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PRELIMINARY RESULTS OF A META-ANALYSIS EVALUATING THE EFFECT OF IMMUNONUTRITION ON OUTCOMES OF ELECTIVE GASTROINTESTINAL SURGERY

Emma Osland
Dept of Nutrition and Dietetics, Ipswich Hospital, Ipswich, Queensland, Australia
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments,
University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: Emma_Osland@health.qld.gov.au

Md Belal Hossain
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments,
University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: hossainm@usq.edu.au

Shahjahan Khan
Department of Mathematics and Computing, Australian Centre for Sustainable Catchments,
University of Southern Queensland, Toowoomba, Queensland, Australia
E-mail: Shahjahan.Khan@usq.edu.au

Muhammed Ashraf Memon
Mayne Medical School, School of Medicine, University of Queensland, Brisbane, Queensland, Australia
Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland, Australia
Faculty of Health Sciences, Bolton University, Bolton, Lancashire, UK
E-mail: mmemon@yahoo.com

ABSTRACT

Providing tube feeds or liquid oral supplements containing additional arginine and/or omega-3 fatty acids and RNA – often referred to as 'immunonutrition' and more recently 'pharmaconutrition' – has been proposed as a strategy to decrease postoperative complications and duration of hospital length of stay for elective surgical patients. However outcomes of individual studies vary and the purported benefits remain controversial. A meta-analysis on this topic was recently published (Zheng et al., 2007), however further randomised controlled trials on this topic have appeared in the literature since this time. This meta-analysis has been undertaken to update the previously published meta-analysis and to attempt to elucidate the potential benefit of providing immune-enhanced nutrition in surgical patients. A search of electronic databases identified all RCTs comparing the use of pre and/or perioperative immunonutrition with standard nutrition provision in elective adult surgical patients between 1990 and 2008. The meta-analysis was prepared in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement. The variables analysed included mortality, total complications, infective complications, anastomotic leak (where applicable), and length of hospital stay. 20 distinct studies were identified that met inclusion criteria involving 1966 patients (immunonutrition n= 1048; standard nutrition n= 918). The provision of immunonutrition was shown to be associated with significant reductions in the incidence of total postoperative complications (OR 0.59, CI 0.41, 0.83, *p*=0.0023, Q=51.5, *p*=0.0001, I^2 = 59%, CI 34.8%, 74.5%), postoperative infective complications (OR 0.49, CI 37, 64, *p*=0.0001, Q=25.2, *p*=0.1939 , I^2 = 23%, CI 0%, 53.3%), anastomotic breakdown (OR 0.51, CI 0.31, 0.84 , *p*=0.0085, Q= 6.31, *p*=0.03 , I^2 = 0%, CI 0%, 7.3%) when compared to standard nutritional provision. No effect of the differences in feed product formulation were seen with relation to mortality (OR 0.94, CI 0.49, 1.8, *p*=0.861, Q=4.49, *p*=0.99, I^2 = 0%, CI 0%, 0%) or length of hospital stay (WMD -2.52, CI -3.71, -1.33, *p*=0.0001, Q= 219, *p*=0.0001, I^2 = 90.2%, CI 87.5%, 93.4%). This meta-analysis lends strong support to the beneficial effects of immune-enhanced nutrition in the management of elective gastrointestinal surgical patients.

Keywords: Meta-analysis; surgery; immunonutrition; pharmaconutrition; surgical complications; human

1. INTRODUCTION

Nutrition provision is recognized to be an important aspect in the perioperative management of elective gastrointestinal surgery patients, and the timely provision of nutrition has been associated with improved postoperative outcomes (Lewis, Andersen and Thomas, 2009). While the benefits of nutritional provision in surgical patients are traditionally thought to arise from the provision of macronutrients such as calories for energy and protein for wound healing, other nutritional components obtained from food or artificial forms of nutrition support are now though to interact with the immune system and modulate the responses to conditions such a trauma, sepsis or surgery (Jones and Heyland, 2008). In view of this, during the early 1990s new artificial nutrition support formulas emerged in the literature and on the commercial market that contained higher quantities of nutrients such as arginine, glutamine, omega-3 fatty acids, and nucleotides: these are thought to enhance the body's immune response. Since that time, the effects of these formulations have been studied in a variety of patient populations including a variety of surgical specialties and in the critically ill (Dupertuis, Meguid and Pichard, 2009). Many of these studies have demonstrated conflicting results (Dupertuis et al., 2009). Further to these individual studies, five meta-analyses on this topic have been conducted, again with conflicting results depending on the patient population investigated. To date only one meta-analysis has been conducted on the use of immunonutrition in elective surgical patients (Zheng et al., 2007)

The current work has been undertaken in an attempt to further explore the literature on immune-enhancing nutritional formations – more recently termed 'pharmoconutrition' – specifically in the area of elective gastrointestinal surgery.

