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Original Contribution

Associations Between Dietary Melatonin Intake and Total and Cause-Specific Mortality Among Japanese Adults in the Takayama Study

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Potential health benefits of melatonin have been suggested. Although melatonin is present in various foods, little is known about the health effects of dietary melatonin intake. We estimated habitual dietary melatonin intake and examined its association with total and cause-specific mortality in a population-based cohort study in Japan. Study subjects included 13,355 men and 15,724 women aged ≥35 years who responded to a self-administered questionnaire in 1992. Their diets were assessed via a food frequency questionnaire at baseline. The melatonin content in various foods on the questionnaire was measured to estimate melatonin intake. Mortality was ascertained during 16 years of follow-up (1992–2008). Hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality were calculated according to melatonin quartiles. A total of 5,339 deaths occurred during follow-up. Melatonin intake was significantly associated with decreased risks of total mortality, cardiovascular mortality, and noncancer, noncardiovascular mortality after controlling for covariates; HRs for the highest quartile of melatonin intake versus the lowest were 0.90 (95% CI: 0.82, 0.98; *P* for trend = 0.05), 0.85 (95% CI: 0.72, 0.99; *P* for trend = 0.10), and 0.77 (95% CI: 0.67, 0.90; *P* for trend = 0.003), respectively. The data suggest a potential benefit of dietary melatonin with regard to mortality rates.

cohort studies; diet; dietary melatonin; Japanese; morality

Abbreviations: aMT6s, 6-sulfatoxymelatonin; CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; ICD-10, *International Classification of Diseases, Tenth Revision*; NCNC, noncancer, noncardiovascular; SD, standard deviation.

Melatonin is a neuroendocrine hormone produced primarily by the pineal gland in the brain (1). Since its discovery, a large variety of physiological features of melatonin have been uncovered. In addition to its well-known role as a circadian-rhythm regulator (2), melatonin is a highly potent antioxidant as well as an effective antiinflammatory agent (3, 4). Melatonin also exhibits immunomodulatory actions, tumor suppression, bone growth enhancement, and hormonal regulation and participates in the regulation of metabolism and energy balance (5–9). These laboratory findings suggest potential benefits of melatonin in human health. In fact, oral administration of melatonin has been shown to improve levels of oxidative, inflammatory, and metabolic biomarkers in humans (10–13). Potential benefits of both endogenous and supplementary melatonin in persons with chronic diseases, such as cancer, cardiovascular disease, diabetes, obesity, and neurodegenerative disorders, have been suggested (14–16).

In 1995, the presence of melatonin in plants was confirmed in 2 independent articles (17, 18), including 1 by one of the current authors (18). Since then, melatonin has been identified and quantified in both animal foods and edible plants (19). Although levels of melatonin in foods are much lower than those in melatonin supplements, consumption of foods rich in melatonin has increased circulating melatonin levels in some studies (20). Dietary melatonin may also have beneficial effects on health by mediating increased circulating melatonin levels. However, because there is no difference between endogenous and exogenously acquired melatonin, how dietary melatonin contributes to overall endogenous melatonin production is unclear (21). Moreover, to our knowledge, there have been no studies

investigating the associations between dietary melatonin intake and disease outcomes. Even the intake levels of melatonin from a usual diet have not been reported. Therefore, we estimated total dietary melatonin intake in a usual diet and examined its relationships to all-cause and cause-specific mortality in a population-based cohort of Japanese men and women (the Takayama Study).

METHODS

The Takayama Study

The Takayama Study is a prospective study launched in Japan in 1992 with the objective of studying associations between dietary and lifestyle factors and morbidity from cancer and various other diseases. The Takayama Study has been described in detail elsewhere (22). A total of 31,552 residents aged 35 years or older in Takayama, Gifu Prefecture, Japan, returned a baseline self-administered questionnaire that included questions on demographic characteristics, cigarette smoking habits, diet, physical activity, and medical and reproductive histories, yielding a participation rate of 85.3%. For the present study, we excluded subjects who reported having or having had cancer (186 men and 540 women) or stroke/coronary heart disease (886 men and 861 women) on the baseline questionnaire; this left 29,079 participants (13,355 men and 15,724 women). Details of the exclusion process are given elsewhere (23). The study has been approved by the institutional ethical committee of Gifu University Graduate School of Medicine (Gifu, Japan).

