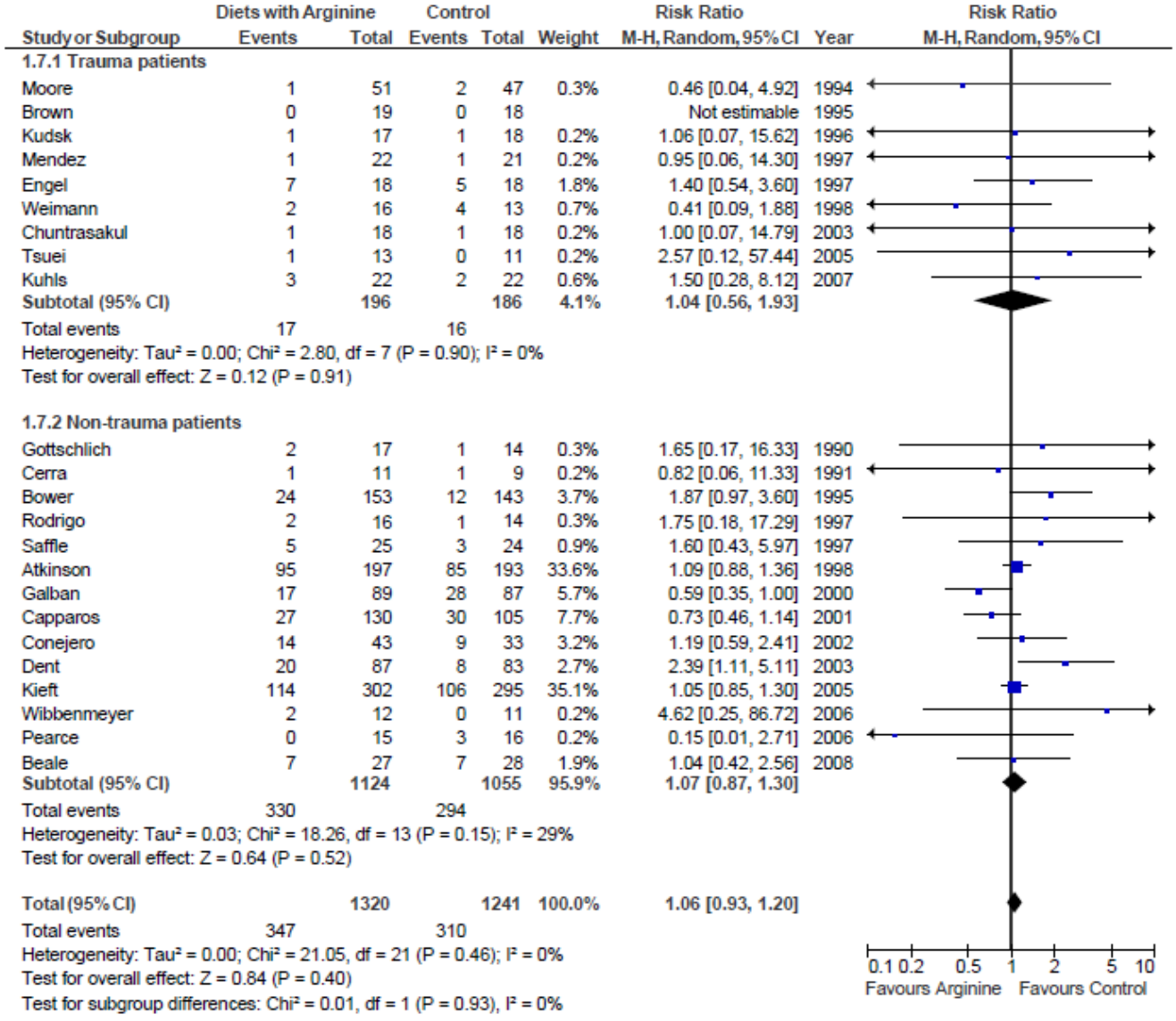


Figure 2b. Mortality in trauma patients (with trauma/non-trauma sub-analyses; excluding Tsuei)

