Nutrition 66 (2019) 62–69

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Relationship between dietary non-enzymatic antioxidant capacity and type 2 diabetes risk in the Japan Public Health Center-based Prospective Study

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ARTICLE INFO

Article History:
Received 25 July 2018
Received in revised form 2 January 2019
Accepted 26 March 2019

Keywords:
NEAC
TAC
Antioxidant capacity
Antioxidant
Cohort study
Diabetes

ABSTRACT

Objective: Intake of antioxidants may reduce the risk for type 2 diabetes (T2D) by reducing oxidative stress. However, it is unclear whether dietary non-enzymatic antioxidant capacity (NEAC), which represents the cumulative action of dietary antioxidants and their synergistic effects in foods, is associated with decreased T2D risk. The aim of this study was to investigate the associations between dietary NEAC and T2D.
Methods: The study included 64 660 adults (27 809 men and 36 851 women), 44 to 76 y of age without history of T2D in the Japan Public Health Center-based Prospective Study. Dietary NEAC was estimated using databases of NEAC measurements compiled from results for three different assays: ferric reducing-antioxidant power (FRAP), oxygen radical absorbance capacity (ORAC), and total radical-trapping antioxidant parameter (TRAP). A multiple logistic regression model was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of self-reported physician-diagnosed T2D over 5 y with adjustment for potential confounders.
Results: In all, 1191 cases of newly diagnosed T2D were reported. Dietary NEACs were not significantly associated with T2D. The multivariate-adjusted ORs were 1.04 (95% CI, 0.88–1.23; $P_{trend} = 0.56$) for FRAP, 1.11 (95% CI, 0.93–1.32; $P_{trend} = 0.26$) for ORAC, and 0.99 (95% CI, 0.84–1.18; $P_{trend} = 0.84$) for TRAP. Similar associations were observed in men and women ($P_{interaction} = 0.46$ for FRAP, 0.35 for ORAC, and 0.63 for TRAP). In stratified analyses of major prooxidant factors, no notable associations with smoking and obesity status were observed.
Conclusions: This finding suggests that dietary NEAC may not be appreciably associated with T2D in Japanese adults.

Introduction

The prevalence of diabetes is increasing worldwide [1]. In 2014, >422 million adults worldwide were found to have diabetes, and individuals living in Asian countries represented 60% of the world diabetic population [1]. In Japan, the prevalence of diabetes is predicted to rise from 7.6% in 2013 to 8.2% in 2035 [2]. Accumulating evidence from both experimental and clinical studies suggests that oxidative stress plays an important role in the development of insulin resistance and diabetes [3]. As such, intake of antioxidants such as vitamin E is hypothesized to reduce the risk for diabetes by

This study was supported by National Cancer Center Research and Development Fund (since 2011), Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (from 1989 to 2010), Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabetes Mellitus (15 ek0210021 h0002) from the Japan Agency for Medical Research. ST was involved in the design of the study as the principal investigator. NS and ST conducted the surveys. IK, MS, KK, SA, TM, AS, MI (M Inoue), MI (M Iwasaki), and MN drafted the plan for data analyses. IK conducted the data analyses and drafted the manuscript. TM provided statistical expertise. and IK and TM had primary responsibility for the final content. All authors were involved in the interpretation of the results and revision of the manuscript and approved the final version of the manuscript. The authors have no conflicts of interest to declare.
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https://doi.org/10.1016/j.nut.2019.03.011
0899-9007/

reducing levels of oxidative stress [3]. Given a variety of antioxidants are consumed from diets, investigating the overall effects of dietary antioxidants in the overall diet could provide additional insight into approaches to prevent T2D.

Measurements of non-enzymatic antioxidant capacity (NEAC) have been developed to assess the free radical-reducing capacity of antioxidants and iron-reducing capacity, in consideration of the synergistic effect of various antioxidants but no single antioxidant present in food and biological samples [4]. Using this concept, some, but not all [5,6], prospective studies in Western counties reported inverse associations between dietary NEAC in the overall diet and incidence of stroke [7], cancer [8], and mortality [9]. There is also some evidence showing that favorable profiles of glucose metabolism markers are associated with high dietary NEAC of the overall diet in western countries [10–12]. To our knowledge, however, only one study has examined the associations between dietary NEAC and incidence of T2D and the result showed an inverse association between them [13]. In addition, the finding from a previous study may be limited due to the inclusion of women only [13]. Moreover, this issue has not been investigated in Asian populations, which have different dietary patterns from Western populations [14]. Additional evidence from Asia is thus needed to enhance the generalizability of the association between dietary NEAC and T2D.

We aimed to examine prospectively the associations between three measures of dietary NEAC—ferric reducing antioxidant potential (FRAP), oxygen radical absorbance capacity (ORAC), and radical trapping antioxidant parameter (TRAP)—and risk for T2D in a large cohort of Japanese adults. In addition, we performed stratified analyses by several factors, including smoking status and obesity, which are closely related to T2D as major contributors to oxidative stress [15,16].

Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard.

Study design and participants

The Japan Public Health Center-based Prospective (JPHC) Study, covering 11 public health center areas nationwide, was launched in 1990 for cohort I and in 1993 for cohort II. For cohort I, the participants were 40 to 59 y of age and residents of five Japanese public health center areas (Iwate, Akita, Nagano, Okinawa-Chubu, and Tokyo), whereas cohort II included participants 40 to 69 y of age who were residents of six public health center areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa-Miyako, and Osaka). The JPHC study population and design have been described in detail elsewhere [17]. The study participants were informed of the study objective and responded to the questionnaire survey, which was regarded as consent from participants.

