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Flavonoid intake in the Japanese population and its effect on the the development of cardiovascular disease

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We examined the association between flavonoid intake and risk of cardiovascular disease using the data of a large Japanese cohort study. We found that higher intake of flavonoids, compared with lower intake, was associated with an decreased risk of cardiovascular disease. Regarding specific flavonoid-rich fruits, we observed significant inverse associations for citrus fruit, strawberry, and grapes.

flavonoid; fruit; cardiovascular disease; cohort study; meta-analysis; prevention

Coronary heart disease and stroke remain the second and fourth leading cause of death in Japan. The prevention of cardiovascular disease remains a huge task in Japan, highlighting the importance of identifying risk factors, in particular modifiable dietary factors. Recently, the importance of flavonoids has been recognized. Flavonoids are synthesized by plants and are an integral part of the human diet, which are widely found in fruits, vegetables, grains, roots, coffee, tea, and wine. They have received much attention in recent years as potentially protective nutrients.

Many knowledge gaps exist in the field of flavonoid intake and cardiovascular disease. Of note, the Japanese Standard Tables of Food Composition, a national database for nutrition research, have no information on flavonoid content. The lack of data about the flavonoid content of foods has limited our ability to estimate the flavonoid intakes in the Japanese population. Accordingly, the question of whether flavonoid intake could prevent cardiovascular disease in the Japanese population has not been answered yet. Also, the underlying mechanisms by which flavonoids provide protective effects against cardiovascular disease have not been fully clarified. In particular, mixed results have been reported regarding flavonoid intakes and hypertension risk. Among various flavonoid-rich foods, strawberries have gained increasing research interest. Although several clinical trials examined the effects of strawberries intervention on cardiovascular risk factors, most of them have a small sample size and the results among studies are inconsistent.

The present study has 4 purposes: (I) estimating the flavonoid intake in the general Japanese population with the use of an international database of flavonoids, (II) determining the prospective association of flavonoid intake with the incidence of cardiovascular disease using the data of a large Japanese cohort study, (III) examining the association between flavonoid intake and hypertension risk by a meta-analysis, (IV) and examining strawberry intervention on cardiovascular risk factors by a meta-analysis.

This study was based on the data of a large Japanese cohort study: the Japan Public Health Center-based prospective Study. A total of 103,802 men and women answered the questionnaire at the fifth-year survey. We excluded 16,625 of them because they had a previous history of cardiovascular disease or cancer, had an extreme body mass index (BMI < 14 or > 40 kg/m²), or had an implausible energy intake (< 800 or > 3600 kcal/day). Ultimately, 87,177 men and women were eligible for analysis.

(1) Dietary assessment

Consumption frequencies and portion sizes of 138 food and beverage items were ascertained by a validated semi-quantitative food-frequency questionnaire. Quantity of food consumption was calculated by multiplying the consumption frequency and usual portion size. The flavonoid intake was determined based on data from the Phenol-Explorer database (http://phenol-explorer.eu/), which is the first comprehensive database on flavonoids and other polyphenol content in foods. For each food, we computed for each flavonoid class by summing the individual compounds of each flavonoid class for each participant.

(2) Outcome assessment

The outcome of this analysis was the first incidence of cardiovascular disease, including coronary heart disease and stroke. Cases of coronary heart disease, including nonfatal myocardial infarction and coronary deaths, were diagnosed in accordance with the criteria of the Monitoring Trends and Determinants of Cardiovascular Disease project. Stroke cases were diagnosed based on the criteria of the National Survey of Stroke, specifically, a sudden or rapid occurrence of a focal, non-convulsive neurological deficit lasting for at least 24 hours or until death.

(3) Statistical analysis

We used a Cox proportional hazards regression model to compute relative risks for cardiovascular disease incidence. All relative risks were adjusted for the following covariates: age, study areas, sex, occupation (unemployed, white-collar worker, blue-collar worker, other, or missing), BMI, use of medication for hypertension and hypercholesterolemia, history of diabetes, smoking status, alcohol use, and physical exercise, and intakes of fish, meat, milk, and total energy. We also examined the associations between flavonoid-rich fruit intake and cardiovascular disease risk. The analyses were performed using SAS 9.4 software.

For meta-analyses, PubMed was searched for relevant studies published up to February 20, 2020. Studies were selected for analysis if they examined the association between flavonoid intakes risk of hypertension or they examined the effects of strawberry intervention on cardiovascular risk factors. The analyses were performed using Stata version 16.0.

(1) We first examined the association between flavonoid intake and cardiovascular risk. After full adjustment for covariates including demographics, lifestyles, and dietary factors, the highest intake group of flavonoids, compared with the lowest intake group, was associated with a decreased risk of cardiovascular disease.

