4.1a EN Composition: Diets Supplemented with Arginine and Select Other Nutrients

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 27 studies reviewed, 5 level 1 studies and 22 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 formula. The Kuhls 2007 study had two interventions including 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: HMB. There was only one study in which arginine was given without other select nutrients (Tsuei 2004***), hence sensitivity analyses were done without this study.

Mortality: All 27 studies reported on mortality and when the results of the 26 studies (Bertolini 2003 excluded) were aggregated, there was no effect on mortality (RR 1.05, 95% CI 0.93, 1.19, p=0.44, 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 0.93, 1.19, p=0.46, heterogeneity I^2=0%; 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 1.08, 95% CI 0.95, 1.23, p=0.23, heterogeneity I^2=0%; figure 1a) and excluding the Tsuei study (RR 1.08, 95% CI 0.94, 1.26, p=0.28, heterogeneity I^2=0%; 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 0.76, 95% CI 0.49, 1.16, p=0.20, heterogeneity I^2=0%; figure 1a). The difference between these two subgroups was not statistically significant (p=0.11). 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 1.05, 95% CI 0.87, 1.26, p=0.60, heterogeneity I^2=21%; figure 2a) were compared, there were no differences in mortality. The difference between these two subgroups was not statistically significant (p=0.88). 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: 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 -1.43, 95% -4.95, 2.10, p=0.43, heterogeneity I^2=83%; figure 5a) and when the Tsuei study was excluded from the analysis (WMD -0.94, 95% CI -4.79, 2.91, p=0.63, p=0.63, heterogeneity I^2=84%; figure 5b); or on ICU length of stay when the Tsuei study was included in the analysis (WMD -0.77, 95% CI -2.31, 0.78, p=0.33, heterogeneity I^2=70%; figure 6a) or when the Tsuei study was excluded from the analysis (WMD -0.50, 95% CI -2.17, 1.17, p=0.56, heterogeneity I^2=72%; 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 significant reduction in mechanical ventilation when the Tsuei study was included in the analysis (WMD -1.67, 95% CI -2.95, -0.39, p=0.01, heterogeneity I^2=63%; figure 7a) and a trend towards a reduction when the Tsuei study was excluded from the analysis (WMD -1.40, 95% CI -2.78, -0.03, p=0.05, heterogeneity I^2=65%; 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 and ICU length of stay
4) Diets supplemented with arginine and other nutrients may be associated with a reduction in duration of mechanical ventilation in critically ill patients, but the presence of significant heterogeneity limits this inference.

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)	0/11 (0) RR 2.57, 95% CI 0.12, 57.44, p=0.55	8/13 (61)	6/11 (55) RR 1.13, 95% CI 0.57, 2.25, p=0.73
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 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
25) Khorana 2009	Moderate to severe head injury patients requiring neurosurgery N=40	C.Random: yes ITT: yes Blinding: double (12)	EN formula Neomune (polymeric, 12.5 g/L arg, 6.25 g/L glutamine) vs EN formula Panenteral (polymeric) modified with the addition of protein.	0/20	0/20	**Wound infection** 0/20 **Chest infection** 7/20 (35) **UTI** 0/20 **GI bleed** 1/20 (5)	**Wound infection** 0/20 **Chest infection** 12/20 (60) **UTI** 1/20 (5) **GI bleed** 0/20
26) Iamsirisaengthong 2017	Major burn patients (>20% TBSA) N=20	C.Random: no ITT: Yes Blinding: no (5)	Neomune (25% protein, gln and arg containing) vs blenderized diet (17% protein). Isocaloric, non-isonitrogenous.	**Hospital** 1/10 (10%)	**Hospital** 1/10 (10%)	**Septic complications** 4/10 (40%) **Wound Healing (days)** 32.3 ± 14.3	**Septic complications** 7/10 (70%) **Wound Healing (days)** 38.3 ± 14.9
27) Nakamura 2020	Mixed ICU population (mostly non trauma) N=88	C.Random: Yes ITT: Yes Blinding: single (12)	Daily 3 grams HMB+14 grams arginine+14 grams of glutamine vs. standard EN	**28 days** 4/45 (8.7%)	**28 days** 6/43 (13.6%)	NA	NA

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 Mean ± SEM	10 ± 2.5 Mean ± SEM
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 (mean ± SEM)	**Hospital** 38 ± 4 (mean ± SEM)	22 ± 3 (mean ± SEM)	21 ± 2 (mean ± SEM)
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
25) Khorana 2009	**ICU** 9.6 days	**ICU** 9.3 days	NR	NR

26) Iamsirisaengthong 2017	**Hospital** 35.4 ± 15.2	**Hospital** 40.4 ± 15.2	NR	NR
27) Nakamura 2020	**Hospital** 21.9 ±8.8 **ICU** 5.4 ±3.5	**Hospital** 24.3 ±7.8, p=0.18 **ICU** 5.8 ±3.8, p=0.83	4.8±2.4	5.3±3.8, p=0.45

C.Random: Concealed randomization NR: Not Reported ITT: intent to treat LOS: Length of stay ICU: intensive care unit

**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.*
*** Tsuei 2004: excluded in sensitivity analyses as only study that gave arginine alone.
****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
‡ 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.
Neomune 48 g sachet: 2.5 g arginine, 1.25 g glutamine, fish oil, 12.5 g protein (Protein: 20% arginine, 10% glutamine; Fat: 20% fish oil) vs *study's prepared formula: 12.5 g/L arginine, 6.25 g/L glutamine, fish oils, 62.5 g/L of protein*