The survey was conducted at baseline as well as at 5- and 10-y follow-ups. Each questionnaire survey was conducted to obtain information on medical histories and health-related lifestyles, including diet. Because the questionnaire that was used for the 5-y follow-up (i.e., the second survey) provided more comprehensive information about food intake than the questionnaire used for the baseline survey, we used data from the second survey as the baseline data for this analysis. This study was approved by the Institutional Review Board of the National Cancer Center and National Cancer for Global Health and Medicine, Japan.

Of the 140 420 individuals who participated in the first survey for cohorts I and II, 113 402 responded to the questionnaire given in the first survey (Fig. 1). Of these, 89 947 responded to the questionnaire survey at the 5-y follow-up (used as baseline data) and 76 901 responded to the questionnaire survey at the 10-y follow up (i.e., follow-up data). We excluded 11 642 participants who reported a history of T2D (n = 5606) or severe disease (n = 5637), including cancer, cerebrovascular disease, myocardial infarction, and chronic liver disease in the first and 5-y follow-up survey, as well as those who reported kidney disease (n = 1467) in the first survey. It should be noted that some of the excluded participants had two or more of the conditions just described. We further excluded 599 participants who reported an extreme amount of total energy intake (i.e., outside the mean ± 3 SD). Finally, 64 660 adults (27 809 men and 36 851 women) were eligible for analysis in the present study.

Food frequency questionnaire

A food frequency questionnaire (FFQ) was used to assess the average intake of 147 food and beverage items over the previous year [18]. For most food items, nine response options were available to describe consumption frequency, which ranged from <1 time/mo to ≥7 times/d. A standard portion size was specified for each food, and respondents were asked to denote their usual portion size from three options (≤0.5 times, standard, and ≥1.5 times). Daily intake of foods was calculated by multiplying the daily consumption frequency and the standard portion size by the individual's usual portion size. Dietary intake of energy and selected nutrients were estimated by referring to the Standard Tables of Food Composition in Japan [19]. In both cohort I and cohort II of the JPHC study, the FFQ has reasonable validity and reproducibility [20,21].

Dietary NEAC levels

Details of estimation of dietary NEAC have been described elsewhere [22]. In short, to estimate the FFQ-based dietary NEAC for each individual, we used published databases in which the NEAC of individual foods was analyzed in the same laboratory by FRAP, which measures the ability of an antioxidant to reduce Fe^{3+} (ferric ion) to Fe^{2+} (ferrous iron) and TRAP, which measures the chain-breaking antioxidant capacity to scavenge peroxyl radicals [23,24]. As another NEAC measure, we used ORAC, which is based on the same chemical principle as TRAP, but measures the area under the curve of radical-induced fluorescence decay [25–29]. To avoid heterogeneity among measurements, we selected most of the foods from an ORAC database of Japanese foods (sweet potato, satoimo [taro root], potato, cabbage, cucumber, radish, onion, tomato, carrot, Chinese cabbage, green sweet pepper, broccoli, spinach, mung bean sprout, lettuce, strawberry, satsuma mandarin, Valencia orange, Japanese persimmon, kiwifruit, watermelon, Japanese pear, banana, grape, melon, peach, apple) [27] and from the largest published ORAC database (peanut, bean, pumpkin, tomato juice, pineapple, milk chocolate, catsup) [25]. Additionally, we selected several food items from other publications (buckwheat, orange juice, apple juice, wine, green tea, white tea, black tea) [26,28,29] to obtain values for foods in the FFQ that were not available in the main ORAC database. If foods were not directly matched to databases, NEAC values were imputed using the following procedures for FRAP, ORAC, and TRAP: For dried foods, NEAC was calculated using the ratio of water between dried and raw as specified in Japanese food composition tables; for Japanese pickled vegetables, NEAC levels were the same as those for the raw vegetable; for Japanese foods for which specific data were not available, such as navel oranges, we used data for the same food that had a different origin, e.g., Valencia oranges. As with previous studies [7–9], our analyses did not take into account NEAC levels from coffee because whether these high-molecular-weight antioxidants are absorbed in vivo is unclear, although Maillard products from the coffee roasting process were shown to be a main contributor to the antioxidant capacity of coffee in vitro [30,31]. Finally, we assigned the NEAC for 58, 55, and 51 food items in the FFQ by FRAP, ORAC, and TRAP, respectively. Overall dietary NEAC was calculated by multiplying the NEAC values of single foods by the amount of each food consumed and then summing the NEAC values for all foods for each participant. Dietary NEAC values were adjusted for energy by the residual method using a regression model.

According to the method just described, we assessed the validity for dietary NEAC from 28-d dietary records (DRs) and FFQ, and the reproducibility was determined based on responses for two FFQs administered at a 1-y interval in a subsample of JPHC study participants (N = 497). Additionally, joint classification was applied to assess agreement between the two methods. For validation, Spearman's rank correlation coefficients (CCs) for the energy-adjusted overall dietary NEAC between FFQ and DR for FRAP, ORAC, and TRAP were 0.52, 0.54, and 0.52 for all participants, respectively. Extreme mis-categorization rates by joint classification analysis were 2% for FRAP and ORAC and 1% for TRAP. In terms of reproducibility, CCs between the energy-adjusted dietary NEACs from two FFQs were 0.64 for FRAP and 0.65 for ORAC and TRAP [22].