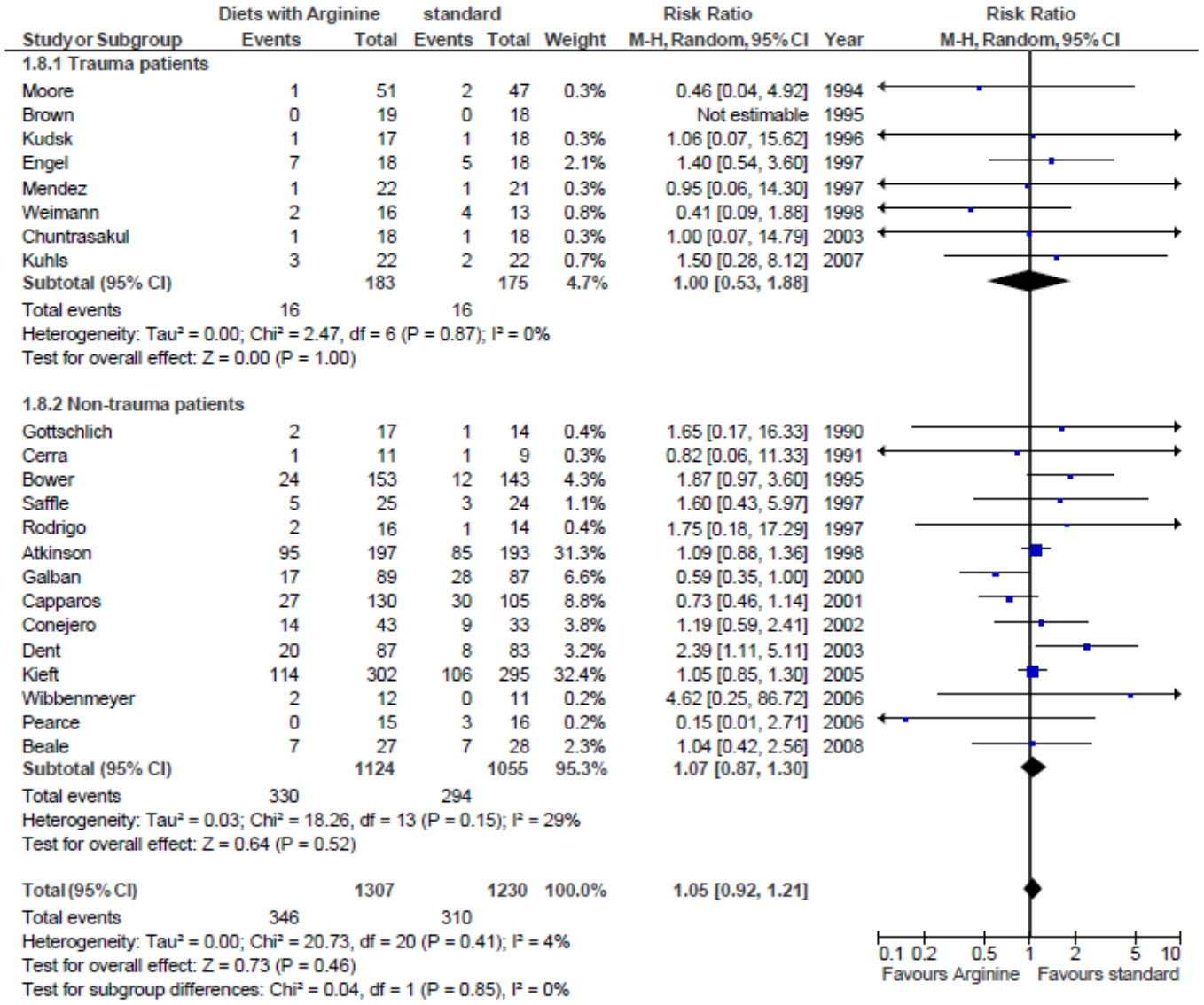


Figure 3a. Infectious complications (with quality sub-analyses)

Study or Subgroup	Diets wih Arginine Events	Total	standard Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.2.1 High Quality Studies (8+)							
Bower	86	153	90	143	15.1%	0.89 [0.74, 1.08]	1995
Kudsk	5	16	11	17	3.1%	0.48 [0.22, 1.08]	1996
Capparos	64	130	37	105	10.8%	1.40 [1.02, 1.91]	2001
Conejero	11	43	17	33	4.9%	0.50 [0.27, 0.91]	2002
Dent	57	87	52	83	13.7%	1.05 [0.83, 1.31]	2003
Kieft 2005	130	302	123	295	15.1%	1.03 [0.86, 1.24]	2005
Tsuei	8	13	6	11	4.0%	1.13 [0.57, 2.25]	2005
Wibbenmeyer	9	12	7	11	5.6%	1.18 [0.68, 2.05]	2006
Subtotal (95% CI)		756		698	72.3%	**0.99 [0.83, 1.17]**	
Total events	370		343				
Heterogeneity: Tau² = 0.03; Chi² = 14.72, df = 7 (P = 0.04); I² = 52%							
Test for overall effect: Z = 0.16 (P = 0.87)							
1.2.2 Low Quality Studies (<8)							
Moore	9	51	10	47	3.1%	0.83 [0.37, 1.86]	1994
Brown	3	19	10	18	1.8%	0.28 [0.09, 0.87]	1995
Engel	6	18	5	18	2.2%	1.20 [0.45, 3.23]	1997
Rodrigo	5	16	3	14	1.5%	1.46 [0.42, 5.03]	1997
Mendez	19	22	12	21	8.3%	1.51 [1.01, 2.27]	1997
Galban	39	89	44	87	10.8%	0.87 [0.63, 1.19]	2000
Subtotal (95% CI)		215		205	27.7%	**0.97 [0.65, 1.45]**	
Total events	81		84				
Heterogeneity: Tau² = 0.12; Chi² = 10.91, df = 5 (P = 0.05); I² = 54%							
Test for overall effect: Z = 0.14 (P = 0.89)							
Total (95% CI)		971		903	100.0%	**0.99 [0.85, 1.15]**	
Total events	451		427				
Heterogeneity: Tau² = 0.03; Chi² = 25.16, df = 13 (P = 0.02); I² = 48%							
Test for overall effect: Z = 0.15 (P = 0.88)							
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%							

