Energy-dense vs routine enteral nutrition in New Zealand Europeans, Māori, and Pacific Peoples who are critically ill

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ABSTRACT

AIMS: To evaluate the effect of energy-dense vs routine enteral nutrition on day-90 mortality by ethnic group in critically ill adults.

METHODS: Pre-planned subgroup analysis of the 1,257 New Zealanders in a 4,000-participant randomised trial comparing energy-dense enteral nutrition (1.5kcal/mL) with routine enteral nutrition (1kcal/mL) in mechanically ventilated intensive care unit (ICU) patients. The primary purpose of this analysis was to evaluate responses to study treatment by ethnic group (European, Māori, and Pacific Peoples) using ethnicity data recorded in the clinical records. The secondary purpose was to compare the characteristics and outcomes of patients by ethnic group. The primary outcome was day-90 mortality.

RESULTS: Among 1,138 patients included in the primary outcome analysis, 165 of 569 (29.0%) assigned to energy-dense nutrition and 156 of 569 patients (27.4%) assigned to routine nutrition died by day 90 (odds ratio; 1.06; 95% CI, 0.92–1.22). There was no statistically significant interaction between treatment allocation and ethnicity with respect to day-90 mortality. Day-90 mortality rates did not vary statistically significantly by ethnic group.

CONCLUSIONS: Among mechanically ventilated adults in New Zealand ICUs, the effect on day-90 mortality of energy-dense vs routine enteral nutrition did not vary by ethnicity.

Over 14,000 critically ill patients are admitted to New Zealand intensive care units (ICUs) annually.[1] Nutrition therapy is an essential standard of care for all patients who require life support (invasive mechanical ventilation) as calorie deficits in such patients are associated with poor outcomes.[2,3] Enteral nutrition delivered through a nasogastric tube is preferred to parenteral nutrition, but typically results in delivery of only ~60% of guideline-recommended calories.[4,5]

The Augmented vs Routine approach to Giving Energy Trial (TARGET) was a multicentre randomised double-blind clinical trial comparing energy-dense nutrition (1.5kcal/mL) with routine nutrition (1kcal/mL) in 4,000 critically ill adults from 46 ICUs in Australia and New Zealand.[6] Use of energy-dense nutrition resulted in delivery of guideline-recommended calories in a large-scale clinical trial for the first time but failed to reduce day-90 mortality or affect a number of important secondary outcomes compared with routine nutrition.[6]

International guidelines recommend the use of weight-based equations to estimate energy requirements[7,8] and these are the most frequently used in clinical practice.[9] Ethnic differences in body composition, socioeconomic status and patterns of prior nutritional intake as well as differences in the prevalence of diseases like obesity and type 2 diabetes mean that it is plausible the calorie requirements of critically ill adults vary by ethnicity. However, whether ethnicity is an important determinant of treatment response when energy-dense nutrition is used to deliver guideline-recommended calories is unknown. This information is important to understanding whether the TARGET results are generalisable to different ethnic groups in New Zealand.

Accordingly, we conducted a pre-planned analysis[10] of the 1,257 participants who were enrolled in the 11 New Zealand ICUs that participated in TARGET. The principal aim of this analysis was to establish whether the effect of energy-dense nutrition on patient outcomes varied by ethnic group. Our hypothesis was that for day-90 mortality there would be a statistically significant interaction between ethnicity and treatment allocation. Our secondary aim was to report the mortality of enrolled participants by ethnic group adjusted for treatment allocation and important baseline covariates.

Method

Trial design

TARGET was an investigator-initiated, randomised, parallel group, double-blind superiority trial. This report outlines the findings from a pre-planned subgroup analysis of response to treatment by ethnicity, which was approved by the Northern B New Zealand Health and Disability Ethics Committee, only included New Zealand participants; ethnicity data were not collected for Australian participants. Details of TARGET trial design are available in the previously published study protocol,[11] statistical analysis plan,[10] and in the primary manuscript.[6]

Patient population

Mechanically ventilated adults, aged 18 or older, who were to commence or had commenced enteral nutrition in the previous 12 hours, and were anticipated to require enteral nutrition in ICU beyond the calendar day following recruitment were eligible for inclusion. Exclusion criteria included a requirement for specific nutritional therapy or when a treating clinician considered the goal feeding rate was clinically contraindicated. As part of baseline data collection, New Zealand study participants had a single ethnicity based on prioritised ethnicity tables[12] recorded from the clinical records.