Ascertainment of type 2 diabetes

Physician-diagnosed T2D during the 5-y period after the second survey was ascertained via a self-administered questionnaire at the third survey, which asked about participant's history of major diseases, including diabetes and time of diagnosis. Only participants who were diagnosed after the second survey (baseline of the present study) were considered as incident cases during the follow-up. In the validation study, 94% of the self-reported diabetes were confirmed by medical reports in a subsample of JPHC study participants [32].

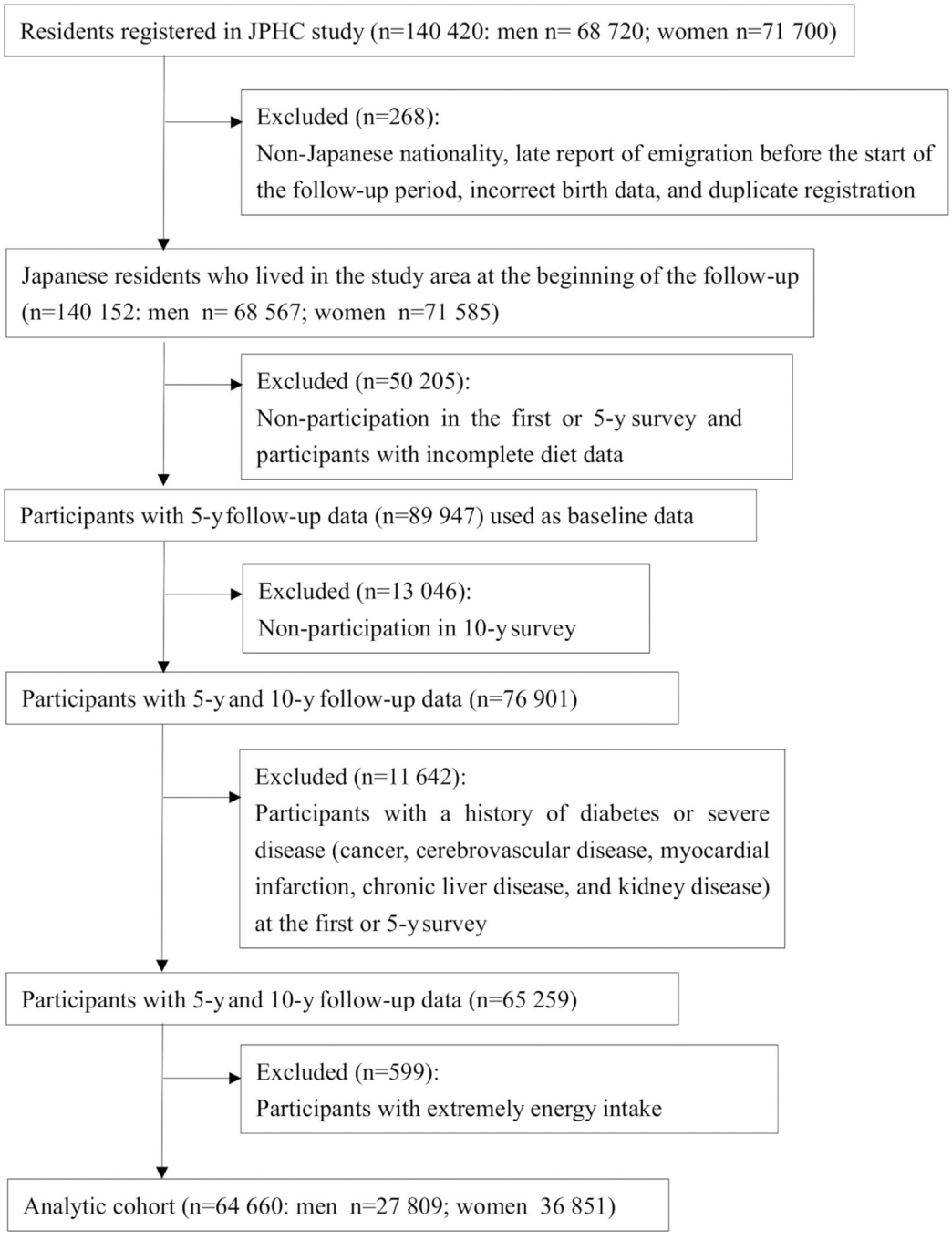

Fig. 1. Flowchart of study population.

Other variables

Information on other variables, including weight, height, smoking status, physical activity level, history of hypertension, use of supplements, and coffee consumption used in the present analysis was derived from the second survey, whereas that for family history of diabetes was derived from the baseline survey. Body mass index (BMI) was calculated as body weight (kg) divided by the square of body height (m^2). Obese status was defined as BMI $\geq$25 kg/m^2 according to definition of the Ministry of Health, Labor and Welfare, Japan. Metabolic equivalents per day (METs/d) were estimated from the average amount of time spent per day engaged in 3 types of physical activity at work and during leisure time.