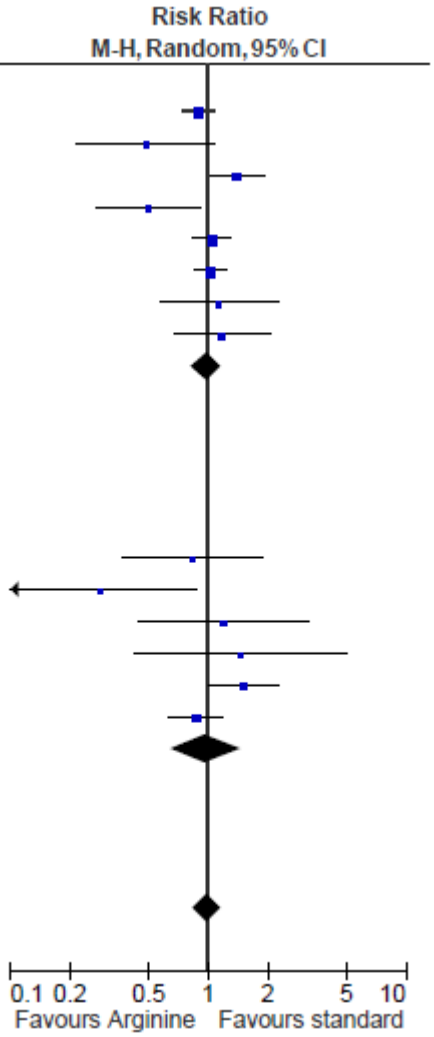


Figure 3b. Infectious complications (with quality sub-analyses; excluding Tsuei)