For this analysis, we excluded patients who were not categorised into one of the three largest ethnic groups (New Zealand European, Māori and Pacific Peoples).

Randomisation and study treatment

Eligible participants were randomised in a 1:1 ratio to 1.5kcal/mL (energy-dense nutrition) or 1kcal/mL (routine nutrition). Randomisation was undertaken using permuted block method with variable block size, stratified by site, via a secure centralised web-based system. Nutrition was delivered via the enteral route at a goal rate of 1mL/kg ideal body weight per hour in both groups, with a maximum goal rate of 100mL per hour, to be achieved within 48 hours. The study feeds were supplied by Fresenius Kabi Deutschland, Germany in identical 1,000mL bags with study-specific labels. Further information regarding feed content is available in the TARGET manuscript.[6] The trial enteral nutrition was administered for up to 28 days, until the patient discontinued enteral nutrition, died or was discharged from ICU, whichever occurred first.

Outcome measures

Primary outcome

The primary outcome was all-cause mortality at day 90 following randomisation.

Secondary outcomes

Secondary outcomes included survival time to day 90; proportion of patients who had each of the following within 28 days of randomisation: vasopressor support; renal replacement therapy in ICU, positive blood cultures to day 28 after randomisation, intravenous antimicrobials to day 28 after randomisation.

Statistical analysis

This analysis was conducted in accordance with a pre-prepared plan.[10] Power calculations were not performed because the number of New Zealand participants in TARGET was determined by the available sample. We conducted analyses on a modified intention to treat population that included all randomised New Zealand participants except those who withdrew consent for the use of all data or were lost to follow up before consent could be obtained and those both who did not meet all eligibility criteria and did not receive any study treatment.

Normally distributed and non-normally distributed continuous variables are reported as mean ± standard deviation and median (interquartile range) respectively. Categorical variables are reported as count and percentages. Baseline characteristics were compared using analysis of variance or Kruskall-Wallis tests for continuous variables with Dunnett posthoc tests when significant and chi-square tests with Bonferonni-adjusted posthoc tests when significant.

The primary outcome, mortality at day 90, was evaluated using logistic regression with results reported as odds ratios with 95% confidence intervals (CIs). As a sensitivity analysis, modified Poisson regression was also used to estimate the relative risks and 95% CIs.

We present survival time as Kaplan–Meier curves and used a Cox proportional-hazards model to calculate hazard ratios for survival. The proportion of patients who had vasopressor support, renal replacement therapy in ICU, positive blood cultures and intravenous antimicrobials were evaluated using logistic regression. A differential effect of treatment across ethnicity groups was evaluated by including the interaction between ethnicity and treatment allocation in all models. Analyses of the independent effects of ethnicity on mortality at day 90 were adjusted for treatment group, and site, as well as the pre-defined covariates of age, ICU admission APACHE-II score, body mass index, gender and admission type and reported as odds ratios and 95% CIs.

Analyses were conducted using SPSS Statistics 25 (IBM Corp, 2017).

Results

Patient characteristics

From June 2016 to November 2017, we enrolled 1,268 patients from 11 adult medical-surgical ICUs in New Zealand into TARGET. A total of 569 patients assigned to energy-dense nutrition and 569 patients assigned to routine nutrition were included in the primary outcome analysis (Figure 1). The energy-dense and routine enteral nutrition groups generally had similar baseline characteristics overall and when treatment groups were compared for New Zealand European, Māori and Pacific Peoples separately (Table 1). However, there were a number of highly statistically significant differences in the baseline characteristics of patients from different ethnic groups. Compared with New Zealand Europeans, Māori and Pacific Peoples were younger, had higher body mass index, were relatively more likely to have end-stage renal failure and insulin-treated diabetes mellitus (Table 2).

