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Enteral and parenteral nutrition in cancer patients, a comparison of complication rates: an updated systematic review and (cumulative) meta-analysis

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ABSTRACT

Introduction

Weight loss in cancer patients is a worrisome constitutional change predicting disease progression and shortened survival time. A logical approach to counter some of the weight loss is to provide nutritional support, administered through enteral nutrition (EN) or parenteral nutrition (PN). The aim of this paper was to update the original systematic review and meta-analysis previously published by Chow *et al*, while also assessing publication quality and effect of RCTs on the meta-conclusion over time.

Methods

A literature search was carried out; screening was conducted for randomized controlled trials published in January 2015 up until December 2018. The primary endpoints were the percentage of patients achieving no infection and no nutrition support complications. Secondary endpoints included proportion of patients achieving no major complications and no mortality. Review Manager (RevMan 5.3) by Cochrane IMS and Comprehensive Meta-Analysis (Version 3) by Biostat were used for meta-analyses of endpoints and assessment of publication quality.

Results

An additional 7 studies were identified since our prior publication, leading to 43 papers included in our review. The results echo those previously published; EN and PN are equivalent in all endpoints except for infection. Subgroup analyses of studies only containing adults indicate identical risks across all endpoints. Cumulative meta-analysis suggests that meta-conclusions have remained the same since the beginning of publication time for all endpoints except for the endpoint of infection, which changed from not favouring to favouring EN after studies published in 1997. There was low risk of bias, as determined by assessment tool and visual inspection of funnel plots.

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Conclusions

The results support the current European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines recommending enteral over parenteral nutrition, when oral nutrition is inadequate, in adult patients. Further studies comparing EN and PN for these critical endpoints appear unnecessary, given the lack of change in meta-conclusion and low publication bias over the past decades.

Keywords: parenteral nutrition (PN), enteral nutrition (EN), cancer patients, malnutrition, tube feeding (TF), standard care (SC)

INTRODUCTION

Unintentional weight loss for cancer patients is a worrisome constitutional change predicting disease progression and shortened survival time [1-2]. A logical approach to counter weight loss is to provide nutritional support, administered through enteral nutrition (EN) or parenteral nutrition (PN) [3-4]. Historically, these approaches are accompanied with concerns of increased complications and costs; EN may hence be the preferred modality, due to its lower costs, fewer complications, and perceived better outcomes [4-6]. Over the past several decades, however, there have been substantial changes in clinical nutrition – the cost effectiveness of nutrition support has significantly increased through adoption of "all-in-one bags" for parenteral nutrition, novel enteral and parenteral formulas, peripheral insertion, and new materials for venous and enteral accesses, just to name a few [7]. New strategies, including standardized "bundles" of evidence-based interventions and strict policies of antisepsis, have also been developed and implemented to reduce the risk of complications [7].

The first meta-analysis comparing complication rates of EN and PN in cancer patients was published in 2016 [7], and looked at endpoints of infection, nutrition support complications, major complications and mortality. It included 36 articles [8-43], and reported that similar rates of nutrition support complications, major complications and mortality were observed between patients receiving EN and PN. Infection rates were reported to be slightly higher among PN patients.

Since the original review, more trials have been published and additional information has the potential for a more comprehensive meta-analysis with greater confidence in the principle conclusions. Moreover, the original review did not assess publication quality, or quantitatively assess for publication bias. With over 1,000 patients randomized to EN and PN each, the current

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meta-analysis may be sufficiently powered to offer a precise point estimate and recommend trial resources be dedicated elsewhere. To determine the effect of the latest randomized controlled trials (RCTs), a cumulative meta-analysis may adequately assess the meta-conclusion over time, as RCTs with new data are published.

The aim of this paper was to compare complication rates for EN and PN cancer patients, through updating the systematic review and meta-analysis previously published, while also assessing publication quality and effect of RCTs on the meta-conclusion over time.

METHODS

Search Strategy

A literature search was carried out in Ovid MEDLINE, Embase Classic and Embase, and Cochrane Central Register of Controlled Trials. The search included studies up until the last week of December 2018 and was limited to English-language studies and RCTs. Search terms included "PN", "EN" and "comparative studies" [Appendix 1], similar to the prior review by Chow *et al* [7]. Reference lists of included studies were also included in the search.

Selection Criteria

Screening was conducted by two authors (RC, LC); where disagreement occurred, discussion and consensus was achieved with input from a third author (NC); Cohen's kappa coefficient documented the inter-rater agreement. Titles and abstracts published after January 2015 and beyond were screened and deemed relevant for full-text review if there was mention of parenteral nutrition and enteral nutrition, and additionally stated that the two nutrition support treatments

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were compared. Following full-text review, studies were included if over 50% of the study population had any form and any stage of cancer, in line with the prior review by Chow *et al* [7].

Endpoints

The primary endpoints were the percentage of patients achieving no infection and no nutrition support complications. Secondary endpoints included proportion of patients achieving no major complications and no mortality.

The definition of endpoints is the same as those reported by the former review published by Chow *et al*. [7]. Minor infections were recorded as reported in studies; when studies provided a breakdown of infection complications, the endpoint "minor infections" was the summation of wound infection, pneumonia and sepsis. Nutrition support complications were recorded as published in studies, or reported as the summation of nausea, vomiting and diarrhea events. Major complication events included major complications and morbidity are reported, as disclosed in studies. Mortality rate was noted as they were recorded in literature.

Additional study characteristics recorded include type of EN (standard care (SC) and tube feeding (TF)), nutrition status of population (including individuals who are malnourished or deemed with protein-energy malnutrition (PEM); studies not mentioning PEM were assumed to have no malnourished patients as we postulated that this demographic would be reported if PEM patients were prevalent) and age of population (children as defined by study, typically 21 years and younger, or adults).

Statistical Analysis

The Mantel-Haenszel model was applied and a random effects analysis model was used to generate risk ratios (RR) and their accompanying 95% confidence intervals (CIs). A *p*-value of less than 0.05 was deemed statistically significant in the test for overall effect; a heterogeneity test with *p*-value greater than 0.05 was considered suitable. For all endpoints, we used the number of patients that did not experience the outcomes as the event numbers, to enable calculation of risks and risk ratios. Test for heterogeneity was conducted to determine whether the size of the effect was equal in all included studies. Review Manager (RevMan 5.3) by Cochrane IMS was used for the aforementioned analyses, to update the previously published analyses and forest plots. Comprehensive Meta-Analysis (Version 3) by Biostat was also used to conduct a cumulative meta-analysis, and assess the effect of studies to the meta-conclusion over publication time.

Assessment of Publication Quality

Funnel plots were generated by Review Manager (RevMan 5.3) to visually assess for publication bias. The Cochrane Risk of Bias assessment tool was employed to assess study quality of the included RCTs.

RESULTS

A total of 216 titles and abstracts were screened, of which 60 were identified for full-text screening (Cohen's kappa = 0.9239). The updated search yielded 7 additional studies [44-50] for inclusion in this systematic review and meta-analysis (Cohen's kappa = 0.7931) [Appendix 2]. The studies all reported on TF and studied adults. The study by Harvey *et al*. [46] included patients classified as PEM.

Infection

PN was slightly statistically superior with respect to infection (RR = 1.11; 95% CI: 1.04-1.19). Subgroup analyses by EN indicated that TF is superior to PN, whereas SC is equivalent. In patients suffering from PEM, PN and EN are equivalent. A higher risk of infection was noted among adult studies; no greater risk was reported among studies in children [Figure 1]. The aforementioned meta-conclusion, favouring PN, has remained unchanged since 1997; the cumulative RR remains in favour of PN with the inclusion of each published study dating to 1997 [Figure 2].

Nutrition Support Complications

Risk of nutrition support complications in EN and PN patients were equivalent (RR = 1.00; 95% CI: 0.96-1.05). Subgroup analyses by modality of EN, nutrition status and age of population reveal that the rate of complications is equivalent within subgroups too [Figure 3]. Since the first study, the meta-conclusion has not favoured EN or PN [Figure 4].

Major Complications

Neither EN nor PN were superior with respect to lower incidence of major complications. No studies on children reported on this endpoint. Subgroup analyses of TF, SC, PEM studies and non-PEM studies reported a similar conclusion [Figure 5]. The meta-conclusion has remained the same since the first publications [Figure 6].

Mortality

Analyses and subgroup analyses indicate equivalent mortality rates between EN and PN [Figure 7]. The meta-conclusion over time has remained the same [Figure 8].

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Heterogeneity

Unsuitable levels of heterogeneity were observed for all analyses of the endpoint "No infection", except for subgroup analyses of studies reporting on children [Figure 1]. Subgroup analyses of "No nutrition support complications" of subgroup SC, non-PEM studies, and child studies had appropriate levels of heterogeneity; other analyses of this endpoint have unsuitable levels [Figure 3]. These unsatisfactory levels may be a consequence of different clinical methodologies, such as different definitions of endpoints across different studies. All analyses of "No major complications" except for subgroup analyses of SC had satisfactory heterogeneity [Figure 5]. Satisfactory levels were observed for all analyses of endpoint "No mortality" [Figure 7].

Publication Quality

The majority of studies had low risk of bias [Appendix 3]. No obvious publication biases exist, as noted by lack of glaring asymmetries upon visual inspection of funnel plots [Appendices 4-7].

DISCUSSION

This systematic review and meta-analysis comparing complication rates between cancer patients administered EN or PN includes 43 studies, which is the highest-powered analysis to date in the cancer setting: the original meta-analysis by Chow *et al*. in 2016 comprised of 36 studies, while Braunschweig *et al*.'s study in 2001 had only 7 studies in their subgroup analyses of cancer patients [51]. The results in this study echo those published in 2016; EN and PN are equivalent in all endpoints except for infection [7]. In fact, cumulative meta-analysis suggests that meta-conclusions have remained the same since the beginning of publication time (i.e. the first published

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RCT) for all endpoints except for the endpoint of infection, which changed from not favouring to favouring EN after studies published in 1997.

Compared to the original review, this review involved additional analyses. The prior review conducted subgroup analyses only by type of EN and nutrition status; this review also investigated endpoints by age of the study population. For studies containing children, PN was equivalent to EN in all three endpoints – infection, nutrition support complications, and mortality; no studies reported on major complications/morbidity. In adults, the conclusion remains unchanged: EN is superior to PN only in infection. These results hence support the current European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines that suggests enteral over parenteral where the gastrointestinal tract works, when oral nutrition is inadequate [52].

Lack of bias, as assessed by the Cochrane Risk of Bias assessment tool and through visual inspection of funnel plots, suggests that the existing literature appropriately documents critical endpoints of PN compared to EN; RCTs, in line with the nature of their study type, did not have critical methodology flaws/biases. This, when considered in conjunction with the results of the cumulative meta-analyses examining studies over the past two decades has only refined our point estimate and has not altered our meta-conclusion, suggests that no new trials are required in this setting to look into these critical endpoints. When considering whether a cancer patient should be administered EN or PN, other considerations should be pondered.

PN has been reported to require less time in improving a patient's nutritional state, which can minimize hospital stays and help expedite turnover of hospital beds to care for more patients [43]. However, EN is nearly half the cost of PN, and may be more fiscally favourable [20]. PN has also been reported to be more beneficial for cancer surgery patients; PN may continue uninterrupted during settings where oral feeding may need to be withheld, such as during some

preoperative diagnostic procedures [13]. However, the results of this meta-analysis suggest that risk of major complications/morbidity and mortality of both nutrition support routes are still equivalent.

This review has its limitations. The reporting of endpoints across studies was not standardized: different definitions and recording methods for infections, nutrition support complications, and major complication outcomes existed. To accurately capture and extract endpoints, we reviewed and contacted corresponding authors when necessary for clarification of endpoints and collection of more data. Overall risk ratios computed by cumulative meta-analyses and standard meta-analysis forest plots differed slightly, due to rounding. Assessment of publication bias via funnel plots did not include accompanying quantitative metrics such as Egger's test; the lack of asymmetry, however, clearly indicates no publication bias.

This systematic review reaffirms the conclusions originally reported by the meta-analysis by Chow *et al*: that neither PN nor EN are superior for all endpoints (major complications, mortality, nutrition support complications) other than infection. Cumulative meta-analyses, in fact, indicate that the meta-conclusion has not changed for several decades; new trials investigating these endpoints are likely unnecessary as they would add little value to the existing body of literature. Subgroup analyses of studies only containing adult patients show no superiority of PN compared to EN, supporting ESPEN's latest guidelines recommending EN should be provided for cancer patients where oral intake is inadequate or they are already malnourished, given that their gastrointestinal tract is functional.

