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Doubly labelled water-calibrated energy intake associations with mortality risk among older adults

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Abstract

Background The body mass index (BMI) is closely related to mortality risk, and energy intake (EI) is essential for maintaining energy balance in weight control. However, self-reported EI has been shown to lead to a systematic underestimation. Total energy expenditure measured using the doubly labelled water (DLW) method is considered an objective biomarker of EI and the gold standard for its estimation in individuals with stable body weight. We aimed to examine the association between DLW-calibrated EI and BMI on overall mortality risk in older adults.

Methods A prospective cohort study was performed using data of 8051 (4267 women and 3784 men) Japanese older adults from the Kyoto–Kameoka Study in Japan. Calibrated EI was calculated from the estimated EI using a food frequency questionnaire and equation developed based on DLW. Participants were classified by quartiles based on their EI stratified by sex. BMI was calculated using self-reported height and body weight. Mortality data were collected between 30 July 2011 and 30 November 2016. Statistical analysis was performed using the multivariable-adjusted Cox proportional hazard model with a restricted cubic spline.

Results The 8051 participants' mean (standard deviation) age and BMI were 73.5 (6.1) years and 22.6 (3.0) kg/m^2, respectively. The mean (standard deviation) EI with and without calibration was 1909 (145) kcal/day and 1569 (358) kcal/day in women and 2383 (160) kcal/day and 1980 (515) kcal/day in men, respectively. During the median 4.75 years of follow-up (36 552 person-years), 661 deaths were recorded. In both women (hazard ratio [HR], 0.63; 95% confidence interval [CI] [0.41, 0.98]) and men (HR, 0.62; 95% CI [0.44, 0.87]), after adjusting for confounders, the top quartile as compared with the bottom calibrated EI quartile showed a negative association with risk of all-cause mortality. The lowest HR for all-cause mortality was 1900–2000 kcal/day in women and 2400–2600 kcal/day in men. However, after adjusting for BMI, no significant association was observed between the calibrated EI and the risk of death. These associations could not be confirmed in the uncalibrated EI. The HR for mortality was minimal at a BMI of 23 kg/m^2 in both men and women, with or without adjustment for the calibrated EI.

Conclusions Calibrated EI was negatively associated with mortality risk but not uncalibrated EI. This may be mediated by an increase in body weight over time. Caution is required when interpreting the association between EI and mortality risk without adjusting for self-reported measurement errors and outcomes.

Keywords body mass index; doubly labelled water; energy intake; food frequency questionnaire; mortality; recovery biomarker

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Introduction

The body weight of older adults is closely related to the risk of death.[1,2] Energy intake (EI) contributes to weight control by maintaining a dynamic equilibrium of energy balance.[3] However, no consistent results have been reported among prospective cohort studies regarding the association between EI and the risk of death in older adults.[4–7] These previous studies have differences in methodology, such as dietary assessment or population, and discrepant findings on EI and mortality may be partially due to errors in self-reported data.[4–7] Self-reported data for dietary assessment are affected by systematic errors related to individuals' characteristics,[8] which hinder accurate evaluation of EI.[9,10]

In nutritional epidemiological studies, it is recommended to use biomarkers in the evaluation of dietary intake.[11] The calibrated regression equation is a method to reduce the effect of factors related to systematic errors in the estimated EI, which uses a food frequency questionnaire (FFQ) and total energy expenditure (TEE) measured by doubly labelled water (DLW) as a biomarker.[12,13] In previous studies, DLW-calibrated EI, as opposed to uncalibrated EI, was found to be associated with cardiovascular disease, cancer and diabetes risk.[10,14,15] Interestingly, most of these associations were reported to be insignificant after adjusting for body mass index (BMI).[10,15] Thus, an analysis of the effects of the presence or absence of an adjustment for BMI may be useful in understanding these causal relationships as it provides knowledge on the relationships between mortality events associated with EI and BMI.[10,15] Considering that EI is negatively associated with the prevalence of frailty with a high risk of future death, even after adjusting for BMI,[9] information regarding EI imbalance could be useful for prolonging the lifespan of older adults.

The objectives of this longitudinal cohort study of community-dwelling older adults were as follows: (1) comparing the associations of DLW-calibrated EI and uncalibrated EI with the risk of death and (2) evaluating the associations of calibrated EI and BMI with the risk of death. Our hypotheses were as follows: (1) only calibrated EI shows a negative association with the risk of death and (2) the association between calibrated EI and the risk of death depends on the presence or absence of adjustment for BMI.

Methods

Study population

This prospective cohort study used data from the Kyoto–Kameoka Study of residents aged 65 years and over in Kameoka City, Kyoto Prefecture, Japan. Details of the study are explained elsewhere.[9,16–21] For a complete survey of residents aged 65 years and over (as of 1 July 2011) in Kameoka, eligible candidates were selected by representatives of the Senior Citizen's Welfare Section of the city office based on demographic data such as name, sex, and birth date in the Basic Resident Register run by the Kameoka City Office (*Figure 1*). On 14 February 2012, 8319 participants provided appropriate responses to the Health and Nutrition Status Survey (additional survey), including the FFQ, and 8051 participants were ultimately included in this study.

The study protocol was approved by the National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN-76-2), Kyoto University of Advanced Science (approval number: 20-1), and Kyoto Prefectural University of Medicine (approval number: RBMR-E-363). All participants provided informed consent by completing and returning the questionnaire by mail. This study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-nut).[11]

Energy intake assessment

EI was evaluated using the previously validated self-administered FFQ[13,22] consisting of 47 food and beverage items. The participants responded to questions on foods and beverages included in the FFQ consumed in the past year. Portion size used a fixed value calculated from a one-day weighted dietary record (DR) by sex.[23] EI was calculated from the intake frequency, and portion size of each food and beverage using a programme developed based on the Standard Tables of Food Composition in Japan.[23] The Spearman's rank correlation coefficient (SCC) between the EI estimated using the FFQ and the EI estimated using the DR was 0.40 and 0.19 for women and men, respectively.[22] EI estimated using the FFQ was 10–13% lower than the EI estimated using DR in both men and women.[22]