2. MATERIALS AND METHODS

Electronic databases (Medline, Pubmed, EMBASE, CINAHL, Cochrane Register of Systematic Reviews, Science Citation Index) were cross-searched using search terms customized to each search engine in an attempt to detect relevant papers comparing the outcomes of provision on immune-enhanced nutritional formulas with those of standard composition provided perioperatively in patients receiving elective surgery. Reference lists of review papers and existing meta-analyses were hand searched for further appropriate citations.

All studies comparing the provision of immune-enhanced nutritional formulations (commercial or experimental) with those of standard nutritional composition providing isocaloric and isonitrogenuous nutritional provision, published in the English language were reviewed. Only randomized controlled trials with primary comparisons between the different nutritional formulations were considered for inclusion. Studies must also have reported on clinically relevant outcomes, and have been conducted in adult (>18 years) elective gastrointestinal surgical cases. Additional exclusion criteria included studies that investigated the effect of parenteral provision supplemented with nutrients believed to be immune-enhancing, unpublished studies and abstracts presented at national and international meetings, and duplicate publications.

The meta-analysis was prepared in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement. Data extraction and critical appraisal of identified studies were carried out by two authors (EO and MAM) for compliance with inclusion criteria and methodological quality. The authors were not blinded to the source of the document or authorship for the purpose of data extraction. The data were compared and discrepancies were addressed with discussion until consensus was achieved.

Evaluation of methodological quality of identified studies was conducted using the Jadad scoring system which provides a numerical quality score based on reporting of randomization, blinding and reporting of withdrawals (Jadad et al., 1996).

Outcomes assessed were those considered to exert influence over practical aspects of surgical practice and policy decisions within institutions such as rates of postoperative complications and mortality outcomes. All studies with reporting on any number of outcomes of this nature were considered and final analyses were run on outcome parameters where numbers were sufficient to allow statistical analysis.

Meta-analyses were performed using odds ratios (ORs) for binary outcomes and weighted mean differences (WMDs) for continuous outcome measures. A slightly amended estimator of OR was used to avoid the computation of reciprocal of zeros among observed values in the calculation of the original OR (Agresti, 1996). Random effects models, developed by using the inverse variance weighted method approach were used to combine the data (Sutton et al., 2000). Heterogeneity among studies was assessed using the Q statistic proposed by Cochran (Cochran, 1954; Hedges and Olkin, 1985; Sutton et al., 2000) and I^2 index introduced by Higgins and Thompson (Higgins and Thompson, 2002). If the observed value of Q is equal to or larger than the critical value at a given significant level (α), in this case 0.05, we conclude that the outcome variable is statistically significant. The drawback of the Q statistic is that its statistical power depends on the number of studies. The I^2 statistic describes the proportion of variation across studies that are due to between-studies heterogeneity rather than chance and unlike Q statistic it does not inherently depend upon the number of studies considered (Huedo-Medina et al., 2006).

Funnel plots were synthesized in order to determine the presence of publication bias in the meta-analysis. Standard error was plotted against the treatment effects (Log OR for the dichotomous and WMD for continuous variables respectively) (Egger et al., 1997; Sutton et al., 2000; Tang and Liu, 2000) to allow 95% confidence interval limits to be displayed. All estimates were obtained using computer programs written in R (Hornik, 2008). All plots were obtained using the 'rmeta' package (Lumley, 2008). In the case of tests of hypotheses, the paper reports p-values for different study variables. In general, the effect is considered to be statistically significant if the p-value is small. If one uses a 5% significance level then the effect is significant only if the associated p-value is less than or equal to 5%.

