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Pneumococcal vaccination, but not influenza vaccination, is negatively associated with incident dementia among Japanese older adults: The JAGES 2013–2022 prospective cohort study

Kousuke Iwai-Saito [a,*], Koryu Sato [b], Masahiro Fujii [c], Katsunori Kondo [d,e]

[a] Division of International Health, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan
[b] Faculty of Policy Management, Keio University, 5322 Endo, Fujisawa-shi, Kanagawa 252-0882, Japan
[c] Division of Virology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan
[d] Department of Social Preventive Medical Sciences, Center for Preventive Medical Sciences, Chiba University, 1-8-1, Inohana, Chuo-ku, Chiba 360-0856, Japan
[e] Department of Gerontological Evaluation, Center for Gerontology and Social Science, Research Institution, National Center for Geriatrics and Gerontology, Aichi, Japan

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ABSTRACT

Background: It is unclear whether inactivated influenza vaccination (IIV) or pneumococcal vaccination are associated with the risk of dementia; however, both types of vaccination are recommended for older adults. Studies have shown that the IIV is negatively associated with incident dementia; however, the uptake of pneumococcal vaccinations has not been considered. We investigated the independent associations of IIV and 23-valent pneumococcal polysaccharide vaccine (PPSV23) with incident dementia in older adults.

Methods: Health-related information on older Japanese adults was obtained through a baseline survey conducted in 2013 (baseline survey). The uptake of IIV and PPSV23 was determined in a second survey conducted in 2016 (second wave). Both surveys were conducted among independent Japanese older adults aged ≥ 65 years at the two surveys and who had not been certified as needing long-term care (LTC). In the second wave, 9,865 participants were followed up for 3.5 years (short-term follow-up), and 6,995 participants were followed up for six years and five months (long-term follow-up) until they required LTC due to dementia onset (incident dementia). A competing risk model with stabilized inverse probability weighting (SIPW) was constructed to calculate the hazard ratios (HRs) and 95 % confidence intervals (CIs) of incident dementia.

Results: PPSV23 uptake was negatively associated with incident dementia among participants in both the short- and long-term follow-up periods after SIPW (short-term follow-up: HR: 0.77, 95 % CI: 0.63 – 0.95; long-term follow-up: HR: 0.83, 95 % CI: 0.70 – 0.97). Conversely, IIV uptake was not associated with incident dementia among participants in either follow-up group (short-term follow-up: HR: 0.86, 95 % CI: 0.63–1.16; long-term follow-up: HR: 0.99, 95 % CI: 0.76–1.29). The PPSV23 uptake was negatively associated with incident dementia in participants without the IIV uptake (short-term follow-up: HR: 0.44, 95 % CI: 0.24 – 0.81; long-term follow-up: HR: 0.47, 95 % CI: 0.29 – 0.76). Conversely, the IIV uptake was not associated with incident dementia regardless of the PPSV23 status (short-term follow-up: HR: 0.87, 95 % CI: 0.62 – 1.23; long-term follow-up: HR: 1.00, 95 % CI: 0.74 – 1.35).

Conclusion: Our results suggest that the PPSV23 uptake was independently associated with the incidence of dementia. However, the IIV uptake was not associated with the incidence of dementia.

1. Introduction

The burden of dementia is rapidly increasing worldwide with the increase in the aging population. The number of people with dementia is predicted to increase from 57.4 million in 2019 to 152.8 million by the year 2050 (Nichols et al., 2022). In Japan, 6.6 million people have been certified as needing long-term care (LTC) and, of these, 1.2 million (18.1 %) needed LTC due to dementia; dementia was the most frequent reason for requiring LTC in 2019 (Cabinet Office, 2022).

Several studies have reported a negative association between

* Corresponding author at: rm334 3rd floor West Research Building, 1-757 Asahimachi, Chuo-ku, Niigata city, Niigata pref. Postal code: 951-8510, Japan.
E-mail addresses: anayoshi@med.niigata-u.ac.jp (K. Iwai-Saito), koryus@sfc.keio.ac.jp (K. Sato), fujiimas@med.niigata-u.ac.jp (M. Fujii), kkondo@kkondo.net (K. Kondo).