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

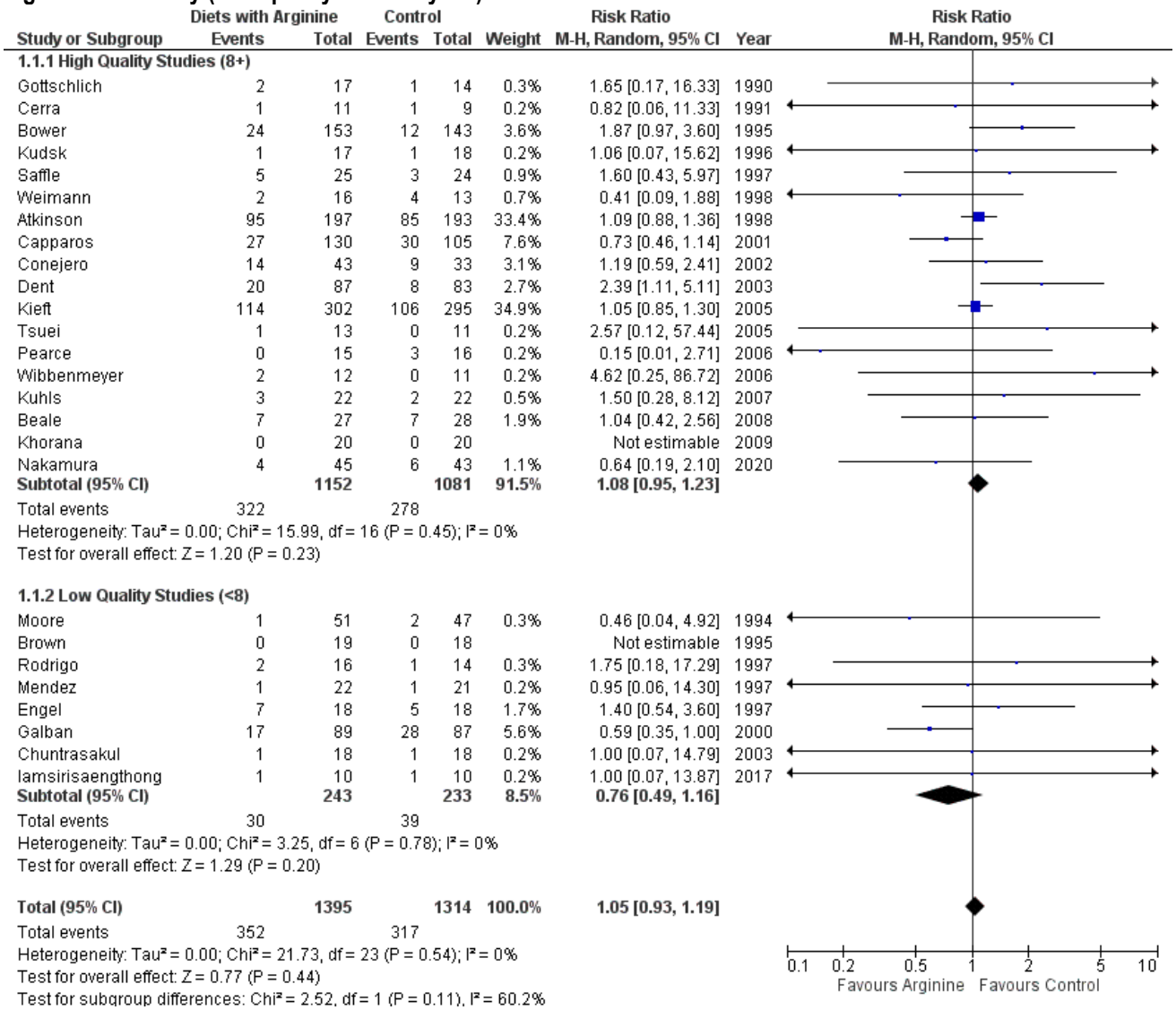


Figure 1b. Mortality (with quality sub-analyses; excluding Tsuei)

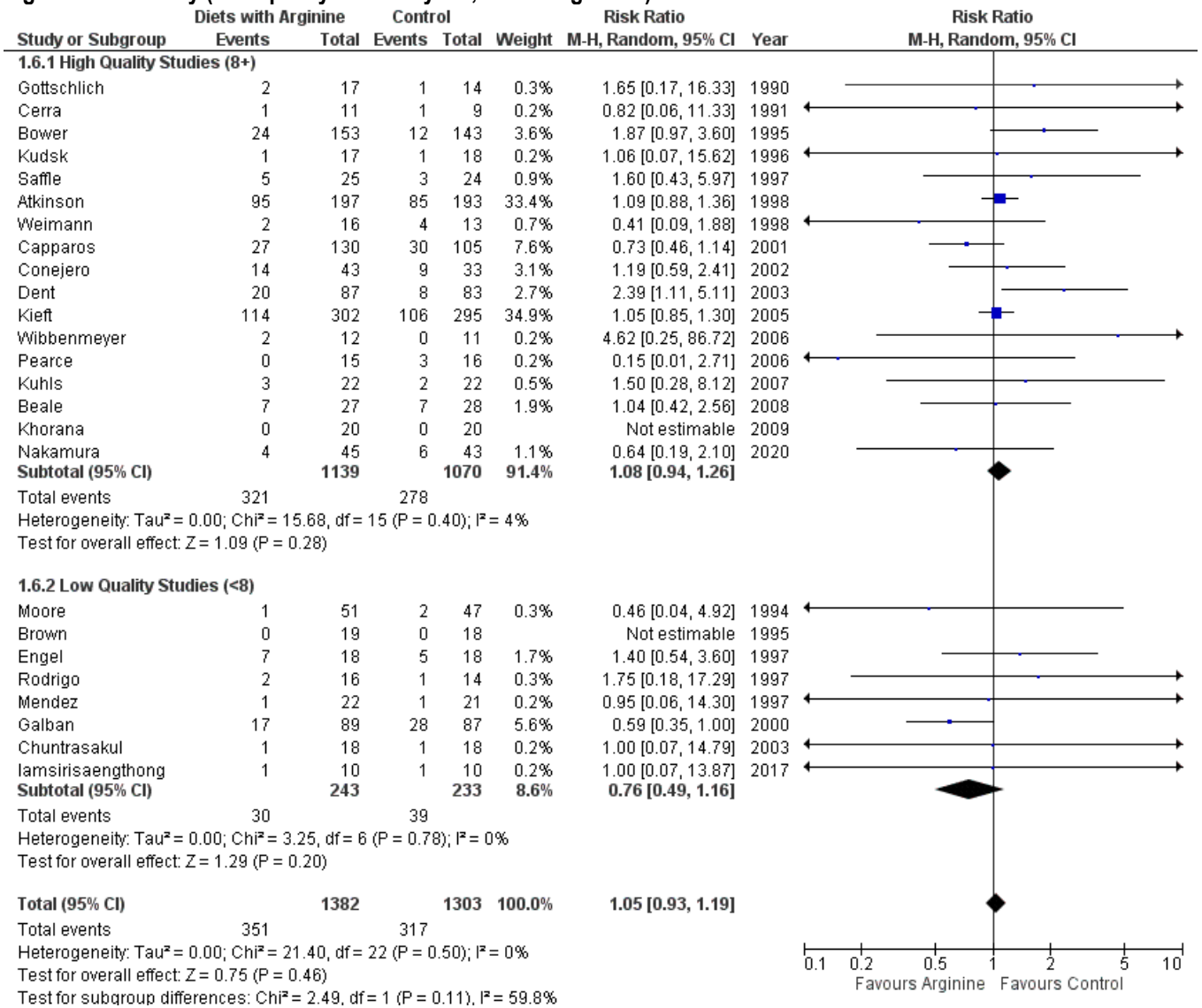


Figure 2a. Mortality (with trauma/non-trauma sub-analyses)