Body mass index evaluation

BMI was calculated as self-reported weight (kg) divided by height (m) squared. We previously found no significant difference between BMI calculated from self-reported height and body weight and objectively measured BMI in a subcohort (n = 1169) of the Kyoto–Kameoka Study (mean difference in women, 0.5 kg/m^2; mean difference in men, 0.4 kg/m^2).[17] The correlation coefficient between BMIs obtained from these self-reports and measurements was 0.912 in women and 0.916 in men.[17] In addition, the interclass correlation coefficient (ICC), as a reproducibility scale of self-reported BMI, was 0.888 and 0.910 for women and men, respectively.[17]

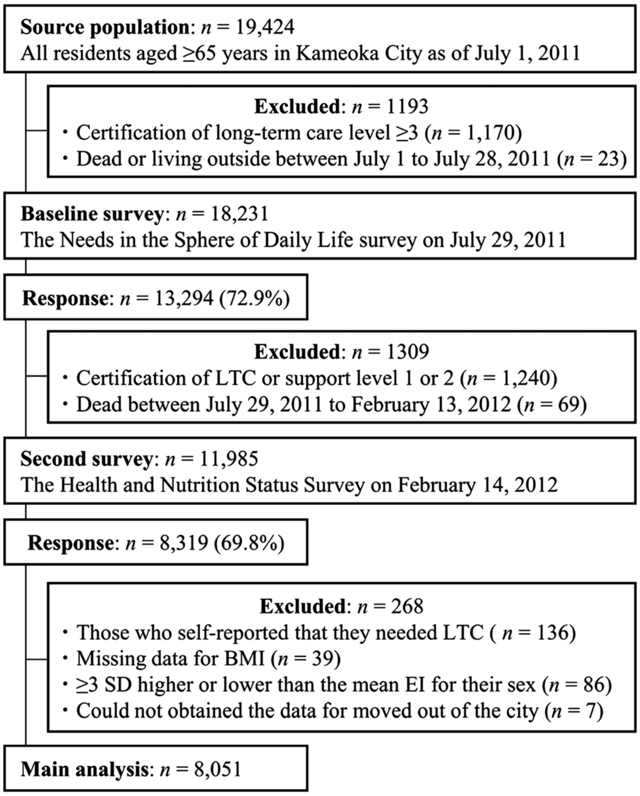

Figure 1 Participant flow diagram for the analysis of energy intake and mortality in Kyoto–Kameoka Study. BMI, body mass index; EI, energy intake; LTC, long-term care; SD, standard deviation.

Other covariates

Questionnaire data at baseline were used for all covariates, such as medical history, socioeconomic status, smoking status, frailty and education. We assessed individuals' socioeconomic status (hard, somewhat hard, somewhat easy or easy) using the following question in the baseline survey: 'Economically, how does your life feel currently?' Self-reported socioeconomic status was categorized as hard/somewhat hard (low status) and somewhat easy/easy (high status). The previous week's physical activity (PA) was evaluated using the International Physical Activity Questionnaire-Short Form (IPAQ-SF).[21,24] It has been reported that PA in older adults calculated using metabolic equivalents (METs) (vigorous PA = 8.0 METs, moderate PA = 4.0 METs and walking = 3.3 METs) allocated to the original version of the IPAQ-SF, compared with objectively measured PA, may be significantly overestimated.[24] PA was calculated as the sum of the product of each PA level (vigorous PA = 5.3 METs, moderate PA = 3.0 METs and walking = 2.5 METs) and the duration of PA (duration and frequency) for each item in older adults in previous studies. PA estimated using a modified PA level on the IPAQ-SF has been validated against PA estimated using an accelerometer in Japanese adults aged 65 years and older (SCC = 0.43 to 0.54).[24] Frailty was evaluated using the self-administered Kihon Checklist (KCL), which comprises 25 previously validated questionnaire items.[19,20,25] The KCL evaluates frailty based not only on the physical component but also on multifaceted aspects (comprehensive frailty), such as social and cognitive factors. Individuals with frailty were defined as those who met at least 7 of 25 items of the KCL.[19,20,25] The ratio of calibrated EI to basal metabolism (calibrated EI/pBMR) was calculated using predicted basal metabolic rate (pBMR), which was estimated using an equation developed by Ganpule et al. using the Japanese population.[26]

Calculation of calibrated energy intake

Calibrated EI was calculated using an equation that was developed using a stepwise multiple regression model with TEE (previously measured using DLW) as a dependent variable.[13] This included 109 older Japanese adults of the sub-cohort in the Kyoto–Kameoka Study, for whom TEE was measured using DLW. TEE was measured using the DLW method over approximately 2 weeks, from May to June 2012. The details are explained elsewhere.[13,27] The multiple regression model used variables identified in the Kyoto–Kameoka Study and was developed to reduce systematic error in the EI estimation using the FFQ. The sub-cohort participants, for whom TEE was measured using DLW, tended to be men, alcohol drinkers and attained higher education than those in the large cohort; however, these differences were minor.[13,27] After confirming the condition of the linear model, such as assumptions of normality, homoscedasticity and independence of the error terms hold, age, sex, BMI and EI estimated from the FFQ were ultimately included in the model as significant independent variables. The determination coefficient (R^2) of this model was 0.36. The model used the following equation:

$$\begin{aligned}\mathrm{C} = \beta_0 + \beta_1\ \mathrm{age}_1(1 \text{ if} \geq 75 \text{ years},\ 0 \text{ if } < 75 \text{ years}) \\ +\beta_2\ \mathrm{sex}_2\ (1 \text{ if female},\ 0 \text{ if male}) \\ +\beta_3\ \mathrm{BMI}_3 + \beta_4\ \mathrm{EI}_4\end{aligned} \quad (1)$$

where *C* represents calibrated EI. The intercept (β_0) of the equation was 1384.92 kcal. The coefficient of binary variables, age (β_1) and sex (β_2), was −166.98 kcal and −354.72 kcal, respectively. The coefficient of continuous variables, BMI (β_3) and EI (β_4), was 25.55 kcal (kg/m^2) and 0.24 kcal (kcal/day), respectively. The product of the above coefficients and all variables for individuals, such as age (1 for 75 years and over; 0 for under 75 years), sex (1 for women; 0 for men), BMI (continuous) and EI (continuous), were calculated. The calibrated EI was calculated as the sum of the above product and the intercept.