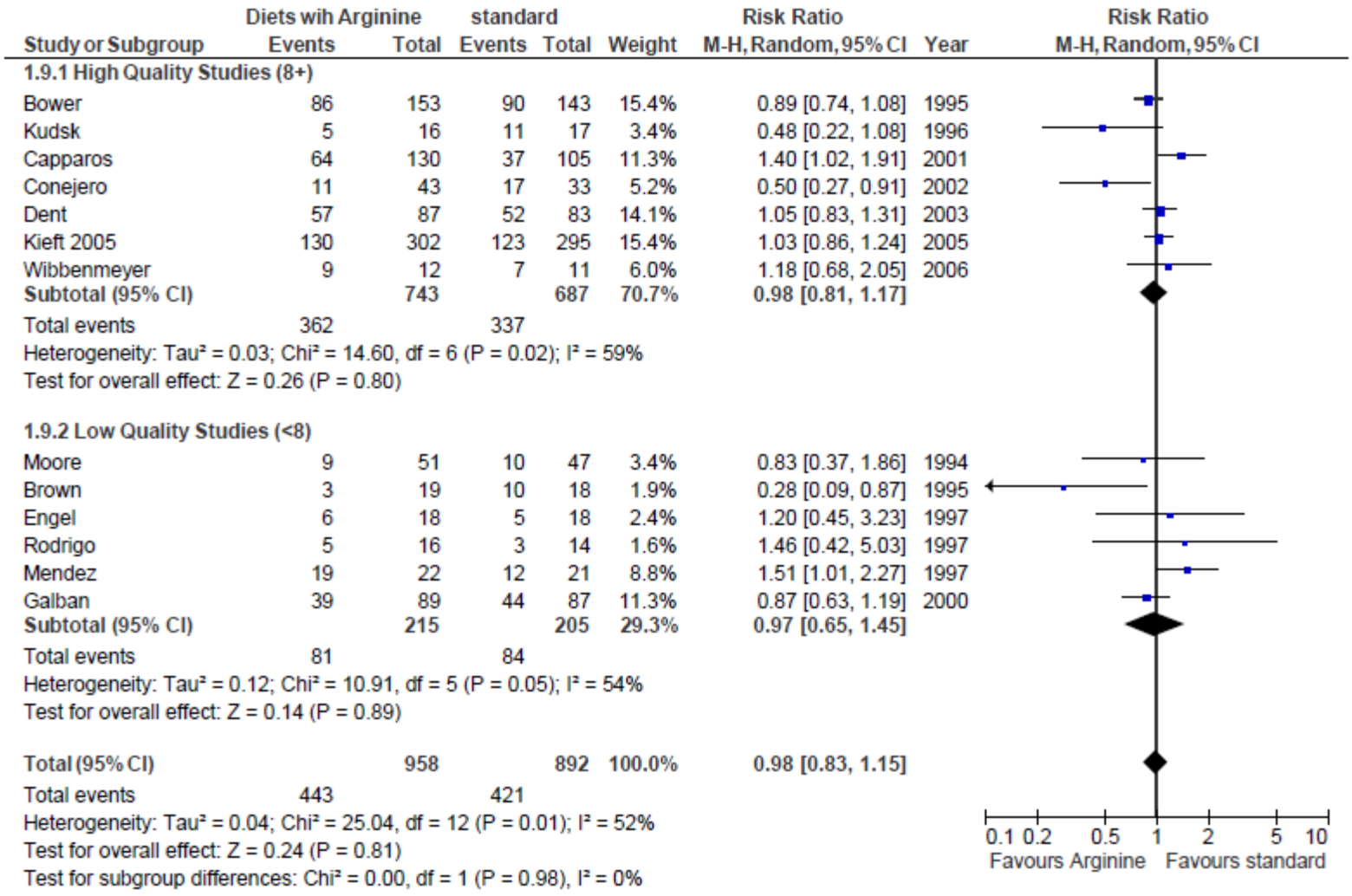


Figure 4a. Infectious complications (with trauma/non-trauma sub-analyses)

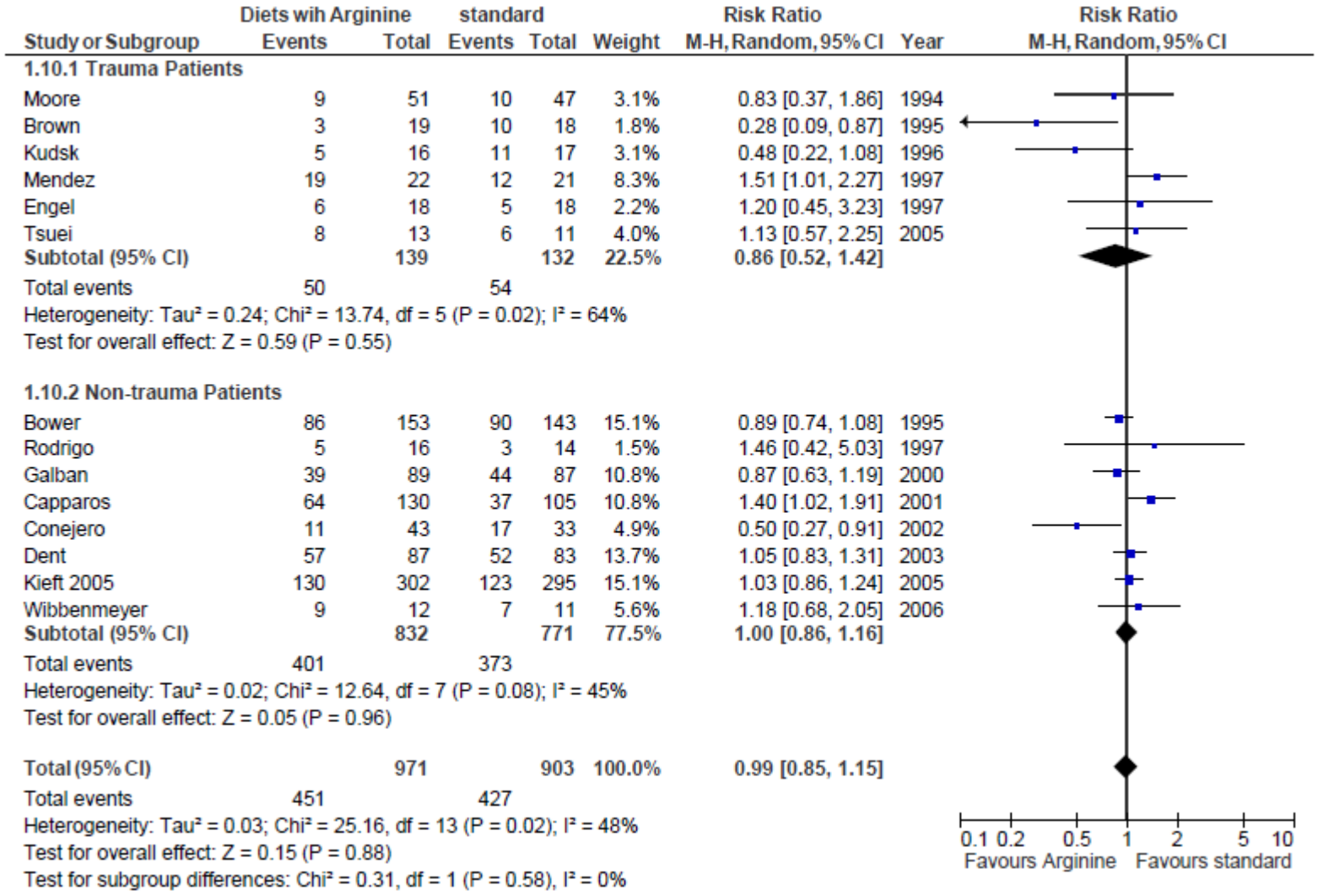


Figure 4b. Infectious complications (with trauma/non-trauma sub-analyses; excluding Tsuei)