Primary outcome

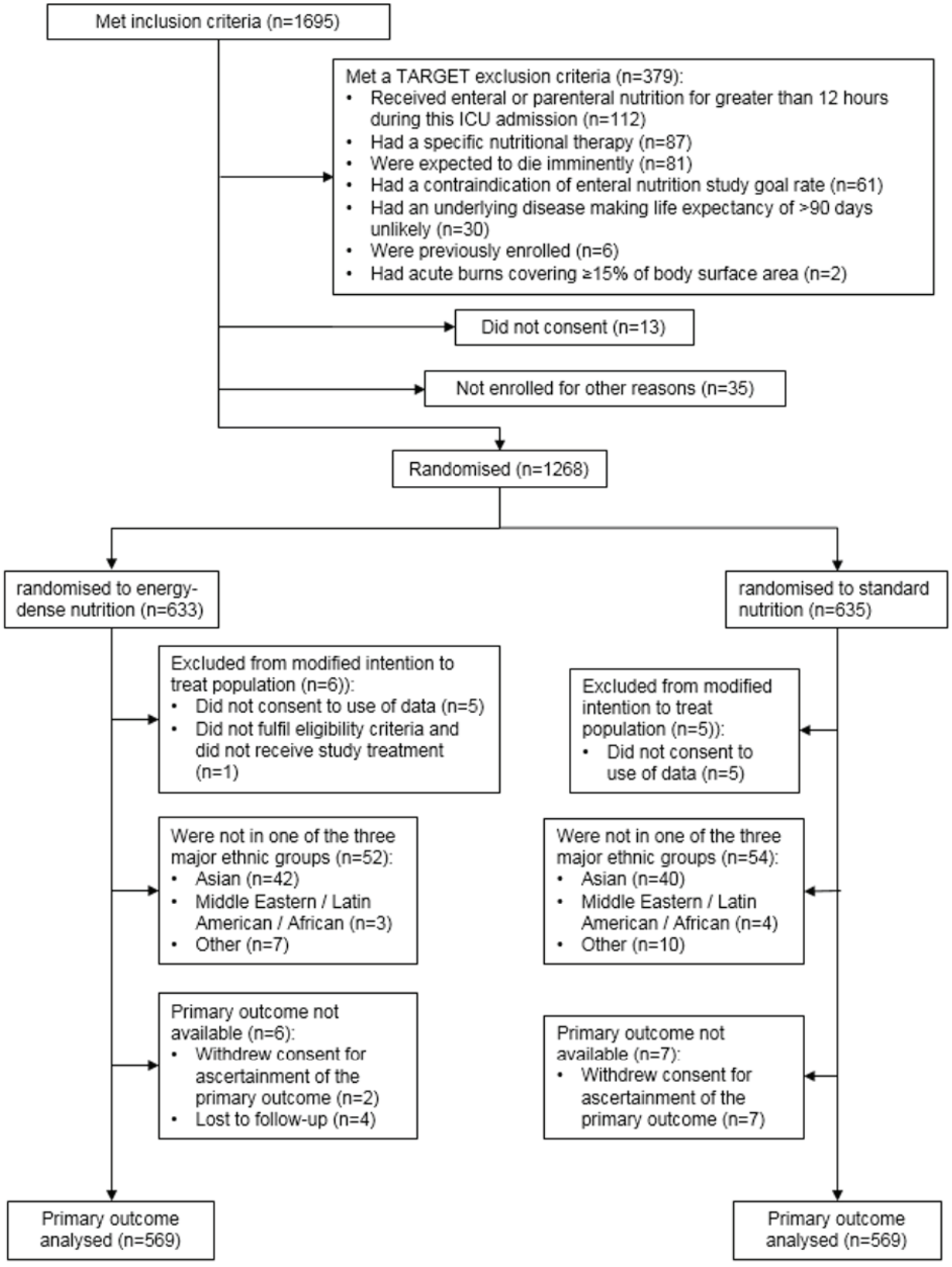
Day-90 mortality by treatment group for each ethnic group is shown in Table 3. There was no statistically significant interaction between study treatment allocation and ethnicity for all-cause mortality at day 90 following randomisation (Table 3 and Figure 2).

A total of 246 of 805 European participants (30.6%), 41 of 189 Māori participants (21.7%), and 34 of 144 Pacific participants (23.6%) had died by day 90. Compared with European participants, the adjusted odds ratio for day-90 mortality for Māori participants was 0.93 (95%CI, 0.56–1.54; P=0.79). Compared with European participants, the adjusted odds ratio for day-90 mortality for Pacific participants was 0.80 (95%CI, 0.53–1.22; P=0.30).

Secondary outcomes

There was no statistically significant interaction between study treatment allocation and ethnicity for survival time following randomisation (Figure 3). There was no statistically significant interaction between ethnicity and treatment allocation for the proportion of patients who had each of the following within 28 days of randomisation: vasopressor support; renal replacement therapy in ICU; positive blood cultures; and intravenous antimicrobials (Table 3).