Statistical analysis

The descriptive data for the study participants were expressed as age-adjusted mean with SD for continuous variables or age-adjusted proportions for categorical variables, according to quartiles of energy-adjusted dietary NEAC intake. Trend associations between the characteristics of participants and dietary NEAC were tested using the linear regression model for continuous variables and logistic regression model for categorical variables. Food and beverage groups were formed on the basis of the Standardized Table of Food Composition, Enlarged Edition in Japan [19]. The contribution of NEAC for each food to the dietary NEAC was computed as:

% NEAC food group = NEAC food group/overall dietary NEAC*100.

To evaluate the associations between dietary NEAC and T2D, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) using multiple logistic regression analysis. The first model was adjusted for age (year, continuous). The second model was further adjusted for sex, study area (11 areas), smoking habits (lifetime non-smoker, former smoker, or current smoker smoking either <20 or $\geq$20 cigarettes/d), total physical activity levels (MET-h/d, quartiles),

history of hypertension (yes or no), family history of diabetes mellitus (yes or no), use of supplements (yes or no), coffee consumption (almost never, <1, 1, or ≥2 cups/d), and total energy intake (kcal/d, continuous). The third model was further adjusted for BMI (<21, 21–22.9, 23–24.9, 25–26.9, or ≥27 kg/m^2). An indicator variable for missing data was created for each covariate. Tests for linear trends were conducted by assigning the median value of dietary NEAC of each quartile to the respective categories and modeling these values as a continuous value.

Additionally, we performed stratified analyses of dietary NEAC and T2D according to sex and smoking (never-smoker or smokers, including ex-smokers) and BMI (<25 or ≥25 kg/m^2), which are major contributors to oxidative stress. Interaction terms by multiplying the dietary NEAC (quartile) and the above-mentioned stratifying variables (dichotomous) were created and included in the model to assess statistical interactions. Two-sided $P < 0.05$ were regarded as statistically significant. All analyses were performed using the SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

During the 5-y period, 1191 participants (692 men and 499 women) were newly diagnosed with T2D. The mean (±SD) level of dietary NEAC excluding NEAC level from coffee was 13 832 ± 10 167 μmol Fe^{2+}/d for FRAP, 7506 ± 4258 μmol TE/d for ORAC, and 5451 ± 4320 μmol TE/d for TRAP. The major food contributors to dietary NEAC values were green tea (FRAP 59.7%, ORAC 34.7%, TRAP 64.7%), fruits (FRAP 17.1%, ORAC 32.9%, TRAP 16.3%), and vegetables (FRAP 11.7%, ORAC 17.7%, TRAP 12.9%). The three measures were strongly correlated among the controls; CCs for FRAP and ORAC, FRAP and TRAP, and ORAC and TRAP were 0.87, 0.99, and 0.86.

Participants with higher dietary NEAC for all measurements were older and more likely to use supplements and have family history of diabetes, but were less likely to be a current smoker and physically active and have higher BMI than those with a lower dietary NEAC at baseline (i.e., at the time of the second survey; Table 1).

A higher dietary NEACs, as derived from FRAP, ORAC, and TRAP were associated with decrease risk for T2D in age-adjusted models (Table 2). The ORs (95% CI) of T2D for the highest quartile of dietary NEAC compared with the lowest dietary NEAC were 0.85 (0.79–0.99) for FRAP, 0.80 (0.68–0.95) for ORAC, and 0.80 (0.68–0.94) for TRAP. However, after further adjusting for confounding variables, we found no statistically significant associations between dietary NEAC and T2D in multivariate-adjusted models. The ORs in the highest quartile of dietary NEAC for FRAP, ORAC, and TRAP were 1.04 (95% CI, 0.88–1.23; $P_{trend} = 0.56$), 1.11 (95% CI, 0.93–1.32; $P_{trend} = 0.26$), and 0.99 (95% CI, 0.84–1.18; $P_{trend} = 0.84$), respectively. A stratified analysis by sex showed no statistically significant interaction between dietary NEAC and T2D for all measurements ($P_{interaction} = 0.46$ for FRAP, 0.35 for ORAC, and 0.63 for TRAP).

Smoking status also did not significantly modify associations between dietary NEAC and T2D ($P_{interaction} = 0.33$ for FRAP, 0.24 for ORAC, and 0.19 for TRAP; Table 3). Similarly, the tests for interactions did not indicate significant differences between normal weight and obesity (BMI <25 or ≥25 kg/m^2; $P_{interaction} = 0.88$ for FRAP, 0.98 for ORAC, and 0.96 for TRAP).

Discussion

In this large prospective population-based study, no significant associations of dietary NEAC excluding NEAC level from coffee determined by several different measurements with T2D were observed overall or according to sex. Moreover, in stratified analyses of major prooxidant factors by smoking and obese status, no notable associations were observed. To our knowledge, this is the first prospective study to examine associations between dietary NEAC and T2D in an Asian population.