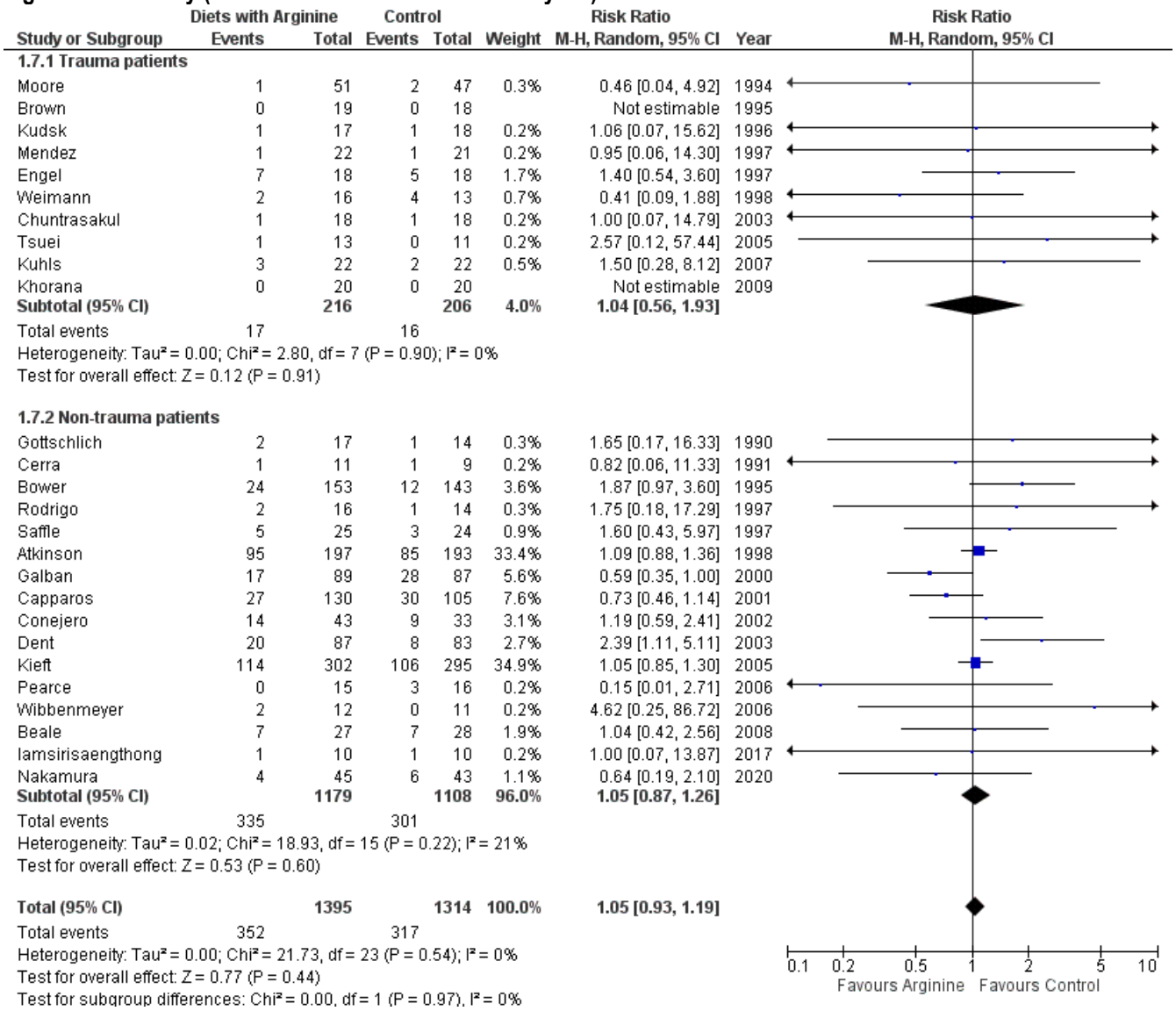


Figure 2b. Mortality in trauma patients (with trauma/non-trauma sub-analyses; excluding Tsuei)