Figure 1: Screening, randomisation and follow-up.



Abbreviations: ICU: intensive care unit.

Table 1: Characteristics of the patients at baseline by ethnicity and treatment group.

	All patients		NZ European		Māori		Pacific Peoples	
Characteristic	**Energy-dense nutrition (n=575)**	**Routine nutrition (n=576)**	**Energy-dense nutrition (n=414)**	**Routine nutrition (n=401)**	**Energy-dense nutrition (n=91)**	**Routine nutrition (n=99)**	**Energy-dense nutrition (n=70)**	**Routine nutrition (n=76)**
Age –yr	57.1±16.6	57.8±16.9	59.3±16.3	60.8±16.3	49.3±15.8	51.9±16.6	53.8±15.8	49.6±16.1
Male sex –no. (%)	378 (66%)	373 (65%)	288 (70%)	266 (66%)	53 (58%)	65 (66%)	37 (53%)	42 (55%)
Actual weight –kg	88.0±23.0	90.0±25.1	84.1±19.7	85.1±19.7	97.5±30.6	94.5±27.3	98.2±23.3	109.7±34.9
Ideal body weight –kg *	66.4±10.4	66.2±10.3	67.1±10.5	66.4±10.2	65.5±10.1	65.5±10.4	63.4±10.2	65.8±10.5
Body mass index –g/m²†	29.7±7.6	30.5±8.5	28.1±6.0	28.8±6.7	33.1±9.7	32.3±9.0	34.5±9.4	37.2±12.1
ICU admission category – no/total no. (%)								
Non-operative –no. (%)	366 (64%)	366 (64%)	279 (67%)	262 (65%)	52 (57%)	61 (62%)	35 (50%)	43 (57%)
Emergency operative –no. (%)	113 (20%)	110 (19%)	76 (18%)	74 (18%)	20 (22%)	22 (22%)	17 (24%)	14 (18%)
Elective operative –no. (%)	96 (17%)	100 (17%)	59 (14%)	65 (16%)	19 (21%)	16 (16%)	18 (26%)	19 (25%)
Co-existing medical conditions								
Chronic cardiovascular disease –no. (%)	21 (4%)	30 (5%)	12 (3%)	23 (6%)	7 (8%)	7 (7%)	2 (3%)	0 (0%)
Chronic respiratory disease –no. (%)	19 (3%)	21 (4%)	13 (3%)	16 (4%)	1 (1%)	0 (0%)	5 (7%)	5 (7%)
Hepatic failure or cirrhosis –no. (%)	7 (1%)	8 (1%)	6 (1%)	8 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
End-stage renal failure, n (%)	6 (1%)	7 (1%)	2 (0.5%)	2 (0.5%)	2 (2%)	2 (2%)	2 (3%)	3 (4%)
Metastatic cancer or haematological malignancy –no. (%)	8 (1%)	12 (2%)	7 (2%)	12 (3%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Immune disease or immunosuppression –no. (%)	18 (3%)	19 (3%)	14 (3%)	17 (4%)	3 (3%)	0 (0%)	1 (1%)	2 (3%)
Insulin dependent diabetes mellitus –no. (%)	18 (3%)	35 (6%)	18 (4%)	14 (3%)	4 (4%)	12 (13%)	9 (13%)	9 (12%)
APACHE-II score ‡	21.7±8.5	22.1±8.8	21.8±8.5	22.3±8.9	22.1±8.1	22.5±8.0	20.8±8.5	20.8±9.5
ANZ Risk Of Death	0.21±0.22	0.22±0.23	0.22±0.22	0.23±0.23	0.19±0.22	0.20±0.21	0.19±0.22	0.19±0.23
Time from ICU admission to randomisation (hours), median (IQR)	13.2 (5.3– 25.9)	12.3 (5.5–24.9)	12.5 (5.0–25.5)	11.8 (5.2–23.6)	13.6 (5.6–28.2)	12.5 (6.2–25.4)	17.3 (6.8–29.7)	12.1 (6.0–27.6)
Sepsis at randomisation –no. (%)	202 (35%)	206 (36%)	151 (36%)	151 (38%)	30 (33%)	26 (26%)	21 (30%)	29 (38%)
Organ support at randomisation –no. (%)								
Invasive ventilation –no. (%) §	574 (100%)	573 (100%)	413 (100%)	398 (100%)	91 (100%)	99 (100%)	70 (100%)	76 (100%)
Vasopressor infusion –no. (%)	394 (69%)	383 (66%)	281 (68%)	257 (64%)	62 (68%)	74 (75%)	51 (73%)	52 (68%)
Acute renal replacement therapy –no. (%)	50 (9%)	38 (7%)	32 (8%)	24 (6%)	6 (7%)	11 (11%)	12 (17%)	3 (4%)