The validity of the calibrated EI calculated using the equation was verified using repeated measurements of TEE measured by the DLW method in the same group from whom the equation was developed (SCC = 0.517).[27] The ICC on the reproducibility scale for estimates of calibrated EI was 0.921 and 0.945 for women and men, respectively.[27] The estimation of the 'true' group mean of the calibrated EI at an error rate of 0.5% within the 95% confidence interval (CI) showed a requirement of 682 women participants and 498 men participants.[27] Therefore, the sample size of this study was sufficient. We previously reported a correlation coefficient (*r*) of 0.95 between the evaluation of once measures of calibrated EI and the 'true' unmeasured mean calibrated EI in both men and women, showing that a dietary assessment accurately reflects habitual EI.[27]

If the target EI is established for the guidelines, absolute EI cannot be applied to individuals with different body sizes. In addition, target EI per actual body weight leads to an increased likelihood of excessive EI prescription in individuals with obesity and reduced EI prescription in underweight individuals. The ideal body weight (IBW) is used in some clinical practice settings and may help to delineate the optimal body weight for a given height. A BMI of 22 kg/m^2 (the square of 22 × height [m^2]) was chosen as the reference point for IBW because previous studies have found that a BMI of approximately 22 kg/m^2 was related to the lowest morbidity rates in Japanese populations.[9,28] The provisional IBW may be appropriate considering the mean BMI of the participants in this study (women, 22.3 kg/m^2; men, 22.9 kg/m^2) and the low risk of death in individuals with a BMI of approximately 22 kg/m^2 in the Japanese population.[2]

Event mortality

During the follow-up, the survival status of the participants was evaluated using the information on the Basic Resident Register run by the Kameoka City Office. Data for the period between 15 February 2012 and 30 November 2016 were obtained. Censoring was applied to the data on former residents whose registration was deleted or those who had left the country (155 individuals [412 person-years] of 8051 individuals [36 552 person-years]).

Statistical analysis

All statistical analyses were stratified by sex. EI was classified into four groups by quartiles. Descriptive statistics of continuous and categorical variables are presented as the mean and standard deviation and the number of individuals and percentage, respectively. Where covariate information pertaining to the family structure (*n* = 625; 7.8%), socioeconomic status (*n* = 389; 4.8%), education attainment (*n* = 939; 11.7%), smoking status (*n* = 366; 4.5%), alcohol drinking (*n* = 312; 3.9%), denture use (*n* = 220; 2.7%), medications (*n* = 648; 8.0%), frailty status (*n* = 1057; 13.1%) and PA (*n* = 248; 3.1%) was missing, we imputed the missing values using the multivariate imputation by chained equation (MICE) package in R Statistical Software (Foundation for Statistical Computing, Vienna, Austria); five datasets were created using multiple imputation.[20,29] All missing values were assumed to be missing at random.

The absolute mortality risk for each EI quartile is presented as the number of events per 1000 person-years. A multivariate Cox proportional hazard model including baseline covariates was used to adjust for confounders on the association between EI and the risk of death. Multivariate analysis was examined using the following three models. Model 1 adjusted for age (continuous) and population density (≥1000 or <1000 people/km^2); Model 2 adjusted for variables in Model 1, as well as living alone (yes or no), socioeconomic status (high or low), educational attainment (<9, 10–12, or ≥13 years), smoking status (never smoker, past smoker or current smoker), alcohol drinking (yes or no), denture use (yes or no), medication use (continuous), number of chronic diseases (continuous), frailty (yes or no) and physical activity (continuous) to Model 1; Model 3 adjusted for variables in Model 2, as well as BMI (continuous) to Model 2. Before statistical analysis, these adjustment factors were determined by referring to covariates used in previous studies that examined the association between EI and mortality.[4–7] It is difficult to determine whether high EI is the cause or effect of a high BMI; therefore, we compared the regression model including BMI and the regression model without including BMI.[9,10] These analysis results are presented as hazard ratio (HR) and 95% CI, with HR calculated with reference to the first quartile of EI. The linear trend was calculated using EI as a continuous exposure variable. We performed a sensitivity analysis using the following two methods: (1) To avoid the possibility of a reversed causal relationship, death events in the first 2 years of the follow-up study (146 men, 64 women) were excluded from the analysis; and (2) a similar analysis was performed using the complete case dataset without missing values.[30]

In addition, to evaluate the curvature between the calibrated EI and mortality risk, we used a restricted cubic spline model using three data points based on the distribution of the calibrated EI.[9] The results are presented as HR and 95% CI, with HR calculated based on the mean of the first quartile of calibrated EI (the group with the lowest EI) for both men and women. Calibrated EI per IBW was also analysed using the same method. Finally, we analysed the association between BMI and the risk of death with and without adjustment for the calibrated EI.

$P < 0.05$ (two-tailed) was considered statistically significant. All analyses were performed using STATA MP, version 15.0 (StataCorp LP, College Station, TX, USA) and/or R software 3.4.3.

Results

The baseline characteristics of the study participants by quartile of absolute calibrated EI distribution stratified by sex are shown in *Tables 1* and *S1*. The results showed that the higher the calibrated EI, the higher the PA, BMI and number of alcohol drinkers in both men and women. Individuals with a high calibrated EI were younger and had a low prevalence of denture use and frailty. In addition, participants in this study had a lower prevalence of frailty and mortality risk compared with participants in the baseline survey (*Table S2*).

