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RESEARCH

One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial

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Abstract

Objective To evaluate the effect of initial low energy permissive underfeeding ("trophic feeding") versus full energy enteral feeding ("full feeding") on physical function and secondary outcomes in patients with acute lung injury.

Design Prospective longitudinal follow-up evaluation of the NHLBI ARDS Clinical Trials Network's EDEN trial

Setting 41hospitals in the United States.

Participants 525 patients with acute lung injury.

Interventions Randomised assignment to trophic or full feeding for up to six days; thereafter, all patients still receiving mechanical ventilation received full feeding.

Measurements Blinded assessment of the age and sex adjusted physical function domain of the SF-36 instrument at 12 months after acute lung injury. Secondary outcome measures included survival; physical, psychological, and cognitive functioning; quality of life; and employment status at six and 12 months.

Results After acute lung injury, patients had substantial physical, psychological, and cognitive impairments, reduced quality of life, and impaired return to work. Initial trophic versus full feeding did not affect mean SF-36 physical function at 12 months (55 (SD 33) *v* 55 (31), P=0.54), survival to 12 months (65% *v* 63%, P=0.63), or nearly all of the secondary outcomes.

Conclusion In survivors of acute lung injury, there was no difference in physical function, survival, or multiple secondary outcomes at 6 and 12 month follow-up after initial trophic or full enteral feeding.

Trial Registration NCT No 00719446

Introduction

Optimal nutritional strategies for mechanically ventilated patients in the intensive care unit are uncertain. There is some evidence and recommendations to support both initial full energy enteral feeding ("full feeding") and low energy permissive underfeeding ("trophic feeding") with different risks and benefits described.[1-7] The Acute Respiratory Distress Syndrome Clinical Trials Network of the National Heart, Lung and Blood Institute published a large, multicentre randomised open label trial of initial trophic compared with full enteral feeding for up to six days in patients with acute lung injury (the "EDEN trial").[8] This trial found no significant difference in short term outcomes, including mortality and days without ventilation. Because nutritional interventions have the potential for longer term effects,[9] and because longer term outcomes of patients in

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Appendix: Eligibility criteria for EDEN trial

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intensive care units might differ from short term results, study outcomes also should be assessed over a longer time frame.[10-15] Evaluation of longer term functional outcomes is especially important in patients with acute lung injury because trophic feeding can exacerbate protein limitations in the intensive care unit,[16] and such malnutrition might underlie important muscle loss,[17] persistent muscle weakness, and functional impairment in these patients.[18-22] Moreover, post hoc data analyses from a previous phase II randomised trial in mechanically ventilated patients in intensive care showed that they were more likely to be discharged to a rehabilitation facility than home with trophic rather than full feeding.[23]

We undertook a prospective longitudinal evaluation of patient outcomes at six and 12 months after acute lung injury in participants from the EDEN study. We assessed patients' physical function, quality of life, functional activities, fatigue, psychological symptoms, cognition, and employment status at six and 12 months after acute lung injury and evaluated the effect of initial trophic compared with full enteral feeding on physical function and secondary outcome measures.

Methods

This study, the ARDS Network Long Term Outcomes Study (ALTOS), was designed to prospectively follow patients enrolled in several ARDS Network trials, including the EDEN trial. Three of the 44 hospitals included in the EDEN study did not participate in this follow-up study. Consenting patients from the 41 participating hospitals were eligible for enrolment into this prospective longitudinal study, with follow-up from April 2008 to April 2012.

Patients

Details of the EDEN eligibility criteria and study intervention have been reported previously (see appendix).[8] Over the first six days of the EDEN trial, the trophic feeding group received, on average, 1672 kJ/day (25% of caloric goal), while the full feeding group received 5434 kJ/day (80% of caloric goal).[8] We excluded patients from the EDEN trial if they met any of the following criteria, based on their status before admission to hospital for acute lung injury: cognitive impairment (evaluated from the medical record and interview with the patient and/or proxy), non-English speaking, homelessness, or aged under 18. The first 272 of 1000 patients enrolled in EDEN were simultaneously randomised to a separate blinded trial (the OMEGA study) that examined a nutritional supplement containing omega 3 fatty acids and antioxidants compared with an isoenergetic isovolemic control in a 2×2 factorial design.[24] All EDEN patients were managed with simplified versions of lung protective ventilation[25] and fluid conservative haemodynamic management[26] protocols, with blood glucose control accomplished with institution specific protocols for insulin targeting about 4-8 mmol/L, with tighter control permitted.[8]

Study procedures

Trained research staff, blinded to treatment allocation, telephoned patients three months after the onset of acute lung injury to provide a reminder about the follow-up study and to obtain updated contact information for the patient and designated proxies. They completed the study assessments at six and 12 months. Published methods were used to minimise loss to follow-up.[27-32] When patients could not complete the assessments by telephone, study assessments were completed by mail (5% of all assessments) and/or by designated proxies (only for the functional performance inventory and the employment secondary outcome measures, representing 9% of these assessments).