Plus-minus values are expressed as mean ± SD.
* Ideal body weight was calculated from patient height, determined in the supine position as follows for men, ideal body weight in kg = 50 + 0.91 (height in cm - 152.4); for females, ideal body weight in kg = 45.5+0.91 (height in cm - 152.4).
† Body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. The score was calculated with the values recorded for each variable during the 24 hours before randomisation that would result in the highest score.
§ n=4 subjects had missing data for this item (1 in the energy-dense group; 3 in the routine nutrition group).

Table 2: Characteristics of TARGET study patients by ethnicity.*

Characteristic	NZ European (N=815)	Māori (N=190)	Pacific Peoples (N=146)
Age -yr	60.0±16.3	50.6±16.2***	51.6±16.1***
Male sex –no. (%)	554 (68%)	118 (62%)	79 (54%)**
Actual weight –kg	84.6±19.7	96.0±28.9***	104.2±30.3***
Ideal body weight –kg †	66.8±10.3	65.5±10.2	64.7±10.4*
Body mass index –g/m^2 ‡	28.4±6.4	32.6±9.3***	35.9±11.0***
ICU admission category			
Non-operative –no. (%)	541 (66%)	112 (59%)	78 (53%)
Emergency operative –no. (%)	150 (18%)	42 (22%)	31 (21%)
Elective operative –no. (%)	124 (15%)	35 (18%)	37 (25%)**
Co-existing medical conditions			
Chronic cardiovascular disease –no. (%)	35 (4%)	14 (7%)	2 (1%)
Chronic respiratory disease –no. (%)	29 (4%)	1 (1%)	10 (7%)
Hepatic failure or cirrhosis –no. (%)	14 (2%)	1 (1%)	0 (0%)
End-stage renal failure, n (%)	4 (0.5%)	4 (2%)*	5 (3%)**
Metastatic cancer or haematological malignancy –no. (%)	19 (2%)	1 (1%)	0 (0%)
Immune disease or immunosuppression –no. (%)	31 (4%)	3 (2%)	3 (2%)
Insulin dependent diabetes mellitus –no. (%)	32 (4%)	16 (8%)*	18 (12%)***
APACHE-II score §	22.1±8.7	22.3±8.0	20.8±9.0
ANZ Risk Of Death	0.23±0.23	0.20±0.21	0.19±0.23
Time from ICU admission to randomisation (hours), median (IQR)	12.3 (5.1–24.7)	12.7 (5.7–26.6)	14.2 (6.6–28.3)
Sepsis at randomisation –no. (%)	302 (37%)	56 (29%)	50 (34%)
Organ support at randomisation –no. (%)			
Invasive ventilation –no. (%)¶	811 (100%)	190 (100%)	146 (100%)
Vasopressor infusion –no. (%)	538 (66%)	136 (72%)	103 (71%)
Acute renal replacement therapy –no. (%)	56 (7%)	17 (9%)	15 (10%)

