conceivable that the same result could be more easily obtained by conventional dialysis, where the dialysate solutions are engineered to target a given strong ion difference. Either way, the manipulation of strong ion difference to achieve specific therapeutic effects is slowly gaining traction, and similar approaches have recently been shown to enhance respiratory support (15, 16). Whatever the future holds for these therapies, it behooves us to start teaching the physicochemical approach to our medical students and junior colleagues sooner rather than later. ■

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Mounting Clarity on Enteral Feeding in Critically Ill Patients

Like many questions in the ICU, best practices for provision of nutrition remain unclear. Several factors contribute to the relative lack of robust ICU nutrition research. Critical care clinical research is immensely difficult for a variety of reasons, not the least of which are extraordinary clinical heterogeneity and multiple overlapping interventions. Furthermore, our understanding of specific nutritional needs during severe physiologic and metabolic stress is poor. Finally, the field is historically fraught with strong opinions on all sides and heavy influence from industry. Despite important questions that remain unanswered, we are fortunate that several large investigator- or network-initiated randomized controlled trials (RCTs) studying enteral calorie delivery in critically ill patients have been published over the past 8 years. In this issue of the *Journal* (pp. 814–822), Deane and colleagues (1) report the 6-month outcomes of nearly 4,000 participants in the TARGET RCT (The Augmented versus Routine Approach to Giving Energy Trial) that investigated delivery of 70% versus 100% caloric requirements in mechanically ventilated critically ill adults.

How Does 100% versus 70% Caloric Intake Affect Critically Ill Patients 6 Months after Study Enrollment?

In the large, initial TARGET trial, the full- and reduced-calorie groups received 103% and 67% of calculated caloric needs, respectively (2). Average age and body mass index (BMI) were 57 years and 29 kg/m^2, respectively. The amount of protein delivered to both groups was similar. Neither 90-day mortality (the primary outcome) nor additional secondary outcomes were significantly different between the two arms. However, recovery does not stop at 90 days, and in their current work, Deane and colleagues (1) undertook telephone contact of over 2,700 survivors 180 days after randomization. The

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major 6-month outcome was quality of life, and additional functional outcomes (workforce participation, disability, and participation in activities), together with mortality, were also assessed. No discernible differences in 6-month functional status or mortality between the two groups were identified.

What Do These Data Mean in the Context of Prior Literature?

Including the TARGET trial, there have now been three large, multicenter RCTs investigating caloric dose in critical illness. The first of these (the EDEN [Early versus Delayed Enteral Feeding to Treat People with Acute Lung Injury or Acute Respiratory Distress Syndrome] trial) was conducted by the NIH Acute Respiratory Distress Syndrome Network and randomized 1,000 patients with acute respiratory distress syndrome to early "trophic" versus full enteral feeding for the first 6 days, with all participants then progressing to full feedings (3). Participants' mean age was 52 years, and their mean BMI was 30 kg/m^2. Participants received roughly 25% and 80% of calculated caloric needs in the trophic and full groups, respectively. Those in the full feeding group received more protein. There were no differences in ventilator-free, ICU-free, and organ failure–free days; 60-day mortality; or infectious complications. Needham and colleagues then assessed 1-year outcomes, both in person and via telephone calls, in patients participating in this RCT, and they found no differences in physical or cognitive function, psychological symptoms, or quality of life (4, 5).

The second RCT (the PermiT [Permissive Underfeeding versus Target Enteral Feeding in Adult Critically Ill Patients] trial), published in 2015 by Arabi and colleagues, randomized 894 critically ill patients (both medical and surgical) to early restricted versus standard enteral feeding for up to 14 days. Participants' mean age was 50 years, and their mean BMI was slightly less than 30 kg/m^2 (6). Although the restricted group received 46% of calculated caloric needs compared with 71% in the standard group, both groups received similar amounts of protein. There were no differences in 90-day mortality or in secondary outcomes, including hospital and ICU lengths of stay and infectious complications.

Taken collectively, data from these three trials and their subsequent analyses, including the paper by Deane and colleagues (1), provide strong evidence that the amount of nonprotein calories delivered during the first 1–2 weeks in the ICU to a general population of critically ill patients who are relatively young and well nourished does not significantly affect short- or longer-term outcomes. Feeding trophically or delivering full calculated calories, or any amount in between, is reasonable in most patients.

Limitations and Remaining Unanswered Questions

Although the authors should be congratulated on a remarkable investigation, there remains work to be done. One important feature of both the PermiT and TARGET RCTs is that protein delivery was equivalent in both arms, thus allowing dissociation from calories. Emerging evidence suggests that although calories are likely not important in many patients, protein delivery may be (7). Research to understand the role of protein supplementation in the recovery of ICU patients, including RCTs of standard-dose versus high-dose protein, are needed. In addition, average BMI in all three RCTs was high; thus, participants were likely well nourished. Although a *post hoc* analysis of the PermiT trial comparing outcomes between participants at high versus low nutritional risk, as measured by the Nutrition Risk in Critically Ill ("NUTRIC") score (8, 9), did not demonstrate any differences in outcomes, trials targeting malnourished high-risk patients remain a high priority. Furthermore, recent trials started enteral feedings very early in the ICU course, as current guidelines recommend (10). Although meta-analyses of many small and mostly single-center RCTs suggest that early enteral feeding (within 48 h of ICU admission) is associated with fewer infectious complications and at least a trend toward improved mortality (11, 12), large multicenter RCTs of early enteral nutrition versus a brief delay are lacking, despite calls for this research for nearly 25 years (13). Finally, we must remember that these RCTs were designed to study superiority, not equivalence. Thus, we cannot conclude that delivery of more or fewer calories is the same, only that it is not different.