Dietary intake was assessed at baseline using a semiquantitative food frequency questionnaire (FFQ) (24). The questionnaire asked about the consumption frequency of foods and dishes (169 items) and the usual portion size over the course of 1 year. Some of the contents of mixed dishes were further classified into several individual foods. For melatonin measurement, 177 foods were selected on the basis of items included in the FFQ. Melatonin in individual foods was measured by liquid chromatography–tandem mass spectrometry. Details on the measurements are given elsewhere (25, 26). When melatonin levels were lower than the quantification limit, a value for the quantification limit was assigned (0.1 pg/g; 0.2 pg/g for some greasy foods). These foods included white bread, biscuits and snacks, oils, sugars, seasonings such as salt, vinegar, and sauces, beer, and wine. For the foods not analyzed for melatonin, the values of similar foods or of a different form of the same foods were assigned. For example, the value for boiled soybeans was assigned to "dried soybeans" after considering the moisture content. The value for kamaboko (boiled fish paste) was assigned to "fish sausage." These assignments covered 88.2% of the cumulative total number of foods (including repetition) on the FFQ, and these foods accounted for 98.6% of the total energy intake in men and 99.3% of that in women. Melatonin values among the measured foods ranged from 0.1 pg/g to 218.04 pg/g. As previously reported (19, 27), melatonin content was relatively high in eggs, seeds, and vegetables. For the remaining foods, we assigned median melatonin values among measured foods in the same food group. For calculation of total melatonin intake for each participant, the estimated melatonin levels of the foods in the FFQ were added together. Melatonin has not been approved for use as a supplement in Japan.

Intakes of other nutrients and food groups were estimated on the basis of this information using the Japanese Standard Tables of Food Composition, fifth revised and enlarged edition (28). A detailed description of the FFQ, along with its reliability and validity for estimation of nutrient and food group intakes, was published previously (24). At the start of the cohort study, the FFQ was validated in a subsample of this population by comparing 12 1-day diet records kept over a 1-year period (23). For the present study, the validity of the melatonin estimation was checked using the same data set. Spearman's correlation coefficients for correlation of melatonin intakes between the questionnaire and the 12 1-day diet records were 0.39 in men and 0.46 in women.

In another sample of women (29), we evaluated the relationship between levels of 6-sulfatoxymelatonin (aMT6s), the principal metabolite of melatonin, in the first morning urine void and melatonin intake estimated on the basis of the same FFQ. The correlation coefficient was 0.10 after controlling for age, body mass index, menopausal status, nightly hours of sleep, asleep/awake status at midnight, and duration of daylight on the day prior to urine collection.

Physical activity was assessed by asking the participant about the average number of hours per week spent performing various kinds of activities during the past year. Weekly metabolic equivalent of task–hours were estimated by multiplying the reported duration of activity by its correspondent energy expenditure requirements. Details, including the measure's validity, are provided elsewhere (30, 31).

Follow-up and endpoints

Information concerning subjects who died or moved away from Takayama City between the baseline date (September 1, 1992) and October 1, 2008, was obtained from residential registers or family registers. The mean duration of follow-up was 14.1 years. Causes of death were identified from death certificates provided by the Legal Affairs Bureau (Japan Ministry of Justice). We classified deaths using the *International Classification of Diseases, Tenth Revision* (ICD-10). We examined mortality due to all causes, all cancers (ICD-10 codes C00–D48), cardiovascular diseases (ICD-10 codes I00–I99), and all noncancer, noncardiovascular (NCNC) causes. During the study period, 941 (6.5%) men and 971 (5.7%) women moved out of Takayama City. They were censored at the time they moved out of the city. The date of moving was unknown for 104 (0.7%) men and 147 (0.9%) women. They were censored at the latest date on which they were known to reside in the city.

Statistical analyses

Dietary intake of melatonin was adjusted for total energy intake using the residual method (32). Baseline characteristics of participants according to quartile of melatonin values were evaluated using analysis of variance or the χ^2 test when appropriate. For each participant, person-years of follow-up were calculated from the date of response to the

baseline questionnaire to the date of death, emigration out of Takayama, or the end of follow-up (October 1, 2008), whichever occurred first. Multivariate Cox regression analyses were performed to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for total and cause-specific mortality for each intake category, considering the lowest quartile as the reference category. Cox regression models included age, total energy intake, sex, marital status (married or not married), duration of education (≤11, 12–14, or ≥15 years, or missing), body mass index (weight (kg)/height $(m)^2$; in quartiles, or missing), physical activity (metabolic equivalent of task–hours/week), alcohol consumption (mg/day; in quartiles), smoking status (never smoker, former smoker, current smoker with ≤30 years of smoking, or current smoker with >30 years of smoking, or missing) histories of diabetes and hypertension (yes, no), hours of sleep per night (≤6, 7–8, or ≥9 hours, or missing), coffee consumption (0.1–6 cups/week or 7 cups/week), and intakes of dietary fiber, polyunsaturated fat, and salt (energy-adjusted). Tests of linear trend across increasing categories were conducted by assigning the median value to each category and treating this variable as continuous.