3. RESULTS

Cross searching of the electronic databases yielded 81 unique abstracts of potential relevance which were retrieved for independent review. Of these, 18 studies met the inclusion criteria. Pooled results yielded 1956 patients, with a near even distribution between feeding interventions (n=1061 immune formulas, n=895 standard composition) from studies dating from 1995 to 2008. The protocol for provision of nutrition differed between studies: 11 studies studied the effects of immunonutrition postoperatively, three studies three operatively and five provided nutrition both pre and postoperatively. All patients receiving postoperative feeding were tube fed distal to the anastomosis within 24hrs post surgery for malignant disease. Five studies report that significant percentages (20-100%) of their study population were malnourished. A summary of the randomised controlled trials included in the final meta-analysis are presented in Table 1.

The included studies collectively demonstrate moderate methodological quality according to the Jadad score with an average score of 2.8 (out of 5), with a range of 1 to 5.

Sufficient data were available for the analysis for five clinically relevant outcomes: total complications; infective complication; anastomotic dehiscence; in-hospital mortality; and length of hospital stay.

Statistically significant reductions in the relative odds of total postoperative complications (OR 0.59 CI 0.41, 0.83, p=0.0023, Q=51.5, p=0.0001, I^2 = 59%, CI 34.8%, 74.5%), infective complications (OR 0.49, CI 37, 64, p=0.0001, Q=25.2, p=0.1939 , I^2=23%, CI 0%, 53.3%), and anastomotic dehiscence (OR 0.51, CI 0.31, 0.84 , p=0.0085, Q= 6.31, p=0.03 , I^2 = 0%, CI 0%, 7.3%) were observed in patients receiving immune- enhancing feeding products. No effect of the differences in feed product formulation were seen with relation to mortality (OR 0.94, CI 0.49, 1.8, p=0.861, Q=4.49, p=0.99,I^2=0%, CI 0%,s 0%) or length of hospital stay (WMD -2.52, CI -3.71, -1.33, p=0.0001, Q= 219, p=0.0001, I^2 = 90.2%, CI 87.5%, 93.4%).

Figure 1 – Forest plot of outcomes for infective complications. Forest plot draws the 95% confidence intervals for treatment effects (odds ratio) as horizontal lines. Confidence intervals show arrows when they exceed specified limits. In the forest plot, squares indicate the estimated treatment effects (odds ratio for immune-nutrition over normal feed groups) with the size of the squares representing the weight attributed to each study. The pooled estimated odds ratio is obtained by combining all the odds ratios of the studies using the inverse weighted method, represented by the diamond and the size of the diamond depicts the 95% confidence interval. Values to the left of the vertical line are at one favour immune-nutrition. Values to right of the vertical line are at one favour Normal feed.

Figure 2 – Forest plot of outcomes for LOS. Forest plot draws the 95% confidence intervals for treatment effects (WMD) as horizontal lines. Confidence intervals show arrows when they exceed specified limits. In the forest plot, squares indicate the estimated treatment effects (WMD for immune-nutrition over normal feed groups) with the size of the squares representing the weight attributed to each study. The pooled estimated odds ratio (WMD) is obtained by combining all the WMD of the studies using the inverse weighted method, represented by the diamond and the size of the diamond depicts the 95% confidence interval. Values to the left of the vertical line are at one favour immune-nutrition. Values to right of the vertical line are at one favour Normal feed.

Funnel plots demonstrate symmetry for mortality, infective complications and anastomotic dehiscence outcomes suggesting the absence of publication bias within the meta-analyses performed for these outcomes. The presence of publication bias is indiciated by asymmetric funnel plots for total complications and length of hospital stay.

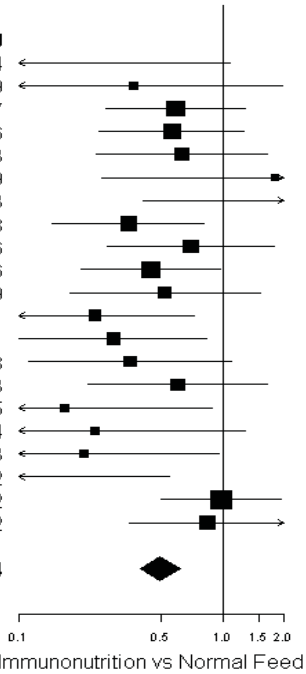
4. COMMENTS AND CONCLUSION

This meta-analysis demonstrates clinically and statistically signficiant reductions in the relative odds of developing postoperative complications (total, infective and that of anastomotic dehiscence) in patients receiving immune-enhancing nutrition formulations following elective gastrointestinal surgery. No effect was seen on postoperative mortality or length of hospital stay.

Sample forest plots are presented in Figures 1 and 2.

