

## Soy products intake and cancer incidence: Findings from the J-MICC Study

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**Background :** Soybeans are rich in nutrients such as protein, vitamins, minerals and isoflavones, and are expected to have an important role in preventing various chronic diseases. It has also been suggested that the health benefits of soy products vary depending on whether they are fermented or non-fermented. The present study aimed to assess the relationship between soy products (fermented/non-fermented), or isoflavone intake and cancer incidence in a large Japanese population.

**Methods :** The data of 49,543 participants in the Japan Multi-Institutional Collaborative Cohort Study were analyzed. Habitual intake of foods including soy products during the past year was examined using the Food Frequency Questionnaire (FFQ). Isoflavone intake from soy foods and total energy intake were estimated from the FFQ. Foods intake including soy products, and isoflavone intake were energy-adjusted using residual method. Information on cancer incidence was collected through national cancer registries, regional cancer registries, patient notifications from hospitals, and reports from subjects confirmed by medical records. Data from the national cancer registries provided to us according to the Cancer Registry Promotion Act were processed and analyzed independently for this study. Cox proportional hazards models adjusted for age, sex and other potential confounders were used to estimate adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) for cancer incidence based on the first quartile group of each soy food (total soy intake, fermented soy intake, non-fermented soy intake) or isoflavone intake.

**Results :** During a mean follow-up of 11.3 years, 4,041 cancer incidences were observed. A higher intake of fermented soy products (HR 0.88, 95% CI 0.80, 0.96) or isoflavone was associated with a lower HR of cancer incidence.

**Conclusion :** The present study suggests that the intake of fermented soy products or isoflavone may be associated with cancer incidence in Japanese adults.

## Addressing Asymmetric Misclassification and Data Separation in Logistic Regression

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In the analysis of binary outcomes, asymmetric misclassification arises when one of the outcomes is misclassified, which leads to biased regression coefficient estimates and reduced prediction accuracy. The asymmetric logistic regression model has been proposed as a solution to address this issue (Komori et al., 2016). However, similar to the standard logistic regression model, the asymmetric logistic regression model suffers from the non-existence of maximum likelihood estimates under data separation, causing computational algorithms to diverge when attempting to estimate regression coefficients. To overcome this issue, we propose a penalized estimation method for the asymmetric logistic regression model, inspired by Firth's method (Firth, 1993). Our method incorporates a penalty term based on the Jeffreys prior distribution into the log-likelihood function. We formally prove that the proposed penalized estimator always exists, even under complete or quasi-complete separation. We further develop an iterative algorithm for computing the penalized estimates based on the JeffreysMPL algorithm (Kosmidis and Firth, 2020). Through extensive simulation studies, we demonstrate the practical utility of our proposed method. The simulation results show that our approach successfully produces stable and meaningful estimates under separation scenarios while maintaining comparable performance to the standard asymmetric logistic regression in non-separation cases. In conclusion, our approach provides researchers with a reliable tool for analyzing binary outcomes with asymmetric misclassification, particularly in small sample or sparse data settings where separation is likely to occur. These situations are commonly encountered in epidemiological research, such as infectious disease epidemiology studies where immunity effects play a role, making our method valuable for epidemiological applications.

## High dietary polyphenol intake is associated with reduced risk of dementia

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**Background :** Dietary polyphenols may play a modifiable role in reducing the risk of dementia; however, current evidence remains limited and inconclusive. This study aimed to determine if dietary polyphenol intake, independent of caffeine intake, is associated with dementia risk in middle-aged and older people.

**Methods :** Participants of this 12-year cohort study were 13,548 community-dwelling individuals aged 40–74 years (52% female). The study was approved by the Niigata University Ethics Committee (Nos. 1324, 2018-0417). Dietary intake data were collected using a validated food frequency questionnaire in 2011–2013. Polyphenol and caffeine intakes were energy-adjusted using the residual method. The outcome was incident dementia determined using Japan's long-term care insurance database. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs).