A sensitivity analysis was performed when the assignment of melatonin values was done for 88.2% of the foods, as mentioned above (the value was considered to be 0 for the remaining foods). Additional sensitivity analyses were conducted by including participants who reported cancer, stroke, or coronary heart disease at baseline and excluding deaths occurring during the first 3 years of follow-up. All statistical analyses were performed using SAS software (SAS Institute, Inc., Cary, North Carolina). Statistical significance was defined as 2-sided $P < 0.05$.

RESULTS

The mean dietary melatonin intake was 30.9 (standard deviation (SD), 14.4) ng/day (32.3 (SD, 14.5) ng/day in men and 29.8 (SD, 14.2) ng/day in women). The main dietary source of melatonin in this population was vegetables (49.4%), followed by cereals (33.6%), eggs (4.8%), and coffee (3.6%). For vegetables and cereals, onions and cabbage (40.0%) and rice (32.5%) were the main sources, respectively.

Table 1 shows the baseline characteristics of participants according to quartile of melatonin intake. Compared with quartile 1, participants in quartile 4 were more likely to be women and never smokers and more likely to have reported a history of diabetes and a shorter nightly duration of sleep. They were less likely to have reported a history of hypertension. Participants in quartile 2 were older and less educated than those in quartile 4. Intakes of energy, polyunsaturated fat, and dietary fiber were lowest in quartiles 2 and 3, and salt intake was lowest in quartile 2. Alcohol intake was lowest in quartile 3, and coffee intake was lowest in quartiles 1 and 2. Although we present mean values for dietary intakes in the table, some of them, including dietary melatonin, may have been overestimated by our questionnaire, because the mean values estimated from the FFQ were generally higher than those estimated from 12 1-day diet records (24).

By the end of the follow-up period, we had recorded 2,901 male deaths and 2,438 female deaths among the 29,079 participants. The associations between melatonin intake and the risk of mortality are presented in Table 2. As compared with the lowest quartile of melatonin intake, the highest quartile of intake was significantly associated with a decreased risk of total, cardiovascular, and NCNC mortality after controlling for covariates; HRs were 0.90 (95% CI: 0.82, 0.98), 0.85 (95% CI: 0.72, 0.99) and 0.77 (95% CI: 0.67, 0.90), respectively. The decreasing trends in risk were statistically significant for total mortality and NCNC mortality (P values for trend were 0.05 and 0.003, respectively). The P values for sex interaction were greater than 0.33.

Because dietary melatonin was significantly inversely associated with NCNC mortality, major causes of death in this category, such as infections (ICD-10 codes A00–A99 and B00–B99), endocrine, nutritional, and metabolic diseases (ICD-10 codes E00–E90), respiratory diseases (ICD-10 codes J00–J99), digestive diseases (ICD-10 codes K00–K93), genitourinary diseases (ICD-10 codes N00–N99), and external causes of injury and poisoning (ICD-10 codes S00–T98) were further assessed. Although melatonin intake was not significantly associated with any of these causes, the lowest risk estimate was observed for digestive diseases; the HR for the highest quartile of melatonin intake versus the lowest was 0.69 (95% CI: 0.41, 1.15; P for trend = 0.09).

Additional adjustment for antioxidant micronutrient intake, vitamin C intake, and adherence to the Japanese food guide (33) did not alter the results substantially (other antioxidants such as vitamin A, vitamin E, or carotene were not included in the models because of their high correlations with dietary fiber ($r > 0.75$)); the HRs for total, cardiovascular, and NCNC mortality for the highest quartile of melatonin intake versus the lowest were 0.90 (95% CI: 0.82, 0.99; P for trend = 0.08), 0.86 (95% CI: 0.73, 1.01; P for trend = 0.15), and 0.78 (95% CI: 0.68, 0.91; P for trend = 0.005), respectively. Intake of tryptophan, a precursor of melatonin, was not associated with total or cause-specific mortality; for example, the HR for total mortality for the highest (vs. lowest) quartile of tryptophan intake was 1.00 (95% CI: 0.90, 1.11; P for trend = 0.68).