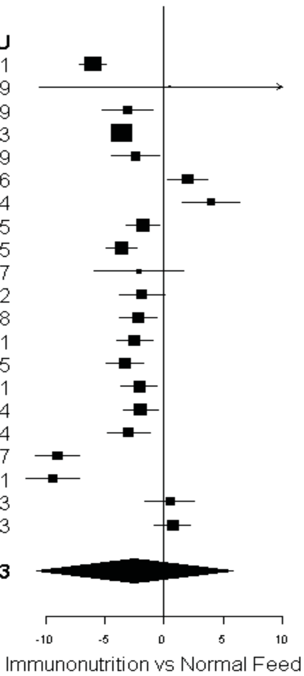
Study	Int n/N	Normal n/N	OR	L	U
Daly et al 95	0/30	7/30	0.055	0.003	1.04
Schilling et al 96	3/14	6/14	0.36	0.07	1.9
Gianotti et al 97	13/87	20/87	0.59	0.27	1.27
Senkal et al 97	12/77	19/77	0.56	0.25	1.26
Braga CCM	9/55	13/55	0.63	0.24	1.63
McCarter Arg	4/14	2/11	1.8	0.26	12.29
McCarter omega 3	5/13	2/11	2.81	0.42	18.73
Braga et al 99	9/85	22/86	0.34	0.14	0.8
Senkal et al 99	9/78	12/76	0.69	0.27	1.76
Snyderman et al 99	19/82	19/47	0.44	0.2	0.96
Gianotti et al 00	6/71	11/73	0.52	0.18	1.49
Braga et al peri 02	5/50	16/50	0.24	0.07	0.71
Braga et al pre 02	6/50	16/50	0.29	0.1	0.81
Braga et al pre/peri 02	5/50	12/50	0.35	0.11	1.08
Braga et al pre/std peri 02	8/50	12/50	0.6	0.22	1.63
Farreras et al 05	2/30	9/30	0.17	0.03	0.85
Xu et al 06	2/30	7/30	0.23	0.04	1.24
Giger et al 07 I-2/7	5/17	10/15	0.21	0.04	0.93
Giger et al 07 I-5/7	2/14	10/15	0.08	0.01	0.52
Klek clin nutr 08	23/92	23/91	0.98	0.5	1.92
Klek ann surg 08	13/52	15/53	0.84	0.35	2
Meta-analysis			**0.49**	**0.37**	**0.64**

Q=25.2 df=19 p=0.1939 I^2=23%



Study	Int mean(sd)	Normal mean(sd)	WMD	L	U
Daly et al 95	16(0.9)	22(2.9)	-6	-7.09	-4.91
Schilling et al 96	14.5(8)	14(19)	0.5	-10.3	11.29
Gianotti et al 97	16.1(6.2)	19.2(7.9)	-3.1	-5.21	-0.99
Senkal et al 97	27(2.3)	30.6(3.1)	-3.6	-4.46	-2.73
Braga CCM	13.7(4.8)	16.1(5.9)	-2.4	-4.41	0.39
McCarter Arg	15(2.4)	13(1.7)	2	0.39	3.6
McCarter omega 3	17(3.7)	13(1.7)	4	1.75	6.24
Braga et al 99	11.1(4.4)	12.9(4.6)	-1.8	-3.14	-0.45
Senkal et al 99	22.2(4.1)	25.8(3.8)	-3.6	-4.84	-2.35
Snyderman et al 99	15.3(9.1)	17.4(11.9)	-2.1	-6.07	1.87
Gianotti et al 00	15.1(5.4)	17.0(6.1)	-1.9	-3.78	-0.02
Braga et al peri 02	9.8(3.1)	12(4.5)	-2.2	-3.71	-0.68
Braga et al pre 02	9.5(2.9)	12(4.5)	-2.5	-3.98	-1.01
Braga et al pre/peri 02	12.0(3.8)	15.3(4.1)	-3.3	-4.84	-1.75
Braga et al pre/std peri 02	13.2(3.5)	15.3(4.1)	-2.1	-3.59	-0.61
Farreras et al 05	13(2.75)	15(3)	-2	-3.45	-0.54
Xu et al 06	9(3.2)	12(3.7)	-3	-4.75	-1.24
Giger et al 07 I-2/7	14.1(1.3)	23.1(3.6)	-9	-10.92	-7.07
Giger et al 07 I-5/7	13.7(2.3)	23.1(3.6)	-9.4	-11.58	-7.21
Klek clin nutr 08	12.9(8)	12.4(5.9)	0.5	-1.53	2.53
Klek ann surg 08	13.1(4.1)	12.4(3.9)	0.7	-0.83	2.23
Meta-analysis			**-2.52**	**-3.71**	**-1.33**