Primary and secondary outcomes

The primary outcome was the physical function domain of SF-36 (version 2) instrument,[33] adjusted for age and sex (range 0-100; higher score is better). Secondary outcomes included the age and sex adjusted SF-36 mental health domain (range 0-100; higher score is better) and the SF-36 physical and mental health summary quality of life norm based scores (range 0-100; higher score is better; mean 50 (SD 10)); the EQ-5D-3L[34] generic quality of life instrument with a utility score[35] (range −0.11-1.0; higher score is better) and visual analogue scale score (range 0-100; higher score is better); the functional performance inventory[36 37] overall functional activity score and subscale scores for physical exercise, maintaining household, and body care (for each, range 0-3; higher score is better); functional assessment of chronic illness therapy[38 39] fatigue interval scale score (range 0-100; higher score is better, with scores ≤68 indicating fatigue); hospital anxiety and depression scale[40] subscale scores for anxiety and depression symptoms (for each, range 0-21; lower score is better, with scores ≥8 indicating substantial symptoms); impact of events scale-revised[41] score for post-traumatic stress disorder symptoms (range 0-4; lower score is better, with scores ≥1.6 indicating substantial symptoms[42]); the mini-mental state examination telephone version converted score[43] for cognition (range 0-30; higher score is better, with scores ≤24 indicating impairment); and employment status (full or part time work *v* unemployed).

Statistical analyses

All analyses were by intention to treat and performed with SAS version 9.2 (SAS Institute, Cary, NC). A two sided $P<0.05$ was considered significant. Statistical analyses were conducted according to an a priori written statistical analysis plan. A Kaplan-Meier curve was used to display survival during the follow-up period, with a comparison of trophic versus full feeding groups with the log rank test. To evaluate change over time (12 *v* six months) for the entire study population, we compared continuous and binary outcome measures, ignoring treatment assignment, using linear and binomial (identity link) regression models, respectively, with generalised estimating equations[44] and an exchangeable correlation model. To quantify the treatment effect for the continuous and binary outcome measures assessed at six and 12 months, we created linear and logistic regression models, using generalised estimating equations with an exchangeable correlation model and an indicator for treatment group (trophic *v* full feeding), follow-up time (12 *v* six months), and the interaction of treatment group and time. In a secondary analysis for the primary outcome variable we extended the above model to test for a statistical interaction between OMEGA randomised assignment and EDEN treatment group (trophic *v* full feeding). We performed additional secondary analyses for the primary outcome variable for a priori patient subgroups at baseline (body mass index (BMI) <25, 25 to <30, ≥30), acute lung injury subgroup ($Pa0_2/Fi0_2$ ≤200 *v* $Pa0_2/Fi0_2$ >200), shock (present *v* absent), and a priori statistical interactions (age and APACHE III score as continuous variables). Missing data were excluded from statistical analyses as only 1-6% of each outcome instrument evaluated had any missing data.

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Results

There were 951 patients enrolled at the EDEN hospitals participating in this study. Baseline patient characteristics were comparable between the trophic and full feeding groups, with a mean age of 52, 49% women, 79% white, and 82% living independently (table 1⇓). Of these 951 patients, 155 (16%) who survived until hospital discharge did not meet eligibility criteria for this follow-up study, leaving 796 patients of whom 508 (64%) survived until 12 months after randomisation (fig 1⇓), with no difference between groups (trophic *v* full feeding estimated 12 month survival 65% *v* 63%; log rank P=0.63).