The sensitivity analysis based on measured foods covering 88.2% of the total number of foods on the FFQ revealed that the results were not substantially altered; the HRs for total, cardiovascular, and NCNC mortality for the highest (vs. lowest) quartile of melatonin intake were 0.90 (95% CI: 0.82, 0.98; P for trend = 0.046), 0.85 (95% CI: 0.73, 1.00; P for trend = 0.11), and 0.77 (95% CI: 0.67, 0.90; P for trend = 0.002), respectively. The results were not altered after including persons who reported cancer, stroke, or coronary heart disease at baseline; the HRs for total, cardiovascular, and NCNC mortality for the highest (vs. lowest) quartile of melatonin intake were 0.89 (95% CI: 0.82, 0.96; P for trend = 0.02), 0.84 (95% CI: 0.73, 0.97; P for trend = 0.049), and 0.79 (95% CI: 0.69, 0.90; P for trend = 0.002), respectively. Exclusion of deaths occurring during the first 3 years of follow-up did not alter the results substantially; the HRs for total, cardiovascular, and NCNC mortality for the highest (vs. lowest) quartile of melatonin

Table 1. Baseline Characteristics of Participants in the Takayama Study According to Quartile of Melatonin Intake, Japan, 1992–2008

Characteristic	Energy-Adjusted Quartile of Melatonin Intake[a]											
	1 (n = 7,270)			2 (n = 7,270)			3 (n = 7,270)			4 (n = 7,269)		
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)
Age, years			53.9 (12.1)			55.3 (13.2)			54.6 (12.8)			54.7 (12.3)
Sex												
Male	4,704	64.7		3,164	43.5		2,807	38.6		2,680	36.9	
Female	2,586	35.3		4,106	56.5		4,463	61.4		4,589	63.1	
Marital status[b]												
Married	6,007	83.6		5,798	81.1		5,885	81.9		6,034	84.1	
Not married	1,176	16.4		1,351	18.9		1,300	18.1		1,144	15.9	
Duration of education, years[b]												
≤11	4,408	61.4		4,586	64.0		4,439	62.0		4,345	60.6	
12–14	2,182	30.4		2,044	28.5		2,182	30.5		2,197	30.6	
≥15	590	8.2		531	7.4		538	7.5		629	8.8	
Cigarette smoking[b]												
Never smoker	2,476	36.2		3,625	53.6		3,811	56.7		3,890	57.8	
Former smoker	1,387	20.1		1,023	15.1		935	13.9		937	13.9	
Current smoker	2,987	43.7		2,111	31.3		1,980	29.4		1,906	28.3	
Duration of sleep, hours/night[b]												
≤6	1,572	22.5		1,605	23.1		1,741	24.9		1,775	25.4	
7–8	4,694	67.2		4,725	68.1		4,650	66.6		4,612	66.0	
≥9	720	10.3		607	8.8		594	8.5		601	8.6	
History of hypertension (yes)	1,407	19.4		1,325	18.2		1,266	17.4		1,256	17.3	
History of diabetes mellitus (yes)	285	3.9		291	4.0		271	3.7		370	5.1	
Body mass index[b,c]			22.3 (2.9)			22.1 (2.9)			22.1 (2.9)			22.3 (2.9)
Alcohol consumption, mg/day			44.7 (47.4)			18.7 (27.4)			14.1 (24.2)			16.3 (27.2)
Physical activity, MET-hours/week			23.6 (38.2)			20.8 (34.4)			21.4 (33.7)			24.6 (36.7)
Dietary intake												
Melatonin, ng/day			25.3 (9.2)			24.7 (8.5)			28.6 (8.6)			45.1 (18.0)
Total energy, kcal/day			2,697 (933)			2,119 (739)			2,122 (727)			2,490 (888)
Polyunsaturated fat, g/day			15.9 (7 6)			13.1 (6.0)			13.4 (6.0)			16.7 (7.7)
Fiber, g/day			15.0 (7.3)			13.5 (6.2)			15.0 (7.1)			22.2 (11.3)
Salt, g/day			14.0 (6.1)			11.7 (5.1)			12.3 (5.2)			16.3 (7.1)
Coffee, mL/day			104 (131)			104 (135)			120 (147)			124 (153)

Abbreviations: MET, metabolic equivalent of task; SD, standard deviation.