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Figure 1.1

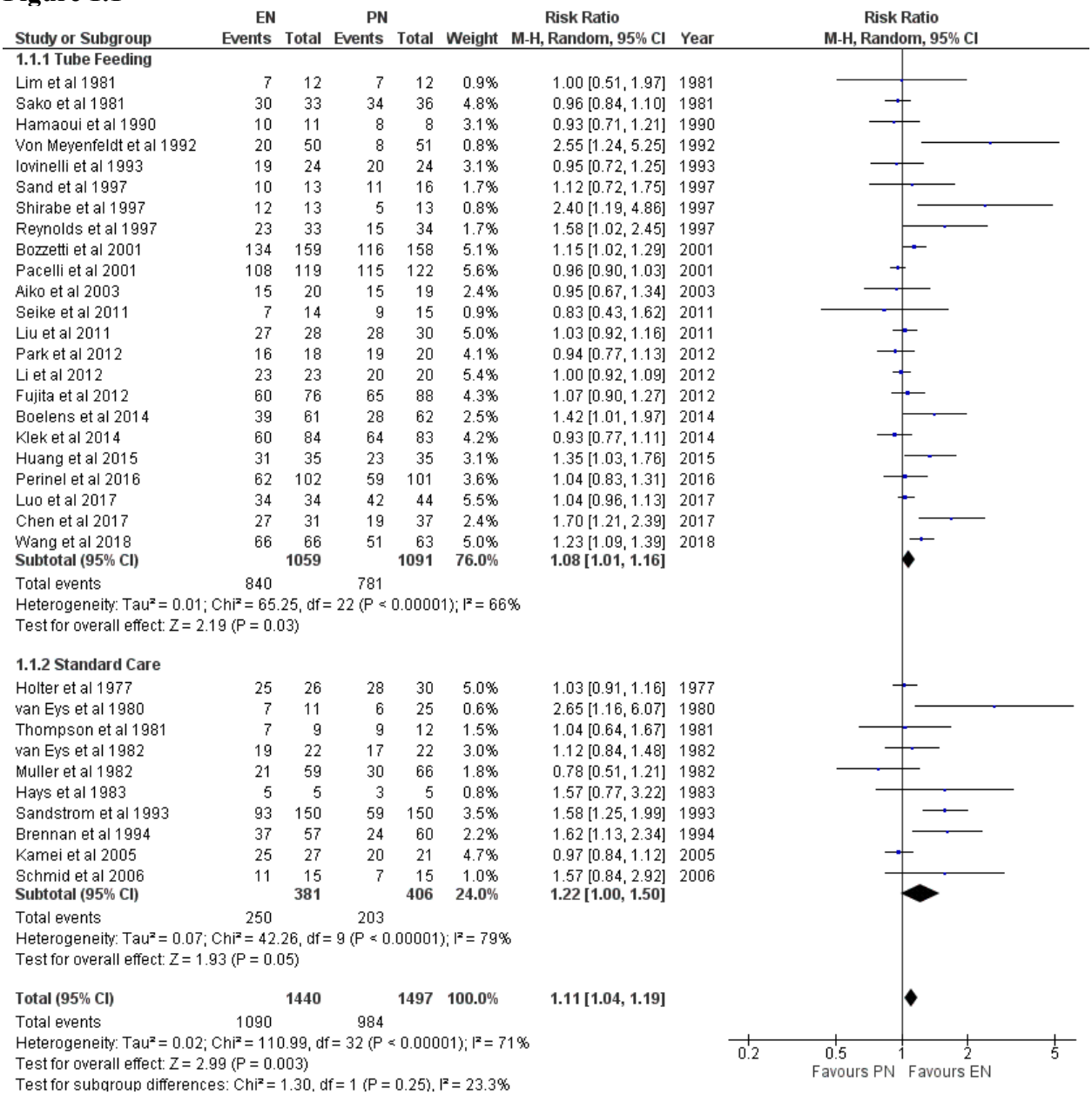

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Figure 1.2

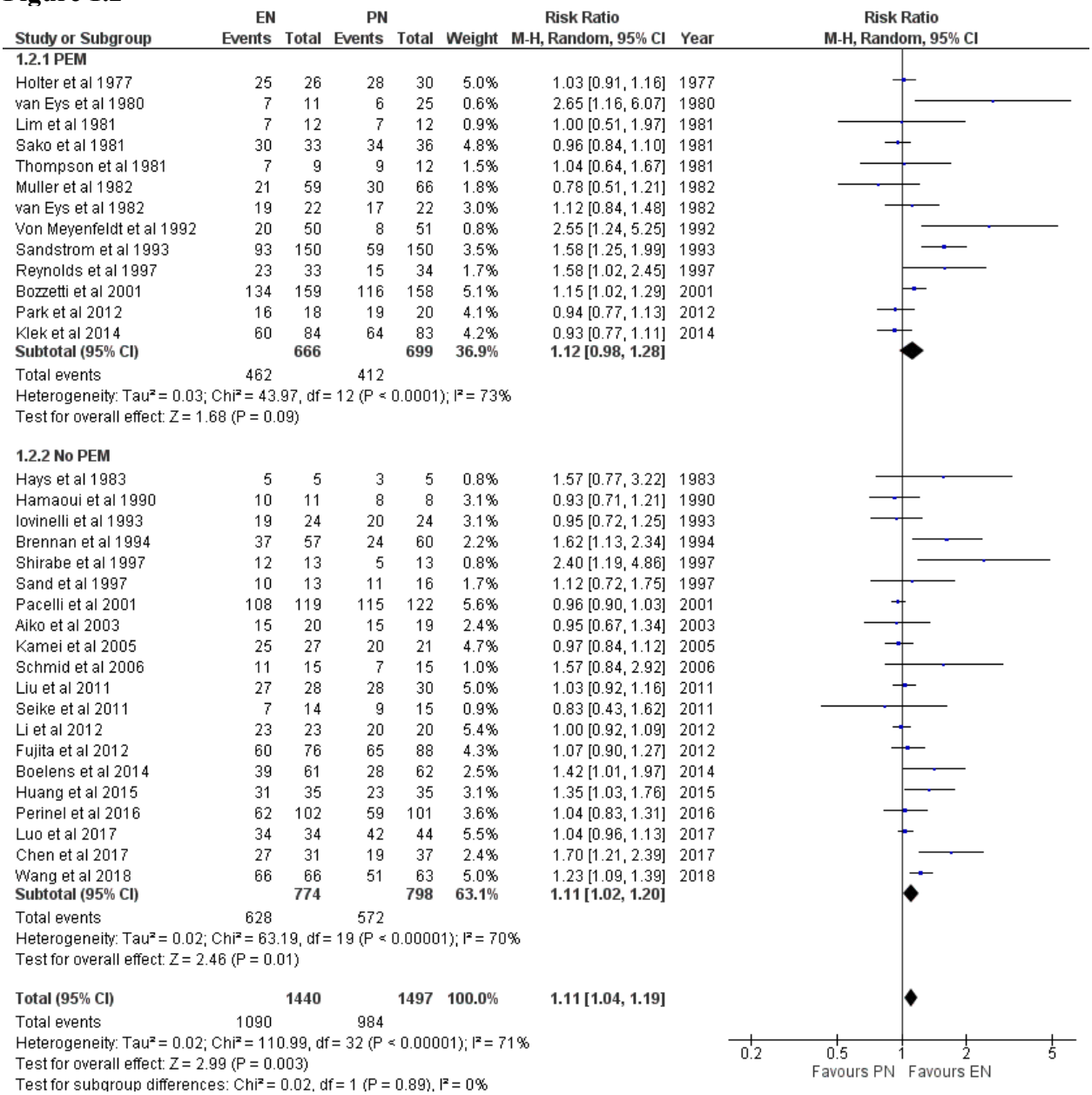

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Figure 1.3

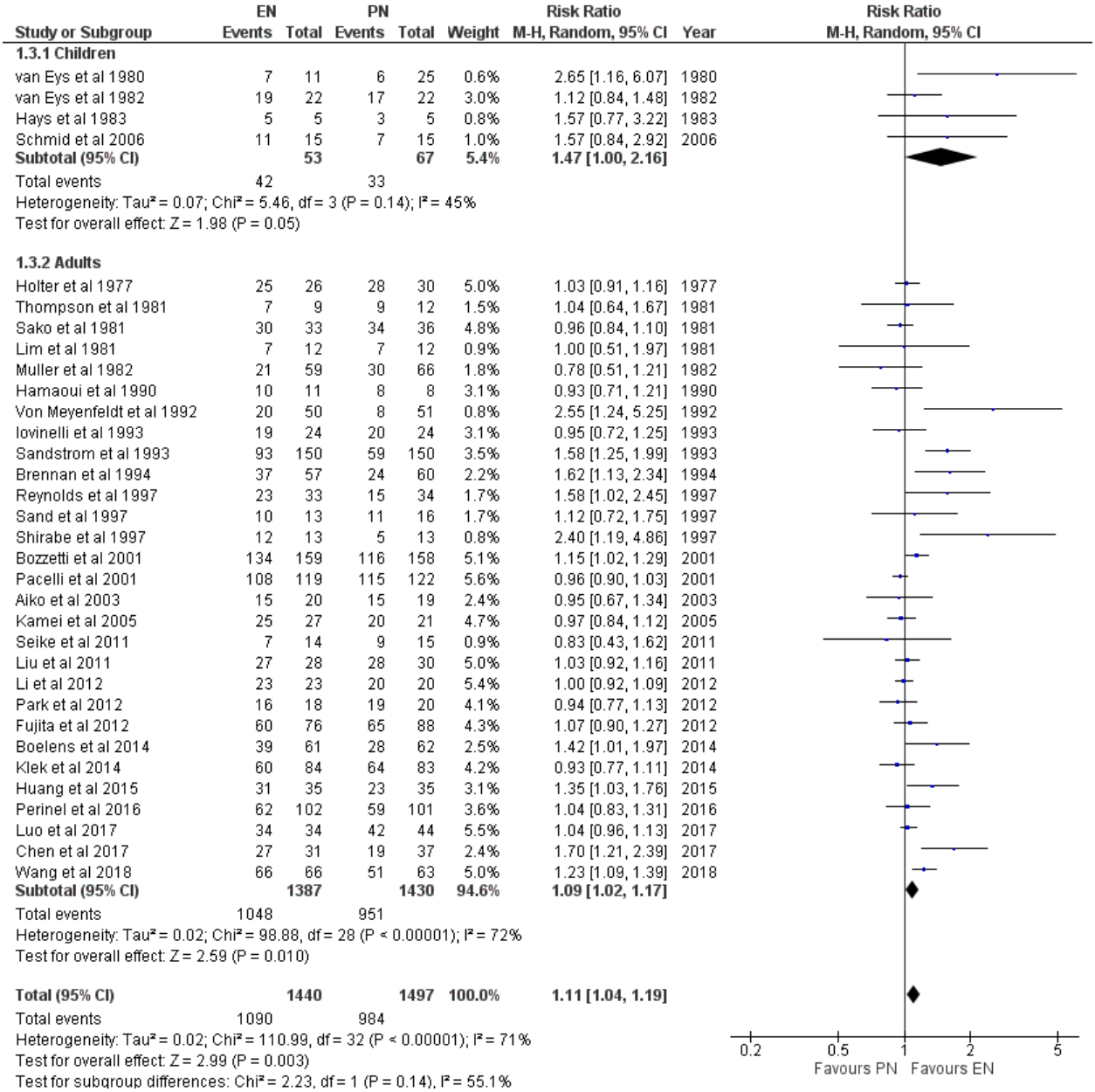

Figure 1. No infection for enteral nutrition (EN) and parenteral nutrition (PN) patients **1.1** Analyses by EN – tube feeding and standard care **1.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **1.3** Analyses by age of population – children and adults

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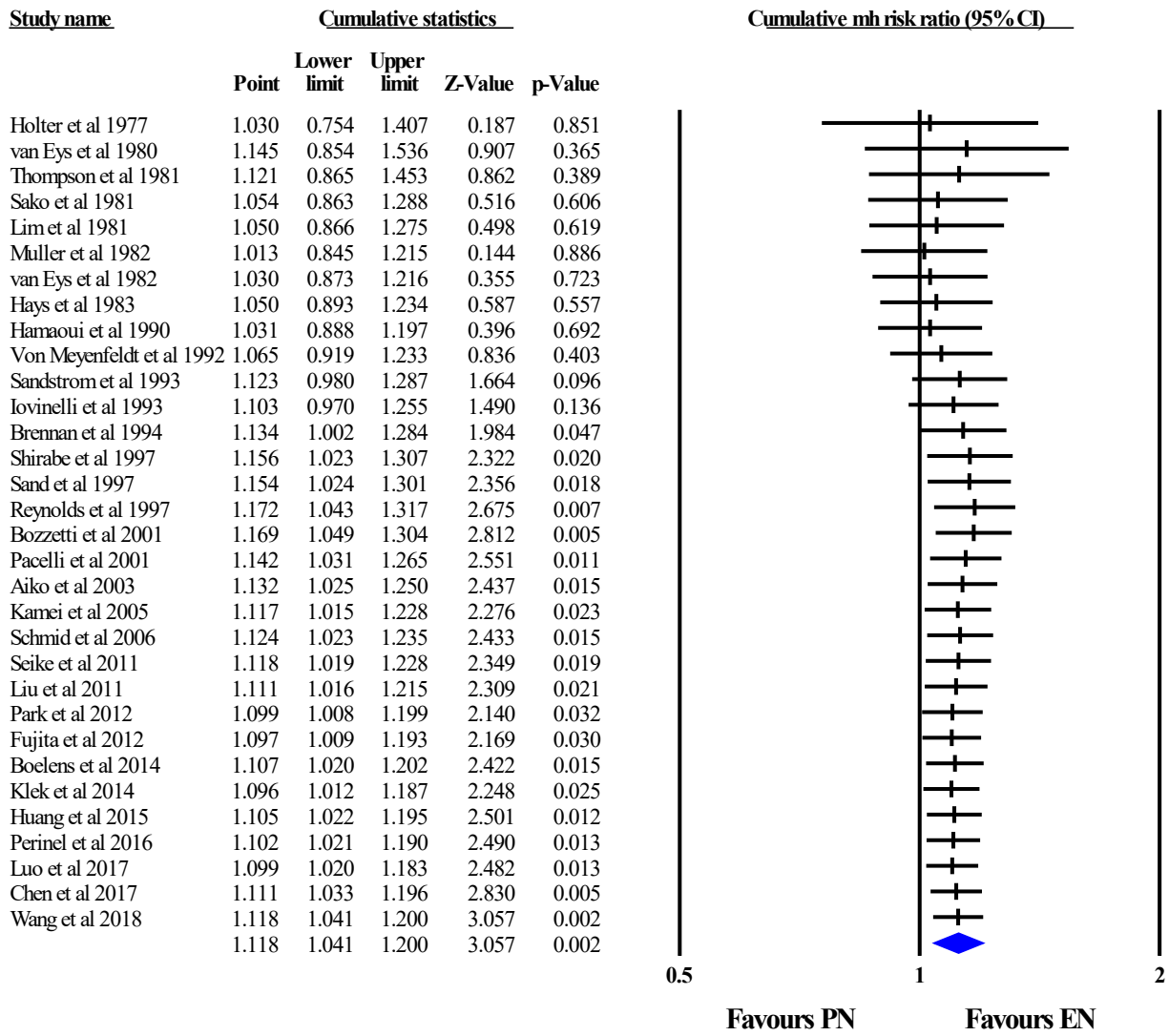

Figure 2. No infection for enteral (EN) and parenteral nutrition (PN) patients, over time