(2) Regarding specific flavonoid-rich fruits, we observed significant inverse associations for citrus fruit, strawberry, and grapes and a borderline inverse association for apple/pear.

(3) We next examined the association between flavonoid intake and hypertension risk, which is one of the most important risk factors of cardiovascular disease. We obtained 5 cohort studies for analysis. A pooled analysis of the 5 cohort studies suggested that flavonoid intake was associated with a non-significant decreased risk of hypertension (**Figure 1**).
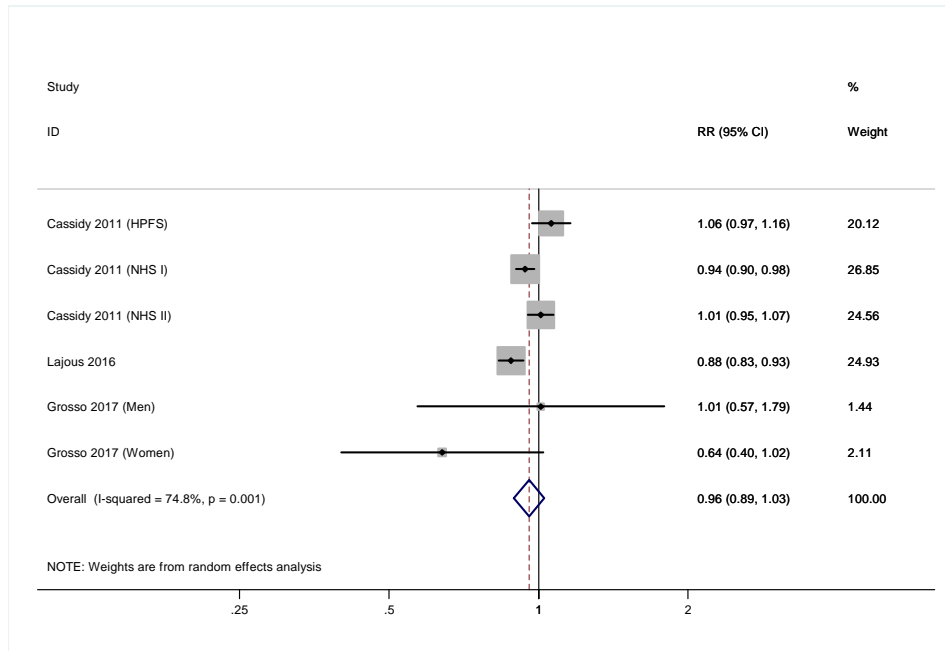

Study ID	RR (95% CI)	% Weight
Cassidy 2011 (HPFS)	1.06 (0.97, 1.16)	20.12
Cassidy 2011 (NHS I)	0.94 (0.90, 0.98)	26.85
Cassidy 2011 (NHS II)	1.01 (0.95, 1.07)	24.56
Lajous 2016	0.88 (0.83, 0.93)	24.93
Grosso 2017 (Men)	1.01 (0.57, 1.79)	1.44
Grosso 2017 (Women)	0.64 (0.40, 1.02)	2.11
Overall (I-squared = 74.8%, p = 0.001)	0.96 (0.89, 1.03)	100.00

NOTE: Weights are from random effects analysis

Figure 1. Meta-analysis for the association between flavonoid intakes and hypertension risk.

(4) Also, we examined the effects of strawberry interventions on cardiovascular risk factors. We included 11 randomized controlled trials in this meta-analysis. Overall, the strawberry interventions significantly reduced C-reactive protein but did not affect blood pressure, lipid profile, or fasting blood glucose (**Table 1**).

Table 1. Meta-analysis for the effects of strawberry intervention on cardiovascular risk factors.

	No. of studies	Effect size (95% CI)	I^2
Systolic blood pressure, mmHg	6	-0.26 (-2.83, 2.31)	0
Diastolic blood pressure, mmHg	6	-0.92 (-2.47, 0.64)	0
Total cholesterol, mmol/L	7	-0.15 (-0.35, 0.05)	25.7
LDL-cholesterol, mmol/L	7	-0.11 (-0.30, 0.08)	1.7
HDL-cholesterol, mmol/L	7	0.00 (-0.08, 0.08)	0
Triglyceride, mmol/L	7	-0.03 (0.25, 0.04)	0
Fasting blood glucose, mmol/L	7	0.04 (-0.10, 0.18)	0
C-reactive protein, mg/L	6	-0.63 (-1.04, -0.22)	9.7

In conclusion, higher intake of dietary flavonoids was associated with a decreased risk of cardiovascular disease. Flavonoid-rich fruits, such as citrus fruits, strawberry, and grape, may be helpful for prevention of cardiovascular disease.

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