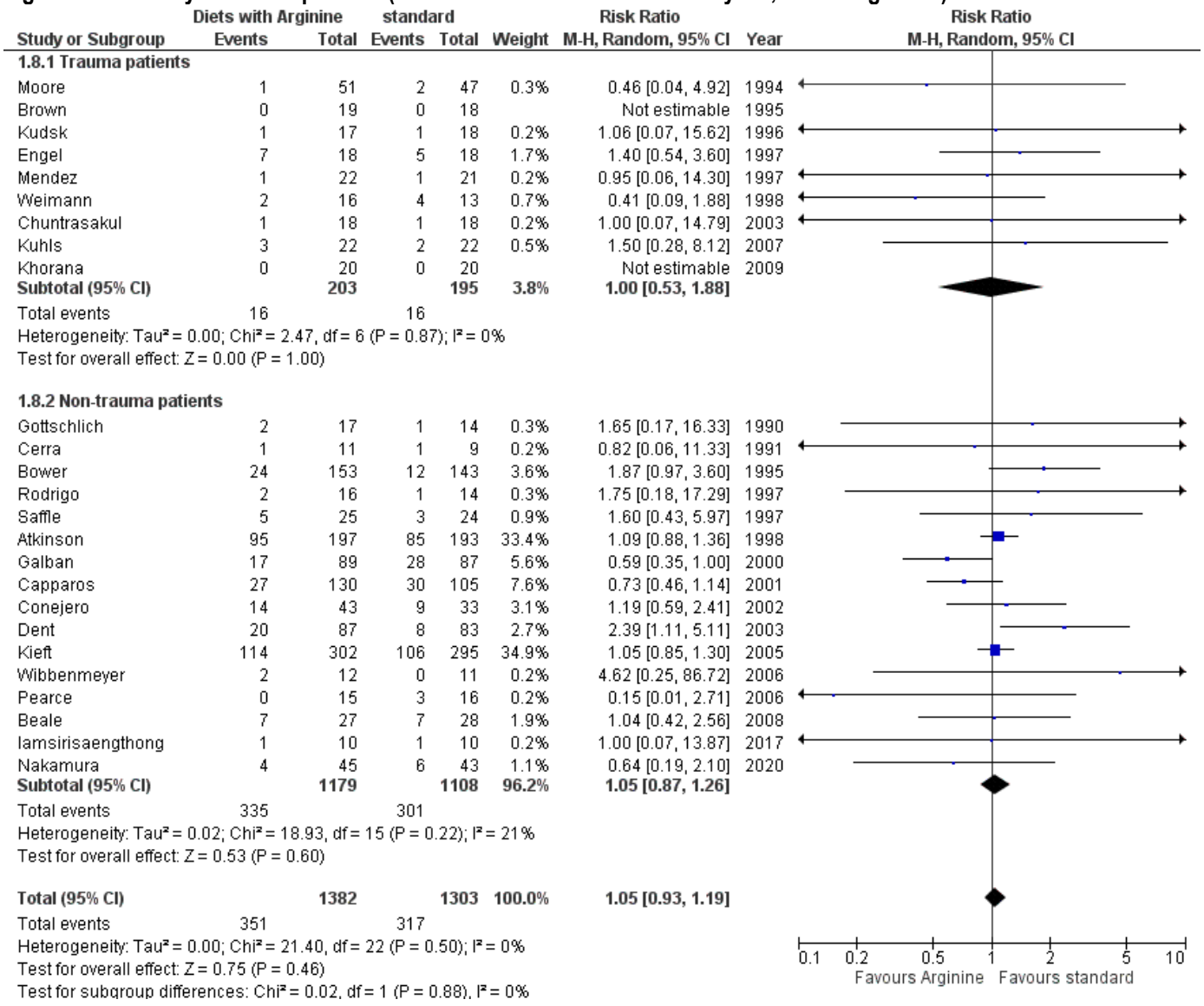


Figure 3a. Infectious complications (with quality sub-analyses)

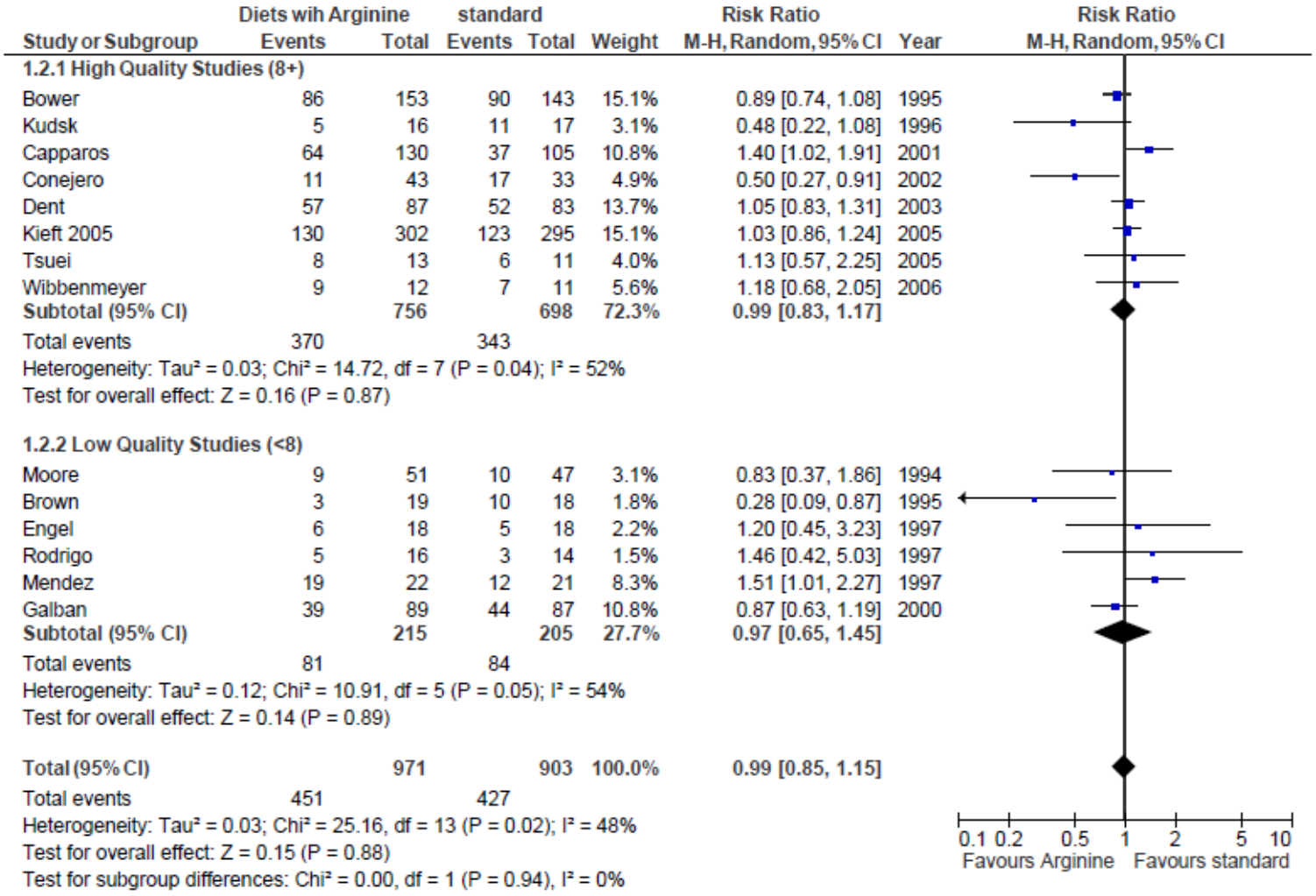


Figure 3b. Infectious complications (with quality sub-analyses; excluding Tsuei)