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Figure 3.1

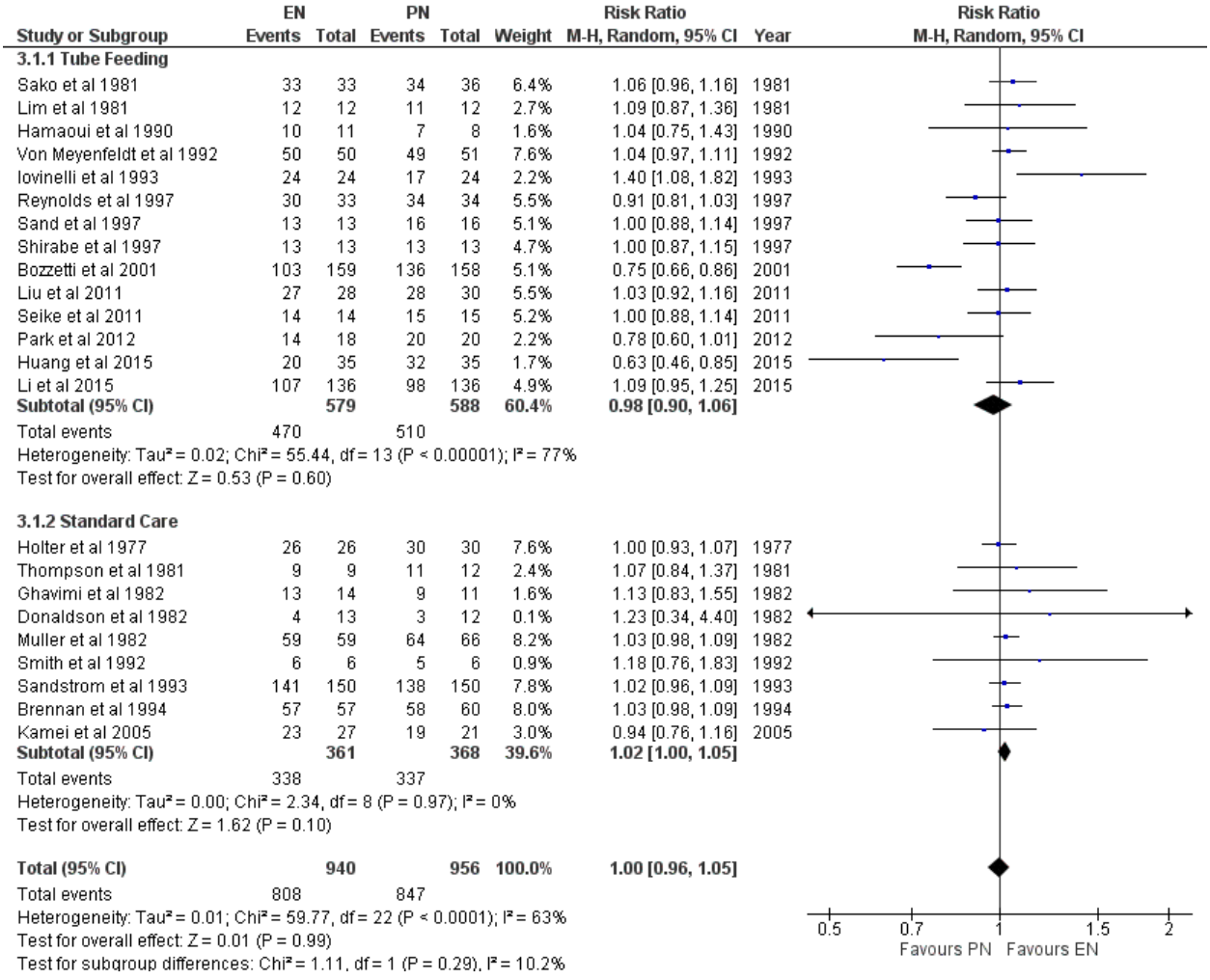

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Figure 3.2

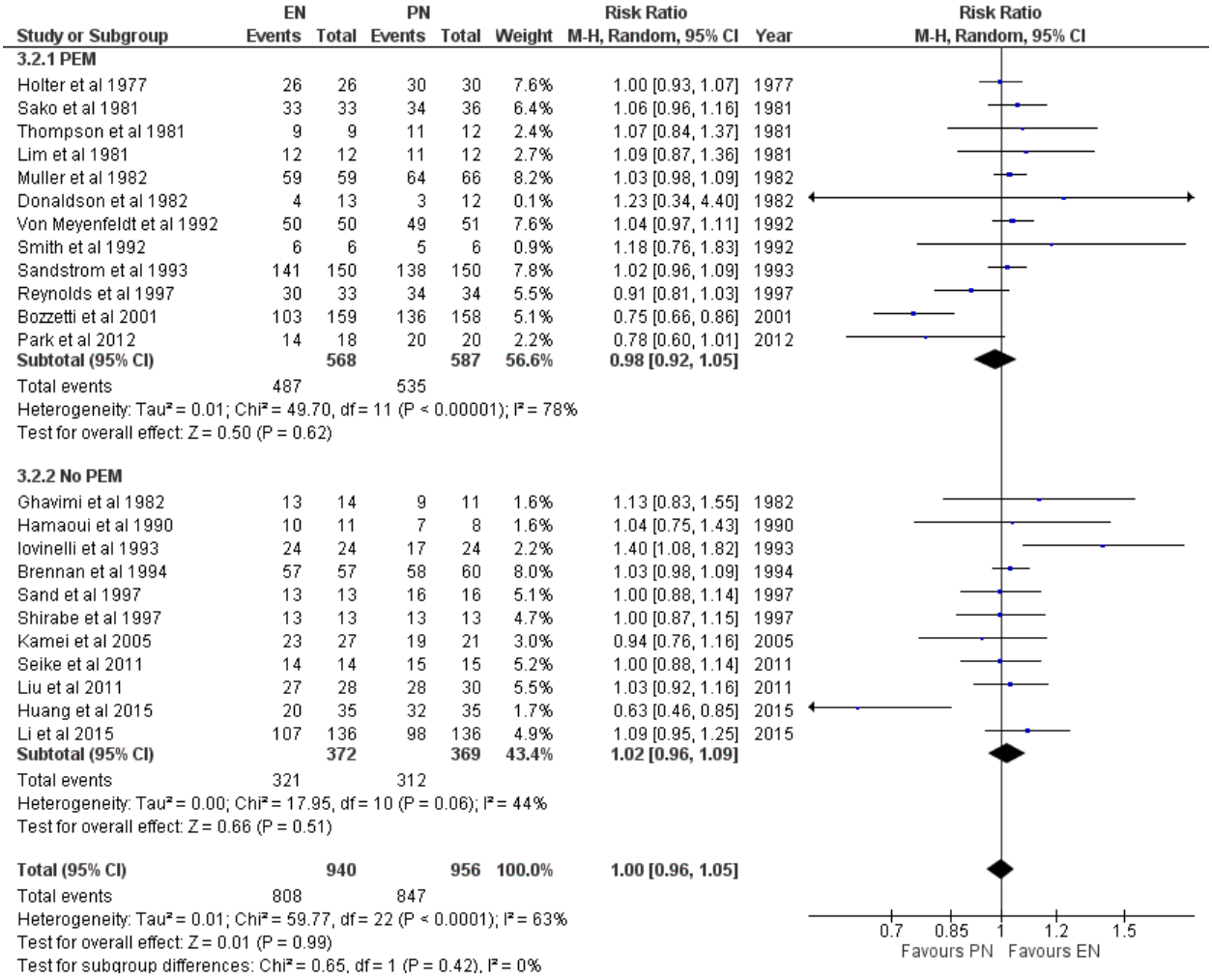

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Figure 3.3

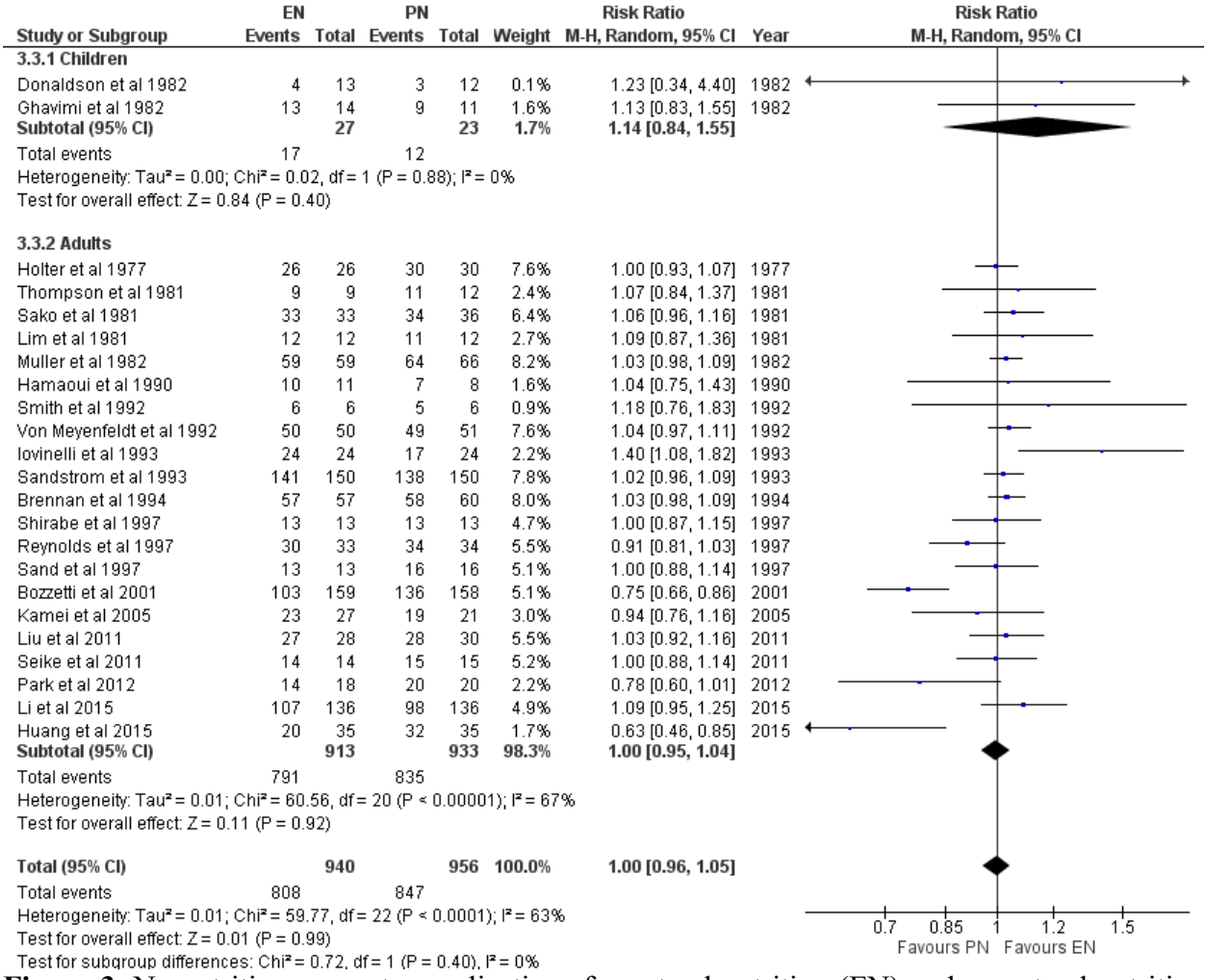

Figure 3. No nutrition support complications for enteral nutrition (EN) and parenteral nutrition (PN) patients **3.1** Analyses by EN – tube feeding and standard care **3.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **3.3** Analyses by age of population – children and adults

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Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Thompson et al 1980	1.074	0.797	1.446	0.469	0.639
Sako et al 1981	1.062	0.901	1.252	0.715	0.475
Lim et al 1981	1.068	0.926	1.232	0.908	0.364
Muller et al 1982	1.053	0.942	1.178	0.912	0.362
Ghavimi et al 1982	1.060	0.953	1.180	1.077	0.281
Donaldson et al 1982	1.062	0.954	1.181	1.099	0.272
Hamaoui et al 1990	1.060	0.957	1.174	1.113	0.266
Von Meyenfeldt et al 1992	1.055	0.965	1.154	1.176	0.240
Smith et al 1992	1.059	0.970	1.157	1.285	0.199
Sandstrom et al 1993	1.052	0.972	1.139	1.258	0.208
Iovinelli et al 1993	1.070	0.991	1.156	1.733	0.083
Brennan et al 1994	1.065	0.992	1.143	1.735	0.083
Reynolds et al 1997	1.048	0.980	1.121	1.366	0.172
Bozzetti et al 2001	1.018	0.955	1.085	0.544	0.587
Kamei et al 2005	1.014	0.952	1.079	0.429	0.668
Liu et al 2011	1.015	0.956	1.078	0.498	0.618
Park et al 2012	1.006	0.949	1.067	0.197	0.843
Li et al 2015	1.011	0.956	1.071	0.392	0.695
Huang et al 2015	0.999	0.945	1.057	-0.034	0.973
	0.999	0.945	1.057	-0.034	0.973

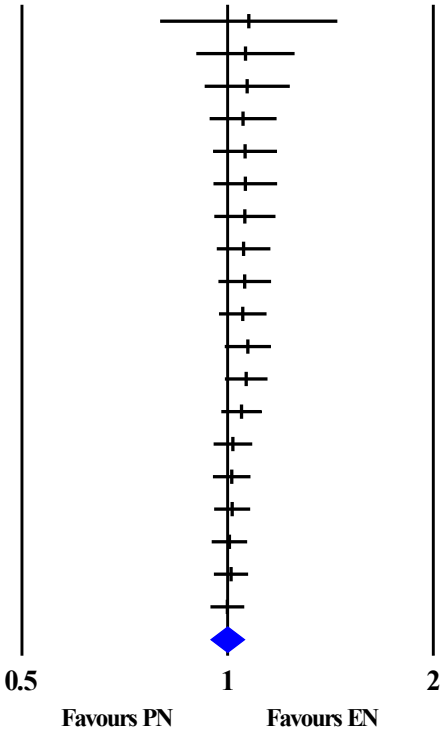

Figure 4. No nutrition support complications for enteral (EN) and parenteral nutrition (PN) patients, over time