In summary, this rigorous and thoughtful investigation comparing 100% versus 70% calorie delivery in critically ill patients helps to end the era of our focus on calorie delivery in the ICU. We should now turn our attention to other ICU nutrition questions. ■

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Rethinking Delivery of Care for Patients Requiring Prolonged Mechanical Ventilation

Patients requiring prolonged mechanical ventilation because of persistent respiratory failure experience a transition from the acute phase of illness responsible for intensive care admission and mechanical ventilation to one of rehabilitative and, in some cases, palliative care. This transition requires adaption of their clinical management plan and the way care is delivered (1). Important domains of care include liberation from ventilation; symptom relief; nutrition; physical, cognitive, and psychological rehabilitation; and discharge planning (2, 3). In the United States, this transition is frequently accompanied by transfer from an ICU to a lower intensity care setting located in a long-term acute care hospital. These hospitals specialize in care delivery for patients requiring extended hospitalization, providing rehabilitation services to patients requiring prolonged mechanical ventilation and those with other prolonged acute conditions (4).

In this issue of the *Journal*, Rak and colleagues (pp. 823–831) report a large and rigorously conducted ethnographic study of delivery and organization of care to patients requiring prolonged mechanical ventilation in eight long-term acute care hospitals (5). Using a positive–negative deviance approach, the study objective was to identify care practices common to high-performing hospitals but infrequent or absent at low-performing hospitals. The overall aim was to develop a framework for optimal care delivery for patients requiring prolonged mechanical ventilation. Participating sites were recruited from those long-term acute care hospitals identified as within the highest or lowest performance quartiles identified using a previously validated model of risk-adjusted mortality. Data comprised 329 hours of direct observation (2–3 observers for 4 d at each site), 196 key informant interviews, and 39 hours of job shadowing.

From these data, the authors identified four important, yet interdependent, domains of effective care practices considered influential for liberation from ventilation: ventilator care; mobilization; nutrition; and management of pain, agitation, and delirium. Identification of these domains in themselves is not novel because other authors have described these care practices as having an important role in successful liberation (6, 7). Importantly, however, Rak and colleagues extend our understanding of these domains through the identification of attributes of effective care within them (i.e., finding the appropriate and individualized balance between aggressiveness and responsiveness of care). As an exemplar, the investigators define aggressiveness of care as the degree to which ventilator management emphasizes physiological progress at the expense of day-to-day patient cues (i.e., continuing a spontaneous breathing trial despite patient distress and request to discontinue). Conversely, responsiveness of care is the degree to which ventilator management emphasizes day-to-day patient cues at the expense of physiological progress (i.e., discontinuing a spontaneous breathing trial at the request of the patient despite respiratory parameters being within normal ranges).

A key finding of the study was that high-performing hospitals achieved the optimal balance between aggressiveness and responsiveness individualized to a patient's needs. This occurred through a mechanism of action that reflects the concept of relational coordination: a mutual process of communicating and relating (i.e., shared goals, shared knowledge, and mutual respect); in other words, interprofessional teamwork and collaboration (8) for the purpose of task integration (9).

The complex, interrelated, dynamic, and frequently emotionally charged care for patients requiring prolonged mechanical ventilation and, indeed, all critically ill patients necessitates effective interprofessional communication and collaboration to enable a shared team approach to care delivery (10). Unfortunately, a substantial body

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ORIGINAL ARTICLE

Outcomes Six Months after Delivering 100% or 70% of Enteral Calorie Requirements during Critical Illness (TARGET)

A Randomized Controlled Trial

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Abstract

Rationale: The long-term effects of delivering approximately 100% of recommended calorie intake via the enteral route during critical illness compared with a lesser amount of calories are unknown.

Objectives: Our hypotheses were that achieving approximately 100% of recommended calorie intake during critical illness would increase quality-of-life scores, return to work, and key life activities and reduce death and disability 6 months later.

Methods: We conducted a multicenter, blinded, parallel group, randomized clinical trial, with 3,957 mechanically ventilated critically ill adults allocated to energy-dense (1.5 kcal/ml) or routine (1.0 kcal/ml) enteral nutrition.

Measurements and Main Results: Participants assigned energy-dense nutrition received more calories (percent recommended energy intake, mean [SD]; energy-dense: 103% [28] vs. usual: 69% [18]). Mortality at Day 180 was similar (560/1,895 [29.6%] vs. 539/1,920 [28.1%]; relative risk 1.05 [95% confidence interval, 0.95–1.16]). At a median (interquartile range) of 185 (182–193) days after randomization, 2,492 survivors were surveyed and reported similar quality of life (EuroQol five dimensions five-level quality-of-life questionnaire visual analog scale, median [interquartile range]: 75 [60–85]; group difference: 0 [95% confidence interval, 0–0]). Similar numbers of participants returned to work with no difference in hours worked or effectiveness at work ($n = 818$). There was no observed difference in disability ($n = 1,208$) or participation in key life activities ($n = 705$).

Conclusions: The delivery of approximately 100% compared with 70% of recommended calorie intake during critical illness does not improve quality of life or functional outcomes or increase the number of survivors 6 months later.

Keywords: critical illness; enteral nutrition; disability and health; quality of life

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A complete list of participating sites and investigators in the TARGET trial is provided in the online supplement.

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

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At a Glance Commentary

Scientific Knowledge on the Subject: The long-term effects of delivering approximately 100% of recommended calorie intake via the enteral route during critical illness compared to lesser calorie delivery were unknown.