A large cohort study of French women showed a significant inverse association between dietary NEAC and T2D [13]. In contrast, we found no associations between any measures of dietary NEAC and T2D. The discrepancy may be partly ascribed to the difference in follow-up duration (5 y in the present study versus 15 y in the French women cohort study). Participants with higher blood glucose levels within non-diabetic range might have changed their diet before baseline, causing a reverse causation, especially when the follow-up period is short. This may be a reason for our null finding. Additionally, we speculate that it might be partly attributable to the difference of foods contributing to the dietary NEAC between the study populations. In the present study population, the dietary NEAC levels in the highest quartile (>17.67 mmol/d) was similar to that reported in the French cohort study (>17.55 mmol/d), but the main contributors to dietary NEAC in the French cohort were fruit (23%), vegetables (19%), alcoholic beverages (15%), and hot beverages such as tea, chicory, and hot chocolate (12%) [13], whereas those in the present cohort were green tea (60%), fruits (17%), and vegetables (12%). Further research would be required to confirm whether the association differs by difference of contributors to dietary NEAC.

Numerous studies have investigated the effect of specific antioxidants on T2D [33,34] or biomarkers of glycemic control [35,36]. In a meta-analysis of western cohort studies, intake of vitamin E was significantly inversely associated with risk of T2D. However, other compounds including vitamin C, flavonoids, carotenoids, or lycopene were not associated with T2D [33]. In meta-analyses of randomized trials of antioxidant supplementation vitamin C [35] or randomized trials of vitamin E [34] and various antioxidants [36], the authors concluded that antioxidant supplementation had no effect on glycemic control [35,36] or T2D [34] in healthy individuals.

We previously reported that higher intake of foods rich in bioactive redox substances such as total vegetables and fruits [37] and consumption of 100% fruit juice and vegetable juice [38], contributing largely to dietary NEAC, were not associated with a lower risk for T2D in the JPHC cohort. Regarding green tea, a major food contributor to dietary NEAC among Japanese, results were inconsistent among prospective cohort studies in Japan; one showed an inverse association [39]; one reported no association [40]; and one found no association in men, but not in women [41].

We found no association between dietary NEAC and T2D among smokers. This finding is consistent with those of a large cohort study, showing no association of T2D risk with dietary antioxidants, including vitamin C, β-carotene, β-cryptoxanthin, and α-tocopherol in male smokers [42]. Dietary NEAC may not be associated with T2D even among those individuals who are at increased exposure to oxidative stress.

The strengths of the present study include its large sample size, the population-based prospective design, use of validated NEAC levels, and extensive adjustment of potentially important confounding factors, including smoking habits, family history of diabetes, physical activity, total energy intake, use of supplements, and coffee consumption. However, the present study has several limitations. First, we could not use a Japanese NEAC database for FRAP, TRAP, and most of ORAC analyses of foods owing to a lack of information in the literature. However, we selected databases analyzed by the same laboratory to ensure that the results were homogeneous and consistent. Second, the diagnosis of T2D

Table 1
Baseline characteristics of study participants according to quartiles of energy-adjusted dietary NEAC intake excluding NEAC from coffee (N = 64 660)

	FRAP					ORAC					TRAP				
	Quartiles of NEAC intake					Quartiles of NEAC intake					Quartiles of NEAC intake				
	Q1 (low)		Q4 (high)			Q1 (low)		Q4 (high)			Q1 (low)		Q4 (high)		
	Mean	SD	Mean	SD	P_{trend}*	Mean	SD	Mean	SD	P_{trend}*	Mean	SD	Mean	SD	P_{trend}*
	16 165		16 165			16 165		16 165			16 165		16 165		
Age (y)					<0.001					<0.001					<0.001
Mean	49.8		53.4			49.8		53.3			49.7		53.5		
SD	7.5		7.8			7.6		7.8			7.4		7.8		
BMI (kg/m^2) †,‡	23.7	0.02	23.4	0.02	<0.001	23.6	0.02	23.4	0.02	<0.001	23.8	0.02	23.4	0.02	<0.001
Current smoker (%)†,§	28.4		19.0		<0.001	35.5		13.5		<0.001	29.0		18.8		<0.001
Total physical activity (MET-h/d) †,‡	33.5	0.1	33.3	0.1	0.002	33.7	0.05	33.1	0.05	<0.001	33.6	0.06	33.2	0.05	0.001
History of hypertension (%)§	16.6		15.6		0.049	16.0		16.0		0.92	16.5		15.8		0.19
Family history of diabetes (%)§	7.5		8.6		0.002	7.3		9.0		<0.001	7.4		8.6		0.003
Food and nutrient intakes‡,‖															
Energy (kcal/d)	2012	6	2000	6	<0.001	2092	6	1964	6	<0.001	2037	6	1969	6	<0.001
β-carotene (μg/d)	2773	21.4	4171	21.5	<0.001	2316	21	4643	21	<0.001	2768	21	4140	22	<0.001
α-tocopherol (mg/d)	6.23	0.02	7.53	0.02	<0.001	5.62	0.02	8.12	0.02	<0.001	6.21	0.02	7.48	0.02	<0.001
β-tocopherol (mg/d)	0.32	0.00	0.36	0.00	<0.001	0.30	0.00	0.37	0.00	<0.001	0.32	0.00	0.36	0.00	<0.001
γ-tocopherol (mg/d)	10.6	0.03	12.0	0.03	<0.001	9.75	0.03	12.5	0.03	<0.001	10.5	0.03	11.9	0.03	<0.001
Cryptoxanthin (μg/d)	776	12	1881	12	<0.001	510	11	2460	11	<0.001	797	12	1.832	12	<0.001
Vitamin C (mg/d)	82.4	0.5	201	0.5	<0.001	68.8	0.4	222	0.4	<0.001	83	0.5	199	0.5	<0.001
Lycopene (μg/d)	2348	42	2981	42	<0.001	1587	42	3609	42	<0.001	2348	42	2997	42	<0.001
Coffee consumption ≥1 cup/d (%)†,§	36.0		28.3		<0.001	36.5		28.9		<0.001	35.7		28.3		<0.001
Use of supplements (%)†,§	11.1		13.4		<0.001	9.7		14.5		<0.001	11.2		13.2		<0.001