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Figure 5.1

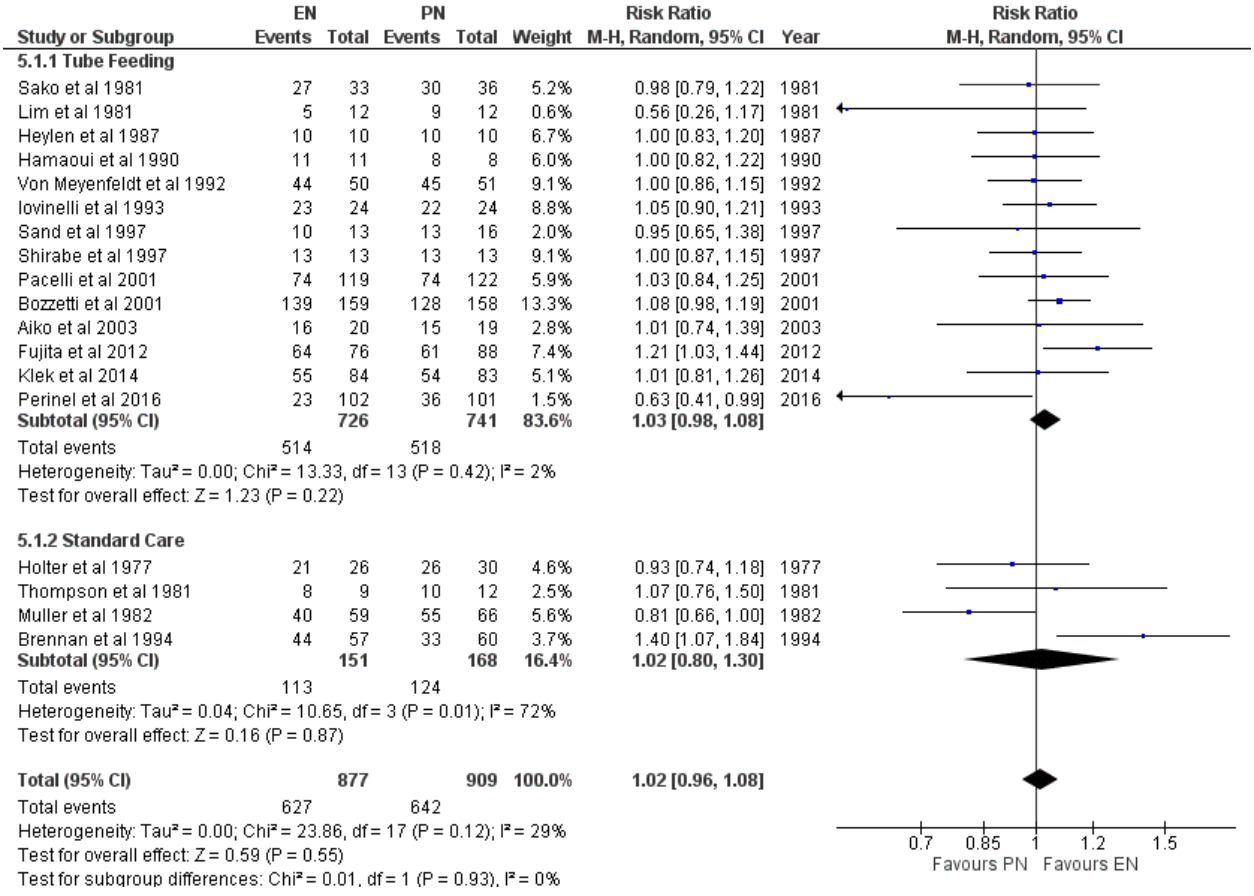

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Figure 5.2

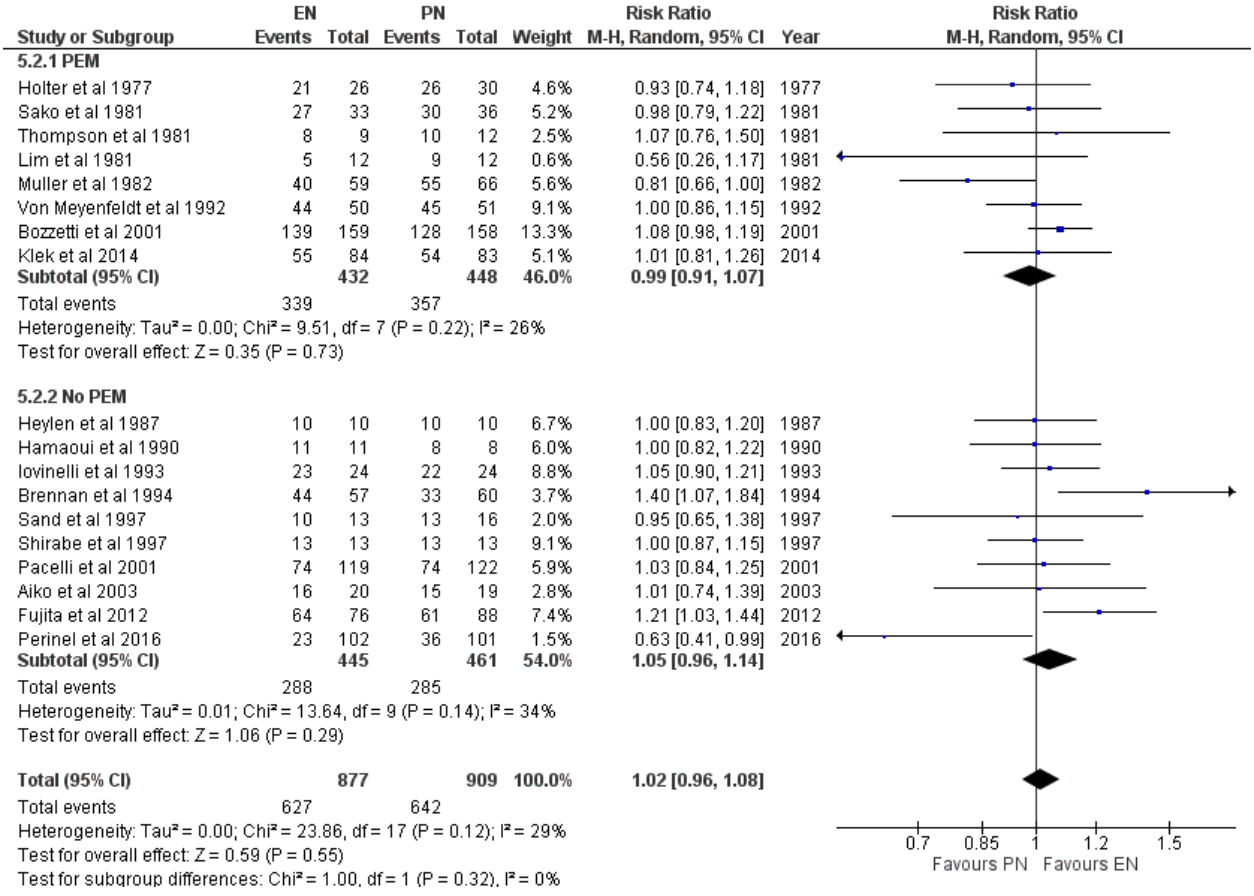

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Figure 5.3

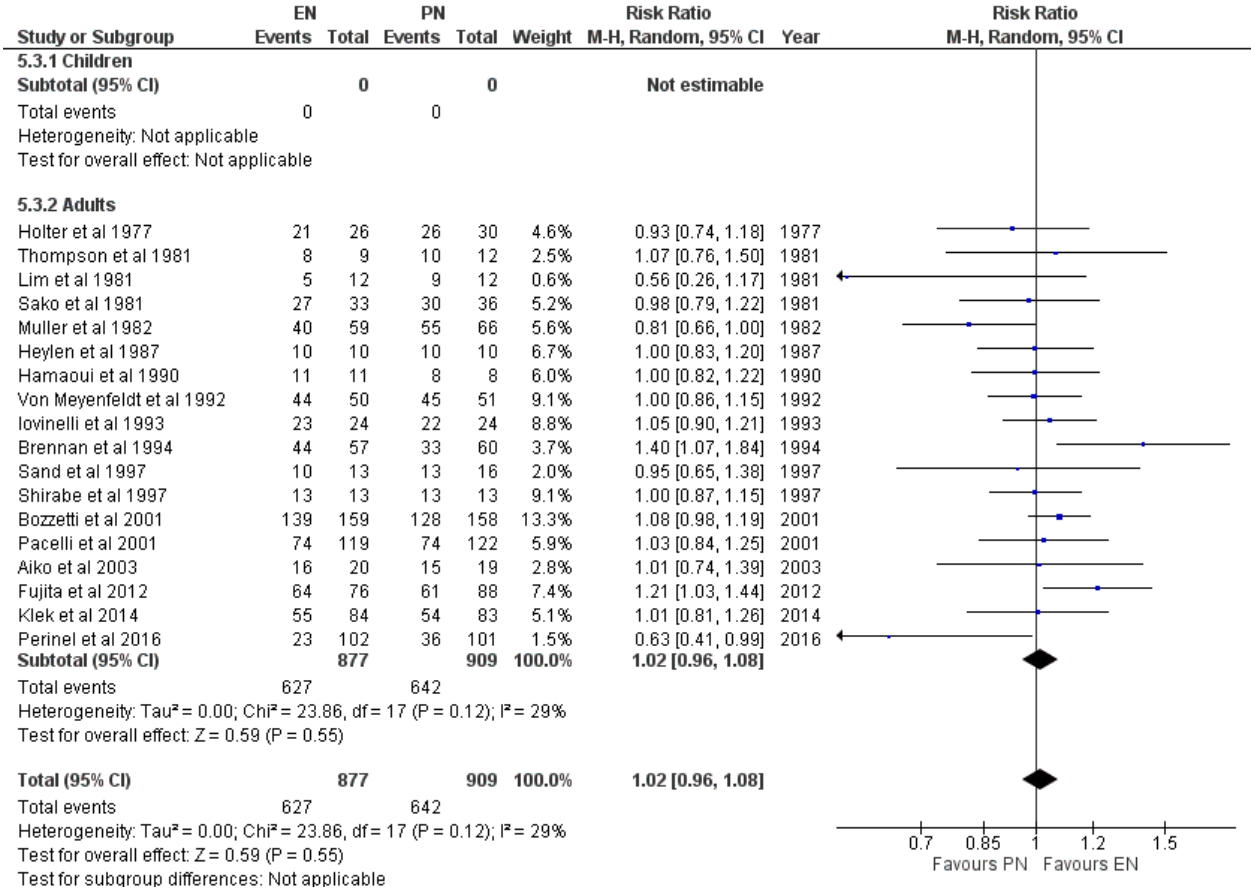

Figure 5. No major complications for enteral nutrition (EN) and parenteral nutrition (PN) patients **5.1** Analyses by EN – tube feeding and standard care **5.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **5.3** Analyses by age of population – children and adults

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Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Holter et al 1977	0.932	0.698	1.244	-0.478	0.632
Thompson et al 1981	0.979	0.777	1.232	-0.182	0.856
Sako et al 1981	0.980	0.821	1.169	-0.223	0.823
Lim et al 1981	0.952	0.802	1.131	-0.557	0.577
Muller et al 1982	0.909	0.787	1.051	-1.291	0.197
Von Meyenfeldt et al 1992	0.935	0.828	1.055	-1.094	0.274
Iovinelli et al 1993	0.959	0.862	1.066	-0.777	0.437
Brennan et al 1994	0.996	0.901	1.102	-0.071	0.943
Sand et al 1997	0.994	0.901	1.096	-0.130	0.897
Bozzetti et al 2001	1.010	0.926	1.103	0.231	0.818
Pacelli et al 2001	1.012	0.931	1.099	0.278	0.781
Aiko et al 2003	1.012	0.933	1.097	0.287	0.774
Fujita et al 2012	1.031	0.955	1.113	0.782	0.434
Klek et al 2014	1.029	0.956	1.108	0.766	0.444
Perinel et al 2016	1.018	0.946	1.095	0.467	0.640
	1.018	0.946	1.095	0.467	0.640

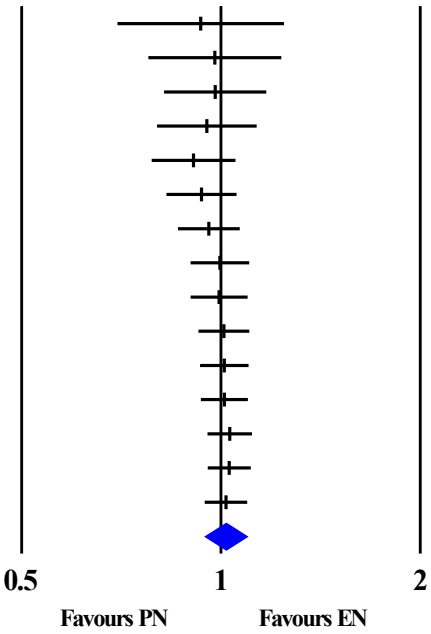

Figure 6. No major complications for enteral (EN) and parenteral nutrition (PN) patients, over time