Patient outcomes at six and 12 months

At six and 12 months, there were 525 and 510 consenting survivors eligible for follow-up, with only 11 (2%) and 23 (<5%) missed at the respective follow-up times (fig 2⇓). Mean (SD) lengths of stay in the intensive care unit and in hospital for the 525 consenting patients surviving until six month follow-up were 14 (12) and 22 (16) days, respectively. Survivors had substantially lower physical and mental quality of life scores compared with age and sex matched population norms (table 2⇓), with a 12 month mean score on the physical function domain of 55 (SD 32) compared with the population norm of 82 (SD 9) (P<0.001). Functional activity level, as measured by the overall mean score on the functional performance inventory, at 12 months was 2.0 (SD 0.7), indicating "some" difficulty. These physical outcomes at 12 months were significantly improved from the six month assessment (table 2). During the 12 month follow-up, 87 (18%) and 57 (12%) patients were admitted to rehabilitation and skilled nursing facilities, respectively, with 267 (56%) requiring either these types of inpatient rehabilitation and nursing care or outpatient physiotherapy. Substantial symptoms of anxiety, depression, and post-traumatic stress disorder were common at 12 months, affecting 42%, 37%, and 23% of survivors, respectively, without significant improvement from the six month assessment (table 2). Cognitive impairment was present in 21% of survivors at 12 months, reduced from 25% at six months (P=0.06). Among survivors at 12 month follow-up, 223 (47%) of the 474 who reported on their employment status before admission to hospital were employed; of these previously employed survivors, 107 (48%) were not working at 12 month follow-up, with 82 (77%) of them attributing their unemployment to health related reasons.

Comparison of trophic *v* full feeding

There was no significant difference in the mean age and sex adjusted SF-36 physical function domain score (55 (SD 33) *v* 55 (SD 31) between the initial trophic and full feeding groups; mean difference adjusted for age and sex 2 (95% confidence interval −4 to 7, P=0.54). There was no interaction between OMEGA randomised assignment and trophic versus full feeding group on the physical function domain score. With the exception of the SF-36 mental health measures that favoured trophic feeding, there were no significant differences between trophic and full feeding groups for all other secondary outcome measures, including functional activities, fatigue, psychological symptoms, cognition, and employment status (table 3⇓, fig 3⇓). Across the primary outcome and almost all secondary outcomes, the treatment effects at the six and 12 month assessment did not significantly differ. In addition, there were no differences in secondary analyses of the a priori subgroups and statistical interactions.

The 12 month cumulative incidence of admission to a physical rehabilitation facility was greater in the trophic group (57 (23%) *v* 30 (14%), P=0.01). There were no significant differences between the trophic and full feeding groups in new residence in a healthcare facility at 90 days (19 (7%) *v* 11 (4%), P=0.21) or in the 12 month cumulative incidence of admission to skilled nursing facilities (29 (12%) *v* 28 (13%), P=0.70) or receipt of outpatient physiotherapy (121 (49%) *v* 99 (46%), P=0.50).

Discussion

Over 12 months of follow-up of patients with acute lung injury from 41 hospitals participating in the EDEN trial, there was no difference in physical function (primary outcome), 12 month survival, or physical, psychological and cognitive function, or employment status at six and 12 months between those randomised to initial trophic versus full enteral feeding. The cumulative mortality was 36%, with survivors showing substantial physical, psychological and cognitive impairments, with reduced quality of life, substantial need for institutionalisation and physical rehabilitation, and impaired return to work.

Comparison with other studies

Consistent with the findings of mainly previous single centre studies of people with acute lung injury,[18 22 45-49] this multicentre study showed impairments across multiple physical, psychological, and cognitive domains, collectively referred to as "post-intensive care syndrome."[50] Unlike physical outcomes, mean scores for psychological and cognitive outcomes did not significantly improve between six and 12 months. It is notable that patients' baseline status for many of these outcomes cannot be measured before onset of acute lung injury, raising the possibility that these were pre-existing impairments; however, the patients evaluated were relatively young, lived independently without assistance at baseline, and were free from cognitive impairments before the illness. Moreover, the observed impairments in quality of life scores at six and 12 months were substantially greater than estimated quality of life scores before intensive care reported in other groups of acute lung injury survivors.[51 52] In addition, other large cohort studies, with prospective measurement of status before intensive care, have shown important new subsequent impairments in physical, psychological, and cognitive outcomes.[53-57] Finally, the magnitude and incidence of these impairments is supported by the high rate of use of rehabilitation, new institutionalisation, and inability to return to work after acute lung injury.