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inactivated influenza vaccination (IIV) and the incidence of dementia (Bukhbinder et al., 2022; Lee et al., 2020; Liu et al., 2016; Luo et al., 2020; Wiemken et al., 2021a). However, previous studies have not examined the association between pneumococcal vaccination and incident dementia (Bukhbinder et al., 2022; Lee et al., 2020; Liu et al., 2016; Luo et al., 2020; Wiemken et al., 2021a). Both IIV and pneumococcal vaccinations are recommended for older adults to prevent severe respiratory illnesses (Grohskopf et al., 2022 and CDC, 2010). These studies were conducted in the United States, Taiwan, and the United Kingdom (Bukhbinder et al., 2022; Lee et al., 2020; Liu et al., 2016; Lophatananon et al., 2023; Luo et al., 2020; Wiemken et al., 2021a), countries in which both vaccinations are recommended for adults aged ≥ 65 or ≥ 75 years and financial support for the vaccinations are available (Chiu et al., 2013; Grohskopf et al., 2022; Agency, 2021; Black et al., 2017; Chen et al., 2018; Lu et al., 2021). The United States national surveillance for vaccination coverage showed that almost 70 % of adults aged ≥ 65 years received both vaccinations (Lu et al., 2021).

However, it remains unknown whether IIV or pneumococcal vaccination is negatively associated with incident dementia.

In Japan, the IIV and 23-valent pneumococcal polysaccharide vaccine (PPSV23) is available through the national immunization program as routine vaccinations for the following individuals: adults aged ≥ 65 years; adults aged 60 to 64 years whose daily activities are extremely limited due to impaired heart, kidney, or respiratory function; and individuals who are almost unable to carry out daily activities because of impaired immune function due to human immunodeficiency virus to prevent related severe respiratory illnesses (Hirota and Kaji, 2008; Murakami et al., 2019). This study investigated the independent association between the IIV and PPSV23 vaccinations and incident dementia in adults aged ≥ 65 years.

2. Methods

2.1. The JAGES surveys

This study adopted a longitudinal design and used data from the Japan Gerontological Evaluation Study (JAGES). The JAGES surveys the social determinants of health among noninstitutionalized and functionally independent persons aged ≥ 65 years who do not receive LTC benefits. The LTC system was introduced in Japan in 2000 to address the demands of older persons with disabilities based on the concept of a user-oriented social insurance system with support for independence. Older adults certified as having LTC service needs can utilize facility-, in-home-, and community-based services, depending on their physical and cognitive impairments (Yamada and Arai, 2020). JAGES survey participants were selected from cities, towns, and villages. Generally, all individuals in a city, town, or village are included if the total number of individuals is less than 5,000, except when budgetary restrictions are in place. If a city, town, or village comprised more than 5,000 individuals, questionnaire booklets were distributed to 5,000 randomly selected individuals (Kondo, 2022).

2.2. Study design and analytical sample

The study design is illustrated in Fig. 1. In a baseline survey conducted between October and December 2013, questionnaires were sent to 193,694 older Japanese adults from 30 municipalities. The survey consisted of five modules (A-E) covering various assessments. Module D assessed the subjective quality of life of the participants, sleep, influenza history, pneumonia history, the PPSV23 uptake, and the IIV uptake. Responses were collected from 137,736 adults (response rate 71.1 %). Of these, 90,896 individuals remained after excluding 46,840 individuals because they were certified as needing LTC, did not include age and/or sex data, or did not have an identification number (ID) to link