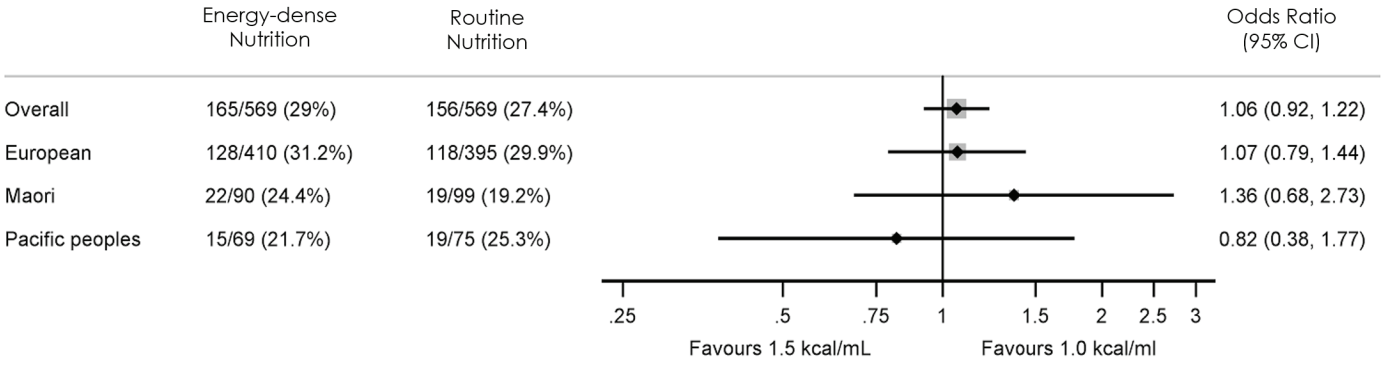
Plus-minus values are expressed as mean ± SD.
* Statistically significant differences between groups compared to the NZ European reference category are indicated by * for P < 0.05, ** for P<0.01, and *** for P<0.001.
† Ideal body weight was calculated from patient height, determined in the supine position as follows for men, ideal body weight in kg = 50 + 0.91 (height in cm - 152.4); for females, ideal body weight in kg = 45.5 + 0.91 (height in cm - 152.4).
‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. The score was calculated with the values recorded for each variable during the 24 hours before randomisation that would result in the highest score.
¶ n=4 NZ European subjects had missing data for this item.

Table 3: Primary and secondary outcome variables.

Outcome	Energy dense nutrition	Routine nutrition	Estimate of difference (95% CI)		Interaction P value*
Day 90 mortality			**Odds ratio**	**Relative risk**	
New Zealand European	128/410 (31.2%)	118/395 (29.9%)	1.07 (0.79–1.44)	1.05 (0.85–1.29)	0.64
Māori	22/90 (24.4%)	19/99 (19.2%)	1.36 (0.68–2.73)	1.27 (0.74–2.19)	
Pacific Peoples	16/69 (21.7%)	19/75 (25.3%)	0.82 (0.38–1.77)	0.86 (0.47–2.19)	
Received vasopressors in the ICU – no/total no. (%) †					
New Zealand European	346/414 (83.6%)	341/399 (85.5%)	0.87 (0.59–1.27)	0.98 (0.92–1.04)	0.91
Māori	76/91 (83.5%)	86/99 (86.9%)	0.77 (0.34–1.71)	0.96 (0.85–1.08)	
Pacific Peoples	59/70 (84.3%)	64/76 (84.2%)	1.01 (0.41–2.45)	1.00 (0.87–1.15)	
Received renal replacement therapy in the ICU – no/total no. (%) †					
New Zealand European	95/414 (22.9%)	72/399 (18.0%)	1.35 (0.96–1.91)	1.27 (0.97–1.67)	0.94
Māori	17/91 (18.7%)	16/99 (16.2%)	1.19 (0.56–2.53)	1.16 (0.62–2.15)	
Pacific Peoples	17/70 (24.3%)	14/76 (18.4%)	1.42 (0.64–3.15)	1.32 (0.70–2.47)	
Had positive blood cultures in the ICU – no/total no. (%) ‡					
New Zealand European	68/414 (16.4%)	65/400 (16.3%)	1.01 (0.70–1.47)	1.01 (0.74–1.38)	0.53
Māori	17/91 (18.7%)	12/99 (12.1%)	1.67 (0.75–3.71)	1.54 (0.78–3.05)	
Pacific Peoples	10/70 (14.3%)	11/76 (14.5%)	0.99 (0.39–2.49)	0.99 (0.45–2.18)	
Received intravenous antimicrobials in ICU – no/total no. (%) ‡					
New Zealand European	314/414 (75.8%)	298/400 (74.5%)	1.08 (0.78–1.48)	1.02 (0.94–1.10)	0.94
Māori	68/91 (74.7%)	70/99 (70.7%)	1.23 (0.65–2.33)	1.06 (0.89–1.26)	
Pacific Peoples	49/70 (70.0%)	52/76 (68.4%)	1.08 (0.53–2.18)	1.02 (0.82–1.27)	