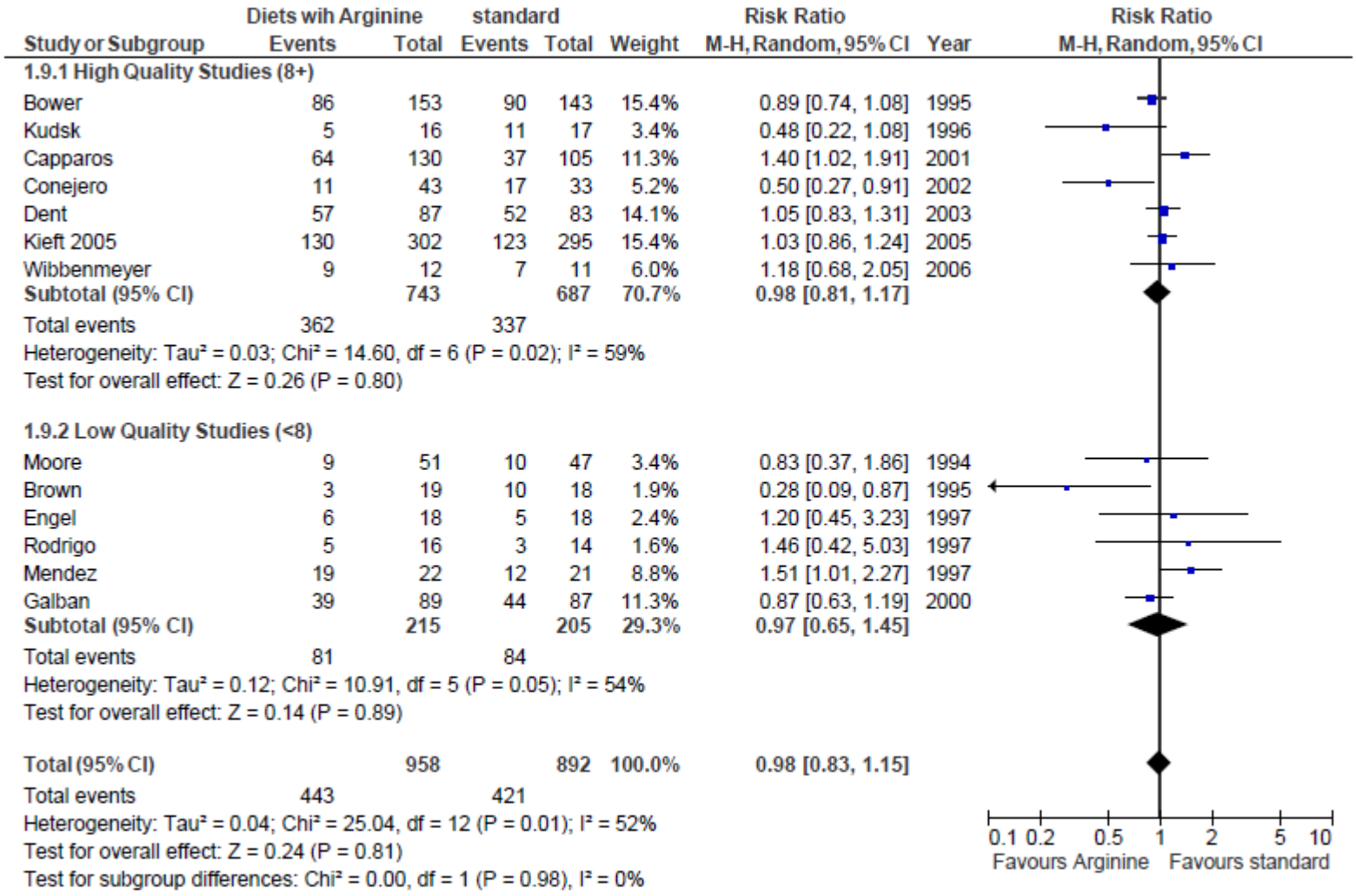


Figure 4a. Infectious complications (with trauma/non-trauma sub-analyses)

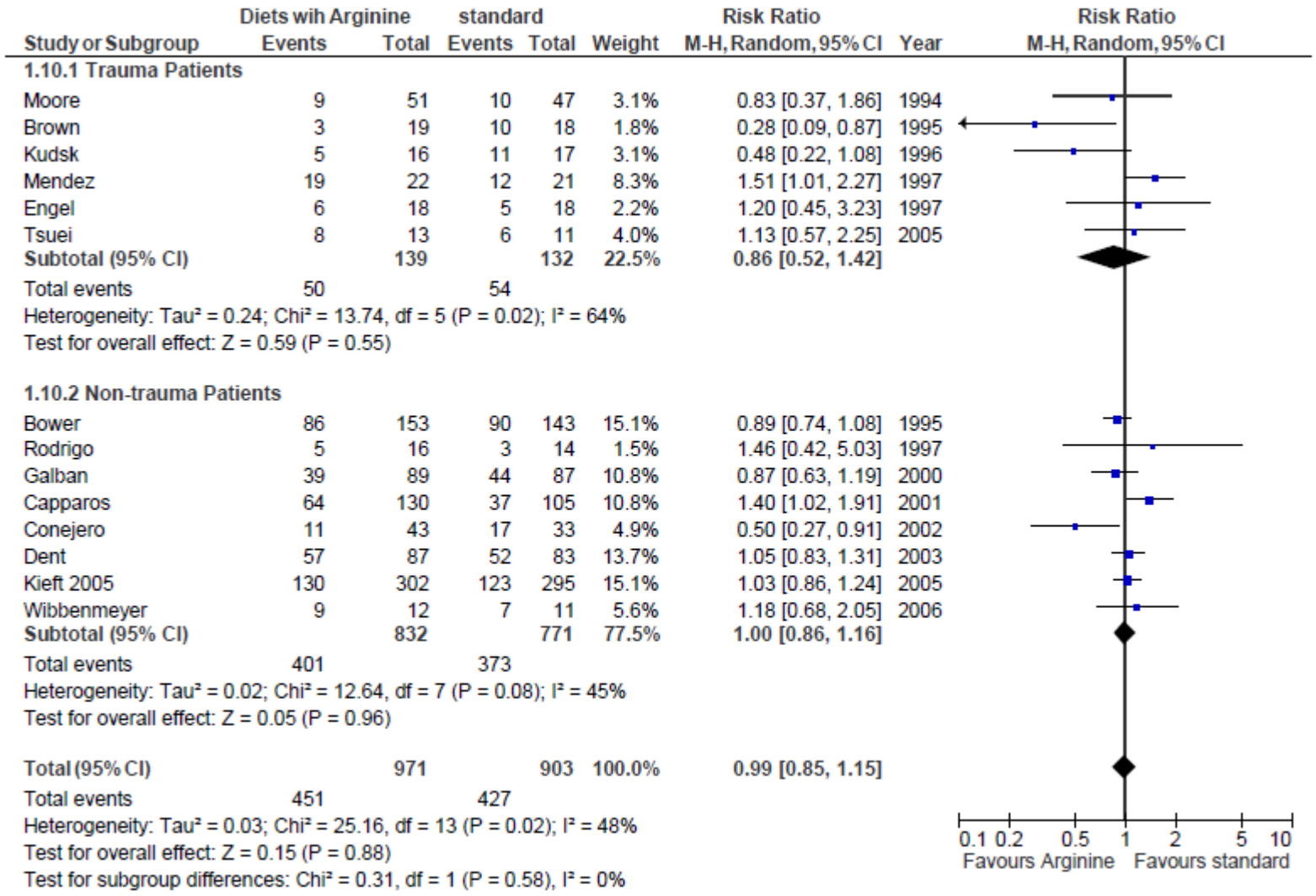


Figure 4b. Infectious complications (with trauma/non-trauma sub-analyses; excluding Tsuei)