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Figure 7.1

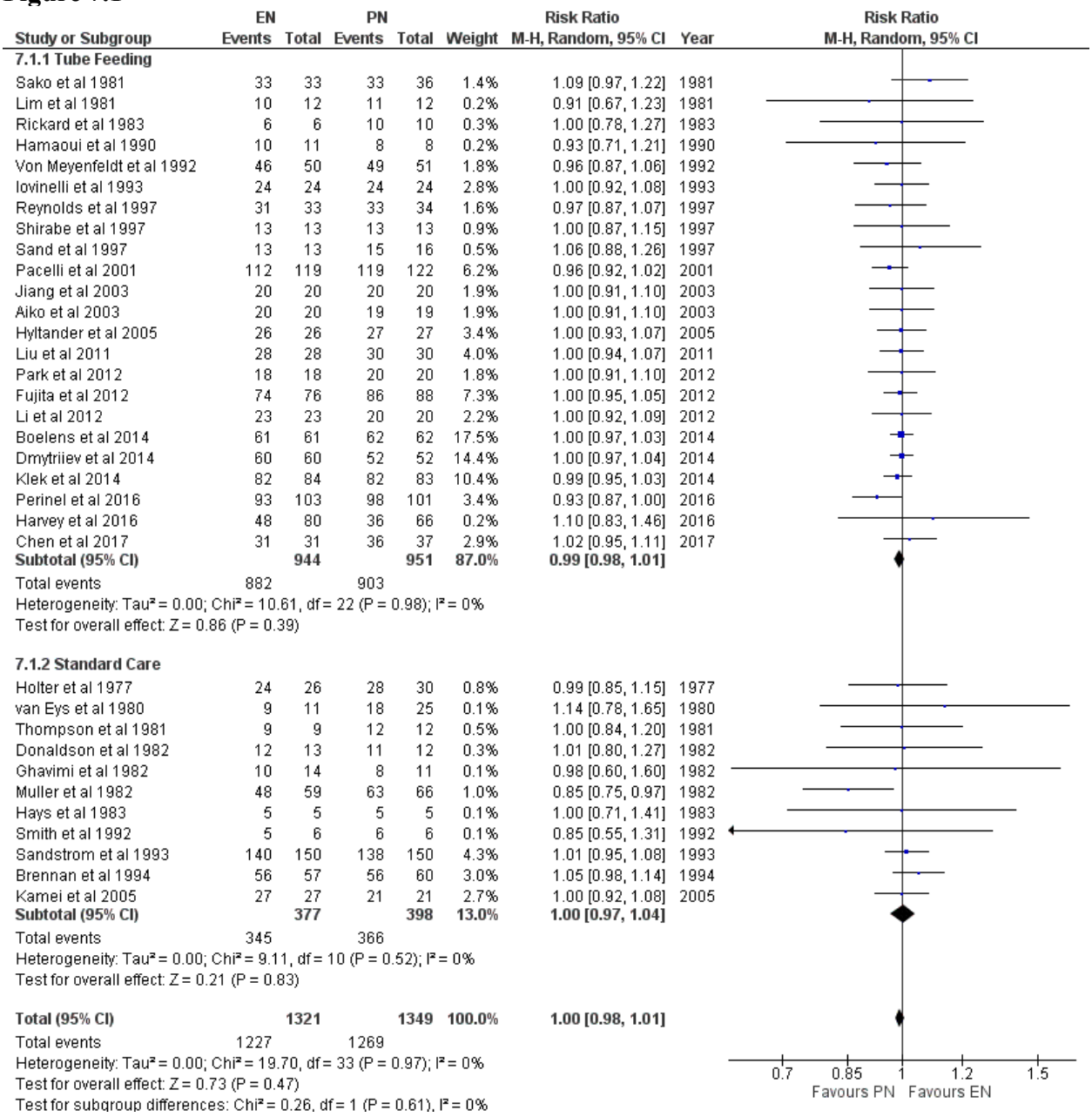

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Figure 7.2

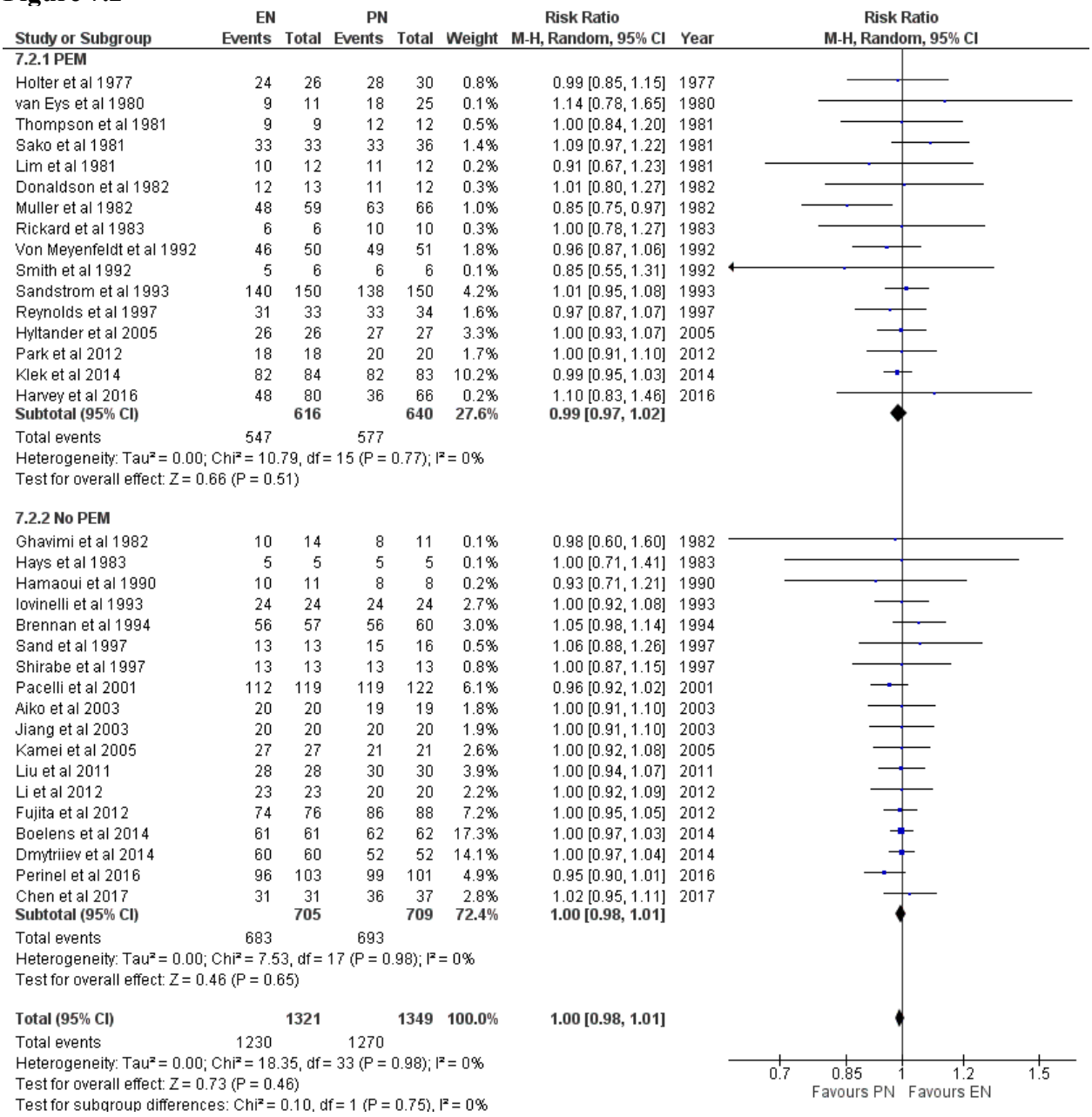

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Figure 7.3

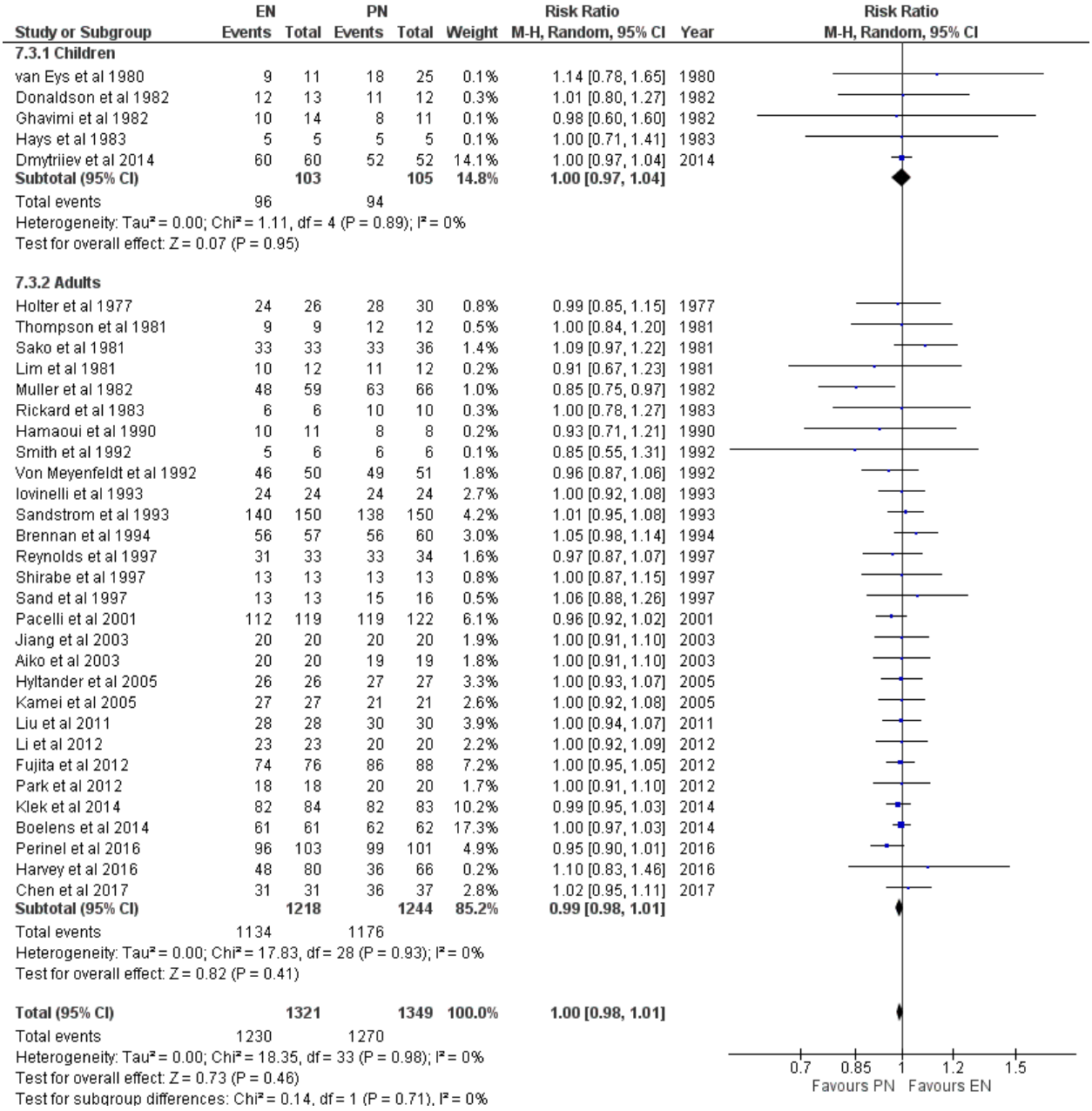

Figure 7. No mortality for enteral nutrition (EN) and parenteral nutrition (PN) patients **7.1** Analyses by EN – tube feeding and standard care **7.2** Analyses by nutrition status – protein energy malnutrition (PEM) and no PEM **7.3** Analyses by age of population – children and adults

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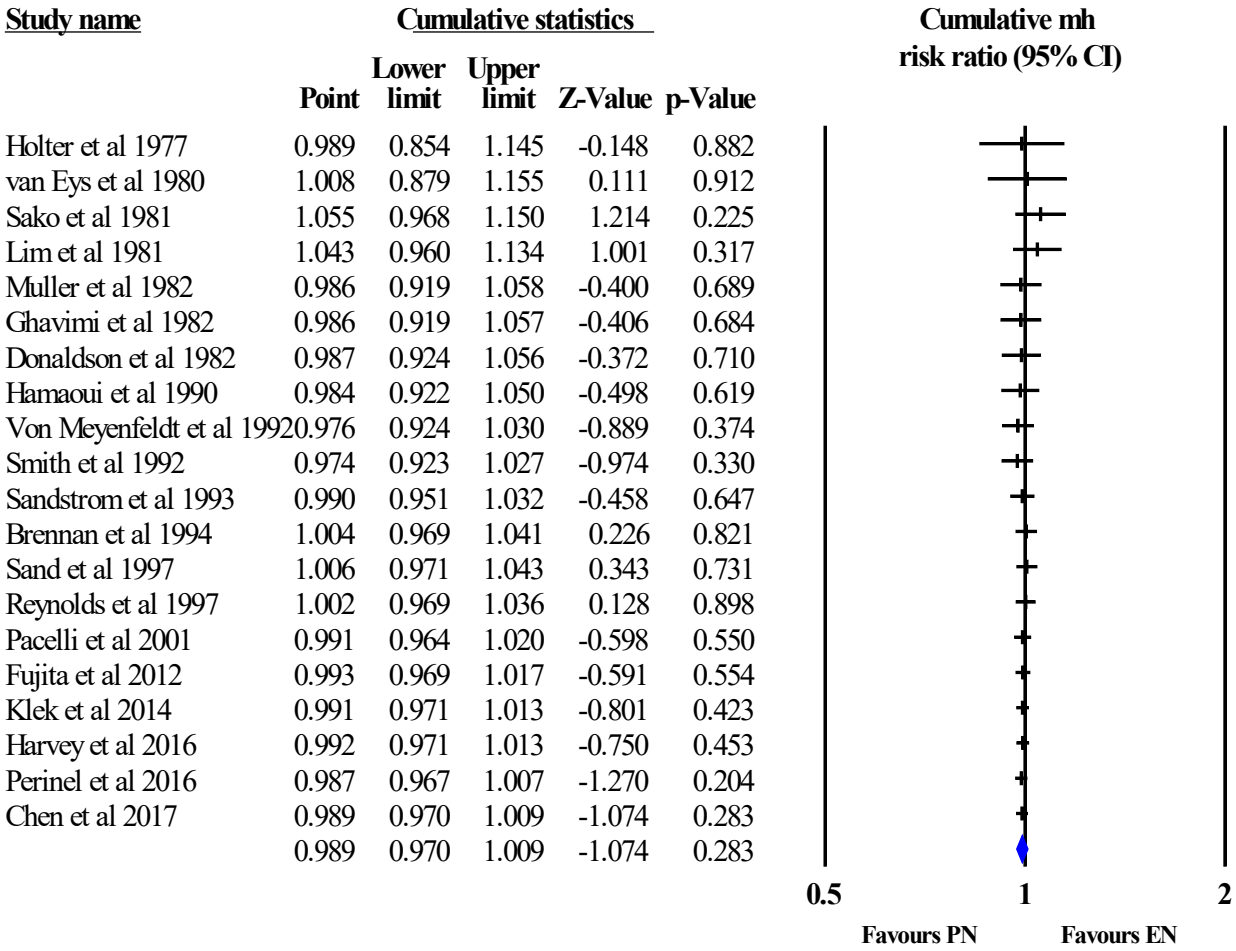