What This Study Adds to the Field: We hypothesized that achieving approximately 100% of recommended calorie intake during critical illness would increase quality-of-life scores, return to work, and key life activities and reduce death and disability 6 months later. However, the enteral delivery of more calories, up to 100% of recommended calorie intake, did not change any of these outcomes. The implication of these data is that the delivery of 100% of recommended calories, when restricted to the acute phase of critical illness, does not improve any measured outcomes that are important to patients and/or communities.

Mechanically ventilated critically ill patients routinely receive enteral nutrition (1–3). In such patients, mean calorie delivery is typically 60–70% of that recommended, with surveys reporting delivery of even fewer calories in North American ICUs (4, 5). Observational studies have reported associations between enteral delivery of approximately 100% of calories and reduced mortality (6).

We recently published the primary outcome from TARGET (The Augmented versus Routine Approach to Giving Energy Trial) (7). Almost 4,000 critically ill adults were randomized to energy-dense or routine enteral nutrition administered in a blinded fashion (7). We were able to deliver approximately 100% and 70% of recommended calories, respectively, to both groups (7). The delivery of approximately 100% of recommended calories had no discernable effect on 90-day mortality (7).

Data from observational studies have also identified associations between calorie deficits during ICU admission and greater muscle loss and reduced quality of life in survivors of critical illness (8, 9). Although there is face-validity that delivering the recommended calories during critical illness will improve quality of life and functional outcomes in survivors (10, 11), data from adequately powered randomized clinical trials are lacking (12).

We therefore prespecified a comprehensive assessment at 6 months after randomization in TARGET to allow us to provide a detailed understanding of the impact of delivering approximately 100% of recommended calories during critical illness (13–15).

We hypothesized that achieving approximately 100% of recommended calorie intake during critical illness would improve recovery, as measured using quality-of-life scores, return to work, disability, and participation in key life activities, and that such benefit would be more apparent in certain subgroups of patients (which we prespecified as those in the labor force, age <65 yr and not in the labor force, age ≥65 yr and living independently, age ≥65 yr and living at home with supports, and age ≥65 yr and living in a long-term health care facility).

Methods

Trial Design

TARGET was an investigator-initiated, parallel-group, blinded, randomized clinical trial. The trial was registered (ClinicalTrials.gov NCT02306746), and the protocol and the statistical analysis plan was published before data-lock (14, 15).

TARGET was designed by the management committee, performed by the investigators, endorsed by the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, and funded by national peer-review organizations (online supplement). Ethics approval was provided by all relevant local institutional review boards. An independent data and safety monitoring board provided trial oversight.

Study Participants

Patients 18 years of age or older in the ICU who were receiving invasive mechanical ventilation, were about to commence enteral nutrition or enteral nutrition had commenced within the previous 12 hours, and were expected to be receiving enteral nutrition in the ICU beyond the calendar day after randomization were eligible for inclusion. A full list of exclusion criteria is provided (online supplement).

Intervention and Comparator

Using a secure web-based system, study participants were randomized to energy-dense enteral nutrition (1.5 kcal/ml, Fresubin Energy Fibre Tube Feed) or routine enteral nutrition (1.0 kcal/ml, Fresubin 1000 Complete Tube Feed) in identical 1,000-ml bags (15). The difference in calorie content between the energy-dense and routine formulations was shared between fat (energy-dense: 58 g/L vs. routine: 27 g/L) and carbohydrate (180 g/L vs. 125 g/L); the protein content of the two formulations was similar (56 g/L vs. 55 g/L) (13). Study enteral nutrition was commenced as soon as possible after randomization. The goal rate for both groups was 1 ml/kg/h on the basis of calculated ideal body weight. Ideal body weight was calculated from patient height, which was determined in the supine position (16, 17). For men, ideal body weight in kg was calculated as $50 + 0.91 \times$ (height in cm $- 152.4$), and for women it was $45.5 + 0.91 \times$ (height in cm $- 152.4$) (16, 17). It was recommended that the goal rate was achieved within 48 hours of commencing the study nutrition (15). Clinician estimation of baseline calorie requirements was recorded but not used to determine the study goal rate. Study enteral nutrition was administered for up to 28 days or until the participant ceased

Data-sharing statement: Nonidentifiable individual participant data that underlie the results reported in this trial will be made available after 3 years following publication and ending 7 years after publication. Availability will only be made to researchers who provide a written proposal for data evaluation that is judged to be methodologically sound by a committee approved by the Australian New Zealand Intensive Care Research Centre (ANZIC-RC). Proposals should be directed to anzicrc@monash.edu. If the proposal is approved, access data requestors will be required to sign a data access agreement prior to accessing data.

The Augmented versus Routine Approach to Giving Energy Trial (TARGET) is a collaboration of the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, the Australian and New Zealand Intensive Care Research Centre, and the Medical Research Institute of New Zealand. The authors assume responsibility for the overall content and integrity of this article.

enteral nutrition, died, or was discharged from ICU, whichever occurred first (15).

Categorization of Participants

A limitation of a single functional outcome for all participants in a trial of a nutritional intervention is that factors, such as patient heterogeneity, add noise and reduce the likelihood of identifying a true difference (12). To ascertain for subtle differences in functional outcomes with TARGET, we chose to measure several variables. Furthermore, we speculated that such longitudinal evaluation could be improved by a novel approach of quantifying outcomes in specific subgroups of participants selected according to baseline characteristics; for example, in those employed prior to their critical illness we hypothesized that their return to work was important to patients and communities (18, 19) and may be modifiable by calories delivered during critical illness (13).