Q=219.57 df=20 p=0.0001 I^2=90.9%



The results of this meta-analysis differ somewhat from the previous meta-analysis on this topic. Zheng et al. (2007) reported signfiicant reductions in infective complications and duration of hospital stay, and no effect on mortality. Investigation of the effect of immunonutrition on total complications or anastomotic dehiscence was not conducted. They also demonstrated an improvement on measures of immune function such as total lymphocytes, CD4 levels, IgG levels and IL6 levels with the provision of immunonutrition. While the latter cluster of immunological outcomes have not been analysed in the current work, it is interesting to note the difference in the length of stay results between this and the Zheng et al. (2007) analysis. The most likely explanation for the difference between outcomes lie in the included studies – the only study included in the 2007 meta-analysis not to report LOS benefits with early feeding was a comparitively by Schilling (1996). Furthermore, this study would have little effect on the pooled outcomes in view of the fixed effects model used and its small study size. In contrast, the present work includes four studies (including two available since the publication of the Zheng et al. (2007) paper) that report increased length of study with the provision of immunonutrition, and utislises a random effects model of meta-analysis that weights smaller studies more heavily than occurs in the fixed effects model.

This is a prelimiary assessment of the data available. To gain a more thorough understanding of the benefits and risks associated with the provision of immunonutrition when compared to standard formulations in this population further analysis of the data is required. For example, as different formulas with different immune-enhancing componant levels have been used (ie Impact®, Stressor®, experimental solutions, etc) stratifying the studies for re-analysis by arginine content may demonstrate differences in outcomes. Similarly, as the presence of malnutrition is known to affect the outcomes of nutritional provision, a sensitivity analysis should be run assessing the impact of this factor on the outcomes seen. Finally, the different protocols used in the 20 studies included in this analysis introduce considerable variablity to the timing and quantity of the immunonutrition provided to the patients involved: these differences should be controlled for to ensure accurate interpretation of the reported outcome data.

In conclusion, this meta-analysis lends support to the beneficial effects of immune-enhanced nutrition in the management of elective gastrointestinal surgical patients. Provision of immunonutrition in preference to standard nutrition appears on preliminary assessment to be associated with statistically and clinically significant reductions in the development of postoperative complications including those of infective origin, anastomotic dehiscence in patients who receive a primary anastomosis, does not show the detrimental mortality outcomes believed to be associated with the use immunonutrition in critically ill populations. It does not, however, concur with previous meta-analysis findings of reduced length of hospital stay associated with the provision of immunonutrition when compared to standard nutritional formulations.

REFERENCES

Agresti, A. (1996). *An Introduction to Categorical Data Analysis*: Wiley & Sons.

Braga, M., Gianotti, L., Nespoli, L., Radaelli, G., and Di Carlo, V. (2002a). Nutritional approach in malnourished surgical patients: a prospective randomized study. *Arch Surg* 137, 174-180.

Braga, M., Gianotti, L., Radaelli, G., *et al.* (1999). Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg* 134, 428-433.

Braga, M., Gianotti, L., Vignali, A., and Carlo, V. D. (2002b). Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery* 132, 805-814.

Braga, M., Gianotti, L., Vignali, A., Cestari, A., Bisagni, P., and Di Carlo, V. (1998). Artificial nutrition after major abdominal surgery: impact of route of administration and composition of the diet. *Crit Care Med* 26, 24-30.

Chen, D. W., Wei Fei, Z., Zhang, Y. C., Ou, J. M., and Xu, J. (2005). Role of enteral immunonutrition in patients with gastric carcinoma undergoing major surgery. *Asian J Surg* 28, 121-124.

Cochran, W. G. (1954). The combination of estimates from different experiments. *Biometrics* 10, 101-129.

Daly, J. M., Weintraub, F. N., Shou, J., Rosato, E. F., and Lucia, M. (1995). Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. *Ann Surg* 221, 327-338.

Dupertuis, Y. M., Meguid, M. M., and Pichard, C. (2009). Advancing from immunonutrition to a pharmaconutrition: a gigantic challenge. *Curr Opin Clin Nutr Metab Care* 12, 398-403.