[a] Cutpoints: quartile 1, <25.56 ng/day; quartile 2, 25.56–29.22 ng/day; quartile 3, 29.23–34.03; quartile 4, ≥34.04 ng/day.

[b] Missing data: marital status, n = 384; years of education, n = 408; smoking status, n = 2,020; sleep duration, n = 1,183; body mass index, n = 1,641.

[c] Weight (kg)/height $(m)^2$.

Table 2. Associations Between Melatonin Intake and Total and Cause-Specific Mortality in the Takayama Study, Japan, 1992–2008

Cause of Death	Energy-Adjusted Quartile of Melatonin Intake[a]												*P* for Trend
	1			2			3			4			
	No. of Deaths[b]	HR	95% CI	No. of Deaths	HR	95% CI	No. of Deaths[c]	HR	95% CI	No. of Deaths	HR	95% CI	
All causes	1,376			1,405			1,325			1,233			
Model 1[d]		1.0	Referent		0.94	0.87, 1.01		0.98	0.91, 1.06		0.91	0.84, 0.98	0.03
Model 2[e]		1.0	Referent		0.91	0.84, 0.98		0.95	0.88, 1.03		0.90	0.82, 0.98	0.05
Cancer	418			410			376			416			
Model 1		1.0	Referent		1.01	0.88, 1.16		1.00	0.87, 1.15		1.09	0.95, 1.25	0.19
Model 2		1.0	Referent		1.04	0.90, 1.20		1.04	0.90, 1.21		1.13	0.96, 1.32	0.14
Cardiovascular disease	404			462			433			379			
Model 1		1.0	Referent		0.94	0.82, 1.07		0.98	0.86, 1.13		0.87	0.76, 1.00	0.08
Model 2		1.0	Referent		0.88	0.76, 1.01		0.93	0.81, 1.08		0.85	0.72, 0.99	0.10
Noncancer, noncardiovascular disease	552			533			515			438			
Model 1		1.0	Referent		0.88	0.78, 0.99		0.95	0.84, 1.08		0.81	0.71, 0.92	0.003
Model 2		1.0	Referent		0.83	0.73, 0.95		0.89	0.79, 1.02		0.77	0.67, 0.90	0.003

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Cutpoints: quartile 1, <25.56 ng/day; quartile 2, 25.56–29.22 ng/day; quartile 3, 29.23–34.03 ng/day; quartile 4, ≥34.04 ng/day.

[b] Cause of death was unknown for 2 persons.

[c] Cause of death was unknown for 1 person.

[d] Results were adjusted for age and sex.

[e] Results were adjusted for age, sex, total energy intake, body mass index, physical activity, smoking status, education, marital status, sleep duration, histories of diabetes and hypertension, and intakes of alcohol, coffee, polyunsaturated fats, dietary fiber, and salt.

intake were 0.89 (95% CI: 0.81, 0.98; *P* for trend = 0.04), 0.87 (95% CI: 0.73, 1.03; *P* for trend = 0.16), and 0.78 (95% CI: 0.67, 0.92; *P* for trend = 0.006), respectively.

Sex-stratified analyses using sex-specific quartiles showed that the results did not differ between men and women; in men, the HRs for total, cardiovascular, and NCNC mortality for the highest (vs. lowest) quartile of melatonin intake were 0.93 (95% CI: 0.83, 1.05; *P* for trend = 0.27), 0.86 (95% CI: 0.69, 1.08; *P* for trend = 0.28), and 0.82 (95% CI: 0.68, 0.99; *P* for trend = 0.06), respectively. The corresponding values in women were 0.87 (95% CI: 0.76, 0.99; *P* for trend = 0.09), 0.87 (95% CI: 0.69, 1.11; *P* for trend = 0.18), and 0.71 (95% CI: 0.56, 0.89; *P* for trend = 0.02), respectively.