The relationships between mortality risk with calibrated EI and uncalibrated EI are shown in *Table 2*. The median follow-up duration was 4.75 years (36 552 person-years). During the follow-up, 262 women (6.1%) and 399 men (10.5%) died. Model 2 showed a negative association between absolute calibrated EI and mortality risk [women, Q1: reference; Q2: HR, 0.67 (95% CI [0.49, 0.92]); Q3: HR, 0.73 (95% CI [0.49, 1.06]); Q4: HR, 0.63 (95% CI [0.41, 0.98]), P for trend = 0.016 and men, Q1: reference; Q2: HR, 0.84 (95% CI [0.66, 1.08]); Q3: HR, 0.63 (95% CI [0.46, 0.86]); Q4: HR, 0.62 (95% CI [0.44, 0.87]), P for trend < 0.001]. However, Model 3, after adjusting for BMI, showed no significant association between these variables in both men and women. Model 2 showed no significant as-

Table 1 Baseline characteristics of the study participants by quartile of absolute calibrated energy intake distribution stratified by sex[a]

	Total		Quartile of the absolute calibrated EI							
			Q1		Q2		Q3		Q4	
Women, *n*	4267		1071		1074		1066		1056	
Age (years)[b]	73.7	(6.3)	79.0	(5.7)	74.5	(6.1)	71.0	(4.9)	70.3	(4.0)
Height (cm)[b]	151	(6)	149	(6)	151	(6)	152	(5)	152	(5)
Body weight (kg)[b]	50.9	(8.1)	45.0	(6.2)	49.1	(6.5)	51.8	(6.1)	57.8	(7.6)
Body mass index (kg/m^2)[b]	22.3	(3.2)	20.2	(2.5)	21.6	(2.7)	22.4	(2.4)	25.1	(3.2)
Ideal body weight (kg)[b]	50.2	(3.9)	49.1	(4.0)	50.1	(4.0)	50.9	(3.6)	50.8	(3.6)
Frailty (*n* [%])[c]	1433	(33.6)	506	(47.3)	379	(35.3)	265	(24.9)	283	(26.8)
PA (MET-min/week)[b]	540	(1198)	354	(999)	543	(1207)	628	(1218)	635	(1326)
Calibrated EI (kcal/day)[b]	1909	(145)	1722	(72)	1867	(31)	1963	(26)	2089	(70)
(kcal/kg IBW/day)[b]	38.2	(3.9)	35.2	(3.3)	37.5	(3.1)	38.7	(2.9)	41.3	(3.4)
pBMR (kcal/day)[b]	1085	(119)	991	(97)	1060	(95)	1110	(90)	1180	(104)
Calibrated EI/pBMR[b]	1.77	(0.16)	1.75	(0.17)	1.77	(0.16)	1.78	(0.15)	1.78	(0.16)
Men, *n*	3784		940		944		955		945	
Age (years)[b]	73.2	(6.0)	77.4	(6.1)	73.8	(5.9)	71.3	(5.0)	70.2	(4.1)
Height (cm)[b]	164	(6)	163	(6)	164	(6)	164	(6)	165	(6)
Body weight (kg)[b]	61.7	(8.8)	56.7	(8.0)	60.4	(7.5)	62.8	(7.5)	67.0	(8.7)
Body mass index (kg/m^2)[b]	22.9	(2.8)	21.3	(2.6)	22.5	(2.4)	23.2	(2.3)	24.6	(2.7)
Ideal body weight (kg)[b]	59.3	(4.4)	58.5	(4.5)	59.2	(4.3)	59.6	(4.2)	60.1	(4.3)
Frailty (*n* [%])[c]	1115	(29.5)	377	(40.1)	275	(29.1)	230	(24.1)	233	(24.7)
PA (MET-min/week)[b]	1023	(1898)	711	(1580)	1062	(1940)	1119	(1946)	1199	(2054)
Calibrated EI (kcal/day)[b]	2383	(160)	2175	(82)	2337	(31)	2435	(28)	2584	(80)
(kcal/kg IBW/day)[b]	40.3	(3.8)	37.4	(3.2)	39.6	(3.0)	41.0	(3.0)	43.2	(3.3)
pBMR (kcal/day)[b]	1415	(129)	1336	(121)	1397	(109)	1436	(111)	1491	(124)
Calibrated EI/pBMR[b]	1.69	(0.15)	1.64	(0.15)	1.68	(0.13)	1.71	(0.13)	1.74	(0.15)

Abbreviations: BMI, body mass index; EI, energy intake; IBW, ideal body weight; MET, metabolic equivalents; PA, physical activity; pBMR, predicted basal metabolic rate; Q, quartiles.

[a] Missing values were supplemented using the multivariate imputation method: frailty status (n = 1,057; 13.1%) and physical activity (n = 248; 3.1%). BMI was calculated as body weight (kg) divided by height squared (m^2).

[b] Continuous values are shown as mean (standard deviation).

[c] Categorical values are shown as number (percentage).

Table 2 Hazard ratios for absolute calibrated or uncalibrated energy intake and all-cause mortality calculated using the multivariate Cox proportional hazards model[a]

				Event/1000 PY		Model 1[b]		Model 2[c]		Model 3[d]	
Absolute EI	*n*	Event	PY	Rate	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Calibrated EI											
Women											
Q1	1,071	133	4,804	27.7	(23.4 to 32.8)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Q2	1,074	59	4,925	12.0	(9.3 to 15.5)	0.67	(0.49 to 0.92)	0.67	(0.49 to 0.92)	0.78	(0.56 to 1.09)
Q3	1,066	40	4,957	8.1	(5.9 to 11.0)	0.71	(0.48 to 1.04)	0.73	(0.49 to 1.06)	0.90	(0.59 to 1.38)
Q4	1,056	30	4,897	6.1	(4.3 to 8.8)	0.62	(0.40 to 0.96)	0.63	(0.41 to 0.98)	0.91	(0.54 to 1.54)
P for trend[e]							0.018		0.016		0.791
Men											
Q1	940	180	4,031	44.7	(38.6 to 51.7)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Q2	944	108	4,238	25.5	(21.1 to 30.8)	0.80	(0.63 to 1.02)	0.84	(0.66 to 1.08)	0.96	(0.74 to 1.24)
Q3	955	61	4,361	14.0	(10.9 to 18.0)	0.58	(0.42 to 0.78)	0.63	(0.46 to 0.86)	0.75	(0.54 to 1.04)
Q4	945	50	4,340	11.5	(8.7 to 15.2)	0.56	(0.40 to 0.79)	0.62	(0.44 to 0.87)	0.81	(0.56 to 1.17)
P for trend[e]							<0.001		0.001		0.123
Uncalibrated EI											
Women											
Q1	1,068	77	4,879	15.8	(12.6 to 19.7)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Q2	1,066	59	4,901	12.0	(9.3 to 15.5)	0.83	(0.59 to 1.16)	0.82	(0.58 to 1.15)	0.81	(0.58 to 1.14)
Q3	1,068	66	4,892	13.5	(10.6 to 17.2)	0.95	(0.68 to 1.32)	0.98	(0.70 to 1.36)	0.94	(0.68 to 1.31)
Q4	1,065	60	4,910	12.2	(9.5 to 15.7)	0.83	(0.59 to 1.17)	0.86	(0.61 to 1.20)	0.84	(0.60 to 1.18)
P for trend[e]							0.601		0.710		0.591
Men											
Q1	946	115	4,173	27.6	(23.0 to 33.1)	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
Q2	947	87	4,268	20.4	(16.5 to 25.1)	0.72	(0.54 to 0.95)	0.73	(0.55 to 0.97)	0.71	(0.53 to 0.93)
Q3	946	109	4,252	25.6	(21.2 to 30.9)	0.85	(0.65 to 1.11)	0.87	(0.67 to 1.14)	0.84	(0.64 to 1.09)
Q4	945	88	4,277	20.6	(16.7 to 25.4)	0.72	(0.54 to 0.95)	0.77	(0.58 to 1.02)	0.74	(0.56 to 0.98)
P for trend[e]							0.045		0.157		0.072