Figure 8. No mortality for enteral (EN) and parenteral nutrition (PN) patients, over time

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Appendix 1. Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to December 20, 2018> Search Strategy:

---

1 exp Parenteral Nutrition/ (23169)
2 exp Enteral Nutrition/ (18501)
3 ((parenteral or intravenous*) adj2 (nutrition or feeding)).mp. (31068)
4 ((enteral or enteric or tube or force) adj2 (nutrition or feeding)).mp. (26309)
5 (1 or 3) and (2 or 4) (6209)
6 exp Comparative Study/ (1815838)
7 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone or prefer* or better).mp. (6846615)
8 or/6-7 (6846615)
9 5 and 8 (2502)
10 limit 9 to english language (2120)
11 limit 10 to randomized controlled trial (288)

****

Database: Embase Classic+Embase <1947 to 2018 Week 51> Search Strategy:

---

1 exp parenteral nutrition/ (47926)
2 exp enteric feeding/ (29141)
3 ((parenteral or intravenous*) adj2 (nutrition or feeding)).mp. (49280)
4 ((enteral or enteric or tube or force) adj2 (nutrition or feeding)).mp. (41156)
5 (1 or 3) and (2 or 4) (10801)
6 exp comparative study/ (1327146)
7 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone or prefer* or better).mp. (9108614)
8 or/6-7 (9108614)
9 5 and 8 (4130)
10 limit 9 to english language (3499)
11 limit 10 to randomized controlled trial (402)

****

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <November 2018> Search Strategy:

---

1 exp Parenteral Nutrition/ (1554)
2 exp Enteral Nutrition/ (1644)
3 ((parenteral or intravenous*) adj2 (nutrition or feeding)).mp. (4161)
4 ((enteral or enteric or tube or force) adj2 (nutrition or feeding)).mp. (4659)
5 (1 or 3) and (2 or 4) (1653)
6 exp Comparative Study/ (11)

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7 (comparison or comparative or compare* or versus or vs or match or rival* or oppose or "side by side" or alone or prefer* or better).mp. (732365)
8 or/6-7 (732365)
9 5 and 8 (826)
10 limit 9 to english language (545)
****

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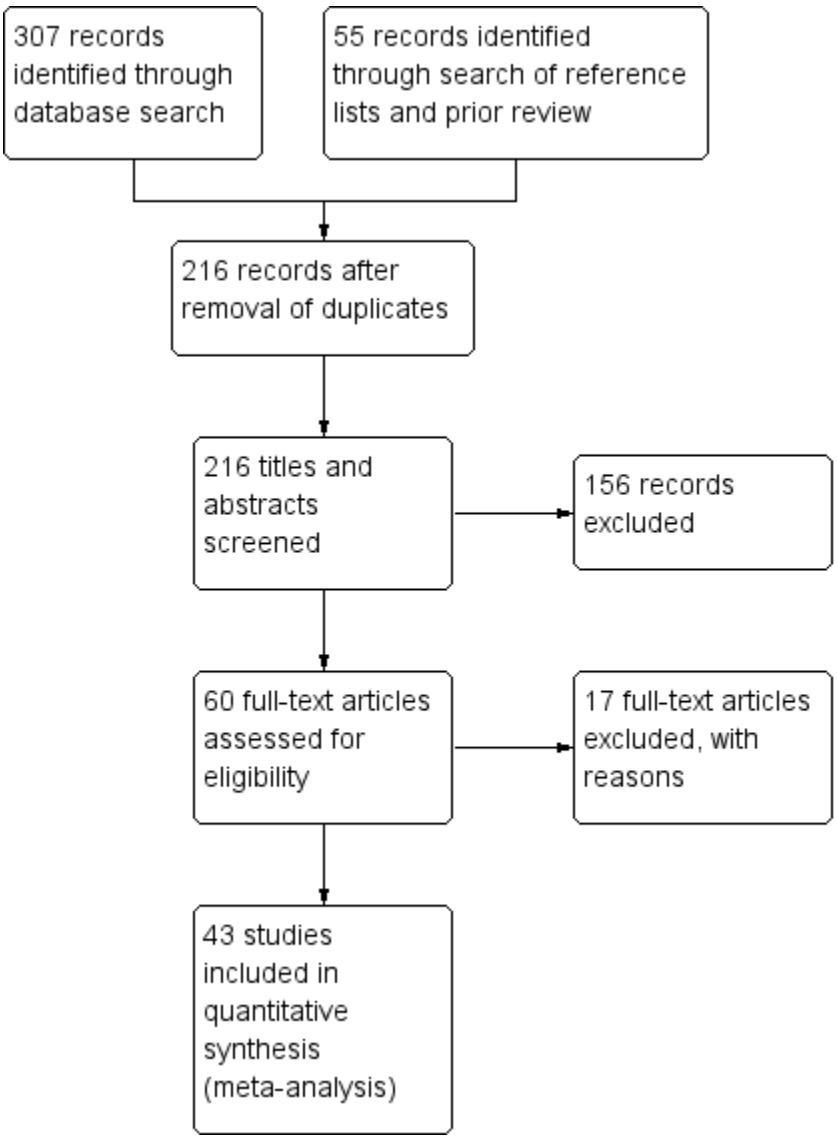
Appendix 2. PRISMA Flow Diagram



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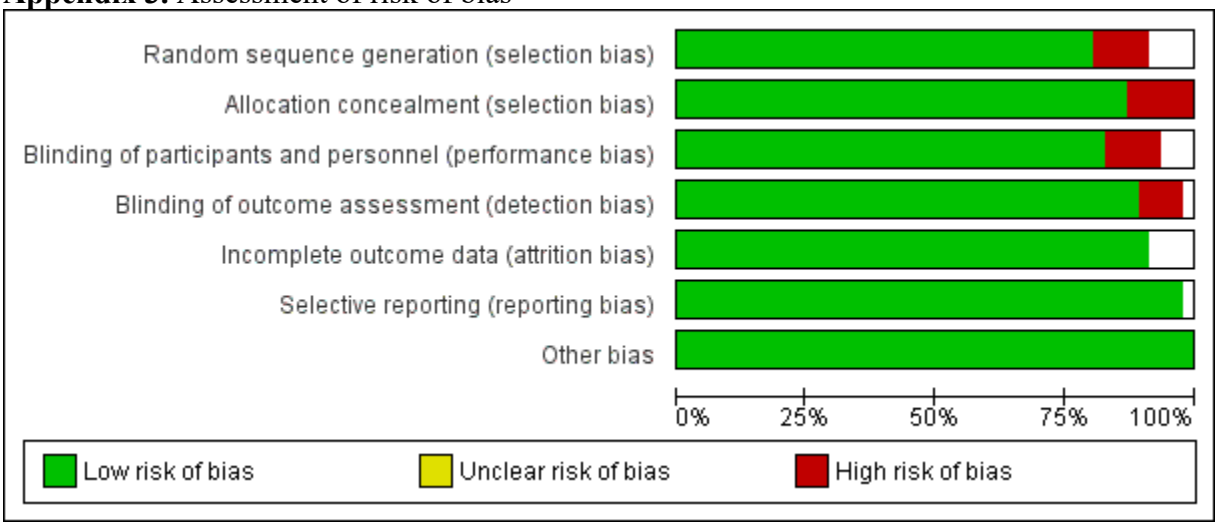
Appendix 3. Assessment of risk of bias



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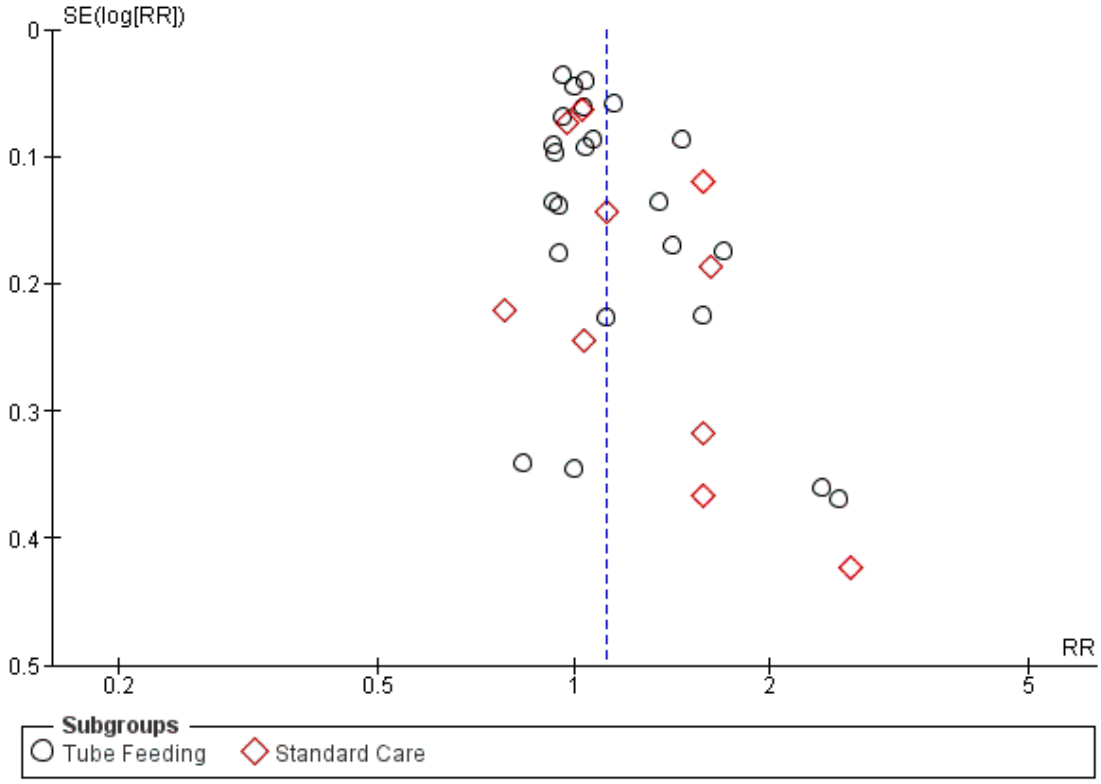
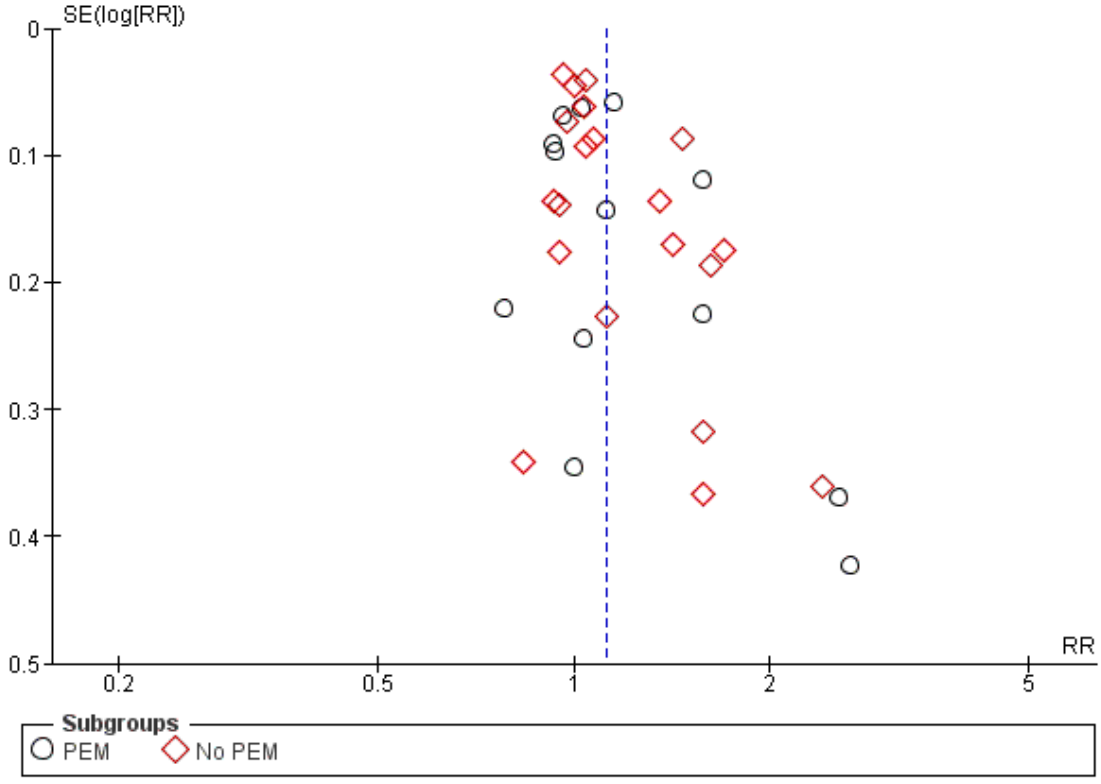
Appendix 4.1