Nutritional strategies in intensive care units, as evaluated in this randomised trial of initial trophic versus full enteral feeding, had no effect on a wide spectrum of outcome measures reported by patients, with no differences between groups for the physical function primary outcome or for nearly all secondary physical, psychological, cognitive and employment outcomes. There is little clinical research investigating the long term outcomes of nutritional strategies in the intensive care unit; hence, limiting specific insights into the potential reasons for these findings and emphasising the importance of further research on this issue. Of note, about half of patients in the trophic feeding group eventually received full feeding after the initial six day period, as per the EDEN protocol. Hence, perhaps the overall duration of differences in feeding strategies in the EDEN patients was not long enough to contribute to differences in outcomes. Alternatively, perhaps within one nutritional strategy, potential benefits were counter balanced by harms, with each mediated by different mechanisms associated with the strategy.

Mean differences in SF-36 mental health scores were significant between the feeding groups, but relatively small in magnitude[58]

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and not supported by significant differences in any of the specific psychological outcome measures (such as symptoms of anxiety, depression, and post-traumatic stress disorder); such differences should therefore be cautiously interpreted. Moreover, as previously observed in a post hoc analysis from a similar phase II randomised trial of nutrition in intensive care,[23] patients in the trophic feeding group were significantly more likely than patients in the full feeding group to be admitted to a rehabilitation facility over 12 month follow-up. Despite this finding, there were no significant differences in other physical, psychological, and cognitive outcomes between groups at six and 12 months, and there were no differences in new residence in a healthcare facility at 90 days or in the 12 month cumulative incidence of admission to a skilled nursing facility or receipt of outpatient physiotherapy. Further exploration of shorter term outcomes and of muscle strength and performance based physical function measures (such as the six minute walk test) could help inform this finding as trophic feeding might have short term effects or physiological effects not evaluated in this study.

Limitations

The study has several strengths, including detailed prospective longitudinal assessment of about 500 patients recruited from 41 hospitals. In addition, at six and 12 month follow-up, only 2% and <5% of consenting patients missed their visits. This study also has potential limitations. Firstly, the EDEN trial primarily evaluated relatively young, well nourished, overweight patients with acute lung injury with pneumonia or non-pulmonary sepsis. The study's findings might not therefore be generalisable to critically ill patients who are older, malnourished, and without infection. Secondly, the study evaluated only patient/proxy reported outcomes obtained by phone or mail, without any performance based assessments (such as the six minute walk test) from direct evaluation. Thirdly, the open label design of the EDEN trial has the potential to introduce bias. In our study, however, the patient outcomes assessors and investigators were blinded to randomised group assignment, and the written statistical analysis plan and study data were finalised before unblinding the treatment allocation. Finally, as functional outcome measures can be assessed only in survivors, mortality after randomisation could introduce bias in understanding the effect of a randomised treatment on functional outcomes.[59] This issue is of less importance in this study, however, because the randomised treatment allocation did not differentially affect mortality.

Conclusion

This multicentre longitudinal study of outcomes at six and 12 months after acute lung injury showed substantial physical, cognitive, and psychological impairments, with reduced quality of life, substantial need for institutionalisation and physical rehabilitation, and impaired return to work. An initial strategy of trophic or full calorie enteral feeding did not affect patients' physical function or multiple secondary outcome measures at six and 12 month follow-up after acute lung injury.

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What is already known on this topic

A large multisite randomised trial showed no difference in short term mortality and days without ventilation in patients with acute lung injury randomised to initial trophic or full enteral feeding in intensive care

Given differences in protein and total caloric intake between these two feeding strategies, evaluation of the effect on patients' longer term functional outcomes is important

What this study adds

In 525 patients with acute lung injury recruited from 41 US hospitals, substantial physical, psychological, and cognitive impairments were common at six and 12 month follow-up

Randomisation to initial trophic or full enteral feeding did not affect physical function (primary outcome), survival, or psychological and cognitive outcomes at six and 12 month follow-up

in the writing of the report; and in the decision to submit the manuscript for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The study was approved by the institutional review boards at each participating hospital, the two centres performing outcome assessments, and the EDEN data and safety monitoring board; and informed consent was given by all patients or their proxy.