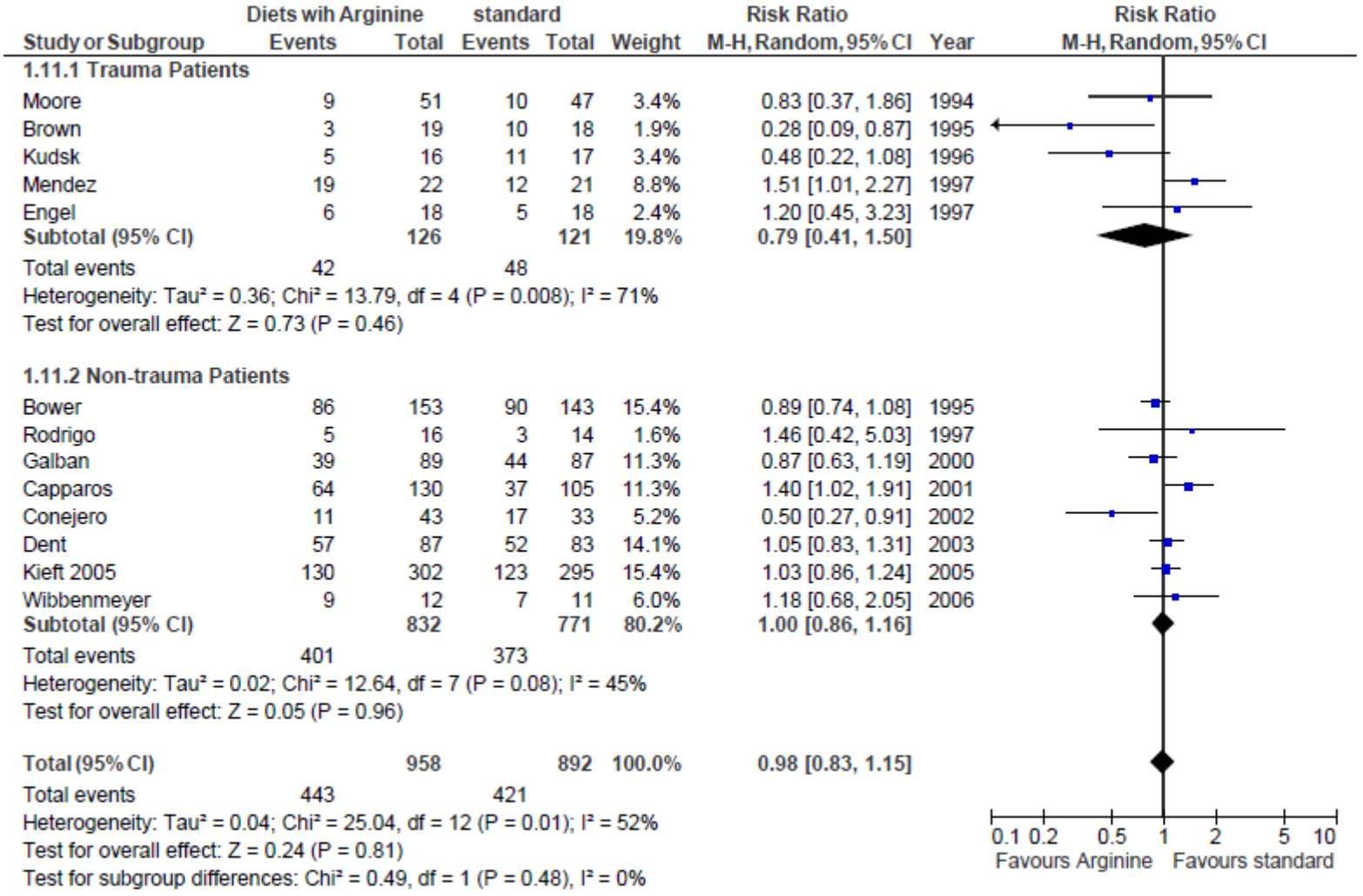
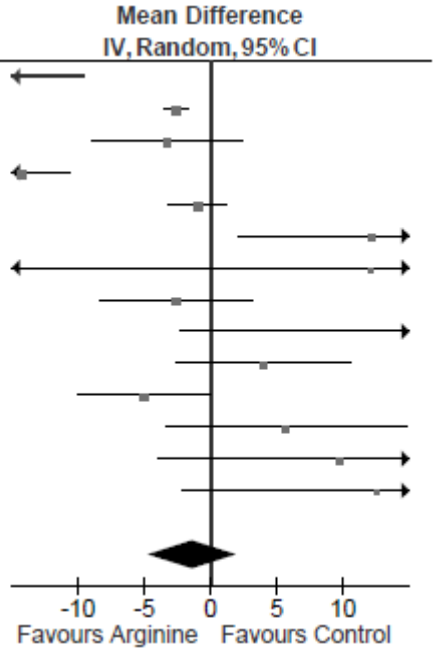