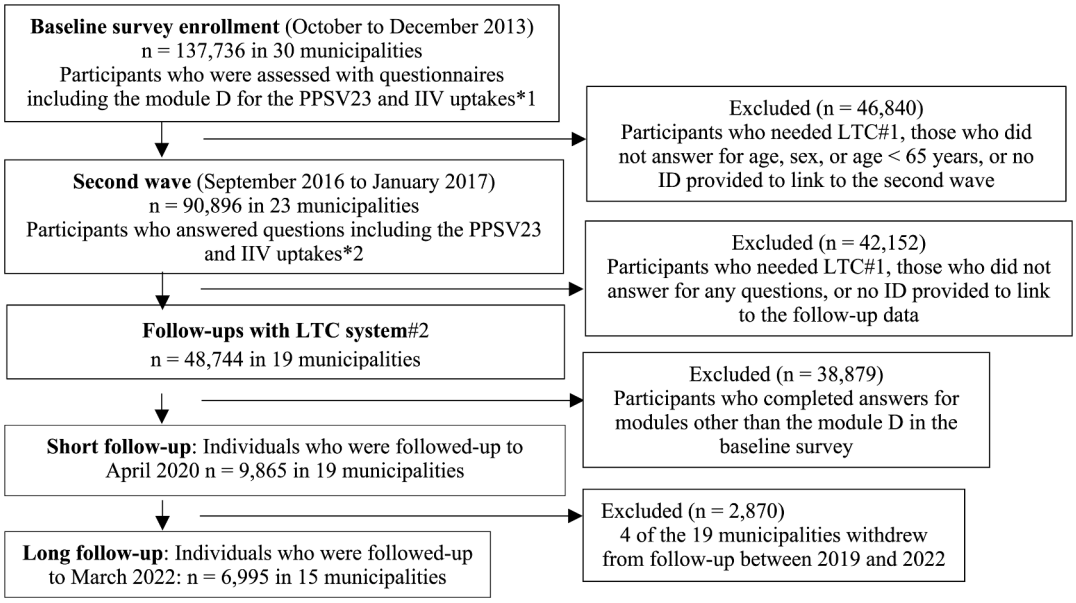

Fig. 1. Study Design. In the baseline survey, we assessed participants' characteristics including age, sex, educational years, equivalized income, marital status, household structure, smoking status, alcohol consumption, BMI ≥ 30, medical checkup, self-rate health, frequency of intense, moderate, and mild physical activities, heart disease, stroke, high blood pressure, diabetes, ear disease, respiratory disease, frailty, pneumococcal and influenza history, pneumococcal and influenza vaccination, social participation, social cohesion, and reciprocity. In the second wave, we assessed the uptake of PPSV23 and IIV. In the follow-ups, trained investigators assessed the participants' cognitive function each time the candidate or their family applied for LTC to the relevant municipal government. #1 and #2. LTC certification has two roles. One was to exclude older adults who were LTC-certified for dementia or other reasons from the baseline and second-wave surveys (#1). The other was to follow up on incidents of certified LTC due to dementia or other reasons after the second wave (#2). *1 and *2: The assessment of the PPSV23 and IIV uptakes in the baseline survey was to adjust for the impact of vaccination at baseline (*1), and the other role of assessing the PPSV23 and IIV uptakes was to investigate whether these two vaccinations were negatively associated with the development of dementia (*2). The finalized data of the short and long-terms follow-up includes only people who participated in all assessments that included the baseline, the second wave, and the follow-up surveys.

to the data from the second wave.

The second wave was conducted between September 2016 and January 2017. Questionnaires were mailed to community-dwelling individuals in 23 municipalities. Data were obtained from 48,744 individuals who completed the self-reported questionnaires, including information about PPSV23 and IIV uptake after excluding data from 42,152 older adults who had been certified as needing LTC, those with no ID, and those who did not answer any questions.

Follow-up surveys were conducted between October 2016 and April 2020 (short-term follow-up: 3.5 years) and between October 2016 and March 2022 (long-term follow-up: 6 years and 5 months) to assess LTC needs and include information on dementia onset. Data regarding participants' LTC needs were collected from their municipality of residence. Registration in the national LTC scheme is mandatory and a certification committee in each municipality assesses the eligibility of each LTC applicant (Tamiya et al., 2011). Data from 9,865 of the 48,744 individuals was used as the short-term follow-up for the statistical analysis because these individuals answered questions of Module D including infections of influenza, pneumonia, the uptakes of PPSV23 and IIV, while the remainder answered other modules. Data from only 6,995 subjects was included in the long-term follow-up because 2,870 individuals in 4 of 19 municipalities withdrew from the follow-up survey.

2.3. Assessment of incident dementia

The outcome of the current study was dementia onset in independent older adults according to the LTC needs to be assessed by municipalities. To be certified for LTC, the applicant or their family applies to the municipality (insurer), which evaluates the individual's level of independence in daily living, dementia, and other care needs (Lin et al., 2018). Trained investigators dispatched by the certification committee in each municipality conducted the primary assessment of LTC program applicants. Investigators visited the home of each applicant to assess their activities of daily living and instrumental activities of daily living status, cognitive function (e.g., short-term memory, orientation, and communication), and the presence of mental or behavioral disorders using a standardized assessment manual of The Ministry of Health, Labour and Welfare [MHLW] (2013). Cognitive disability grade is categorized into eight levels: 0, I, IIa, IIb, IIIa, IIIb, IV, and M (0 = Independent, M = Needs constant treatment in a specialized medical facility). Cognitive impairment categorization strongly correlates with Mini-Mental State Examination scores (Hisano, 2009), and level "I" corresponds to a 0.5-point rating on the Clinical Dementia Rating scale (Meguro et al., 2012). The dementia cases were defined as a person with grade IIa or higher dementia, as defined by the MHLW assessment manual as "individuals with dementia-related symptoms, behavioral disturbance and/or difficulty in communication that limit daily living outside the home, but who are capable of daily living under someone's care". The criteria of the MHLW manual have been validated by a previous study (Noda et al., 2018). LTC certification has two roles. One is to exclude older adults who were LTC-certified for dementia in the baseline survey and second wave. The other is to follow-up certified LTC cases due to incident dementia or other reasons after the second wave. The baseline survey and second wave included older adults who were not LTC-certified. (Fig. 1).