Data sharing: No additional data available

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Tables

Table 1| Characteristics of patients with acute lung injury according to randomisation to initial trophic or full enteral feeding. Figures are means (SD) unless stated otherwise*

Characteristic	All patients (n=951)	Trophic feeding (n=481)	Full feeding (n=470)
Baseline patient data			
Age (years)	52 (16)	52 (16)	52 (15)
No (%) women	468 (49)	227 (47)	241 (51)
No (%) white	717 (79)	362 (79)	355 (79)
No (%) by previous residence:			
Home independently	780 (82)	396 (82)	384 (82)
Home with help or professional help	108 (11)	53 (11)	55 (12)
Nursing, intermediate care, or rehabilitation facility	42 (4)	19 (4)	23 (5)
Other	21 (2)	13 (3)	8 (2)
BMI	30 (8)	30 (8)	30 (8)
No (%) with diabetes	263 (28)	130 (27)	133 (28)
No (%) with previous stroke with sequelae	36 (4)	11 (2)	25 (5)
No (%) receiving chronic haemodialysis	30 (3)	12 (2)	18 (4)
Baseline intensive care data			
No (%) admitted to medical intensive care unit	576 (61)	287 (60)	289 (62)
APACHE III score	91 (27)	92 (28)	90 (27)
PaO_2/FiO_2 ratio	165 (81)	167 (80)	163 (82)
No (%) with PaO_2/FiO_2 ratio ≤200	673 (72)	338 (73)	335(72)
Albumin (g/L)	23 (7)	23 (7)	23 (7)
No (%) by primary lung injury risk factor:			
Pneumonia	617 (65)	321 (67)	296 (63)
Sepsis	139 (15)	78 (16)	61 (13)
Aspiration	91 (10)	40 (8)	51 (11)
Trauma	36 (4)	17 (4)	19 (4)
Transfusions	16 (2)	4 (1)	12 (3)
Other	52 (5)	21 (4)	31 (7)
Daily intensive care data†			
Morning glucose (mmol/L)	7.38 (1.83)	7.10 (1.38)	7.66 (1.38)
Minimum glucose (mmol/L)	6.33 (1.5)	6.16 (1.39)	6.49 (1.55)
Cumulative net fluid balance until day 7 (L)	1.3 (8.3)	0.5 (8.4)	2.0 (8.2)
No (%) with any dialysis during admission	178 (19)	84 (18)	94 (20)
No (%) with any vasopressor use	450 (48)	231 (48)	219 (47)
Proportion of days per patient	22 (31)	22 (30)	23 (32)
No (%) with any corticosteroids	327 (36)	178 (38)	149 (33)
Proportion of days per patient	23 (36)	25 (37)	21 (35)
No (%) with any narcotics	895 (94)	451 (94)	444 (95)
Proportion of days per patient	75 (30)	74 (31)	77 (30)
No (%) with any neuromuscular blocker	186 (20)	84 (18)	102 (22)
Proportion of days per patient	7 (20)	7 (19)	8 (20)
Days without organ failure to day 28:			
Cardiovascular	19 (10)	19 (10)	19 (10)
Renal	20 (11)	20 (11)	19 (11)
Hepatic	22 (10)	22 (10)	23 (10)
Coagulation	23 (9)	22 (10)	23 (9)

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Table 1 (continued)

Characteristic	All patients (n=951)	Trophic feeding (n=481)	Full feeding (n=470)

APACHE III=acute physiology and chronic health evaluation III; PaO_2=partial pressure of oxygen in arterial blood; FiO_2=fraction of inspired oxygen, BMI=body mass index.

*Proportions might not add to 100% because of rounding. Unknown or missing data: race=43, BMI=3, APACHE III score=24, PaO_2/FiO_2=18, albumin=35, morning glucose=4, minimum glucose=4, dialysis=1, daily fluid balance=301, vasopressor use=4, corticosteroids=41, narcotics=2, neuromuscular blocker=2.

†Data presented as overall average for each patient's mean value of available daily data. Medication data available until earlier of 48 hours after cessation of mechanical ventilation or day 10 for corticosteroids and vasopressors, and day 12 for narcotics and neuromuscular blockers. Proportions calculated among days in intensive care unit in which medication data were available. Glucose data available until earlier of 48 hours after cessation of mechanical ventilation or day 12. Days without organ failure until day 28 calculated as previously published.[8]

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Table 2| **Outcomes* at six and 12 months in patients with acute lung injury. Figures are means (SD) unless stated otherwise**