Appendix 4.2



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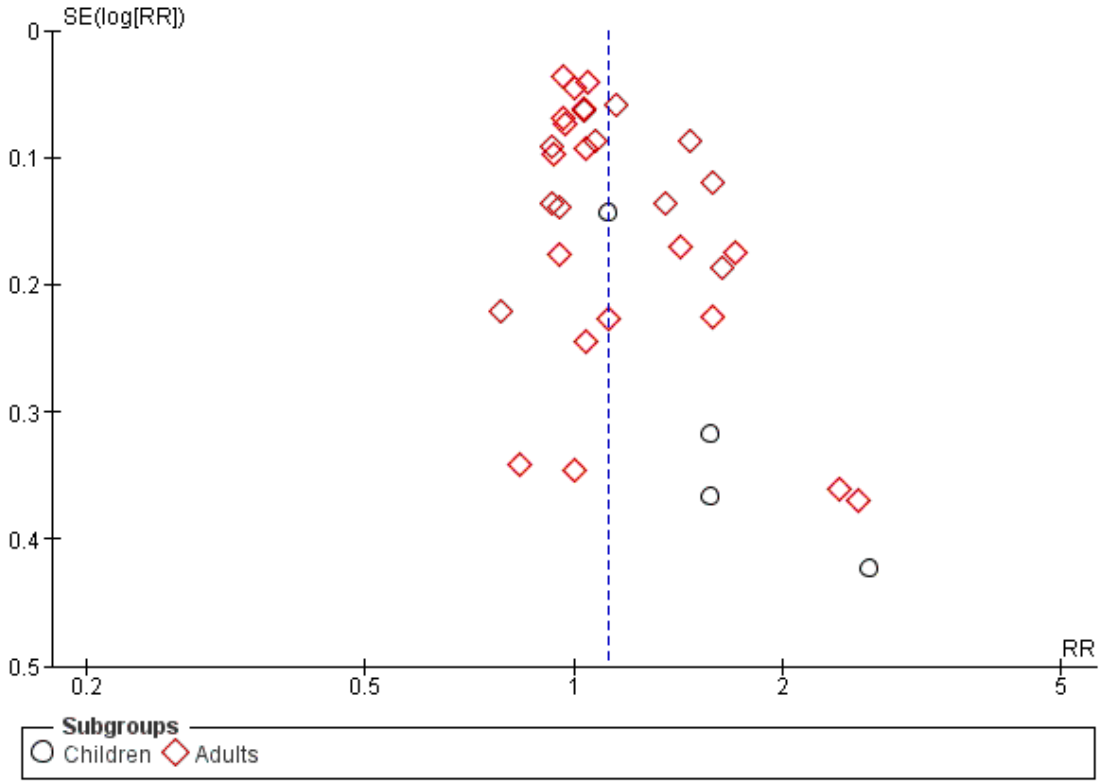
Appendix 4.3



Appendix 4. Assessment of publication bias for endpoint "No infection" **4.1** Assessment by enteral nutrition (EN) – tube feeding and standard care **4.2** Assessment by nutrition status – protein energy malnutrition (PEM) and PEM **4.3** Assessment by age of population – children and adults

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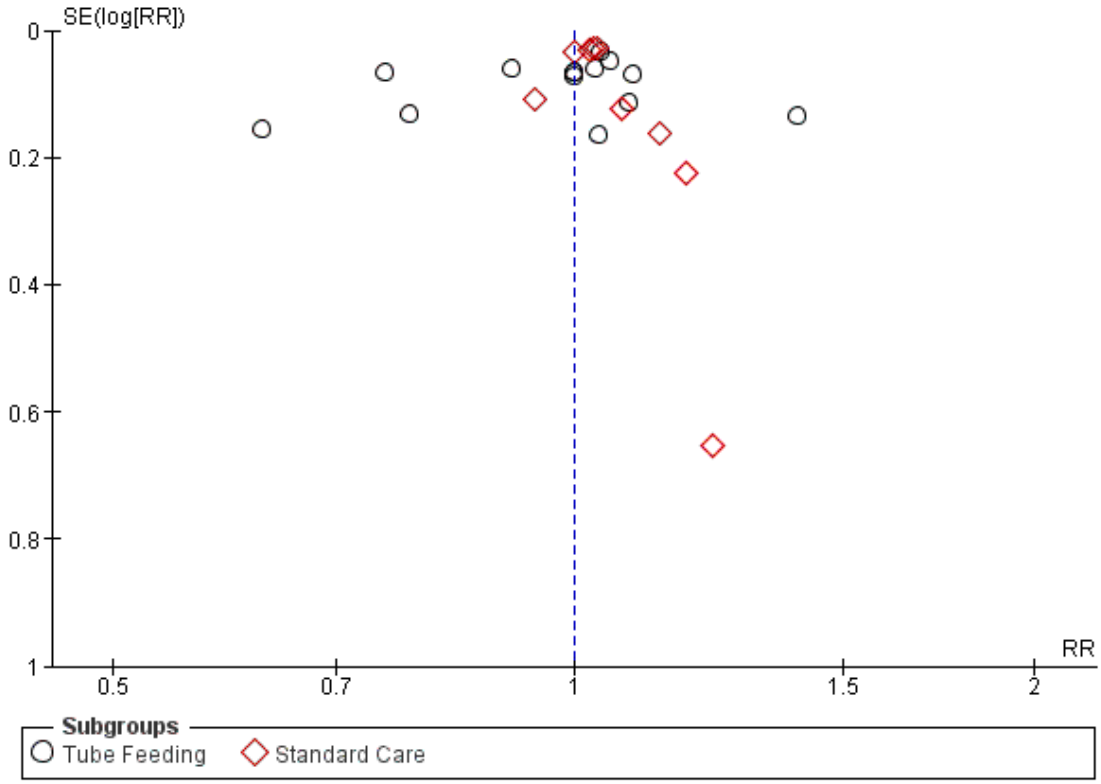
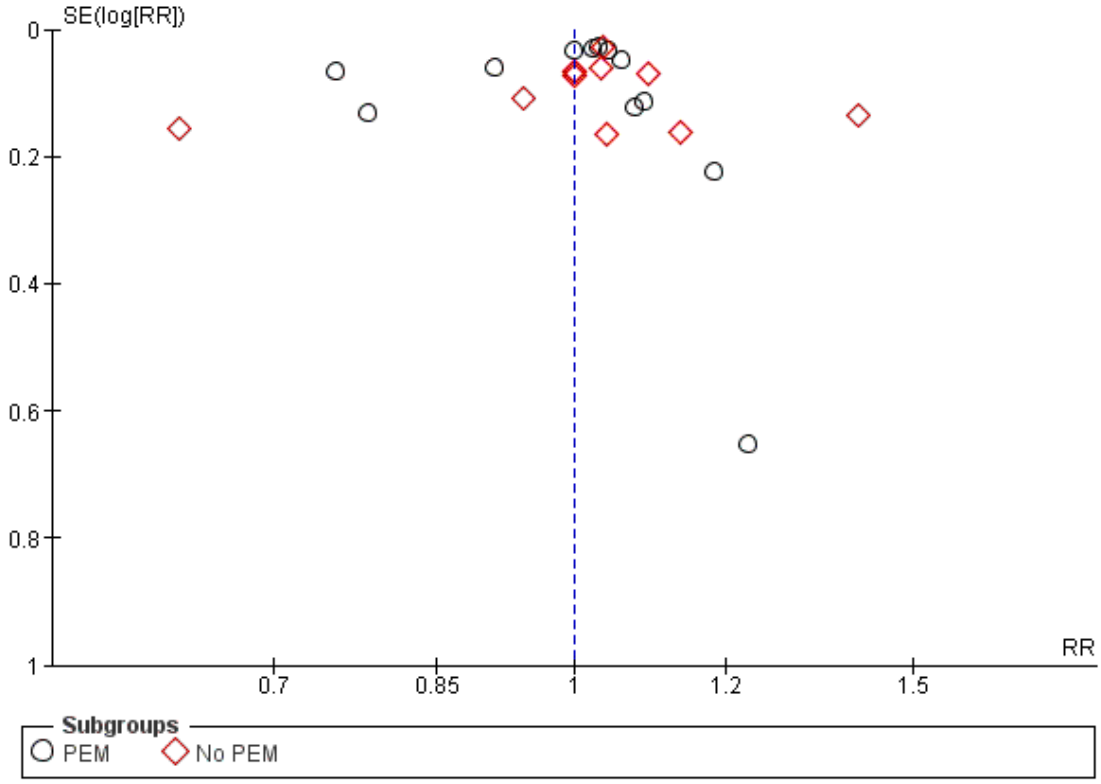
Appendix 5.1



Appendix 5.2



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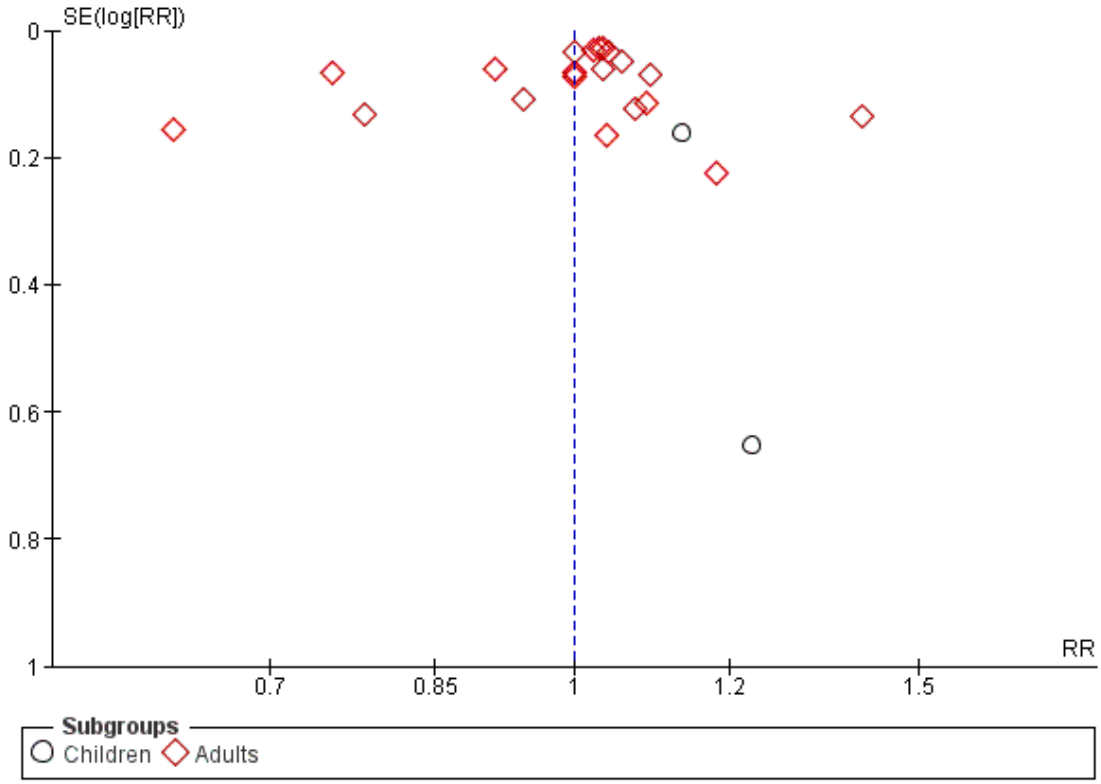
Appendix 5.3



Appendix 5. Assessment of publication bias for endpoint "No nutrition support complications" **5.1** Assessment by enteral nutrition (EN) – tube feeding and standard care **5.2** Assessment by nutrition status – protein energy malnutrition (PEM) and PEM **5.3** Assessment by age of population – children and adults

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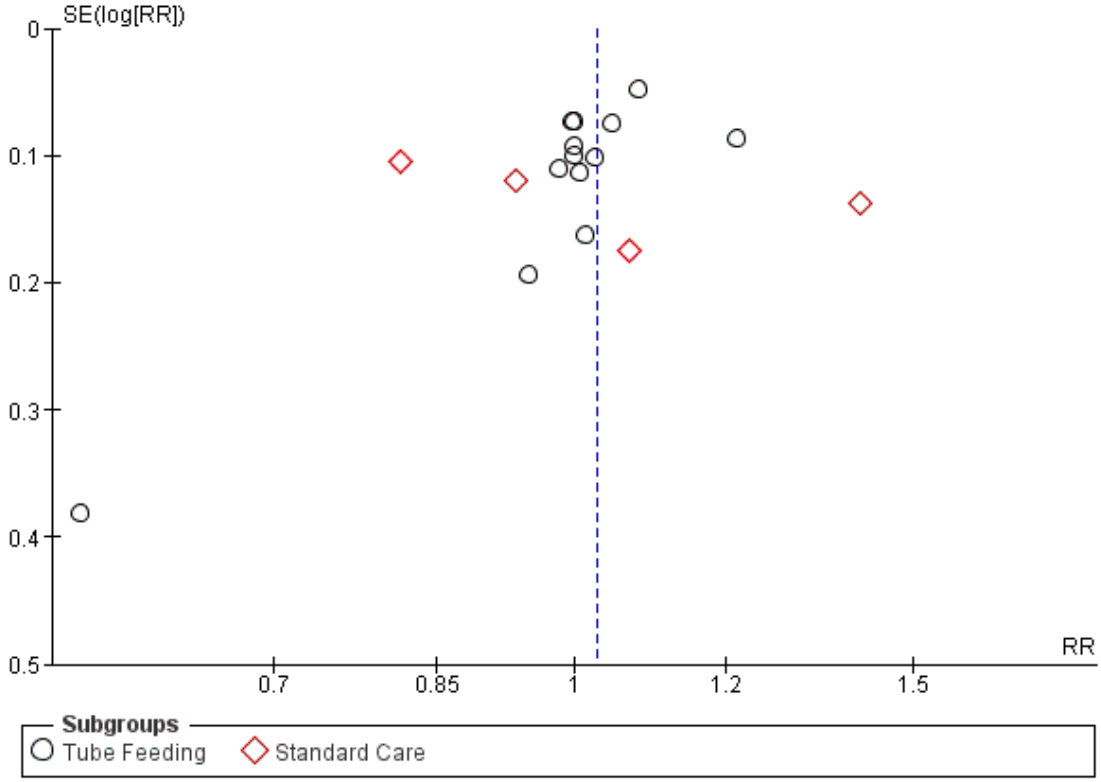
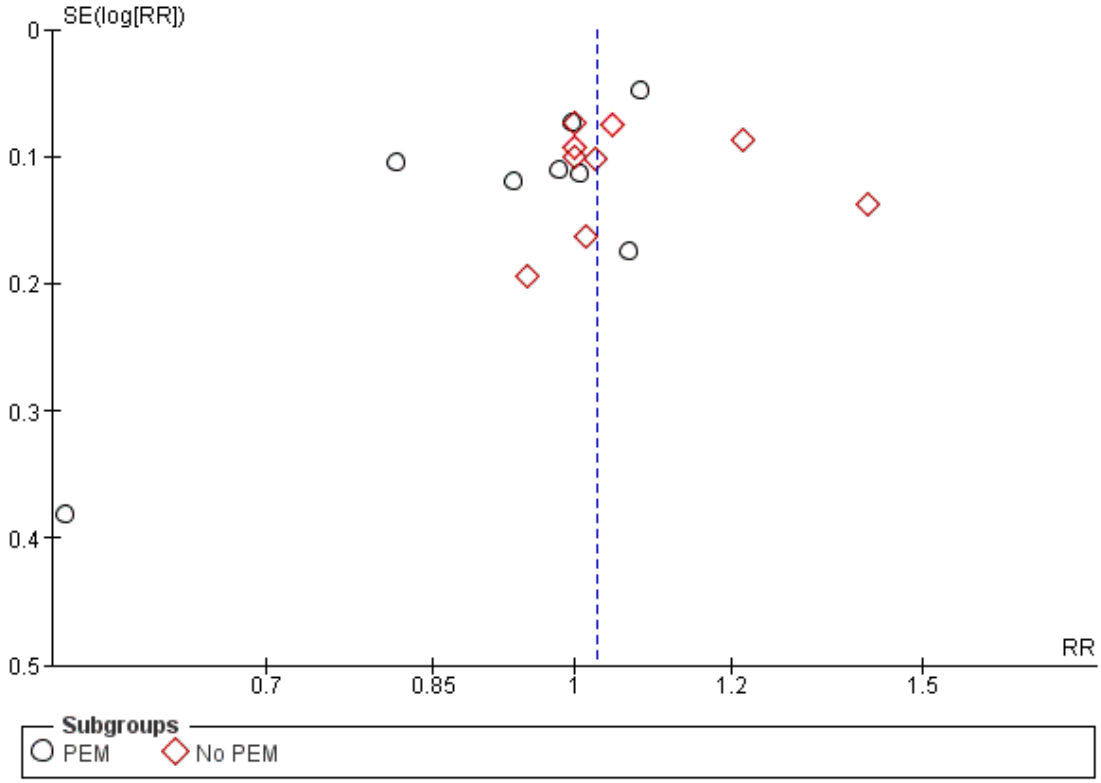
Appendix 6.1