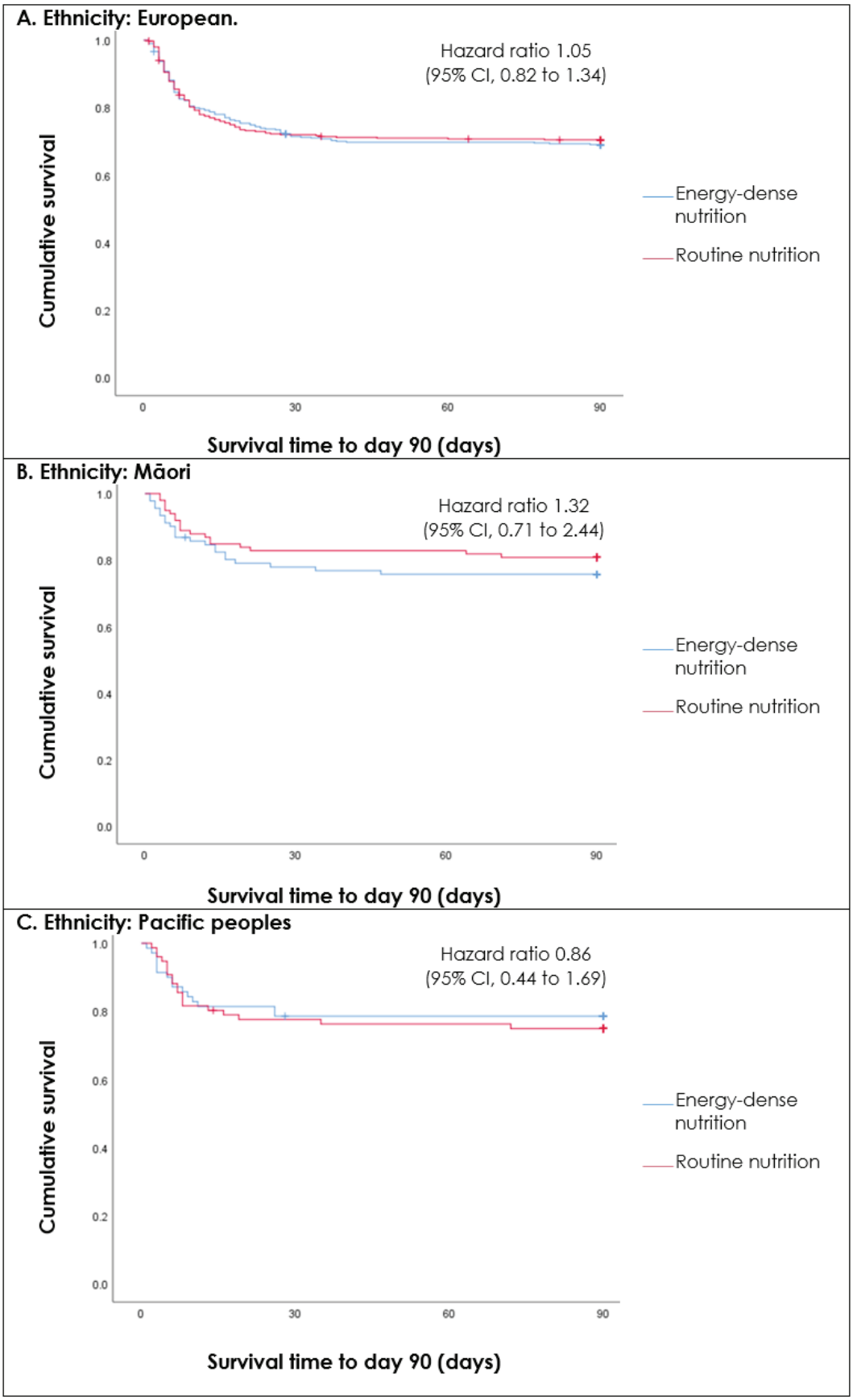
* Interaction P values for comparisons of differences in proportions by treatment group and ethnicity are based on the logistic regression model (P values from sensitivity analyses based on the Poisson regression model were similar).
† Data were missing for two subjects in the routine nutrition group.
‡ Data were missing for one subject in the routine nutrition group.
Abbreviations: ICU: intensive care unit; ANZ: Australia and New Zealand; APACHE: Acute Physiology and Chronic Health Evaluation.

Figure 2: Primary outcome—day 90 mortality by ethnicity.*



* There was no statistically significant interaction between treatment effect and ethnicity; interaction P value from logistic regression model equals 0.64; interaction P value from modified Poisson regression model equals 0.63.