	6 Months (n=514)	12 Months (n=487)	Difference† (95% CI)	P Value†
Quality of life—SF-36 (population norm):				
Physical function (82, SD 9)	51 (32)	55 (32)	4 (2 to 5)	<0.001
Physical health summary (50, SD 10)	38 (12)	39 (13)	2 (1 to 2)	<0.001
Mental health (76, SD 3)	64 (26)	65 (25)	1 (–1 to 3)	0.28
Mental health summary (50, SD 10)	45 (15)	45 (15)	0 (–1 to 1)	0.94
Quality of life—EQ-5D:				
Utility score	0.68 (0.25)	0.71 (0.24)	0.02 (0.00 to 0.04)	0.02
Visual analogue scale	68 (22)	69 (22)	2 (0 to 4)	0.08
Functional activities—functional performance inventory:				
Overall score	1.9 (0.7)	2.0 (0.7)	0.1 (0.1 to 0.1)	<0.001
Physical exercise subscale	1.6 (0.9)	1.6 (0.9)	0.1 (0.0 to 0.1)	0.03
Maintaining house subscale	1.8 (0.9)	1.9 (0.9)	0.1 (0.1 to 0.2)	<0.001
Body care subscale	2.5 (0.7)	2.5 (0.7)	0.0 (0.0 to 0.1)	0.03
Fatigue—FACIT:				
Interval score	60 (17)	62 (18)	2 (1 to 3)	0.001
No (%) with score ≤68	342 (71)	304 (67)	–4 (–8 to –1)	0.02
Psychological symptoms‡:				
Anxiety score	7 (5)	7 (5)	0 (–1 0)	0.21
No (%) with score ≥8	218 (45)	195 (42)	–3 (–7 to 2)	0.21
Depression score	6 (5)	6 (5)	0 (0 to 0)	0.83
No (%) with score ≥8	179 (37)	170 (37)	0 (–4 to 4)	0.88
Post-traumatic stress disorder score	1.1 (0.9)	1.0 (1.0)	–0.1 (–0.1 to 0.0)	0.05
No (%) with score ≥1.6	122 (26)	107 (23)	–2 (–6 to 1)	0.23
Cognition—mini-mental state exam:				
Score	25 (2)	25 (2)	0 (0 to 0)	0.15
No (%) with score ≤24	120 (25)	96 (21)	–4 (–8 to 0)	0.06
No (%) employed§	132 (26)	137 (29)	2 (–1 to 6)	0.13

FACIT=functional assessment of chronic illness therapy; FPI=functional performance inventory

*Unknown or missing data: SF-36 physical function=29 (six months), 31 (12 months); SF-36 physical health summary=30, 33; SF-36 mental health=30, 32; SF-36 mental health summary=30, 33; EQ-5D utility score=28, 29; EQ-5D visual analogue scale=28, 30; FPI overall score=16, 15; FPI physical exercise subscale=14, 15; FPI maintaining house subscale=13, 14; FPI body care subscale=13, 14; FACIT score=34, 32; anxiety score=31, 28; depression score=31, 29; post-traumatic stress disorder score=37, 31; mini-mental state exam score=31, 37; employment status=9, 7.

†Calculations from linear or binomial (identity link) regression models based on generalising estimating equations with exchangeable correlation structure[44] and indicator for time (12 *v* 6 month follow-up). "Difference" represents difference between 12 and 6 months in mean score for continuous measures or in proportion for binary measures.

‡Depression and anxiety symptoms measured with hospital anxiety and depression scale; symptoms of post-traumatic stress disorder measured with impact of events scale-revised.

§Employment at 6 and 12 months calculated for all patients regardless of reported baseline employment status.

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Table 3| **Outcomes* at 12 months in patients with acute lung injury according to randomisation to initial trophic or full enteral feeding * Figures are means (SD) unless stated otherwise**