BMI, body mass index; FRAP, ferric reducing-antioxidant power; MET, metabolic equivalents; NEAC, non-enzymatic antioxidant capacity; ORAC, oxygen radical absorbance capacity; TRAP, total radical-trapping antioxidant parameter.
*On the basis of logistic regression analyses for categorical variables and linear regression analysis for continuous variables.
†Participants with incomplete information were excluded (BMI: 1457; total physical activity: 11 092; smoking status: 2969; coffee consumption: 3328; use of supplements: 2039).
‡Age-adjusted means and SE.
§Age-adjusted proportion.
‖Energy-adjusted using the residual method excepting energy intake and coffee consumption.

was ascertained by self-reporting, although a validation study of a subpopulation of the JPHC study showed that 94% of self-reported diabetes could be confirmed with medical records [32]. Third, dietary intakes were assessed only at one point, and thus may not reflect long-term intake levels. Fourth, the follow-up period was relatively short (5 y), which might have attenuated the association by reverse causation. Finally, although we adjusted for potentially important confounding variables, the possibility of bias owing to residual confounding and unmeasured factors cannot be ruled out.

Conclusion

Dietary NEAC (free radical–reducing capacity and ferric-reducing antioxidant power) was not significantly associated with T2D. This finding suggests that dietary NEAC might not be a strong determining factor of T2D among Japanese. These findings require further investigation, including characterization of NEAC biomarkers, to obtain additional insight into how NEAC might influence the risk for T2D.

Acknowledgments

The members of the JPHC study group are S. Tsugane (principal investigator), N. Sawada, M. Iwasaki, S. Sasazuki, T. Yamaji, T. Shimazu, and T. Hanaoka (National Cancer Center, Tokyo); J. Ogata, S. Baba, T. Mannami, A. Okayama, and Y. Kokubo (National Cerebral and Cardiovascular Center, Osaka); K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta, Y. Tanaba, H. Sato, Y. Roppongi, T. Takashima, and H. Suzuki (Iwate Prefectural Ninohe Public Health Center, Iwate); Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, N. Nagai, Y. Ito, S. Komatsu, and T. Minamizono (Akita Prefectural Yokote Public Health Center, Akita); H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, Y. Kobayashi, M. Machida, K. Kobayashi, and M. Tsukada (Nagano Prefectural Saku Public Health Center, Nagano); Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, and H. Sakiyama (Okinawa Prefectural Chubu Public Health Center, Okinawa); K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji, and R Saito (Katsushika Public Health Center, Tokyo); A. Murata, K. Minato, K. Motegi, T. Fujieda, and S. Yamato (Ibaraki Prefectural Mito Public Health Center, Ibaraki); K. Matsui, T. Abe, M. Katagiri, M Suzuki, and K. Matsui (Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata); M. Doi, A. Terao, Y. Ishikawa, and T. Tagami (Kochi Prefectural Chuo-higashi Public Health Center, Kochi); H. Sueta, H. Doi, M. Urata, N. Okamoto, F. Ide, H. Goto, and R. Fujita (Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki); H. Sakiyama, N. Onga, H. Takaesu, M. Uehara, T. Nakasone, and M. Yamakawa (Okinawa Prefectural Miyako Public Health Center, Okinawa); F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, and M. Takano (Osaka Prefectural Suita Public Health Center, Osaka); Y. Tsubono (Tohoku University, Miyagi); K. Suzuki (Research Institute for Brain and Blood Vessels Akita, Akita); Y. Honda, K. Yamagishi, S. Sakurai, and N. Tsuchiya (University of Tsukuba, Ibaraki); M Kabuto (National Institute for Environmental Studies, Ibaraki); M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe (National Institute of Health and Nutrition, Tokyo); M. Akabane (Tokyo University of Agriculture, Tokyo); T. Kadowaki and M. Inoue (The University of Tokyo, Tokyo); M. Noda and T. Mizoue (National Center for Global Health and Medicine, Tokyo); Y. Kawaguchi (Tokyo Medical and Dental University, Tokyo); Y. Takashima and Y Yoshida (Kyorin University, Tokyo); K. Nakamura and R. Takachi (Niigata University, Niigata); J. Ishihara (Sagami Women's University, Kanagawa); S. Matsushima

Table 2
Odds ratios (OR) and 95% confidence intervals (95% CI) of risk for type 2 diabetes according to quartiles of energy-adjusted dietary NEAC excluding NEAC from coffee (N = 64 660)