Figure 5a. Hospital LOS

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Cerra	36.7	8.5	11	54.7	10.5	9	6.8%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	12.0%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	9.0%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	10.6%	-14.30 [-17.90, -10.70]	1996
Saffle	37	4	25	38	4	24	11.5%	-1.00 [-3.24, 1.24]	1997
Mendez	34	21.2	22	21.9	11	21	5.8%	12.10 [2.07, 22.13]	1997
Weimann	70.2	53	16	58.1	30	13	1.1%	12.10 [-18.57, 42.77]	1998
Atkinson	20.6	26	197	23.2	32	193	8.9%	-2.60 [-8.39, 3.19]	1998
Chuntrasakul	45	30	18	29	26	18	2.6%	16.00 [-2.34, 34.34]	2003
Dent	25	26	87	21	17	83	8.2%	4.00 [-2.57, 10.57]	2003
Tsuei	22	9	61	27	17	55	9.5%	-5.00 [-10.03, 0.03]	2005
Pearce	19.1	14.4	15	13.4	11.1	16	6.4%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	4.0%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	3.7%	12.50 [-2.10, 27.10]	2008
Total (95% CI)			721			689	100.0%	-1.38 [-4.73, 1.97]	

Heterogeneity: Tau² = 24.16; Chi² = 83.24, df = 13 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.81 (P = 0.42)



Revised Figure 5b. Hospital LOS (excluding Tsuei)

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Cerra	36.7	8.5	11	54.7	10.5	9	7.6%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	12.9%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	9.9%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	11.5%	-14.30 [-17.90, -10.70]	1996
Mendez	34	21.2	22	21.9	11	21	6.5%	12.10 [2.07, 22.13]	1997
Saffle	37	4	25	38	4	24	12.4%	-1.00 [-3.24, 1.24]	1997
Atkinson	20.6	26	197	23.2	32	193	9.8%	-2.60 [-8.39, 3.19]	1998
Weimann	70.2	53	16	58.1	30	13	1.3%	12.10 [-18.57, 42.77]	1998
Dent	25	26	87	21	17	83	9.1%	4.00 [-2.57, 10.57]	2003
Chuntrasakul	45	30	18	29	26	18	3.0%	16.00 [-2.34, 34.34]	2003
Pearce	19.1	14.4	15	13.4	11.1	16	7.2%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	4.6%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	4.2%	12.50 [-2.10, 27.10]	2008
Total (95% CI)			660			634	100.0%	-0.89 [-4.53, 2.74]	

Heterogeneity: Tau² = 26.39; Chi² = 82.47, df = 12 (P < 0.00001); I² = 85%
Test for overall effect: Z = 0.48 (P = 0.63)

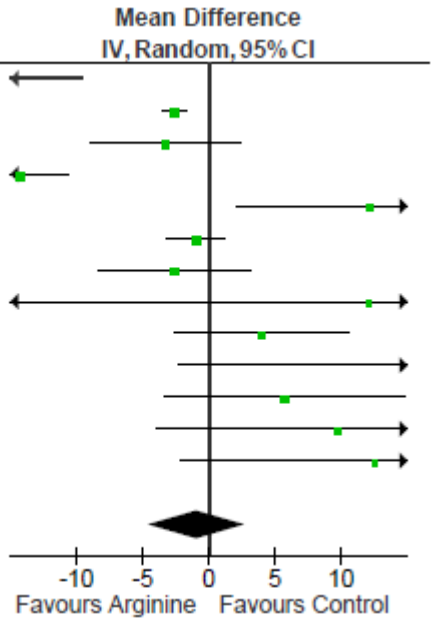


Figure 6a. ICU LOS

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Moore	5.3	0.8	51	8.6	3.1	47	14.6%	-3.30 [-4.21, -2.39]	1994
Kudsk	5.8	1.8	16	9.5	2.3	17	13.8%	-3.70 [-5.10, -2.30]	1996
Rodrigo	8	7.3	16	10	2.7	14	8.5%	-2.00 [-5.85, 1.85]	1997
Mendez	18.9	20.7	22	11.1	6.7	21	2.8%	7.80 [-1.31, 16.91]	1997
Engel	19	7.4	18	20.5	5.3	18	7.9%	-1.50 [-5.70, 2.70]	1997
Atkinson	10.5	13.1	197	12.2	23.2	193	8.7%	-1.70 [-5.45, 2.05]	1998
Weimann	31.4	23.1	16	47.4	32.8	13	0.6%	-16.00 [-37.12, 5.12]	1998
Galban	18.2	12.6	89	16.6	12.9	89	8.7%	1.60 [-2.15, 5.35]	2000
Dent	14.8	19.6	87	12	10.9	83	6.9%	2.80 [-1.94, 7.54]	2003
Chuntrasakul	3.4	5.8	18	7.8	13.6	18	4.4%	-4.40 [-11.23, 2.43]	2003
Tsuei	13	6	61	16	10	55	10.2%	-3.00 [-6.04, 0.04]	2005
Pearce	11	9.5	15	4	3.6	16	6.4%	7.00 [1.88, 12.12]	2006
Kuhls	27.8	17.82	22	22.4	17.35	22	2.3%	5.40 [-4.99, 15.79]	2007
Beale	16.6	14.8	27	13.4	11.5	28	4.2%	3.20 [-3.82, 10.22]	2008
Total (95% CI)			655			634	100.0%	-0.77 [-2.46, 0.92]	