DISCUSSION

In this prospective cohort study, we observed a modest but significantly decreased risk of total mortality among persons with a high intake of melatonin. Significant risk decreases were also observed for cardiovascular mortality and NCNC mortality. Our findings suggest a potential benefit of dietary melatonin with regard to these types of mortality. The biological plausibility of this relationship (mentioned in the Introduction) lends support to our results. The observed inverse association of melatonin intake with NCNC mortality may reflect the association with digestive disease mortality. Melatonin is produced by the gastrointestinal tract, including the liver, and melatonin levels in these organs are higher than levels in the blood or the pineal gland (34, 35). Melatonin protects against liver injury by inhibiting oxidation, inflammation, proliferation of hepatic stellate cells, and hepatocyte apoptosis (35, 36). Melatonin also regulates gastrointestinal motility and reduces the severity of intestinal inflammatory pathology (34, 37). Therefore, protective effects of melatonin against various digestive diseases, including gastric ulcer, pancreatitis, colonic disease, cholangiopathy, liver cirrhosis, and liver injuries (34–39), have been suggested, and such effects may also be expected for dietary melatonin. To the best of our knowledge, this is the first study to have examined the association between melatonin intake and total mortality. Furthermore, no other study has examined the association between melatonin intake and disease outcomes other than total mortality.

Even studies using biomarkers of melatonin, such as urinary aMT6s level, to assess their relationship to disease outcomes are scarce, except for studies on breast cancer incidence. A recent meta-analysis of 6 prospective case-control studies did not suggest a significant association between urinary aMT6s level and breast cancer risk (40). Only 1 study (the Osteoporotic Fracture in Men Study) has examined the association between urinary aMT6s level and total mortality, and there was no significant association among older men (41). Investigators in the Nurses' Health Study and Nurses' Health Study II found that a higher urinary aMT6s level was prospectively associated with decreased risks of diabetes, hypertension, and myocardial infarction (42), which are not contradictive of our results on melatonin intake and cardiovascular mortality. However, in the other study, carried out among women from the Women's Health Initiative Observational Study, Perez-Caraballo et al. (43) did not find a significant association between urinary aMT6s level and the risk of incident hypertension. In a recent review by Amorim Pereira et al. (20), the consumption of melatonin-rich foods, such as cherries, grapes, bananas, pineapples, and dark green vegetables, increased circulatory melatonin level in some intervention studies, including our previous study (27). However, considering that the previous findings on the relationship between urinary melatonin level and disease risk have not been confirmed, it is too early to imply that our observed inverse associations with mortality risk should be ascribed to increased circulating melatonin levels due to a high intake of melatonin. In addition, some authors have criticized studies investigating the measurement of blood or urinary melatonin levels after intake of foods containing melatonin, suggesting that the increase in circulating melatonin is not consistent with the amount of dietary melatonin ingested (44). In fact, the correlation between total melatonin intake and urinary aMT6s level in our different sample group was not high, although we cannot deny the possibility of low validity of our FFQ. Dietary melatonin may be directly relevant to the risk of mortality, unmediated by circulating melatonin levels. It is also possible that the observed inverse association may have been due not to melatonin but to other components of foods or to synergetic effects of dietary melatonin and other components.

The strengths of our study include the prospective design, representation of the general population, information on potential confounders, and a high rate of follow-up. It is challenging to estimate total melatonin intake in the usual diet. For unequivocal assessment of the amount of melatonin in foods, the use of reliable techniques, such as liquid chromatography–tandem mass spectrometry, is strongly encouraged (45). We utilized liquid chromatography–tandem mass spectrometry to measure melatonin in foods. However, there are some limitations to the use of this method. Although we measured melatonin content in numerous foods for the present study, the melatonin content values for some foods, especially in mixed dishes, could be affected by certain ingredients or components. Despite the accumulating data on melatonin content in foods, there is still a lack of standardized methods for determining melatonin concentration in foods. There is no available complete database on melatonin content in various foods. The correlation coefficient for dietary melatonin intake between the FFQ and 12 days of diet records was not high, and this measurement error is also likely to have affected the ranking of individuals for melatonin intake. Although we accounted for several potential lifestyle and dietary confounders, unmeasured confounders, such as nighttime light exposure and history of night-shift work, may have affected the results. The sample size was limited, which precluded analyses of causes with small numbers of deaths, especially NCNC causes. Finally, we could not distinguish the effect of dietary melatonin on incidence, survival, or both.

In summary, we found that a high intake of dietary melatonin was associated with decreased risks of total, cardiovascular, and NCNC mortality in Japanese adults. This study highlights a potential role of dietary melatonin in longevity.

Our findings are new and should be confirmed in other studies. There is also a need to evaluate the content of melatonin in more foods to estimate the total melatonin intake in a usual diet and to better explore its potential impact on health.

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The data sets generated during and/or analyzed in the current study are not publicly available due to lack of a corresponding explicit agreement phrase in the consent forms used, but the data are available from the corresponding author upon reasonable request.

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