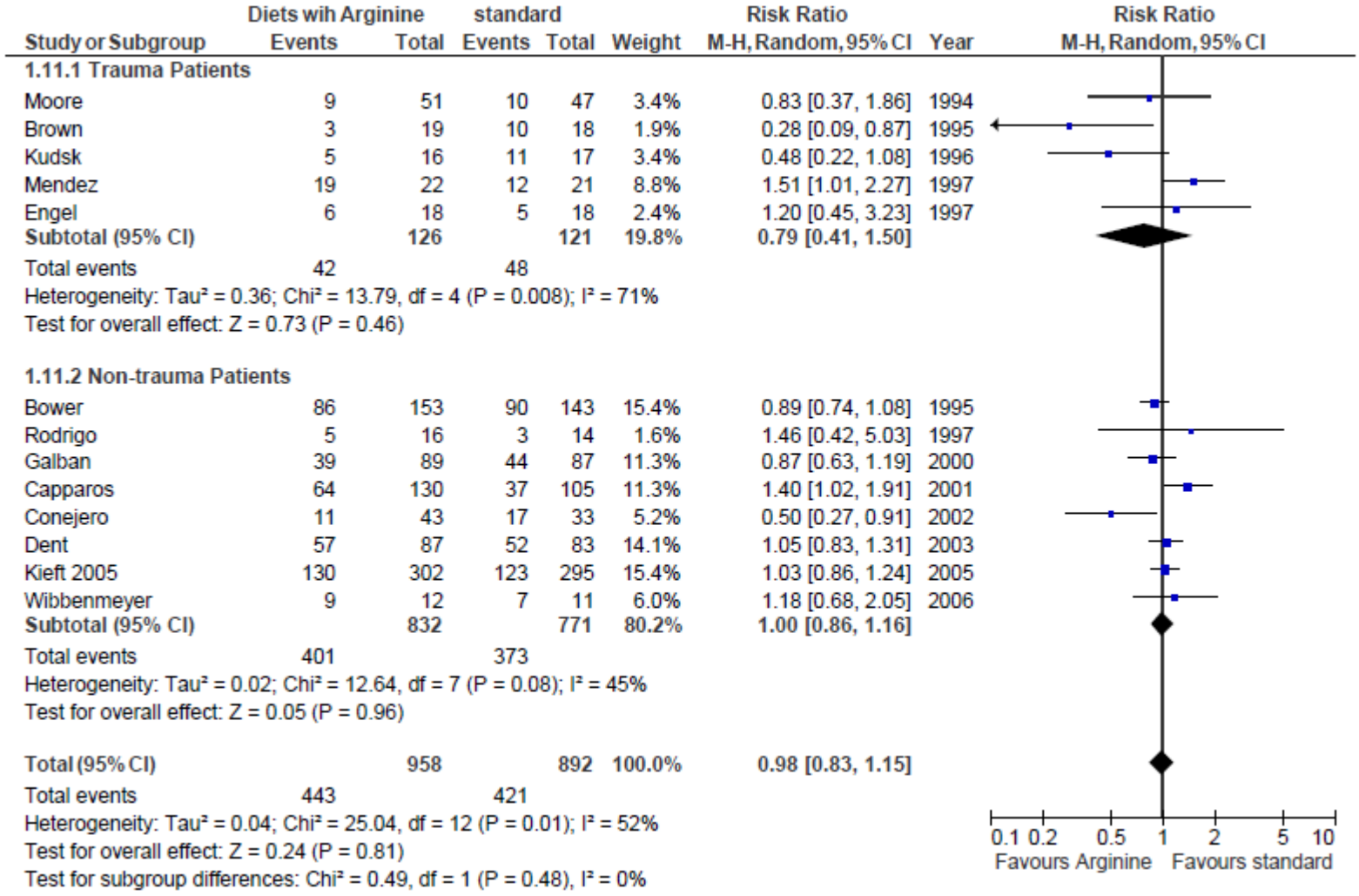


Figure 5a. Hospital LOS

	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	6.7%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	11.0%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	8.6%	-3.30 [-8.91, 2.31]	1995
Kudsk	18.3	2.8	16	32.6	7	17	9.9%	-14.30 [-17.90, -10.70]	1996
Mendez	34	21.2	22	21.9	11	21	5.8%	12.10 [2.07, 22.13]	1997
Atkinson	20.6	26	197	23.2	32	193	8.5%	-2.60 [-8.39, 3.19]	1998
Weimann	70.2	53	16	58.1	30	13	1.2%	12.10 [-18.57, 42.77]	1998
Dent	25.4	26	87	20.9	17	83	8.0%	4.50 [-2.07, 11.07]	2003
Chuntrasakul	44.9	30.2	18	28.8	25.7	18	2.8%	16.10 [-2.22, 34.42]	2003
Tsuei	22	9	61	27	17	55	9.0%	-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	4.1%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	3.8%	12.50 [-2.10, 27.10]	2008
Iamsirisaengthong	35.4	15.2	10	40.4	15.2	10	4.3%	-5.00 [-18.32, 8.32]	2017
Nakamura	21.9	8.8	45	24.3	7.8	43	10.0%	-2.40 [-5.87, 1.07]	2020
Total (95% CI)			**751**			**718**	**100.0%**	**-1.43 [-4.95, 2.10]**	

Heterogeneity: Tau² = 29.29; Chi² = 81.41, df = 14 (P < 0.00001); I² = 83%
Test for overall effect: Z = 0.79 (P = 0.43)