Patients were grouped or categorized on the basis of their prerandomization circumstances as proximate to randomization as possible (13). We tested the process of grouping into categories according to baseline characteristics prior to TARGET commencing (20). On the basis of this study, we implemented a discrete decision tree with five categories of TARGET participants (Figure E1 in the online supplement). These groups were aged <65 years and in the labor force, aged <65 years and not in the labor force, aged ⩾65 years and living independently, aged ⩾65 years and living at home with supports, and aged ⩾65 years and living in a long-term health care facility (Figure E1).

Outcomes

Surviving participants were contacted by trained assessors at approximately Day 180 after randomization. These assessors conducted questionnaires via telephone with participants or with their proxy if the participants were unable to complete these. Questionnaires were completed prior to any investigator, assessor, study participant, or proxy becoming aware of treatment allocation.

The prespecified major outcome of our TARGET Day-180 assessment was survivor quality of life, as quantified using the EuroQol five dimensions five-level questionnaire (EQ5D5L) visual analog scale score (21).

The EQ5D5L descriptive system may be converted into a single index value after adjustment to country-specific value sets (22). Because there are no country-specific value sets for Australia or New Zealand we present EQ5D5L single index values adjusted to value sets for England and Canada (22). The EQ5D5L scale evaluates mobility, personal care, usual activities, pain/discomfort, and anxiety/depression and separates each of these health domains into five levels (23). We also report health profiles from each of the five EQ5D5L domains and dichotomized domains into "no problems" (level 1) or "problems" (levels 2–5) (24).

Additional Functional Outcome Assessment Relative to Category

For those categorized as age <65 years and in the labor force, we measured workforce participation using the Australian Labor Force Survey (25).

For those categorized as *1*) age <65 years and not in the labor force, *2*) age ⩾65 years and living at home with essential supports, or *3*) age ⩾65 years and living in a long-term care facility, we assessed disability using the World Health Organization Disability Assessment Schedule (WHODAS) survey, version 2.0 (26). Each of the 12 items on the WHODAS were scored 0–4 and summarized as a percentage of the maximum possible score of 48 (27). This score was then dichotomized to "no or mild disability" (WHODAS score 0–24%) or "moderate to severe disability" (25–100%) (27). Day-180 "disability free survival" was also calculated as those patients alive and with a WHODAS score <25% (27).

For those categorized as age ⩾65 years and living independently at baseline, we quantified participation using the Adelaide Activities Profile (28). This validated tool quantifies participation for people in the study region aged ⩾65 years across four domains: domestic chores, household maintenance, service to others, and social activities (28). The assessment includes 21 activities rated 0–3 according to increasing frequency of participation, with a lesser sum score representing less activity.

Statistical Analyses

The calculations underlying the sample size have been published (7). In brief, a sample of 3,774 patients providing 80% power to detect a difference of 3.8–4.3 percentage points in 90-day mortality, assuming a baseline mortality of 20–30% with 6% sample-size inflation ($n = 4{,}000$), allowed for losses during follow-up.

The original TARGET-modified intention-to-treat population included all randomized participants, regardless of treatment compliance, except for those participants who *1*) were not eligible for randomization and did not receive the study intervention and *2*) withdrew consent to continue, and permission to use all data was refused (7). Our major outcome for Day 180 was conducted in survivors and for whom an EQ5D5L result could be obtained (Figure 1). Mortality at Day 180 was evaluable for all those in the original TARGET-modified intention-to-treat population minus those who withdrew from ongoing contact or were lost to follow-up (Figure 1).

Data are summarized as mean (SD), median (interquartile range [IQR]), or difference (with 95% confidence intervals [CIs]). We compared median differences between the groups using the Hodges-Lehmann method, and relative risks were calculated using log-binomial regression. We also conducted sensitivity analyses for our major outcome and all functional outcomes, using the worst value for each score for patients who died before assessment (29).

For the mortality analysis only confirmed deaths prior to Day 180 were counted. To evaluate the effect of the intervention on mortality, relative risks were adjusted in models, including *1*) a random effect for site and *2*) fixed effects for age, APACHE-II score, body mass index, region (Australia or New Zealand), sex, and ICU admission type (medical/elective or surgical/emergency surgical). Time to event (death) is presented as a Kaplan-Meier plot. Given missing data from those whom we could not contact and establish survival at Day 180, we also present time to event (death) at Day 180 in the original TARGET-modified