Abbreviations: CI, confidence interval; EI, energy intake; HR, hazard ratio; PY, person-years; Q, quartiles; Ref, reference.

[a] The EIs ranges in Q1, Q2, Q3 and Q4 are as follows: <1811, 1811–1916, 1917–2009 and ≥2010 kcal for calibrated EI in women, respectively; <2278, 2278–2385, 2386–2485 and ≥2486 kcal for calibrated EI in men, respectively; <1408, 1408–1566, 1567–1750 and ≥1751 kcal for uncalibrated EI in women, respectively; and <1730, 1730–1968, 1969–2249 and ≥2250 kcal for uncalibrated EI in men, respectively.

[b] Model 1: Adjusted for age and population density.

[c] Model 2: In addition to the factors listed in Model 1, adjusted for family structure, economic status, educational attainment, smoking status, alcohol consumption status, denture use, medication use, number of chronic diseases, frailty status and physical activity.

[d] Model 3: In addition to the factors listed in Model 2, adjusted for body mass index.

[e] Linear trend *P* values were calculated using the likelihood ratio test and a continuous variable of EIs.

sociation between uncalibrated EI and mortality risk (*Tables 2* and *S3*). In addition, a sensitivity analysis showed similar results (*Tables S4–S7*).

The dose–response relationship between the calibrated EI and the risk of death in a restricted cubic spline model is shown in *Figures 2*, *3*, *S1* and *S2*. In Model 2, if the first quartile of calibrated EI (1722 kcal in women and 2174 kcal in men) was used as the reference, HR for all-cause mortality was minimal at a calibrated EI of 1900–2000 kcal in women and 2400–2600 kcal in men. In these relationships, the calibrated EI per IBW was optimal at 38–40 kcal/kg IBW and 42–46 kcal/kg IBW in women and men, respectively. However, Model 3 showed no significant association between mortality and calibrated EI. In the analysis stratified by BMI, there was a significant association between low EI and the risk of death in individuals with a BMI $<$ 22 kg/m^2, but not in those with a BMI $\geq$ 22 kg/m^2 (*Figure S2*). Furthermore, HR for mortality was minimal at a BMI of 23 kg/m^2 in both men and women, with or without adjustment for the *calibrated EI* (*Figures 4 and S3*).

Discussion

This is the first study to examine the association of DLW-calibrated EI and BMI with older adults' mortality risk. Additionally, the dose–response relationship between these relationships has not been examined.[4] We indicate that the calibrated EI showed the lowest HR for mortality at 1900–2000 kcal in women and 2400–2600 kcal in men, whereas the uncalibrated EI showed no significant results. Furthermore, no significant association was observed between the calibrated EI and the risk of death after adjusting for BMI. However, there was a significant association between BMI and the risk of death, even after adjusting for calibrated EI.