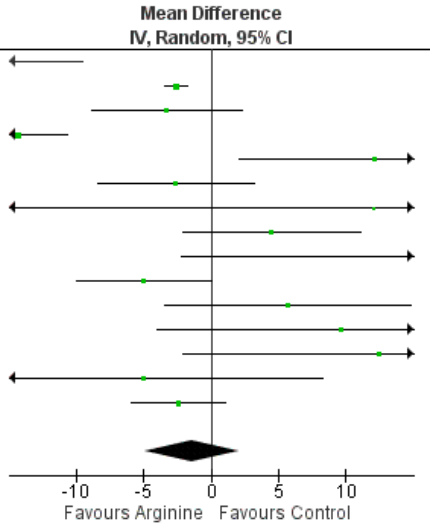


Figure 5b. Hospital LOS (excluding Tsuei)

	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	7.5%	-18.00 [-26.50, -9.50]	1991
Moore	14.6	1.3	51	17.2	2.8	47	11.6%	-2.60 [-3.48, -1.72]	1994
Bower	27.6	23	153	30.9	26	143	9.4%	-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
Mendez	34	21.2	22	21.9	11	21	6.5%	12.10 [2.07, 22.13]	1997
Weimann	70.2	53	16	58.1	30	13	1.4%	12.10 [-18.57, 42.77]	1998
Atkinson	20.6	26	197	23.2	32	193	9.3%	-2.60 [-8.39, 3.19]	1998
Chuntrasakul	44.9	30.2	18	28.8	25.7	18	3.2%	16.10 [-2.22, 34.42]	2003
Dent	25.4	26	87	20.9	17	83	8.7%	4.50 [-2.07, 11.07]	2003
Pearce	19.1	14.4	15	13.4	11.1	16	7.1%	5.70 [-3.39, 14.79]	2006
Kuhls	40	23.45	22	30.3	22.98	22	4.7%	9.70 [-4.02, 23.42]	2007
Beale	43.8	28	27	31.3	27.2	28	4.4%	12.50 [-2.10, 27.10]	2008
Iamsirisaengthong	35.4	15.2	10	40.4	15.2	10	4.9%	-5.00 [-18.32, 8.32]	2017
Nakamura	21.9	8.8	45	24.3	7.8	43	10.7%	-2.40 [-5.87, 1.07]	2020
Total (95% CI)			**690**			**663**	**100.0%**	**-0.94 [-4.79, 2.91]**	

Heterogeneity: Tau² = 32.99; Chi² = 80.77, df = 13 (P < 0.00001); I² = 84%
Test for overall effect: Z = 0.48 (P = 0.63)

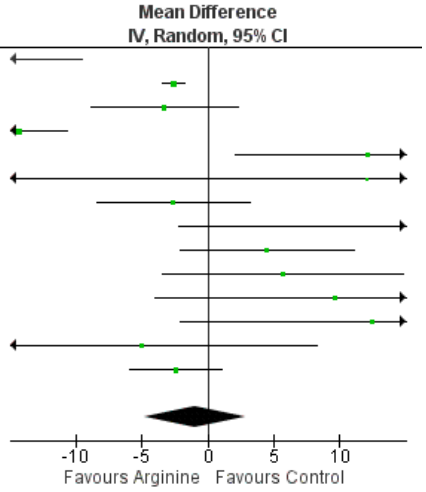


Figure 6a. ICU LOS

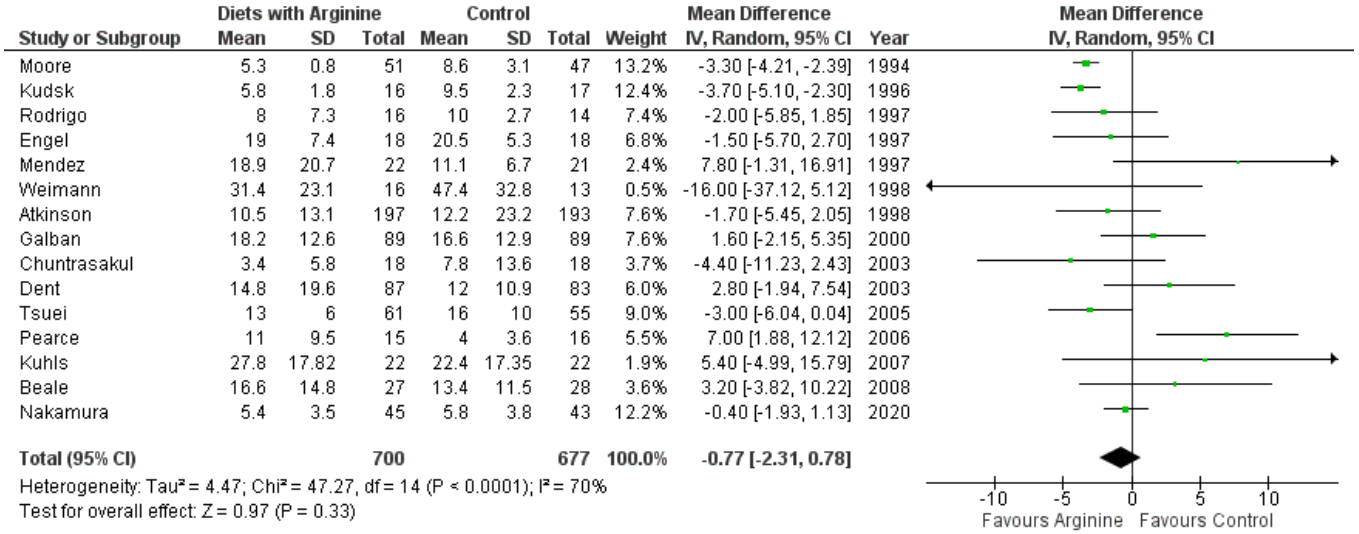


Figure 6b. ICU LOS (excluding Tsuei)