Heterogeneity: Tau² = 4.89; Chi² = 40.26, df = 13 (P = 0.0001); I² = 68%
Test for overall effect: Z = 0.89 (P = 0.37)

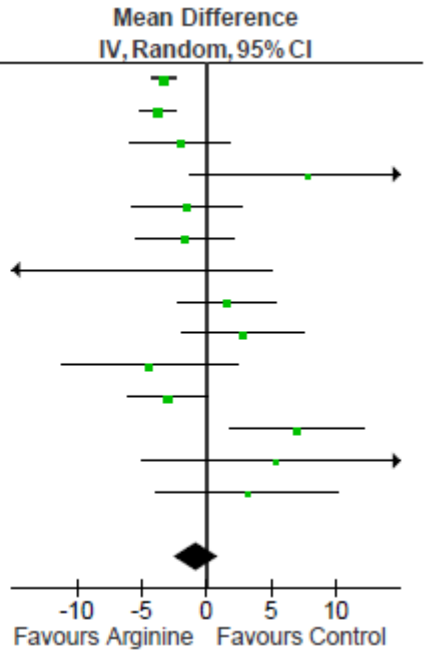


Figure 6b. ICU LOS (excluding Tsuei)

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Moore	5.3	0.8	51	8.6	3.1	47	15.5%	-3.30 [-4.21, -2.39]	1994
Kudsk	5.8	1.8	16	9.5	2.3	17	14.8%	-3.70 [-5.10, -2.30]	1996
Mendez	18.9	20.7	22	11.1	6.7	21	3.3%	7.80 [-1.31, 16.91]	1997
Engel	19	7.4	18	20.5	5.3	18	8.8%	-1.50 [-5.70, 2.70]	1997
Rodrigo	8	7.3	16	10	2.7	14	9.5%	-2.00 [-5.85, 1.85]	1997
Atkinson	10.5	13.1	197	12.2	23.2	193	9.7%	-1.70 [-5.45, 2.05]	1998
Weimann	31.4	23.1	16	47.4	32.8	13	0.7%	-16.00 [-37.12, 5.12]	1998
Galban	18.2	12.6	89	16.6	12.9	89	9.7%	1.60 [-2.15, 5.35]	2000
Chuntrasakul	3.4	5.8	18	7.8	13.6	18	5.1%	-4.40 [-11.23, 2.43]	2003
Dent	14.8	19.6	87	12	10.9	83	7.9%	2.80 [-1.94, 7.54]	2003
Pearce	11	9.5	15	4	3.6	16	7.3%	7.00 [1.88, 12.12]	2006
Kuhls	27.8	17.82	22	22.4	17.35	22	2.7%	5.40 [-4.99, 15.79]	2007
Beale	16.6	14.8	27	13.4	11.5	28	4.9%	3.20 [-3.82, 10.22]	2008
Total (95% CI)			594			579	100.0%	-0.44 [-2.31, 1.42]	

Heterogeneity: Tau² = 5.60; Chi² = 40.21, df = 12 (P < 0.0001); I² = 70%

Test for overall effect: Z = 0.47 (P = 0.64)