**Results :** In analyses adjusted for demographic factors, body size, lifestyle habits, and disease histories, higher polyphenol intake was associated with a lower risk of dementia ( $P$  for trend  $< 0.0001$ ), with the highest quintile (Q5) having a reduced risk of dementia  $HR=0.63$ , 95%CI: 0.50–0.79) compare to the lowest quintile (Q1, reference); after further adjusted for caffeine intake, this association remained significant ( $P$  for trend = 0.0213), with Q5 having an  $HR$  of 0.73 (95% CI: 0.54–0.98). In females, higher polyphenol intake had a significantly lower risk of dementia in the full-adjusted model, with  $HR$  of Q5 vs Q1, 0.63 (95% CI: 0.41–0.97,  $P$  for trend = 0.0152). In males, a significant association between higher polyphenol intake and a lower risk of dementia was observed ( $HR$  of Q5 vs Q1, 0.56 (95% CI: 0.41-0.77,  $P$  for trend = 0.0003), but this association was attenuated when accounting for caffeine intake.

**Conclusion :** High polyphenol intake is associated with decreased risk of dementia in middle-aged and older Japanese individuals, independent of caffeine intake, especially in females.

## Association Between Cerebral White Matter Lesions with Cognitive Decline and Circulating serum APP

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**Background and Objectives :** White matter lesions (WMLs) , which reflect cerebral small vessel disease and microvascular fragility, are increasingly recognized as markers of age-related brain pathology(Kuriyama et al., 2017). Recent studies have shown that aging induces the expression of amyloid precursor protein 770 (APP770) in cerebral vascular endothelial cells, which may contribute to cognitive impairment. In this study, we investigated the relationship between circulating APP levels and WMLs with cognitive decline using brain MRI data from a community-dwelling older population.

**Methods :** A total of 214 community-dwelling older adults (126 men, 88 women; 75.8 years) were included. Deep WMLs were evaluated on brain MRI using the Fazekas classification. All participants underwent brain MRI, self-administered lifestyle questionnaires, neuropsychological tests, blood tests, and the association with serum APP770 levels was examined.

**Results :** The mean serum APP770 level was 39.3 ng/mL. APP770 levels were 22.3 pg/mL in the G0 group (48 patients), 31.5 in G1 (94 patients), 48.0 in G2 (45 patients), 74.3 in G3 (21 patients), and 102.7 in G4 (6 patients), showing a significant increase with disease progression. Neuropsychological tests, including the Mini-Mental State Examination (MMSE), Word Fluency Test, and Symbol Digit Modalities Test, showed significant declines with increasing WML grade. A significant negative correlation was observed between APP770 and the word fluency test and SDMT ( $p < 0.05$ ).

**Conclusion :** Elevated circulating APP770 levels were significantly associated with WMLs accompanied by cognitive decline, suggesting that APP770 may serve as a potential biomarker for vascular cognitive impairment. Stratification based on APP770 levels may offer a novel approach for epidemiological screening and early detection of vascular-related cognitive decline in aging populations.

## Development of Visualization App for Childhood Vaccination Coverage in Japan

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**Backgrounds :** Routine vaccination for children covers 14 infectious diseases (e.g., Japanese encephalitis [JE] virus, rotavirus, etc.) in Japan. Although the number of vaccinations is made public on the Ministry of Health, Labour and Welfare website, age-, year-, and region-specific coverage is not easily accessible. This study aimed to develop an open-access web app to support decision-making by providing stakeholders detailed vaccination coverage.

**Methods :** The app targeted children aged 0–15 years. We used vaccination and population data provided in e-Stat, a portal site for Japanese Government Statistics. The vaccination data between 2010 and 2023 was provided as vaccinations per year by age and 47 prefectures in CSV format or via Application Programming Interface (API) services. The population data were obtained using the API from Vital Statistics and the Number of Births. The app was developed to visualize cumulative vaccination coverage based on birth year or the number of vaccinations by line, bar, and geographical chart.

**Results :** The vaccination app visualized the trend of vaccination coverage. For example, the JE vaccination for specific ages was restricted due to undershipment for manufacturing reasons in 2021, and the under-vaccination was a concern. The app showed that the vaccination coverage in the second period at 9-year-olds in 2021 was 10% compared to about 40% in the same age group in other years. However, the vaccination coverage recovered to the same level (about 60%) as in different age groups in 11-year-olds in 2023. In addition, the geographical chart clarified the regional characteristics of JE vaccination coverage. The coverage of 1-year-olds was less than 10% in half of the prefectures. On the other hand, Oita, Miyazaki, Yamaguchi, Kumamoto, and Chiba prefectures showed more than 50% in 2022.

**Conclusion :** The app would be useful for monitoring vaccination coverage and identifying the characteristics of prefectures in Japan.