Egger, M., Davey Smith, G., Schneider, M., and Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629-634.

Farreras, N., Artigas, V., Cardona, D., Rius, X., Trias, M., and Gonzalez, J. A. (2005). Effect of early postoperative enteral immunonutrition on wound healing in patients undergoing surgery for gastric cancer. *Clin Nutr* 24, 55-65.

Gianotti, L., Braga, M., Fortis, C.*, et al.* (1999). A prospective, randomized clinical trial on perioperative feeding with an arginine-, omega-3 fatty acid-, and RNA-enriched enteral diet: effect on host response and nutritional status. *JPEN J Parenter Enteral Nutr* 23, 314-320.

Gianotti, L., Braga, M., Vignali, A.*, et al.* (1997). Effect of route of delivery and formulation of postoperative nutritional support in patients undergoing major operations for malignant neoplasms. *Arch Surg* 132, 1222-1229; discussion 1229-1230.

Giger, U., Buchler, M., Farhadi, J.*, et al.* (2007). Preoperative immunonutrition suppresses perioperative inflammatory response in patients with major abdominal surgery-a randomized controlled pilot study. *Ann Surg Oncol* 14, 2798-2806.

Hedges, L. V., and Olkin, I. (1985). *Statisical methods for meta-analysis*. Orlando: Academic Press.

Higgins, J. P., and Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med* 21, 1539-1558.

Hornik, K. (2008). R: A language and environment for statistical computing. Vienna: Foundation for Statistical Computing.

Huedo-Medina, T. B., Sanchez-Meca, J., Marin-Martinez, F., and Botella, J. (2006). Assessing heterogeneity in meta-analysis: Q statistic or I2 index? *Psychol Methods* 11, 193-206.

Jones, N. E., and Heyland, D. K. (2008). Pharmaconutrition: a new emerging paradigm. *Curr Opin Gastroenterol* 24, 215-222.

Klek, S., Kulig, J., Sierzega, M.*, et al.* (2008a). Standard and immunomodulating enteral nutrition in patients after extended gastrointestinal surgery--a prospective, randomized, controlled clinical trial. *Clin Nutr* 27, 504-512.

Klek, S., Kulig, J., Sierzega, M.*, et al.* (2008b). The impact of immunostimulating nutrition on infectious complications after upper gastrointestinal surgery: a prospective, randomized, clinical trial. *Ann Surg* 248, 212-220.

Lewis, S. J., Andersen, H. K., and Thomas, S. (2009). Early enteral nutrition within 24 h of intestinal surgery versus later commencement of feeding: a systematic review and meta-analysis. *J Gastrointest Surg* 13, 569-575.

Lumley, T. (2008). The rmeta Package version 2.14.

McCarter, M. D., Gentilini, O. D., Gomez, M. E., and Daly, J. M. (1998). Preoperative oral supplement with immunonutrients in cancer patients. *JPEN J Parenter Enteral Nutr* 22, 206-211.

Schilling, J., Vranjes, N., Fierz, W., *et al.* (1996). Clinical outcome and immunology of postoperative arginine, omega-3 fatty acids, and nucleotide-enriched enteral feeding: a randomized prospective comparison with standard enteral and low calorie/low fat i.v. solutions. *Nutrition* 12, 423-429.

Senkal, M., Mumme, A., Eickhoff, U., *et al.* (1997). Early postoperative enteral immunonutrition: clinical outcome and cost-comparison analysis in surgical patients. *Crit Care Med* 25, 1489-1496.

Senkal, M., Zumtobel, V., Bauer, K. H., *et al.* (1999). Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study. *Arch Surg* 134, 1309-1316.

Sutton, A. J., Abrams, K. R., Jones, D. R., Sheldon, T. A., and Song, F. (2000). *Methods for Meta-analysis in Medical Meta-analysis*: John Wiley.

Tang, J. L., and Liu, J. L. (2000). Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol* 53, 477-484.

Xu, J., Zhong, Y., Jing, D., and Wu, Z. (2006). Preoperative enteral immunonutrition improves postoperative outcome in patients with gastrointestinal cancer. *World J Surg* 30, 1284-1289.

Zheng, Y., Li, F., Qi, B., *et al.* (2007). Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. *Asia Pac J Clin Nutr* 16 Suppl 1, 253-257.