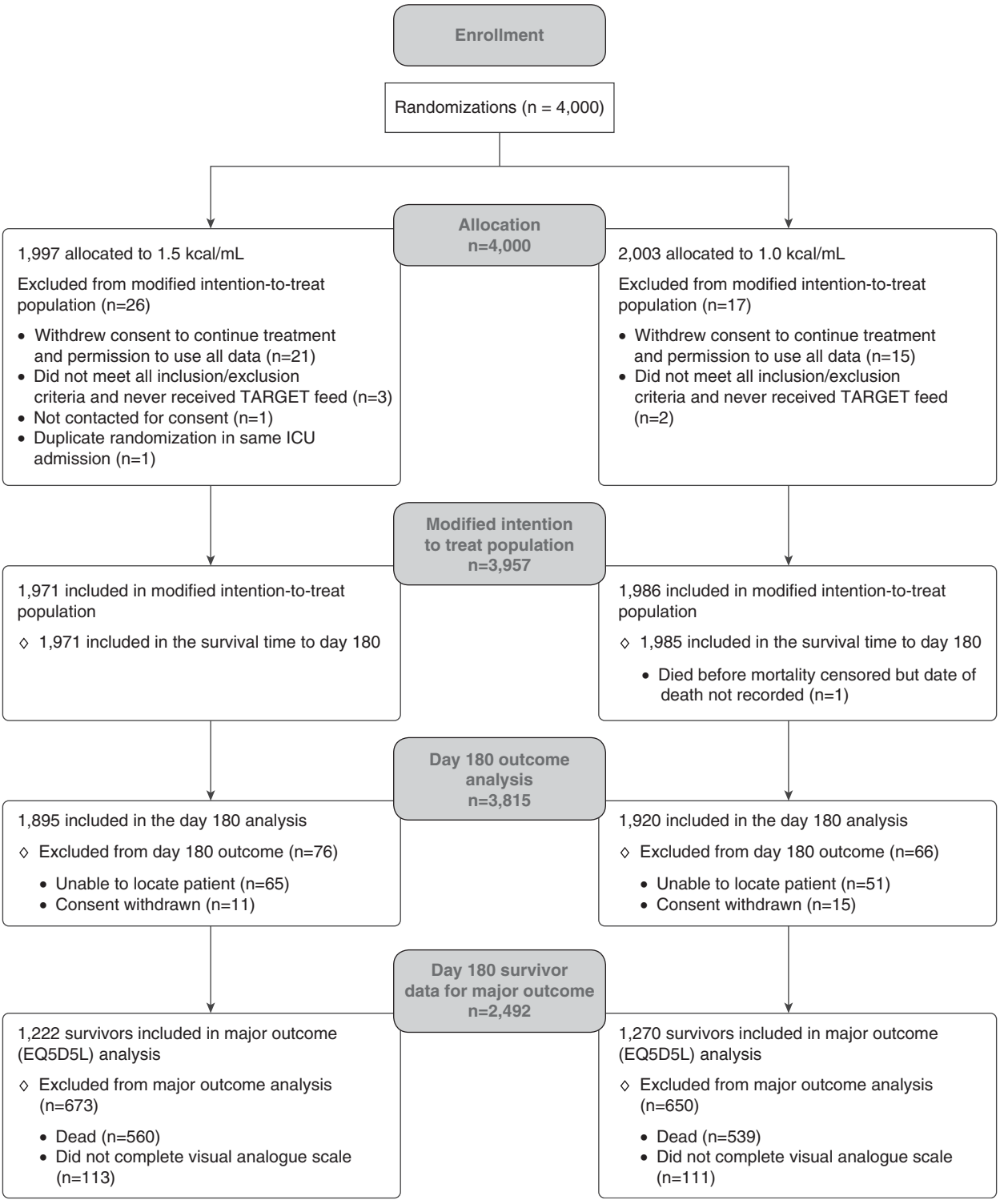

Figure 1. Participant flow diagram. EQ5D5L = EuroQol five dimensions five-level questionnaire; TARGET = The Augmented versus Routine Approach to Giving Energy Trial.

intention-to-treat population censored observation at their last known date of being alive. Data were analyzed using SPSS Statistics 25.0 (IBM, 2017).

The primary outcome of TARGET was at Day 90 (mortality), and this manuscript was our preplanned Day-180 analysis of data from TARGET (7). For this reason we provide point estimates and accompanying 95% CIs unadjusted for multiple comparisons and did not generate any *P* values with these estimates.

Results

Study Participants

As reported, randomization was performed 4,000 times in 3,997 patients (3 patients were inadvertently randomized twice), with 43 patients excluded from the modified intention-to-treat cohort (10). Of the original TARGET intention-to-treat population ($n = 3,957$), 142 participants withdrew consent or were lost to follow-up, with 3,815 (96.4%) of participants with known vital status or outcome assessments at Day 180 (Figure 1).

The EQ5D5L visual analog scale score was available for 2,492 (65.3%) participants but was not available for 1,099 (28.8%) participants who died and 224 survivors who did not complete an EQ5D5L visual analog scale score (5.9%) (Figure 1).

The scheduled Day-180 assessments were completed at a median (IQR) of 185 (182–193) days following randomization.

There was no evidence of important differences in baseline characteristics for participants assigned energy-dense or routine enteral nutrition (Table E1). There were similar proportions of patients and similar baseline characteristics in each category, regardless of treatment allocation or loss to follow-up (Tables E1 and E2). Survivors who did not complete the EQ5D5L visual analog scale score had similar baseline characteristics and exposure to the intervention when compared with those survivors who did (Table E3).

The trial enteral nutrition was commenced early during ICU admission, and study participants were exposed to the study intervention for a median (IQR) of 6 (3–11) days (Table E4). The volume and protein delivered were similar between groups, whereas the group allocated energy-dense nutrition received substantially more calories (mean group difference: 605 kcal/d [95% CI, 579–630]; percent recommended calorie intake mean group difference 34% [95% CI, 32–36]; Tables E4 and E5 and Figures E2 and E3). The latter difference remained whether calorie intake was measured as calories per day or calories per kilogram of body weight (ideal or actual).

Outcomes

There were no between-group differences in the EQ5D5L visual analog scale scores (Table 1). When converted into single index values there were no between-group differences (Table 1). Similarly, there were no between-group differences within any of the EQ5D5L domains, whether visualized according to level (Figure 2), dichotomized within each domain (Table 1), or including deaths as the worst score, zero (Table E6).