2.4. Vaccinations

The exposures included pneumococcal and influenza vaccinations. In Japan, the PPSV23 vaccine was introduced in 1983 as a voluntary vaccination and became a routine vaccination when the national immunization program for PPSV23 was implemented in October 2014 (Iwai-Saito et al., 2021; Murakami et al., 2019; Shono and Kondo, 2015). The baseline survey in 2013 was conducted before the implementation of the national immunization program. Vaccination was assessed by asking the respondents, "Did you receive a pneumococcal vaccination in recent years?" in the baseline survey. The second wave was conducted between September 2016 and January 2017, after the implementation of the national immunization program for PPSV23. The second wave assessed the pneumococcal vaccination status of the survey participants by asking the following questions: "Have you received a pneumococcal vaccination in the last 5 years?" Respondents chose from the following options: "No," "Yes, I used my municipality's subsidy," and "Yes, but I did not use my municipality's subsidy." The second and third responses were evaluated as indicators of PPSV23 uptake. Only 8.3 % of the participants answered "Yes" in the 2013 survey, with 35.6 % of participants answering "No" in the 2013 survey and "Yes" in the 2016 survey, and 56.1 % of participants answering "No" in both surveys. Based on these results, we concluded that most participants showed PPSV23 uptake after the implementation of the national immunization program. The IIV immunization program was introduced in 2001 to prevent severe illness in adults aged $\geq$ 65 years and those who met the eligibility criteria (Hirota and Kaji, 2008). The 4-valent IIV contains hemagglutinin proteins of the two influenza virus subtypes, types A and B. This vaccine was introduced in 2015 to prevent seasonal influenza epidemics and replaced the 3-valent IIV, which contains viral proteins of two subtypes of type A virus and one subtype of type B virus. No adjuvants have been added to these vaccines in Japan (Nakayama, 2015; Seki et al., 2017). Influenza vaccination status was assessed by asking participants "Have you had the flu shot in the past year?" in the baseline and second wave, respectively).

2.5. Covariates

The covariates potentially associated with dementia were age, sex, socioeconomic status (SES), health behaviors, BMI, chronic diseases, geriatric factors, history of vaccination and infection, and social capital.

The covariates related to SES included years of education, equivalized income, marital status, and household structure. Evidence indicates that years of education and income are associated with the incidence of dementia among older adults (Takasugi et al., 2019) Marital status and household structure are associated with incident dementia (Roystonn et al., 2020). These factors were assessed as previously described (Iwai-Saito et al., 2021). Covariates related to health behaviors consisted of smoking, alcohol consumption, medical checkups, self-rated health, and frequency of intense, moderate, and mild physical exercise. Smoking and high alcohol consumption are risk factors for dementia in older adults (Beydoun et al., 2014). Smoking status was assessed by asking "Do you smoke cigarettes?", and the participants selected an appropriate answer. Alcohol consumption was assessed by asking, "Do you drink alcohol?", and the participants selected an appropriate answer. Regular health check-ups are associated with a lower incidence of dementia among older adults (Nakagomi et al., 2021). The frequency of medical checkups was assessed by asking participants, "Have you ever had a checkup at a health center, your workplace, a medical institution, or another place?", and the participants selected an appropriate answer. Poor self-rated health is associated with the risk of dementia (Stephan et al., 2021). Self-rated health was assessed by asking participants "How is your current health status?" The participants selected appropriate ratings from the following response options: excellent, good, fair, and poor (Iwai-Saito et al., 2022). The frequency of intense, moderate, and mild nonoccupational physical activities is associated with lower incident dementia among older adults (Arafa et al., 2021). Activity frequency was assessed by asking participants "The following questions are about your physical movement in regular daily life (exercise, sport, activities, or housework requiring physical effort). Do not include movement for work." "Do you exert yourself strenuously, moderately, or lightly in the following activities?" The participants selected one of four options for the intensity of physical activity. Obesity (body mass index [BMI] of $\geq$ 30 kg/m^2) is associated with an increased risk of dementia in older adults (Im et al., 2019). Heart disease, stroke, high blood pressure, diabetes, respiratory diseases, and