Appendix 6.2



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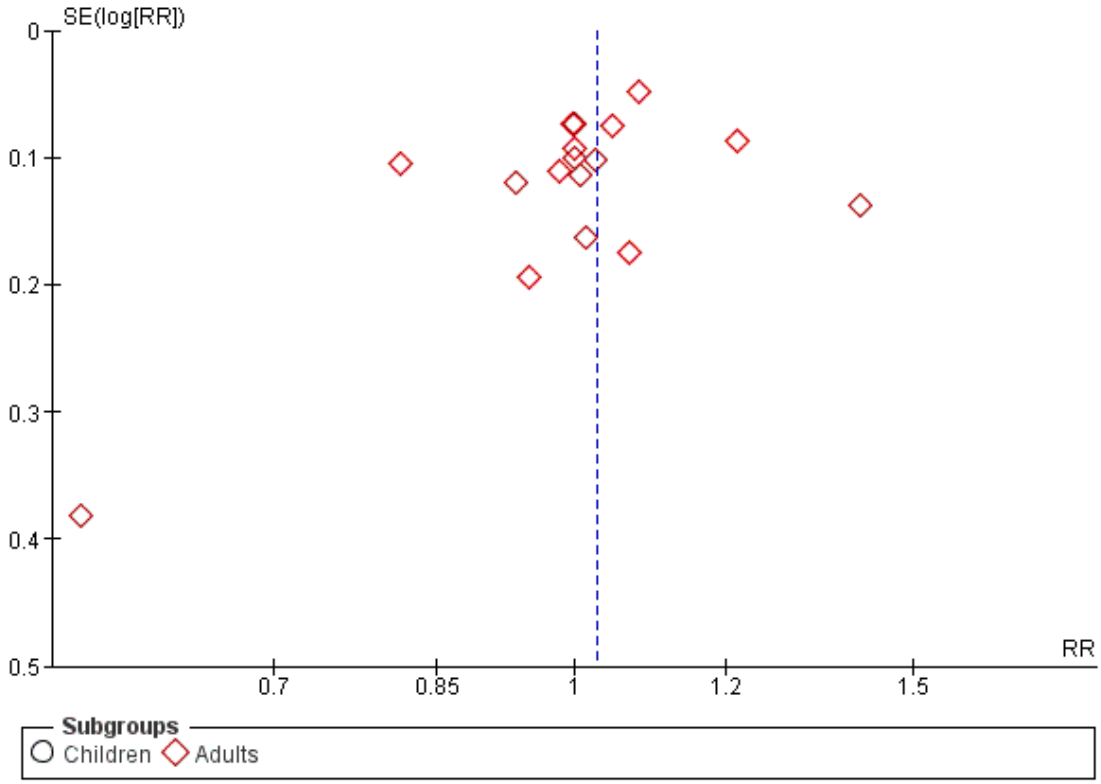
Appendix 6.3



Appendix 6. Assessment of publication bias for endpoint "No major complications" **6.1** Assessment by enteral nutrition (EN) – tube feeding and standard care **6.2** Assessment by nutrition status – protein energy malnutrition (PEM) and PEM **6.3** Assessment by age of population – children and adults

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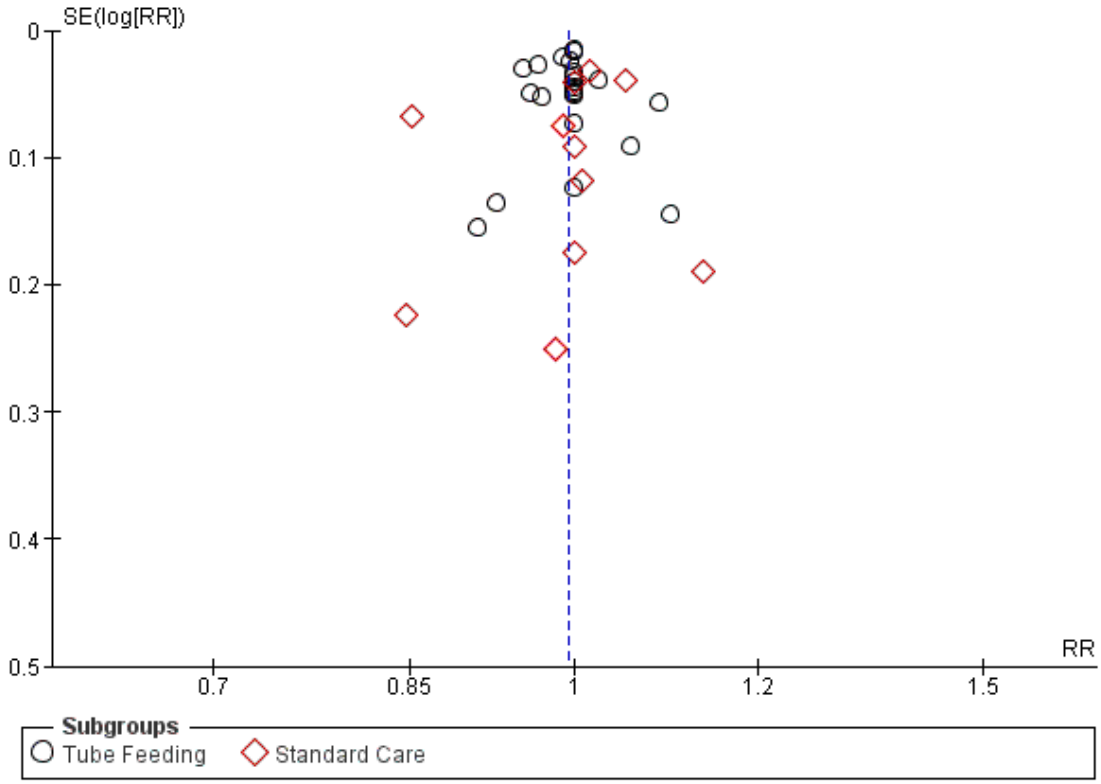
Appendix 7.1



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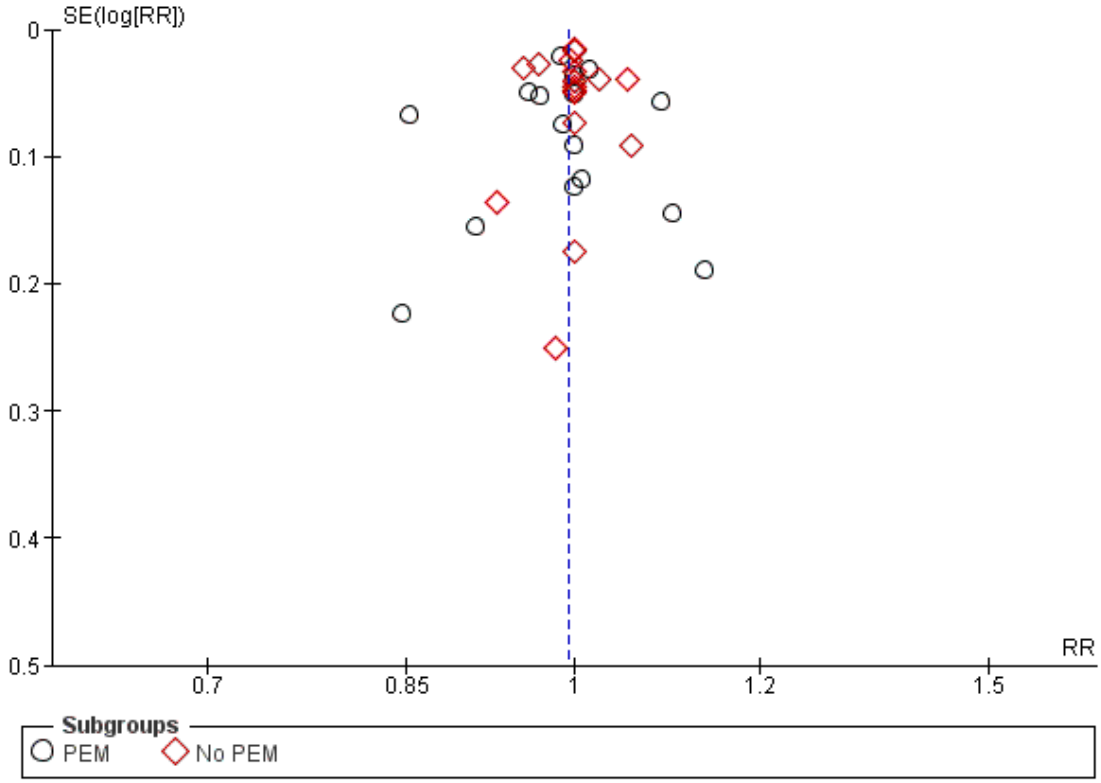

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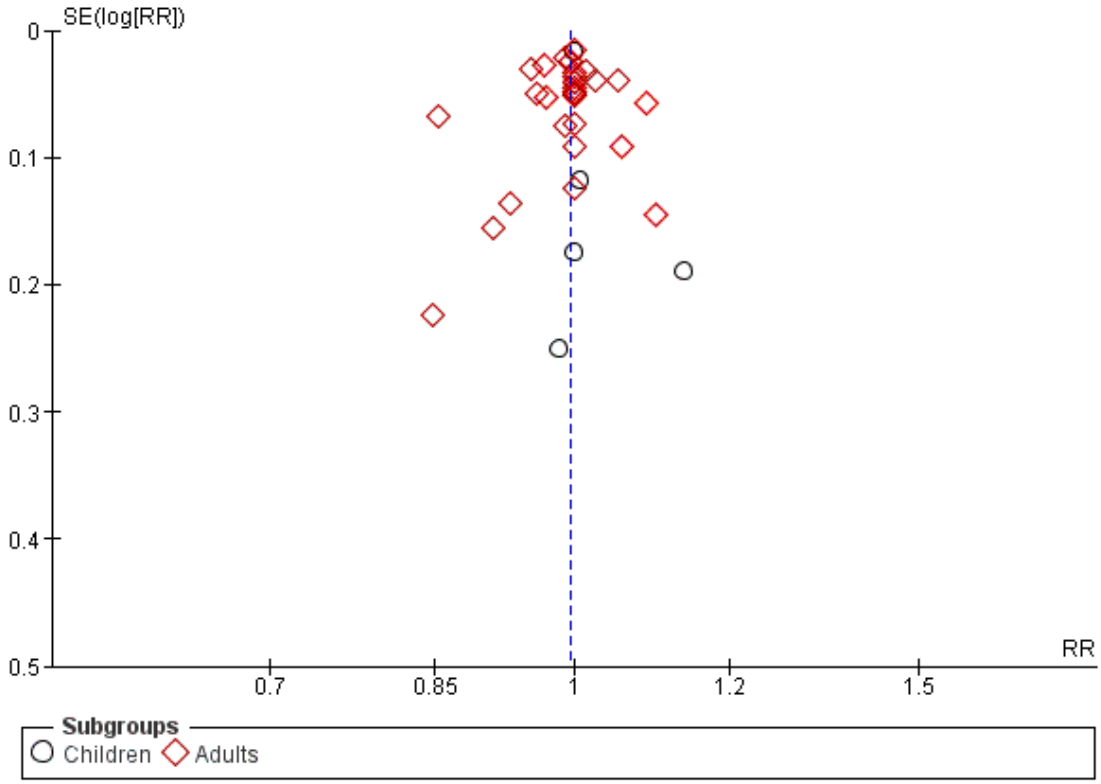
Appendix 7.3



Appendix 7. Assessment of publication bias for endpoint "No mortality" **7.1** Assessment by enteral nutrition (EN) – tube feeding and standard care **7.2** Assessment by nutrition status – protein energy malnutrition (PEM) and PEM **7.3** Assessment by age of population – children and adults

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