By Day 180, 560 of 1,895 patients (29.6%) in the energy-dense nutrition group and 539 of 1,920 patients (28.1%) in the routine enteral nutrition group had died (unadjusted relative risk: 1.05 [95% CI, 0.95–1.16]). Within each of the five categories used to assess functional outcomes, mortality point estimates were similar, except for those aged ⩾65 years and living at home with support (Table E7). The point estimate for this

Table 1. Functional Outcomes Assessed at Day 180 Using the EQ5D5L Questionnaire (Survivors Only)

	Treatment Group			
	1.5 kcal/ml	1.0 kcal/ml	Total	Group Difference
Primary outcome				
EQ5D5L visual analog scale, median (IQR)	75 (60–85) ($n = 1,222$)	75 (60–85) ($n = 1,270$)	75 (60–85) ($N = 2,492$)	0 (0–0)*
Secondary outcomes using EQ5D5L questionnaire				
Single index value				
EQ5D5L single index value, England value set, median (IQR)	0.86 (0.66–0.95) ($n = 1,215$)	0.85 (0.66–0.95) ($n = 1,254$)	0.85 (0.66–0.95) ($N = 2,469$)	0 (0–0)*
EQ5D5L single index value, Canada value set, median (IQR)	0.85 (0.66–0.93) ($n = 1,215$)	0.85 (0.66–0.93) ($n = 1,254$)	0.85 (0.66–0.93) ($N = 2,469$)	0 (0–0)*
Domain data dichotomized				
Mobility, *n* (%)				
No problems	713 (58)	695 (55)	1,408 (57)	0.92 (0.84–1.01)†
Problems	509 (42)	572 (45)	1,081 (43)	
Self-care, *n* (%)				
No problems	909 (74)	931 (73)	1,840 (74)	0.96 (0.84–1.10)†
Problems	313 (26)	338 (27)	651 (26)	
Usual activity, *n* (%)				
No problems	570 (47)	573 (45)	1,143 (46)	0.97 (0.91–1.05)†
Problems	652 (53)	694 (55)	1,346 (54)	
Pain/discomfort, *n* (%)				
No problems	617 (51)	621 (49)	1,238 (50)	0.97 (0.90–1.05)†
Problems	604 (49)	642 (51)	1,246 (50)	
Anxiety/depression, *n* (%)				
No problems	661 (54)	717 (57)	1,378 (56)	1.06 (0.97–1.16)†
Problems	554 (46)	541 (43)	1,095 (44)	

Definition of abbreviations: CI = confidence interval; EQ5D5L = EuroQol five dimensions five-level questionnaire; IQR = interquartile range.
*Median difference (95% CI) calculated using the Hodges-Lehmann method.
†Unadjusted relative risk (95% CI) from log-binomial regression of reported problems; 1.5 versus 1.0 kcal/ml.

category was in the direction of harm for those who received energy-dense nutrition (Table E7). For the Day-180 mortality cohort, time-to-event (death) curves were similar between groups (Figure 3A), with appearance unaffected when plotted including those who withdrew from ongoing contact or were lost to follow-up (Figure 3B).

Of the 818 participants <65 years and in the labor force prior to TARGET, 456 (56%) had returned to work by Day 180. There were no differences between groups who received energy-dense or routine enteral nutrition on the proportion that returned to work, the hours worked, the shifts missed at work, effectiveness at work, or major changes in the kind of work done (Table 2). The cumulative WHODAS scores, the proportion of respondents reporting no or mild disability and moderate to severe disability, and disability-free days were also similar (Table E8). For those aged >65 years the results from the Adelaide Activities Profile survey did not identify differences between groups (Table E9). Inferences were unchanged within sensitivity analyses imputing deaths as the worst score (Table E6).