ear diseases are risk factors for incident dementia (Cheng et al., 2012; de Heus et al., 2021; Johnson et al., 2021; Kuzma et al., 2018; Russ et al., 2020; Wolters et al., 2018). These diseases were assessed by asking participants to "Circle the number of all diseases for which you are currently receiving treatment or experiencing aftereffects." The covariates related to geriatric factors included depression and frailty. A history of depression is associated with all-cause dementia (Kuring et al., 2020). Geriatric depression was evaluated using the short form of the Geriatric Depression Scale (Burke et al., 1991). Frailty is a predictor of Alzheimer's disease (AD), vascular dementia, and other types of dementia (Kojima et al., 2016). Frailty was assessed using the Kihon Checklist (Fukutomi et al., 2015). which was validated using cardiovascular health study criteria (Satake et al., 2016). Two infectious diseases, pneumonia, and influenza, and two vaccinations, PPSV23 and IIV (at the baseline, but not at the exposure), were used as covariates. A history of pneumonia or influenza was associated with the risk of dementia (Levine et al., 2023). Covariates related to social capital consisted of social participation, social cohesion, and reciprocity. Social participation, social cohesion, and reciprocity were associated with a lower risk of incident dementia (Takahashi et al., 2019; Murayama et al., 2018; Saito et al., 2018). These three types of social capital were evaluated as previously described (Kousuke Iwai-Saito, 2021). Age was treated as a continuous variable, while all other variables were categorized into several groups. Details of each categorical variable are listed in Table 1.

2.6. Statistical analysis

In the baseline survey, data had minor missingness on almost all study variables. (Supplemental Tables 1 and 4), In the second wave, data for PPSV23 or IIV uptake had minor missingness (Supplemental Table 3), whereas there were no missing data for the following variables: age, sex, body mass index, LTC needs, and days until the participants needed LTC or loss of LTC eligibility due to death. Imputation can handle missing data if they are missing at random (MAR). Twenty imputed datasets were generated to handle missing data using Markov chains as previously described (Li, 1988). The stabilized average treatment effect on incident dementia was calculated using the stabilized inverse probability weighting (SIPW) method (Kusama et al., 2019). A logistic regression model was used to predict the propensity score for participants with the PPSV23 or IIV uptake and those without one of the two vaccinations; all covariates were included as possible confounders and the stabilized average treatment effect of the PPSV23 or IIV uptake was calculated. The stabilized average treatment effect was used to avoid instability in the estimated effect size owing to extreme weighting (Xu et al., 2010). The standardized difference (SD) was used to check the balance of the covariates between participants with the PPSV23 or IIV uptake and those without one of the two vaccinations. If the SD of all covariates was < 0.1 and > -0.1 after weighting, it was considered well-balanced. Competing risk analysis was conducted using a cause-specific hazard model (Fine and Gray, 1999). Competing risk analysis is a type of survival analysis that statistically accounts for the presence of competing events (e.g., death) that preclude future outcomes of interest (Lau et al., 2009). Cox proportional hazard models for incident dementia were developed; hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated after the SIPW. Stabilized average treatment effect-weighted HRs were calculated for each dataset with good balance, and Rubin's rule was used to combine all estimators (Knol and VanderWeele, 2012). All P values were two-tailed, and the significance level was set at 5 %. We tested whether the model satisfied the proportional hazard assumption (PH assumption) with the method using a time-dependent covariate (Cox, 1972). We confirmed that all the models satisfied the PH assumption, except for models in 4 of the 20 imputations among participants with the PPSV23 uptake, but without the IIV uptake in the short-term follow-up. We calculated the HRs and 95 % CI for associations with incident dementia in those excluding the datasets with the

Table 1
Baseline characteristics of participants in the short-term follow-up (n = 9,865).