	Trophic feeding (n=259)	Full feeding (n=228)	Treatment effect (95% CI)†	P value†
Quality of life—SF-36 (population norm)				
Physical function (82, SD 9)‡	55 (33)	55 (31)	2 (–4 to 7)	0.54
Physical health summary (50, SD 10)	39 (14)	40 (13)	0 (–2 to 3)	0.76
Mental health (76, SD 3) ‡	67 (25)	63 (26)	6 (1 to 10)	0.02
Mental health summary (50, SD 10)	46 (15)	43 (15)	4 (1 to 6)	0.01
Quality of life—EQ-5D				
Utility score	0.70 (0.25)	0.71 (0.23)	0.00 (–0.04 to 0.05)	0.75
Visual analogue scale	71 (22)	68 (23)	3 (–1 to 7)	0.14
Functional activities—functional performance inventory:				
Overall score	2.0 (0.7)	2.1 (0.7)	–0.1 (–0.2 to 0.1)	0.28
Physical exercise subscale	1.6 (0.9)	1.7 (0.9)	–0.1 (–0.2 to 0.1)	0.48
Maintaining house subscale	1.9 (0.9)	2.0 (0.9)	0.0 (–0.2 to 0.1)	0.54
Body care subscale	2.5 (0.7)	2.6 (0.6)	–0.1 (–0.2 to 0.0)	0.12
Fatigue—FACIT:				
Interval score	63 (19)	61 (17)	2 (–1 to 6)	0.16
No (%) with score ≤68	154 (66)	150 (68)	0.85 (0.58 to 1.24)	0.39
Psychological symptoms§:				
Anxiety score	7 (5)	7 (5)	0 (–1 to 0)	0.31
No (%) score ≥8	93 (39)	102 (46)	0.71 (0.49 to 1.02)	0.07
Depression score	6 (5)	6 (5)	0 (–1 to 0)	0.28
No (%) with score ≥8	85 (36)	85 (39)	0.86 (0.59 to 1.25)	0.44
Post-traumatic stress disorder score	0.9 (0.9)	1.1 (1.0)	–0.1 (–0.3 to 0.1)	0.20
No (%) with score ≥1.6	53 (22)	54 (25)	0.86 (0.57 to 1.32)	0.50
Cognition—mini-mental state exam:				
Score	25 (2)	26 (2)	0 (0 to 0)	0.45
No (%) with score ≤24	52 (22)	44 (21)	1.08 (0.69 to 1.69)	0.75
No (%) employed	69 (27)	68 (30)	0.86 (0.58 to 1.28)	0.46

FACIT= functional assessment of chronic illness therapy; FPI=functional performance inventory.

*Unknown or missing data: SF-36=physical function 11 (full), 20 (trophic); SF-36=physical health summary=12, 21; SF-36 mental health=11, 21; SF-36 mental health summary=12, 21; EQ-5D utility score=8, 21; EQ-5D visual analogue scale=9, 21; FPI overall score=3, 12; FPI physical exercise subscale=3, 12; FPI maintaining house subscale=3, 11; FPI body care subscale=3, 11; FACIT score=8, 24; anxiety score=8, 20; depression score=8, 21; post-traumatic stress disorder score=9, 22; mini-mental state exam score=17, 20; employment status=2, 5.

†Calculated from linear or logistic regression models based on generalising estimating equations with exchangeable correlation structure[44] and indicator for treatment (trophic *v* full feeding group), time (12 *v* 6 month follow-up), and interaction of treatment group and time. Treatment effect represents mean difference in score for continuous measures and odds ratio for binary measures.

‡Adjusted for age and sex within linear regression model described above.

§Depression and anxiety symptoms measured with hospital anxiety and depression Scale and symptoms of post-traumatic stress disorder measured with impact of events scale-revised.

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Figures

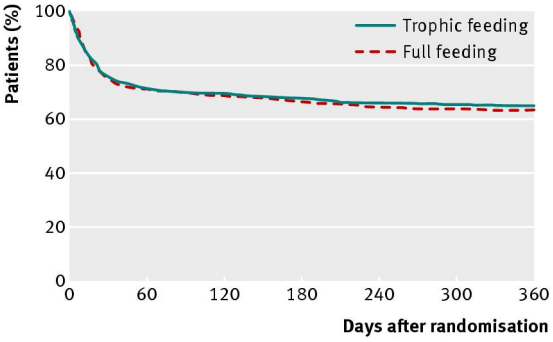

Fig 1 Survival until 12 months after randomisation. Curves at any time point represent proportion of patients surviving in study at that time. Two consenting patients were censored at date of six month assessment because of loss to follow-up thereafter. Patients known to be alive but who missed their 12 month follow-up were administratively censored at expected date of their 12 month assessment