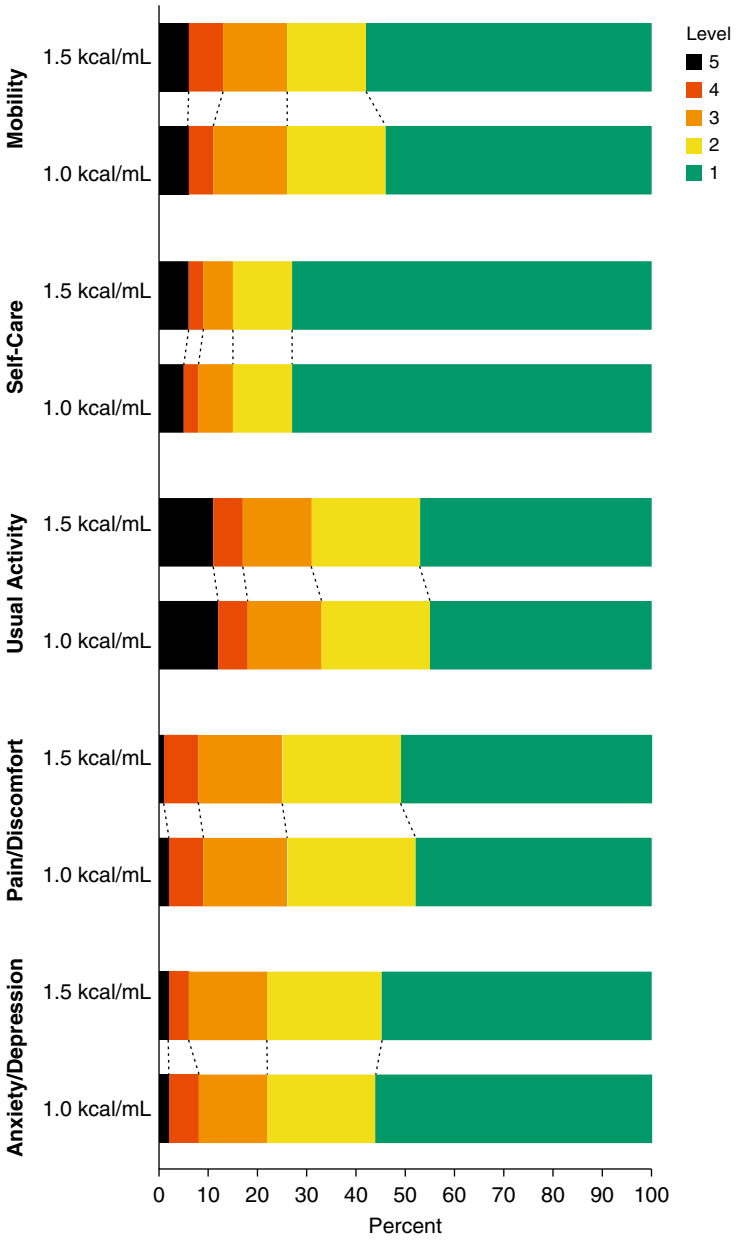

Figure 2. Health-related questionnaire dimensions visualized according to level. EuroQol five dimensions five-level quality-of-life questionnaire: Level 1, no problem; level 2, slight problem/pain/anxiety; level 3, moderate problem/pain/anxiety; level 4, severe problem/pain/anxiety; and level 5, unable to complete or extreme pain/anxiety.

Discussion

We assessed participants approximately 6 months after randomization to evaluate the effect of an energy-dense enteral nutrition formula compared with a standard formula during critical illness on longer-term outcomes. Although the use of the energy-dense nutrition markedly increased energy delivery to approximately 100% of guideline goal calories during ICU admission, such additional calories did not affect quality of life or mortality at 180 days. Furthermore, additional calorie delivery did not affect functional outcomes when quantified as capacity to return to work, disability, or participation.

Quality of life is markedly diminished in survivors of critical illness, alongside substantial reductions in employment and social participation and increases in disabilities (30, 31). There is, however, sparse evidence from multicenter randomized clinical trials about the impact of enteral calorie delivery during critical illness on such long-term outcomes. The most comprehensive data are from a study of survivors who consented to participate in long-term follow-up as part of the EDEN (Initial Trophic vs. Full Enteral Feeding in Patients with Acute Lung Injury) trial. The EDEN trial randomly assigned 1,000 patients with acute lung injury to "trophic feeding" or "full energy feeding" for a maximum of 5 days in ICU (32, 33). At 6 and 12 months after randomization, 525 and then 510 survivors had quality-of-life evaluations (32, 33). In EDEN, usual care of "full calorie feeding" resulted in delivery of approximately 1,300 kcal/d, which is a similar amount of calories as delivered to the routine enteral nutrition (1.0 kcal/ml) group in TARGET. In TARGET, the intervention delivered almost 1,900 kcal/d. In EDEN, the intervention of trophic feeding delivered approximately 400 kcal/d

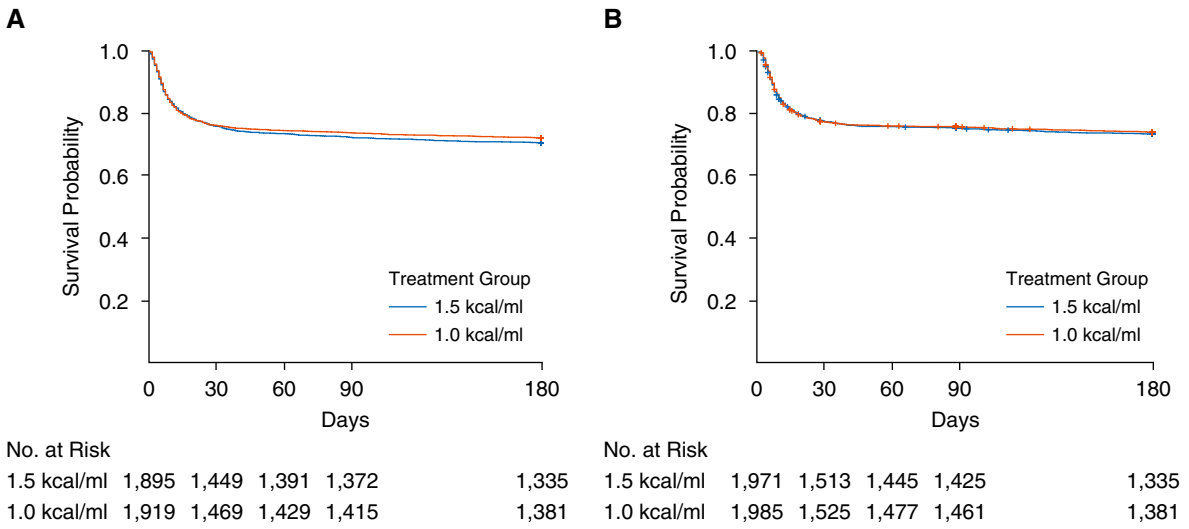

Figure 3. Time-to-event (death) curves. (*A*) Participants with known Day-180 status (i.e., only those in whom we were able to determine survival status at Day 180), with missing data from those unable to be located (energy-dense $n = 65$ and routine energy $n = 51$) and those who withdrew consent ($n = 11$ and $n = 15$) removed from plot. (*B*) Including all participants from the modified intention-to-treat population. For time-to-event plots, one patient allocated to 1.0 kcal/ml died prior to censor date in another country, and date of death was unable to be ascertained. This patient was included in mortality analysis but not time-to-event curves.

and did not affect quality-of-life scores at 6 or 12 months (32). Of 223 survivors who participated in EDEN and were employed at baseline, 48% were not working at 12-month follow-up, with no differences between groups, and the majority of participants attributing the lack of employment to health-related reasons (32).