		Mean	Frequency of mild physical activity	≥4 times/ week	48.7
Age (years)	–	73.0		2 – 3 times/ week	21.4
		%		1 time/ week	8.5
Sex	Male	46.1		≤1 – 3 times/ month	5.8
	Female	53.9		A few times/year	3.5
Number of years of education (years)	<6	1.3		Almost no activity	12.1
	6 – 9	38.3	BMI (kg/m^2)	<30	94.3
	10 – 12	40.0		≥30	5.7
	≥13	19.8	Heart disease	Yes	90.0
	Other	0.5		No	10.0
Equivalized income (million yen)	<2.00	54.1	Stroke	No	97.1
	2.00 – 3.99	37.2		Yes	2.9
	≥4.00	8.7	High blood pressure	No	54.9
Marital status	Married	75.0		Yes	45.1
	Widowed	19.2	Diabetes	No	87.4
	Divorced	2.9		Yes	12.6
	Never married	2.1	Ear diseases	No	93.8
	Other	0.8		Yes	6.2
Household structure (Living with someone or alone)	A spouse	41.2	Respiratory diseases	No	95.7
	Alone	12.5		Yes	4.3
	Children	7.4	Geriatric depression	Not depressed	78.0
	A spouse and children	16.7		Depression tendency	17.2
	Three generations	14.4		Depression	4.8
	Other	7.7	Frailty	Nonfrail	59.2
Smoking	Currently	9.4		Prefrail	29.9
	Quit	16.0		Frail	10.9
	Never	74.5	Pneumonia	No	96.4
Alcohol consumption	Currently	37.7		Yes	3.6
	Quit	4.8	Influenza	No	98.9
	Do not drink	57.5		Yes	1.1
Medical checkup	Within 1 year	63.8	PPSV23	No	96.4
	1–4 years ago	11.7		Yes	3.6
	≥4 years ago	9.8	IIV	No	39.9
	Never	14.8		Yes	60.1
Self-rated health	Excellent	13.6	Social participation	No	60.8
	Good	72.4		Yes	39.2
	Fair	12.7	Social cohesion	No	14.5
	Poor	1.4		Yes	85.5
Frequency of intense physical activity	≥4 times/ week	5.7	Reciprocity	No	3.4
	2 – 3 times/ week	8.6		Yes	96.6
	1 time/ week	6.9			
	≤1 – 3 times/ month	6.4			
	A few times/year	9.4			
	Almost no activity	63.0			
Frequency of moderate physical activity	≥4 times/ week	32.6			
	2 – 3 times/ week	21.4			
	1 time/ week	10.3			
	≤1 – 3 times/ month	10.0			

(continued on next page)

Table 1 (*continued*)

	A few times/year	6.9
	Almost no activity	18.9

The short-term follow-up: 3.5 years follow-up period.

four imputations. For the sensitivity analysis, we used extended competitive risk models to obtain separate HRs within different follow-up durations (≤1,200 or > 1,200 days in the short-term follow-up; ≤2,200 or > 2,200 in the long-term follow-up) (Kleinbaum and Klein, 2012). The associations calculated using the Cox proportional hazards models were assessed to determine whether they were dependent on SIPW (Supplemental Figs. 1 and 2). Stata version 17 (Stata Corp., College Station, TX, USA) was used for all statistical analyses.

3. Results

Table 1 shows the characteristics of the participants during the short-term follow-up period. The most prevalent characteristics per category were: female sex; 10 to 12 years of education; income < 2.00 million yen; married status; living with a spouse; never smoking; do not drink alcohol; medical checkup within 1 year; self-rated health "good;" almost no intense physical activity, moderate physical activity ≥ 4 times a week, mild physical activity ≥ 4 times a week; BMI < 30 kg/m^2; not currently receiving treatment or experiencing complications of any of the following: heart disease, stroke, high blood pressure, diabetes, ear diseases, and respiratory diseases; not depressed; non-frail; no history of influenza; no history of pneumonia; without the PPSV23 uptake; with the IIV uptake; no social participation; with social cohesion; with reciprocity. Supplemental Table 5 shows that the prevalence of almost all characteristics in the long-term follow-up was the same as that in the short-term follow-up, except for educational background, as six – to nine years of education was the most prevalent response in the long-term follow-up. Supplemental Table 2 shows that the basic characteristics of the participants in the short- and long-term follow-up were almost equivalent to those of the participants with valid responses in the baseline survey because the SDs in the short- or long-term follow-up and the baseline survey were smaller than or approximately 0.1. The only exception was that the SDs for frailty were greater than 0.7 when comparing participants in the short- and long-term follow-up periods. This finding may be explained by the fact that the baseline sample included frail participants who became dependent on LTC after the baseline survey and were thus ineligible for the second wave.