Figure 3: Survival by ethnicity and treatment group.*



* There was no statistically significant interaction between treatment effect and ethnicity; interaction P value from Cox proportional hazards regression equals 0.64.

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Discussion

In this pre-planned subgroup analysis of New Zealand participants enrolled in a large multicentre critical care nutrition trial comparing energy-dense and routine nutrition we found no evidence of a statistically significant interaction between treatment group assignment and ethnicity for day-90 mortality. There was also no evidence of a differential treatment effect based on ethnicity for a range of secondary outcomes, including patients who received vasopressor support, renal replacement therapy, positive blood cultures or receiving intravenous antimicrobials.

While previous studies have suggested that empiric calculations of energy requirements may be inaccurate in non-Caucasians populations,[13] our findings suggest that despite differences in calculated energy requirements, patient outcomes with energy-dense vs routine nutrition do not vary among the New Zealand's most common ethnic groups. The absence of inter-ethnicity heterogeneity of treatment response was confirmed in analyses adjusting for important baseline covariates. As our study had relatively few exclusion criteria, our findings are generalisable to patients who receive enteral nutrition in New Zealand ICUs, irrespective of their ethnicity.

Equity of outcomes among patients admitted to New Zealand ICUs has not been reported previously. In the New Zealand TARGET study cohort, the observed day 90 mortality was 21.7%, 23.6%, and 30.6% for Māori, Pacific Peoples, and New Zealand European respectively. There were a number of important differences in the baseline characteristics of patients by ethnic group including that Māori and Pacific Peoples were younger, had higher body mass index and more frequently had insulin-treated diabetes mellitus and end-stage renal failure than New Zealand European participants. The day-90 mortality rate of Māori and Pacific Peoples did not differ significantly from New Zealand European mortality rate in analyses adjusting for important baseline covariates, including illness severity. Notably, given the observed differences in the rates of insulin-treated diabetes mellitus and end-stage renal failure by ethnic group, adjustment for illness severity was based on the APACHE-II score, which accounts for comorbid conditions including end-stage renal failure and for acute physiological derangements such as hyperglycaemia, which is the major predictor of mortality in patients with diabetes mellitus who are critically ill. These data provide a degree of reassurance that Māori and Pacific patients who are admitted to New Zealand ICUs have similar mortality outcomes to New Zealand European patients. However, it is notable that relatively few studies evaluating the independent association between ethnicity and outcome among New Zealanders admitted to ICU have been undertaken[14] and it is uncertain whether the cohort of patients enrolled in TARGET is representative.

Our study is noteworthy because it is the first time that the potential impact of ethnicity on outcome has been systematically evaluated in a large-scale intensive care randomised clinical trial; it has some limitations. We did not record data on socioeconomic status, which may be an important confounding variable. Because participants were critically unwell, documented ethnicity could not be verified reliably by asking participants and the ethnicity documented in the clinical records, or the prioritisation of ethnicity made at the time of data collection may have been inaccurate. However, ethnicity data and prioritised ethnicity data are routinely recorded for Ministry of Health reporting purposes in the New Zealand health system, and ethnicity data are usually available in clinical records, having been documented during previous healthcare encounters. Randomisation was not stratified by ethnicity; however, the groups were well balanced and sensitivity analyses adjusting for important baseline covariates was consistent with the unadjusted analyses. Categorisation in ethnic groups was performed on a post-hoc basis; however, different methods of categorisation were not feasible because other ethnic group categories were too small to allow for meaningful analysis to occur. This also means it is uncertain whether the effects of energy dense vs routine enteral nutrition are similar for other ethnic groups. Confidence intervals around treatment effect estimates were relatively large, particularly

in the Māori and Pacific subgroups, and do not exclude the possibility of clinically important treatment effects in individual subgroups. However, the absence of statistically significant heterogeneity in an analysis including more than 1,100 New Zealand participants constitutes high-level evidence that treatment responses to energy-dense nutrition do not vary among the three major ethnic groups in New Zealand.

In conclusion, our findings do not support the hypothesis that in critically ill adults the effect of energy-dense nutrition on day-90 mortality varies for European, Māori and Pacific ethnic groups in New Zealand.

Competing interests:
Mrs Mackle reports grants from Health Research Council of NZ during the conduct of the study; Dr Ridley reports grants from Baxter Healthcare Corporation, personal fees from Nutricia Australia, personal fees from Baxter Australia, outside the submitted work.

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