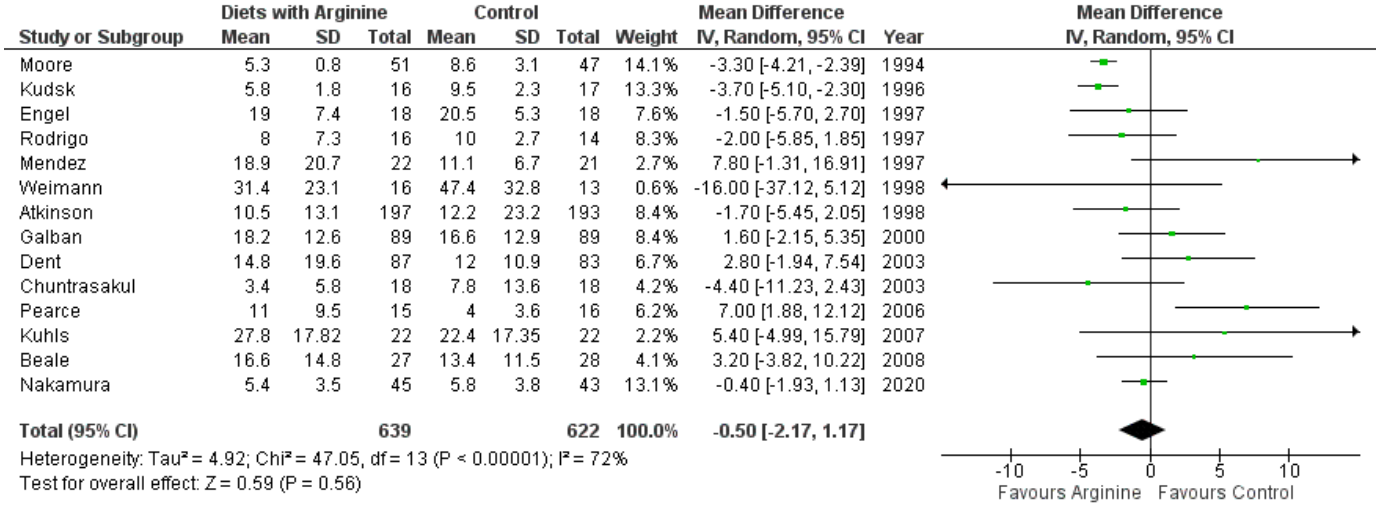


Figure 7a. Duration of Mechanical Ventilation (days)

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Moore	1.9	0.9	51	5.3	3.1	47	17.6%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	16.8%	-3.00 [-4.14, -1.86]	1996
Mendez	16.5	19.4	22	9.3	6	21	2.0%	7.20 [-1.30, 15.70]	1997
Engel	14.8	5.6	18	16	5.6	18	7.5%	-1.20 [-4.86, 2.46]	1997
Atkinson	8	11.1	197	9.4	17.7	193	9.6%	-1.40 [-4.34, 1.54]	1998
Weimann	21.4	10.8	16	27.8	14.6	13	1.7%	-6.40 [-15.94, 3.14]	1998
Galban	12.4	10.4	89	12.2	10.3	87	9.2%	0.20 [-2.86, 3.26]	2000
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.1%	-4.70 [-11.38, 1.98]	2003
Dent	14.3	22.4	87	10.8	12.8	83	4.3%	3.50 [-1.95, 8.95]	2003
Tsuei	10	5	61	14	10	55	9.6%	-4.00 [-6.93, -1.07]	2005
Kuhls	23.1	12.66	22	20.9	12.66	22	2.6%	2.20 [-5.28, 9.68]	2007
Nakamura	4.8	2.4	45	5.3	3.8	43	16.0%	-0.50 [-1.83, 0.83]	2020
Total (95% CI)			**642**			**617**	**100.0%**	**-1.67 [-2.95, -0.39]**	

Heterogeneity: Tau² = 2.22; Chi² = 30.13, df = 11 (P = 0.002); I² = 63%
Test for overall effect: Z = 2.55 (P = 0.01)

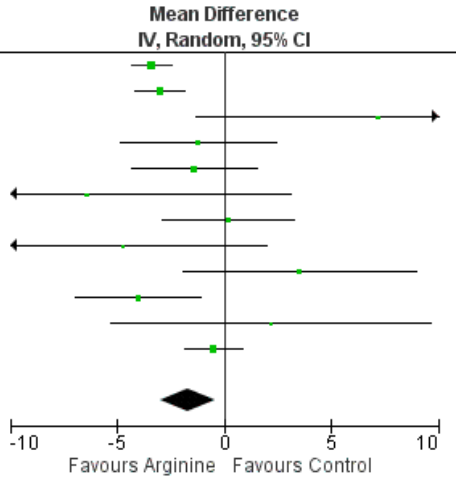
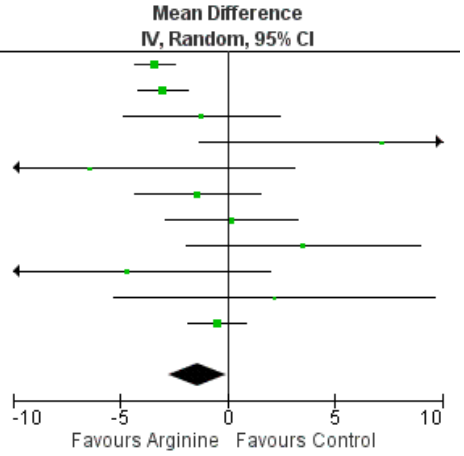


Figure 7b. Duration of Mechanical Ventilation (days) (excluding Tsuei)

Study or Subgroup	Diets with Arginine Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Moore	1.9	0.9	51	5.3	3.1	47	19.2%	-3.40 [-4.32, -2.48]	1994
Kudsk	2.4	1.3	16	5.4	2	17	18.3%	-3.00 [-4.14, -1.86]	1996
Engel	14.8	5.6	18	16	5.6	18	8.4%	-1.20 [-4.86, 2.46]	1997
Mendez	16.5	19.4	22	9.3	6	21	2.3%	7.20 [-1.30, 15.70]	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	10.7%	-1.40 [-4.34, 1.54]	1998
Galban	12.4	10.4	89	12.2	10.3	87	10.3%	0.20 [-2.86, 3.26]	2000
Dent	14.3	22.4	87	10.8	12.8	83	4.9%	3.50 [-1.95, 8.95]	2003
Chuntrasakul	2.7	5.2	18	7.4	13.5	18	3.5%	-4.70 [-11.38, 1.98]	2003
Kuhls	23.1	12.66	22	20.9	12.66	22	2.9%	2.20 [-5.28, 9.68]	2007
Nakamura	4.8	2.4	45	5.3	3.8	43	17.5%	-0.50 [-1.83, 0.83]	2020
Total (95% CI)			**581**			**562**	**100.0%**	**-1.40 [-2.78, -0.03]**	

Heterogeneity: Tau² = 2.34; Chi² = 28.92, df = 10 (P = 0.001); I² = 65%
Test for overall effect: Z = 2.00 (P = 0.05)



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