	Q1 (low)		Q2		Q3		Q4 (high)			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	P_{trend}*	$P_{interaction}$
FRAP										
Overall										
Cases (n)		332		293		272		294		
Participants (n)		16 165		16 165		16 165		16 165		
Median (μmol Fe^{2+}/d)		4478		8898		14 127		25 631		
Model 1†	1.00	(Reference)	0.87	(0.74–1.02)	0.80	(0.68–0.94)	0.85	(0.72–0.99)	0.07	
Model 2‡	1.00	(Reference)	0.95	(0.81–1.12)	0.93	(0.78–1.10)	1.02	(0.86–1.20)	0.71	
Model 3§	1.00	(Reference)	0.97	(0.82–1.14)	0.96	(0.81–1.13)	1.04	(0.88–1.23)	0.56	
Men										
Cases (n)		179		187		151		175		
Participants (n)		6952		6952		6953		6952		
Median (μmol Fe^{2+}/d)		3927		7642		12 055		22 620		
Model 3§	1.00	(Reference)	1.11	(0.90–1.38)	0.89	(0.71–1.12)	1.00	(0.80–1.26)	0.71	0.46
Women										
Cases (n)		118		124		125		132		
Participants (n)		9212		9213		9213		9213		
Median (μmol Fe^{2+}/d)		5074		10 027		15 731		27 878		
Model 3§	1.00	(Reference)	1.16	(0.89–1.51)	1.19	(0.91–1.56)	1.19	(0.91–1.55)	0.30	
ORAC										
Overall										
Cases (n)		332		303		276		280		
Participants (n)		16 165		16 165		16 165		16 165		
Median (μmol TE/d)		3235		5592		8009		12 294		
Model 1†	1.00	(Reference)	0.90	(0.77–1.05)	0.81	(0.69–0.95)	0.80	(0.68–0.95)	<0.01	
Model 2‡	1.00	(Reference)	1.04	(0.89–1.22)	1.04	(0.88–1.24)	1.12	(0.94–1.34)	0.23	
Model 3§	1.00	(Reference)	1.03	(0.88–1.21)	1.04	(0.88–1.24)	1.11	(0.93–1.32)	0.26	
Men										
Cases (n)		176		182		163		171		
Participants (n)		6952		6952		6953		6952		
Median (μmol TE/d)		2617		4451		6411		10 084		
Model 3§	1.00	(Reference)	1.05	(0.85–1.30)	0.94	(0.75–1.17)	0.96	(0.77–1.21)	0.57	0.35
Women										
Cases (n)		111		126		132		130		
Participants (n)		9212		9213		9213		9213		
Median (μmol TE/d)		4126		6651		9106		13 475		
Model 3§	1.00	(Reference)	1.25	(0.96–1.62)	1.31	(1.00–1.71)	1.24	(0.95–1.63)	0.18	
TRAP										
Overall										
Cases (n)		343		285		274		289		
Participants (n)		16, 165		16, 165		16 165		16 165		
Median (μmol TE/d)		1501		3341		5540		10 399		
Model 1†	1.00	(Reference)	0.82	(0.70–0.96)	0.77	(0.66–0.91)	0.80	(0.68–0.94)	0.02	
Model 2‡	1.00	(Reference)	0.90	(0.76–1.05)	0.91	(0.77–1.07)	0.96	(0.81–1.14)	0.95	
Model 3§	1.00	(Reference)	0.93	(0.79–1.09)	0.94	(0.79–1.11)	0.99	(0.84–1.18)	0.84	
Men										
Cases (n)		185		178		149		180		
Participants (n)		6952		6952		6953		6952		
Median (μmol TE/d)		1228		2746		4609		9087		
Model 3§	1.00	(Reference)	1.01	(0.82–1.26)	0.84	(0.67–1.06)	0.99	(0.80–1.24)	0.89	0.63
Women										
Cases (n)		119		125		123		132		
Participants (n)		9212		9213		9213		9213		
Median (μmol TE/d)		1828		3893		6284		11 379		
Model 3§	1.00	(Reference)	1.17	(0.90–1.52)	1.16	(0.89–1.52)	1.18	(0.91–1.54)	0.34	

FRAP, ferric reducing-antioxidant power; NEAC, non-enzymatic antioxidant capacity; ORAC, oxygen radical absorbance capacity; TE/d, Trolox equivalents/d; TRAP, total radical-trapping antioxidant parameter.
*Linear trends across quartiles of dietary NEAC intake were tested using the median intake value for each quartile value as an ordinal variable.
†Adjusted for age.
‡Also adjusted for sex, public health center area, smoking status, total physical activity, history of hypertension, family history of diabetes, coffee consumption, energy intake, and use of supplements.
§Also adjusted for body mass index.

and S. Natsukawa (Saku General Hospital, Nagano); H. Shimizu (Sakihae Institute, Gifu); H. Sugimura (Hamamatsu University School of Medicine, Shizuoka); S. Tominaga (Aichi Cancer Center, Aichi); N. Hamajima (Nagoya University, Aichi); H. Iso and T. Sobue (Osaka University, Osaka); M. Iida, W. Ajiki, and A. Ioka (Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka); S. Sato (Chiba Prefectural Institute of Public Health, Chiba); E. Maruyama (Kobe University, Hyogo); M. Konishi, K. Okada, and I. Saito (Ehime University, Ehime); N. Yasuda (Kochi University, Kochi); S. Kono (Kyushu University, Fukuoka); S. Akiba (Kagoshima University, Kagoshima); T. Isobe (Keio University); and Y. Sato (Tokyo Gakugei University).