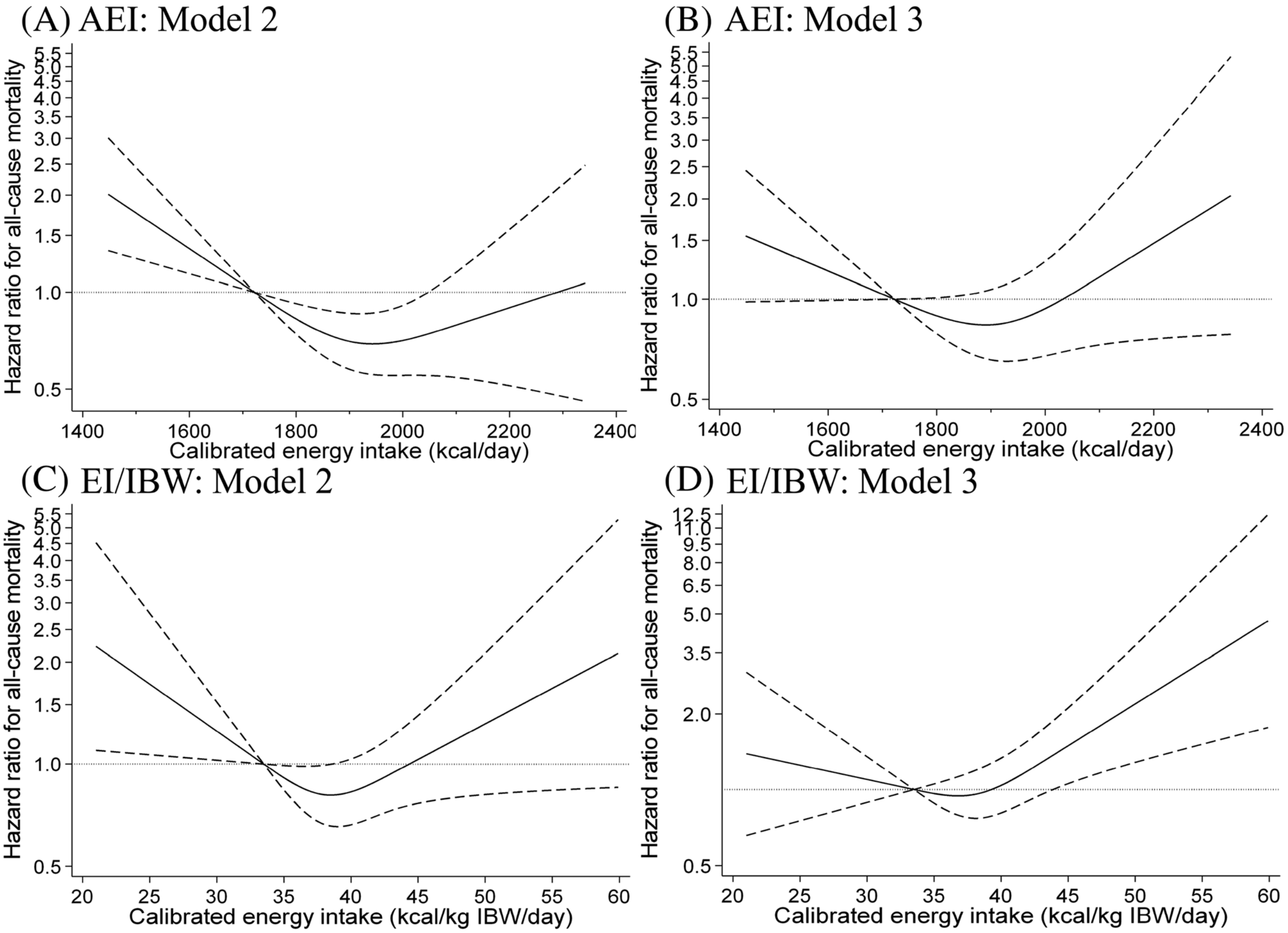

Figure 2 Dose–response relationship between calibrated energy intake and mortality in Japanese older women. The *x*-axis of each panel is (*A*) absolute energy intake (AEI) in Model 2 (*P* value = 0.001), (*B*) AEI in Model 3 (*P* value = 0.139), (*C*) calibrated energy intake per ideal body weight (EI/IBW) in Model 2 (*P* value = 0.051), (*D*) EI/IBW in Model 3 (*P* value = 0.625). The solid line shows the hazard ratio, and the broken lines show the 95% confidence intervals. The adjustment factors for Model 2 were age, population density, family structure, economic status, educational attainment, smoking status, alcohol consumption status, denture use, medication use, number of chronic diseases, frailty status and physical activity. Model 3 adjusted for body mass index in addition to the factors listed in Model 2.

The comparison between calibrated EI and uncalibrated EI suggested that systematic bias in the self-reported dietary assessment significantly impacts the results of nutritional epidemiological study. In general, regarding uncalibrated nutrient intake estimated using the FFQ, the reliability of the energy-adjusted nutrient intake is considered higher than that of the estimated absolute nutrient intake.[31,32] Under-reporting of EI by individuals with a high BMI[8] may make it difficult to understand the relationship between EI and the risk of death. However, the difficulty in accurately measuring dietary intake based on self-reported dietary assessments may be the cause of the difficulty in elucidating the relationship between EI and mortality events.[4–7] Therefore, examination of the association between EI and the risk of death using the biomarker calibration approach may partially resolve the problems of measurement errors in nutritional epidemiological studies, providing the optimal target EI for public health and clinical nutrition guidelines.

EI is one 'half' or part of energy balance, BMI is a marker of long-term EI and physical activity,[3] and use of self-report or DLW provides a short-term measure of EI.[14] An important aspect of our hypothesis is that EI is not associated with the risk of death independent of BMI. In other words, BMI may not be a confounder but a mediator of the relationship between EI and the risk of death.[10,14] If body fat accumulation (high BMI) is a mediator of the association between the risk of death and EI, the results without adjusting for BMI may be most appropriate in understanding the relationship between the calibrated EI and risk of death.[10,14] BMI and calibrated EI are closely related because our calibration equation for the biomarker includes