Our findings have important implications for clinical practice. Although there are substantial differences between TARGET and EDEN in terms of duration of exposure to the nutritional intervention, the number of patients involved who participated at long-term follow-up, and the instruments used to quantify outcomes, the consistent signal is that delivery of calories of various amounts up to the full recommended goals during the acute phase of critical illness does not appear to improve any outcome measured so far that is important to patients and/or communities (34).

Strengths of our Day-180 outcome assessment include that researchers were blinded to treatment allocation, and quality of life was evaluated in almost 2,500 participants, return to work in more than 800 participants, disability in more than 1,200 participants, and participation of over 700 older participants in key life activities. This allowed robust estimates of no effect. Necessarily, functional outcomes were only ascertainable in survivors, but conclusions based on these results are supported by sensitivity analyses imputing worst scores to those who died (35). In an attempt to identify particular subgroups or categories of participants that may have benefited from the intervention we also conducted additional exploratory analyses in categories of patients on the basis of baseline function. None of the main or exploratory analyses identified evidence of a benefit, or harm, from providing approximately 100% of recommended calories. A strength of our study is that protein delivery was similar between groups (approximately 1.08 g/kg/d), and therefore protein was not a confounding variable. However, international guidelines recommend greater amounts of protein (2, 3, 36). Large randomized clinical trials are required to inform clinicians as to whether more protein would be of benefit, harm, or have no effect on critically ill populations (37, 38).

The limitations of our Day-180 assessment include that the study was conducted in Australia and New Zealand, where the rate of overweight or obese adults is approximately two thirds of the population (and this may explain the mean body mass index of 29.2 kg/m^2 in those that participated in TARGET); that patients who were determined by treating clinicians as needing a specific nutritional therapy were excluded; energy expenditure was not measured; and that nutritional intervention was commenced early, limited to ICU admission, ceased at 28 days, and administered for a mean of 6 days (39). Accordingly, our results may not be generalizable to healthcare settings where populations are leaner and/or there are large proportions of the population who require specific nutritional therapies. Our results may also not necessarily apply to nutrition delivered in ICU when measuring energy expenditure, or interventions after ICU, or for those who are anticipated to require tube feeding in ICU for prolonged periods (29, 40).

We used existing quality-of-life instruments, and the EQ5D5L visual analog scale was verbally administered by data collectors (41). These tools and their administration may not be adequate to detect all differences that are important to survivors (42, 43). We also did not attempt to quantify quality of life prior to critical illness, and this may allow greater precision in detecting differences due to a single intervention (44). However, the 95% CIs around no effect for many of the outcomes suggest that any substantial differences with various amounts of calories during ICU admission are unlikely.

A further limitation is that, in our attempt to account for heterogeneity and provide greater clarity in relation to potential benefits of energy, we grouped study participants into categories. This process has not been used in previous trials of nutritional therapy in the critically ill, and categorization and associated outcomes we chose were based on value judgments.

Table 2. Employment Outcomes at Day 180 in Those in the Labor Force at Enrollment (Survivors Only)

	Treatment Group		Total	Group Difference
	1.5 kcal/ml	1.0 kcal/ml		
Returned to work, yes, *n* (%)	229 (56) (*n* = 412)	227 (56) (*n* = 406)	456 (56) (*N* = 818)	0.99 (0.88 to 1.12)*
Days from randomization to starting back at work, median (IQR)†	81 (42 to 115)	81 (49 to 132)	81(46 to 124)	−6 (−15 to 3)‡
Hours worked last week, median (IQR)§	35 (20 to 40)	38 (24 to 40)	38 (22 to 40)	0 (−3 to 0)‡
Hours worked last 4 wk, median (IQR)‖	38 (24 to 40)	38 (25 to 40)	38 (24 to 40)	0 (−2 to 0)‡
Days/shifts of work missed in last 4 wk, median (IQR)¶	0 (0 to 2)	0 (0 to 2)	0 (0 to 2)	0 (0 to 0)‡
Effectiveness at work, self-reported scale, median (IQR)	90 (80 to 100)	90 (71 to 100)	90 (75 to 100)	0 (0 to 0)‡
Major changes in the kind of work, yes, *n* (%)**	108 (47)	103 (46)	211 (46)	1.03 (0.85 to 1.23)*

Definition of abbreviation: IQR = interquartile range.
*Unadjusted relative risk (95% confidence interval) from log-binomial regression.
†Excludes 10 subjects with missing data (2 in 1.5 kcal/ml group and 8 in 1.0 kcal/ml group).
‡Median difference (95% confidence interval) calculated using the Hodges-Lehmann method.
§Excludes two subjects in 1.0 kcal/ml group with missing data.
‖Excludes three subjects in 1.0 kcal/ml group with missing data.
¶Excludes five subjects with missing data (1 in 1.5 kcal/ml group and 4 in 1.0 kcal/ml group).
**Excludes two subjects in 1.0 kcal/ml group with missing data.

Finally, any subgroup analyses risk identifying apparent differences within a single group that may not represent a true difference (45). Given the subgroup aged ⩾65 years and living at home with supports included only 219 participants with 97 events (deaths), and our *a priori* hypothesis was that they would be most likely to benefit from increased calorie delivery, yet the signal was for harm with greater calories, we recommend caution against overinterpretation within this subgroup.

Conclusions

Six months after randomization into TARGET, we measured quality of life, mortality, and functional outcomes. We observed that increasing calorie delivery during critical illness to approximately 100% of recommended intake did not affect any of these outcomes. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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