Table 3
Odds ratios (OR) and 95% confidence intervals (95% CI) of type 2 diabetes risk according to quartiles of energy-adjusted dietary NEAC excluding NEAC from coffee, stratified by smoking status and BMI

	Q1 (low)		Q2		Q3		Q4 (high)			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	P_{trend}*	$P_{interaction}$
FRAP										
Never-smoker										
Cases (n)		182		169		139		162		
Participants (n)		10 542		10 542		10 542		10 542		
Median (μmol Fe^{2+}/d)		4779		9462		14 895		26 541		
Multivariate model†	1.00	(Reference)	1.04	(0.84–1.30)	0.89	(0.71–1.13)	1.02	(0.81–1.29)	1.00	0.33
Smoker										
Cases (n)		115		124		121		128		
Participants (n)		4880		4881		4881		4881		
Median (μmol Fe^{2+}/d)		3959		7729		12 241		23 326		
Multivariate model†	1.00	(Reference)	1.14	(0.88–1.49)	1.09	(0.83–1.43)	1.18	(0.90–1.54)	0.33	
BMI <25 kg/m^2										
Cases (n)		147		153		139		143		
Participants (n)		11 441		11 441		11 441		11 441		
Median (μmol Fe^{2+}/d)		4653		9096		14 275		25 624		
Multivariate model‡	1.00	(Reference)	1.10	(0.87–1.39)	1.04	(0.81–1.32)	1.05	(0.82–1.35)	0.88	0.88
BMI ≥25 kg/m^2										
Cases (n)		163		139		141		146		
Participants (n)		4359		4360		4360		4360		
Median (μmol Fe^{2+}/d)		4145		8354		13 621		25 387		
Multivariate model‡	1.00	(Reference)	0.91	(0.71–1.15)	0.98	(0.77–1.24)	1.04	(0.81–1.33)	0.52	
ORAC										
Never-smoker										
Cases (n)		196		153		141		162		
Participants (n)		10 542		10 542		10 542		10 542		
Median (μmol TE/d)		3698		6163		8586		12 828		
Multivariate model†	1.00	(Reference)	0.88	(0.71–1.10)	0.86	(0.69–1.09)	1.00	(0.79–1.26)	0.89	0.24
Smoker										
Cases (n)		116		118		121		133		
Participants (n)		4880		4881		4881		4881		
Median (μmol TE/d)		2601		4461		6448		10 267		
Multivariate model†	1.00	(Reference)	1.03	(0.79–1.34)	1.06	(0.81–1.38)	1.17	(0.89–1.53)	0.23	
BMI <25 kg/m^2										
Cases (n)		160		156		131		135		
Participants (n)		11 441		11 441		11 441		11 441		
Median (μmol TE/d)		3291		5658		8065		12 279		
Multivariate model‡	1.00	(Reference)	1.11	(0.88–1.39)	1.01	(0.79–1.29)	1.06	(0.82–1.37)	0.81	0.98
BMI ≥25 kg/m^2										
Cases (n)		163		140		150		136		
Participants (n)		4359		4360		4360		4360		
Median (μmol TE/d)		3118		5433		7818		12 205		
Multivariate model‡	1.00	(Reference)	0.94	(0.74–1.19)	1.09	(0.86–1.39)	1.06	(0.82–1.37)	0.49	
TRAP										
Never-smoker										
Cases (n)		189		159		145		159		
Participants (n)		10 542		10 542		10 542		10 542		
Median (μmol TE/d)		1662		3614		5894		10 762		
Multivariate model†	1.00	(Reference)	0.94	(0.76–1.17)	0.90	(0.72–1.14)	0.96	(0.76–1.21)	0.79	0.19
Smoker										
Cases (n)		118		118		121		131		
Participants (n)		4880		4881		4881		4881		
Median (μmol TE/d)		1245		2782		4713		9408		
Multivariate model†	1.00	(Reference)	1.04	(0.80–1.36)	1.07	(0.82–1.40)	1.17	(0.90–1.53)	0.23	
BMI <25 kg/m^2										
Cases (n)		154		149		140		139		
Participants (n)		11 441		11 441		11 441		11 441		
Median (μmol TE/d)		1565		3424		5612		10 405		
Multivariate model‡	1.00	(Reference)	1.02	(0.81–1.29)	1.00	(0.79–1.27)	0.97	(0.76–1.24)	0.73	0.96
BMI ≥25 kg/m^2										
Cases (n)		168		139		136		146		
Participants (n)		4359		4360		4360		4360		
Median (μmol TE/d)		1368		3113		5323		10 257		
Multivariate model‡	1.00	(Reference)	0.89	(0.70–1.12)	0.92	(0.72–1.17)	1.02	(0.80–1.30)	0.61	

BMI, body mass index; FRAP, ferric reducing-antioxidant power; NEAC, non-enzymatic antioxidant capacity; ORAC, oxygen radical absorbance capacity; TE/d, Trolox equivalents/d; TRAP, total radical-trapping antioxidant parameter.

*Linear trends across quartiles of dietary NEAC intake were tested using the median intake value for each quartile value as an ordinal variable.

†Adjusted for age, sex, public health center area, BMI, total physical activity, history of hypertension, family history of diabetes, coffee consumption, energy intake, and use of supplements.

‡Adjusted for age, sex, public health center area, BMI, smoking status, total physical activity, history of hypertension, family history of diabetes, coffee consumption, energy intake, and use of supplements.

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