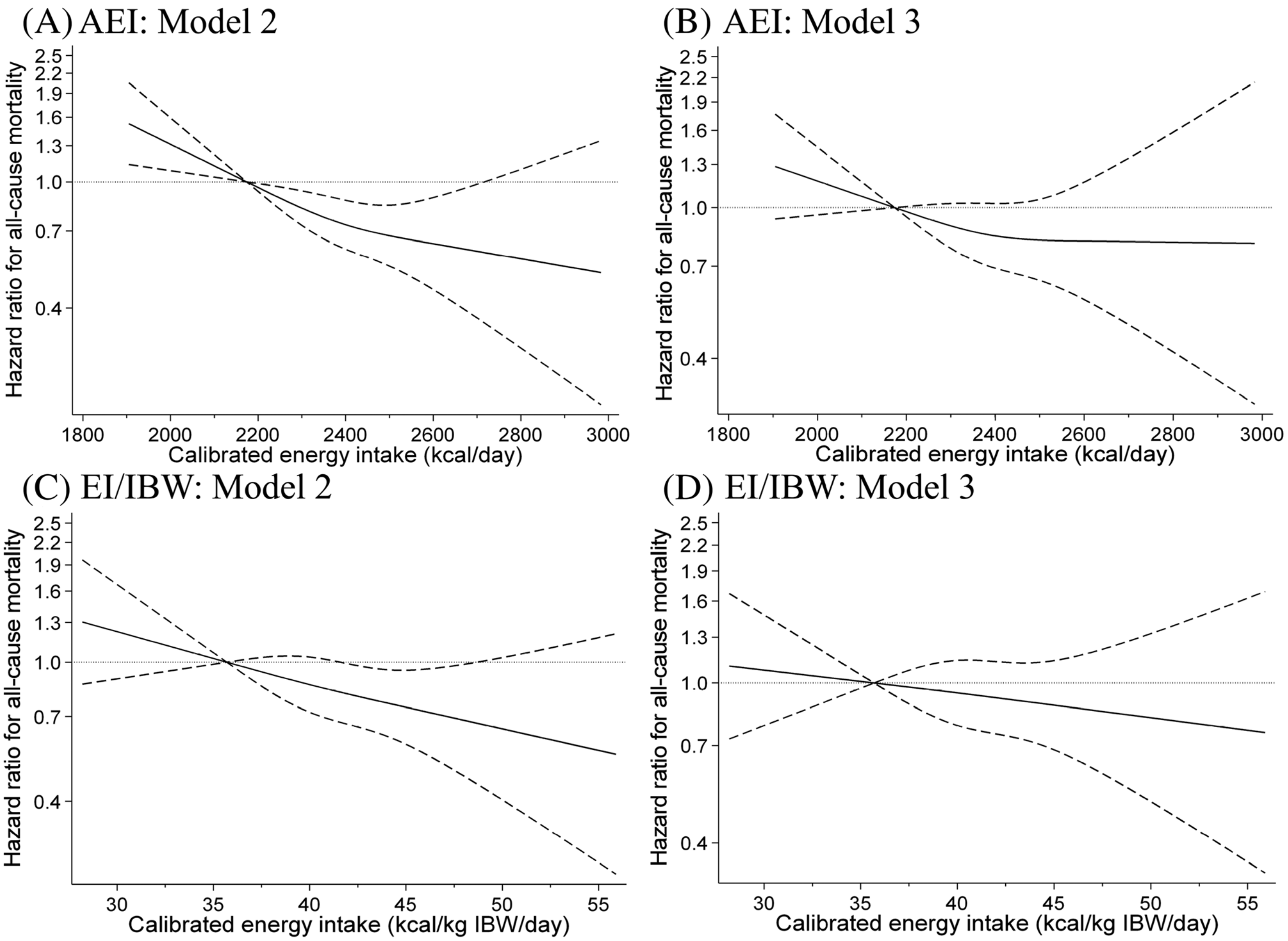

Figure 3 Dose–response relationship between calibrated energy intake and mortality in Japanese older men. The *x*-axis of each panel is (*A*) absolute energy intake (AEI) in Model 2 (*P* value = 0.004), (*B*) AEI in Model 3 (*P* value = 0.604), (*C*) calibrated energy intake per ideal body weight (EI/IBW) in Model 2 (*P* value = 0.032), (*D*) EI/IBW in Model 3 (*P* value = 0.837). The solid line shows the hazard ratio, and the broken lines show the 95% confidence intervals. The adjustment factors for Model 2 were age, population density, family structure, economic status, educational attainment, smoking status, alcohol consumption status, denture use, medication use, number of chronic diseases, frailty status and physical activity. Model 3 adjusted for body mass index in addition to the factors listed in Model 2.

BMI as an important factor. In addition, because it is necessary to average the increase in EI to sustain the increased weight in a mathematical modelling approach for adult human metabolism,[3] BMI may be considered an intermediator in a causal diagram of EI and mortality. Therefore, the inclusion of BMI in a statistical model leads to over-adjustment.[15] In the analysis stratified by BMI to overcome the limitation as much as possible, we demonstrated the association between low EI and the risk of death in individuals with a BMI $<$ 22 kg/m^2. Although our hypothesis could not be fully tested with the available data, the most probable interpretation of our results regarding the relationship between EI and the risk of death was that weight loss due to reduced EI may mediate the risk of death (especially in individuals with low BMI).

Adequate dietary intake, including EI and protein intake, is important to prevent malnutrition and improve protein synthesis and skeletal muscle maintenance/synthesis in older adults.[9,33,34] Especially, many previous studies have supported that protein intake increases skeletal muscle.[33] However, this may contribute not only to the impact of an increased protein intake but also to the increase in EI. We previously reported the dose–response relationship of the effects of protein intake on lean mass by meta-analysis using data from a randomized controlled trial.[33] Although this meta-analysis indicated that increasing protein intake may increase dose-dependent lean mass, these relationships were attenuated by adjusting for the change in body weight for the intervention period as an indicator of energy balance.[33] In addition, the anabolic effect of protein feeding has a higher