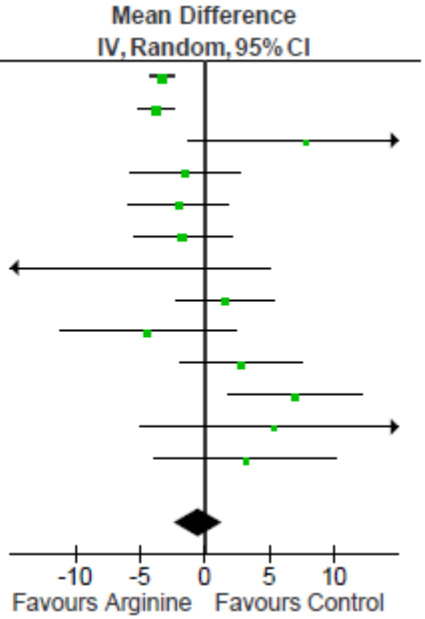


Figure 7a. Ventilated days

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Gottschlich	9	4.5	17	10	2.5	14	10.1%	-1.00 [-3.51, 1.51]	1990
Moore	1.9	0.9	51	5.3	3.1	47	13.9%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	13.5%	-3.00 [-4.14, -1.86]	1996
Mendez	16.5	19.4	22	9.3	6	21	2.4%	7.20 [-1.30, 15.70]	1997
Saffle	22	3	25	21	2	24	12.9%	1.00 [-0.42, 2.42]	1997
Engel	14.8	5.6	18	16	5.6	18	7.5%	-1.20 [-4.86, 2.46]	1997
Weimann	21.4	10.8	16	27.8	14.6	13	1.9%	-6.40 [-15.94, 3.14]	1998
Atkinson	8	11.1	197	9.4	17.7	193	9.1%	-1.40 [-4.34, 1.54]	1998
Galban	12.4	10.4	89	12.2	10.3	87	8.8%	0.20 [-2.86, 3.26]	2000
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.5%	-4.70 [-11.38, 1.98]	2003
Dent	14.3	22.4	87	10.8	12.8	83	4.7%	3.50 [-1.95, 8.95]	2003
Tsuei	10	5	61	14	10	55	9.1%	-4.00 [-6.93, -1.07]	2005
Kuhls	23.1	12.66	22	20.9	12.66	22	2.9%	2.20 [-5.28, 9.68]	2007
Total (95% CI)			639			612	100.0%	**-1.30 [-2.72, 0.12]**	

Heterogeneity: Tau² = 3.57; Chi² = 44.55, df = 12 (P < 0.0001); I² = 73%
Test for overall effect: Z = 1.79 (P = 0.07)

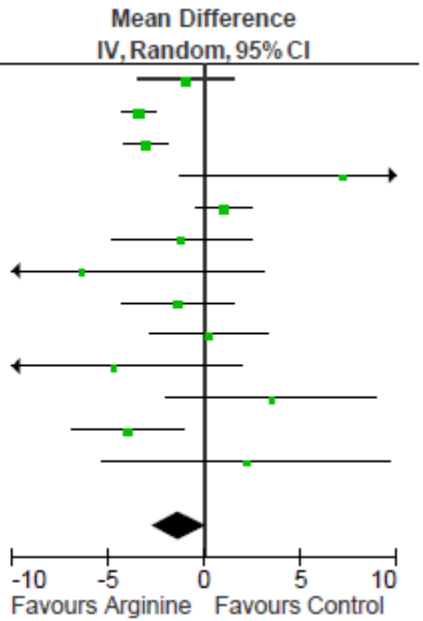
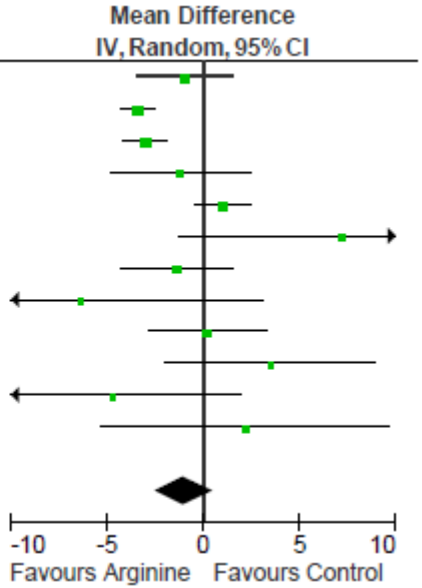


Figure 7b. Ventilated days (excluding Tsuei)

	Diets with Arginine			Control				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Gottschlich	9	4.5	17	10	2.5	14	11.1%	-1.00 [-3.51, 1.51]	1990
Moore	1.9	0.9	51	5.3	3.1	47	15.1%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	14.7%	-3.00 [-4.14, -1.86]	1996
Engel	14.8	5.6	18	16	5.6	18	8.3%	-1.20 [-4.86, 2.46]	1997
Saffle	22	3	25	21	2	24	14.0%	1.00 [-0.42, 2.42]	1997
Mendez	16.5	19.4	22	9.3	6	21	2.6%	7.20 [-1.30, 15.70]	1997
Atkinson	8	11.1	197	9.4	17.7	193	10.0%	-1.40 [-4.34, 1.54]	1998
Weimann	21.4	10.8	16	27.8	14.6	13	2.2%	-6.40 [-15.94, 3.14]	1998
Galban	12.4	10.4	89	12.2	10.3	87	9.7%	0.20 [-2.86, 3.26]	2000
Dent	14.3	22.4	87	10.8	12.8	83	5.2%	3.50 [-1.95, 8.95]	2003
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.9%	-4.70 [-11.38, 1.98]	2003
Kuhls	23.1	12.66	22	20.9	12.66	22	3.3%	2.20 [-5.28, 9.68]	2007
Total (95% CI)			578			557	100.0%	-1.02 [-2.53, 0.49]	

Heterogeneity: Tau² = 3.72; Chi² = 42.90, df = 11 (P < 0.0001); I² = 74%

Test for overall effect: Z = 1.32 (P = 0.19)