Supplemental Table 3 shows the proportions of cases with cumulative incident dementia and death as competitive events and others with or without PPSV23 or IIV uptake in the short- and long-term follow-ups with missing data. The incident dementia and death rates were 5.7 % and 1.5 %, respectively, among all participants in the short-term follow-up period. Incident dementia and death were most prevalent in missing cases related to both PPSV23 and IIV uptake in the short- and long-term follow-ups. The high prevalence of incident dementia and death in the missing data was likely due to the possibility that frail older adults in the baseline survey could not answer the question related to PPSV23 and IIV uptake because of their inability to recall past vaccinations. Missing data could cause a bias in underestimating the association between incident dementia and the two vaccinations, which should be handled with imputation. Table 2 shows the proportion of cases of cumulative incident dementia and other competitive events among participants with or without PPSV23 or IIV uptake at two follow-ups after imputation. Incident dementia was most prevalent among participants with the IIV uptake in the two follow-up periods (participants with IIV uptake in the short-term follow-up was 6.1 % and long-term follow-up was 13.8 %).

Table 3 shows the basic characteristics of the participants with or without PPSV23 uptake during the short-term follow-up period before and after SIPW. Before the SIPW, the mean values of the following categories varied between the vaccinated and unvaccinated groups, with an SD greater than 0.1: age, smoking status, frequency of medical checkups, frequency of mild physical activity, respiratory disease, pneumococcal and influenza vaccination status, social participation, and social cohesion. After SIPW, these values equalized to SD of less than 0.1. We confirmed that all the mean values of these categories were equalized with an SD smaller than 0.1 in all imputations. Balancing (SD < 0.1 and > -0.1) was successful between the participants with and without PPSV23 uptake across all 20 imputations. Supplemental Table 6 shows the basic characteristics of participants with and without IIV uptake during the short-term follow-up period before and after SIPW. The equalization of the mean values was successful in 4 of the 20 imputations after SIPW. Supplemental Table 7 shows the basic characteristics of participants with PPSSV23 uptake before and after SIPW during the long-term follow-up period. Balancing was successful between patients with and without PPSV23 uptake in all 20 imputations. Supplemental Table 8 shows the basic characteristics of participants with IIV uptake before and after SIPW. Balancing was successful between those with and those without IIV uptake in 11 of the 20 imputations during the long-term follow-up period.

Table 2
Proportion of cumulative incident dementia cases and competitive events with or without PPSV23 or IIV uptake among participants in the short- and long-term follow-up periods.

Follow-up			Number of participants	No LTC need	Incident dementia	Death	Other
Short-term follow-up			N	%	%	%	%
(n = 9,865)	All participants	–	9,865	87.9	5.7	0.9	5.6
	PPSV23	No	5,618*	87.9	5.9	1.0	5.3
		Yes	4,220*	87.8	5.5	0.8	5.9
	IIV	No	3,317**	88.4	5.1	0.9	5.5
		Yes	6,508**	87.6	6.1	0.9	5.6
Long-term follow-up	All participants	–	6,995	75.2	12.9	3.6	8.3
(n = 6,995)	PPSV23	No	3,966#	76.5	12.8	3.2	7.5
		Yes	3,011#	73.6	13.0	4.0	9.4
	IIV	No	2,079##	78.9	11.1	3.1	6.9
		Yes	4,615##	73.4	13.8	3.8	9.0

PPSV23:23-valent pneumococcal polysaccharide vaccination; IIV: inactivated influenza vaccination; the short-term follow-up: 3.5 years follow-up period; the long-term follow-up: 6 years and 5 months follow-up period; no LTC need: participants who were not certified as requiring LTC; incident dementia: participants who were certified as requiring LTC because of incident dementia; death: participants who lost LTC eligibility due to death; Others: participants who were certified as requiring LTC because of low function for activity in daily living other than the incident dementia or those who lost LTC eligibility due to moving or those who needed care but were not certified as requiring LTC; *, **, #, and ##: sum of participants with or without the PPSV23 or IIV uptake was not equal to the total number of participants because total number of participants in 20 imputed data sets varied due to the imputation and the total number was adjusted to minimum number of the total participants in the 20 imputed data sets.

Table 3
Basic characteristics of participants according to the PPSV23 uptake before and after SIPW in the short-term follow-up (n = 9,865).