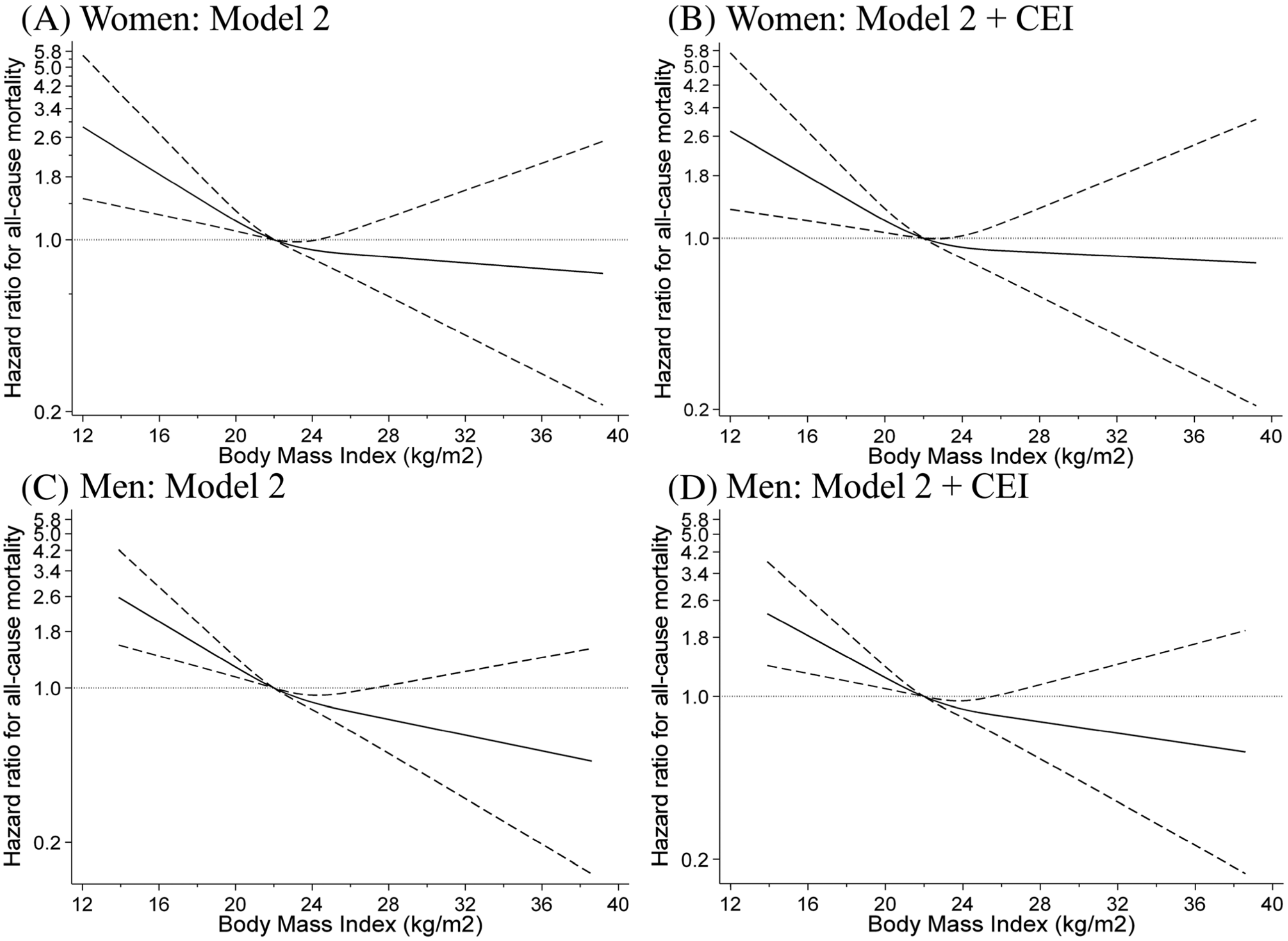

Figure 4 Association between body mass index and mortality adjusted for with and without calibrated energy intake in Japanese older women and men. The *x*-axis of each panel is the association between body mass index (BMI) and mortality results adjusted for (*A*) Model 2 (*P* value = 0.002) and (*B*) Model 2 + calibrated energy intake (CEI) (*P* value = 0.007) in women and (*C*) Model 2 (*P* value $<$ 0.001) and (*D*) Model 2 + CEI (*P* value = 0.003) in men. The solid line shows the hazard ratio, and the broken lines show the 95% confidence intervals, and the hazard ratio based on BMI of 22.0 kg/m^2 as reference was calculated. The adjustment factors for Model 2 were age, population density, family structure, economic status, educational attainment, smoking status, alcohol consumption status, denture use, medication use, number of chronic diseases, frailty status and physical activity.

nitrogen balance trend in older adults with a positive energy balance than in those with a negative energy balance.[34] Therefore, maintaining a dynamic equilibrium of energy balance by an adequate EI may be an important determinant of the anabolic effect of protein feeding. Therefore, evaluating protein intake and EI in older adults is necessary. These data suggest that providing older adults with opportunities for nutrition education and dietary assessment could be important for identifying inadequate EI.

Energy balance is important not only for EI but also for energy expenditure, including PA.[35–37] Some epidemiological studies indicated a U-[35] or J-shaped[36] relationship between the PA level and EI, and the lowest PA groups have higher EI and body weight. Conversely, an experimental study using metabolic chambers has shown that EI does not change, but energy balance differs at different levels of PA.[37] These data imply that EI is not automatically matched to the PA level. Although we adjusted for self-reported PA as a confounder, we could not evaluate the relationship between energy balance and mortality risk. Moreover, although we calculated age-calibrated PA based on PA intensities for Japanese older adults used in a previous study,[21,24] self-reported assessments may inflate estimates of habitual PA compared with objective PA estimated from DLW or triaxial accelerometer. The individuals in the highest tertile of free-living activity energy expenditure calculated by the DLW method have a lower mortality risk than the community-dwelling older adults in the lowest tertile.[38] Therefore, it is necessary to further study and evaluate the association of objectively assessed energy balance, including EI and TEE, with mortality.

In addition, our findings showed the lowest HR for mortality at a BMI of approximately 23 kg/m^2 in both men and women, even after adjusting for calibrated EI. Our previous study has reported that BMI can be accurately self-evaluated,[17] and BMI may be an ideal surrogate marker for managing energy balance compared with self-reported EI. In addition, considering the significant association between EI/IBW and the risk of death, the intake of the target EI/IBW may lead to optimal BMI control by optimal EI considering body size. Although our results have not demonstrated a significant inverse association between high BMI and mortality risk, the HR shown in our results suggests a trend of lower mortality risk in participants with high BMI. Therefore, it is necessary to conduct a further study and evaluate the association of high EI and high BMI with mortality to elucidate the obesity paradox.[39]

The strength of this large-scale cohort study in community-dwelling older residents was the use of the calibrated EI calculated using a previously validated equation that was developed based on TEE measured by the DLW method as a recovery biomarker of EI. This may be essential for the accurate evaluation of the association of EI with BMI and mortality. However, this study has some methodological limitations. First, TEE measured by the DLW method is assumed to reflect the actual EI of individuals with stable body weight.[13] Therefore, if the population in this study consisted of some individuals with unstable body weight, the estimated calibrated EI may have a systematic error. In addition, the equation may not include other covariates related to the systematic error that could not be obtained in the Kyoto–Kameoka Study. This may be the reason for the low coefficient of determination (R^2). Furthermore, our present cohort study did not develop a calibrated equation using biomarkers of nutrients for energy production, such as protein. Therefore, analyses were limited to the association between EI and the risk of death. Second, although the Kyoto–Kameoka Study conducted a complete survey of residents aged 65 years and over in Kameoka, the baseline characteristics of participants in the baseline survey and those in this study were different, which may have led to selection bias. Third, the follow-up period of the present study was relatively short. Furthermore, due to the lack of data on the cause of death, this study could not examine the association between calibrated EI and the cause of death. Lastly, although this study included an adjustment for confounders, there may be residual confounders in the association between calibrated EI and mortality risk. Therefore, re-evaluating the results of the present prospective study with a long-term follow-up using repeated measurement data of individuals, such as calibrated EI and BMI, may be useful for understanding the causal relationship between the risk of death in these data and its mechanism.

In conclusion, this study suggested that the maintenance or increase in body mass by modulating EI might substantially contribute to a negative association between calibrated EI and the risk of death. Previous findings using the international DLW database that we are sharing show that TEE starts decreasing at 60 years in both men and women.[40] Considering the above-mentioned results, our present findings may contribute to the maintenance of optimal body size by providing the optimal target EI to reduce the risk of death in older adults with changing energy balance.

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Conflict of interest

None of the authors report a conflict of interest related to research presented in this article.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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