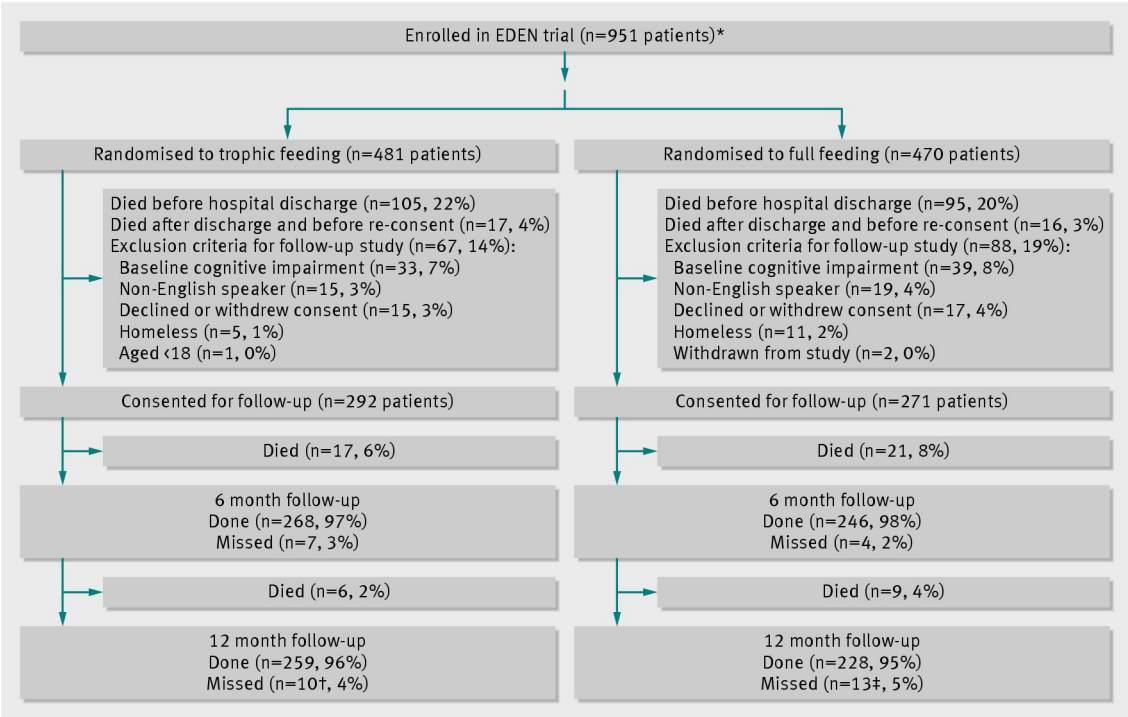

Fig 2 Enrolment and follow-up of patients with acute lung injury according to initial feeding regimen. *Three of 44 hospitals in EDEN trial did not participate in follow-up study, reducing original sample size from 1000 to 951; †eight known to be alive at 12 months, two others were censored for survival analysis; ‡known to be alive at 12 months

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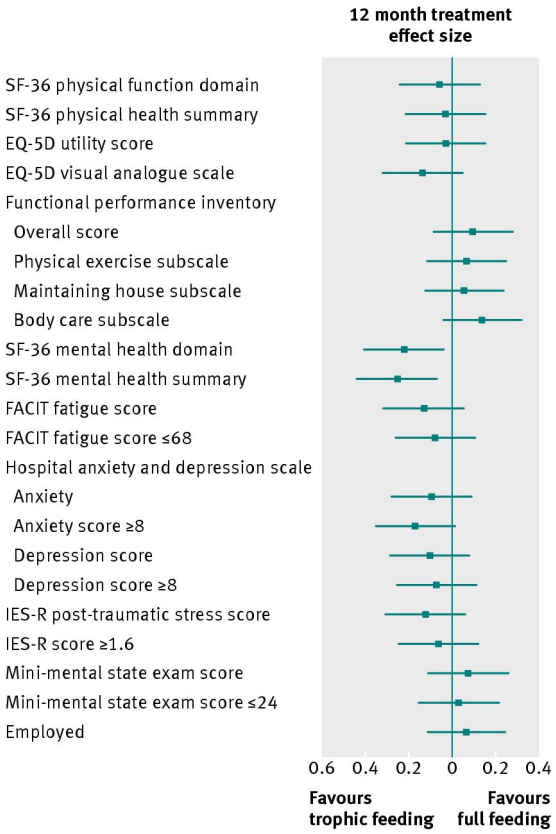

Fig 3 Effect size (treatment effect) of treatment intervention on primary outcome (SF-36 physical function domain adjusted for age and sex) and all secondary outcomes at 12 months. Effect size calculated as treatment effect (difference in means or proportions, see table 3) divided by pooled SD from trophic and full feeding groups.[60 61] FACIT=functional assessment of chronic illness therapy, IES-R=impact of events scale-revised

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