		Before SIPW			After SIPW		
	–	Vaccination			Vaccination		
		*Yes	**No	SD	*Yes	**No	SD
Age (years)		73.91	72.29	0.296	73.00	73.06	−0.010
Sex	1: male; 2: female	1.56	1.53	0.066	1.55	1.54	0.012
Number of years of education (years)	1: >6; 2: 6–9; 3: 10–12 4: ≥13; 5: the other	2.80	2.79	0.015	2.78	2.78	0.001
Equivalized income (million yen)	1: <2.00; 2: 2.00 − 3.99;3: ≥4.00	1.62	1.58	0.050	1.60	1.61	−0.015
Marital status	1: married; 2: widowed;3: divorced; 4: never married; 5: other	1.33	1.36	−0.042	1.34	1.34	0.005
Household structure(Living with whom or alone)	1: a spouse; 2: alone; 3: children; 4: a spouse and children; 5: three generations; 6: other	2.76	2.75	0.006	2.77	2.76	0.005
Smoking status	1: currently; 2: quit; 3: never	2.70	2.63	0.110	2.67	2.66	0.006
Alcohol consumption	1: currently; 2: quit3: do not drink	2.24	2.18	0.063	2.21	2.22	0.014
Frequency of medical checkup	1: within 1 year; 2: 1–4 years ago; 3: ≥4 years ago; 4: never	1.61	1.88	−0.246	1.73	1.75	−0.021
Self-rated health	1: excellent; 2: good3: fair; 4: poor	2.03	2.02	0.013	2.03	2.04	−0.013
Frequency of intense physical activity	1: ≥4 times/week 2: 2 − 3 times/week 3: 1 time/week 4: ≤1 − 3 times/month5: A few times/year6: Almost no activity	4.94	5.07	−0.082	5.02	4.99	0.018
Frequency of moderate physical activity	1: ≥4 times/week 2: 2 − 3 times/week 3: 1 time/week 4: ≤1 − 3 times/month5: A few times/year6: Almost no activity	2.86	3.05	−0.098	2.95	2.97	−0.007
Frequency of mild physical activity	1: ≥4 times/week 2: 2 − 3 times/week 3: 1 time/week 4: ≤1 − 3 times/month5: A few times/year6: Almost no activity	2.21	2.41	−0.117	2.30	2.32	−0.012
Body mass index	0: <30 kg/m^2; 1: ≥30 kg/m^2	0.05	0.06	−0.024	0.06	0.06	0.006
Heart disease	0: No; 1: Yes	0.12	0.10	0.068	0.10	0.10	−0.003
Stroke	0: No; 1: Yes	0.03	0.03	0.023	0.03	0.03	0.009
High blood pressure	0: No; 1: Yes	0.49	0.45	0.091	0.47	0.47	0.013
Diabetes	0: No; 1: Yes	0.14	0.13	0.027	0.13	0.13	0.001
Ear diseases	0: No; 1: Yes	0.07	0.07	0.002	0.07	0.07	0.004
Respiratory diseases	0: No; 1: Yes	0.06	0.03	0.121	0.05	0.05	0.004
Geriatric depression	1: not depressed2: depression tendency3: depression	1.28	1.32	−0.080	1.31	1.31	0.013
Frailty	0: non-frail; 1: prefrail; 2: frail	0.55	0.59	−0.047	0.57	0.58	−0.012
Pneumonia history	0: No; 1: Yes	0.02	0.01	0.067	0.02	0.02	0.018
Influenza history	0: No; 1: Yes	0.05	0.04	0.059	0.05	0.05	0.002
PPSV23	0: No; 1: Yes	0.18	0.01	0.582	0.09	0.09	0.021
IIV	0: No; 1: Yes	0.80	0.49	0.705	0.63	0.63	0.002
Social participation	0: No; 1: Yes	0.51	0.44	0.141	0.46	0.47	−0.008
Social cohesion	0: No; 1: Yes	0.89	0.85	0.111	0.88	0.87	0.029
Reciprocity	0: No; 1: Yes	0.99	0.99	0.056	0.99	0.99	0.011

PPSV23:23-valent pneumococcal polysaccharide vaccination; short-term follow-up: 3.5 years follow-up period; SIPW: stabilized inverse probability weighting; SD: standardized difference; * mean of each variable among participants with PPSV23 uptake. **Mean of each variable among participants without the PPSV23 uptake. This table presents the results for 1 of the 20 imputed datasets before and after SIPW.

Fig. 2 shows the competing risk analysis of incident dementia among the participants with PPSV23 or IIV uptake after SIPW during a short-term follow-up period. First, we calculated the HR and 95 % CI for incident dementia in participants with PPSV23 uptake, including those with IIV uptake. In other words, both groups with and without PPSV23 uptake may have received IIV. Uptake of the PPSV23 was negatively associated with incident dementia in participants with all the follow-up days (HR: 0.77; 95 % CI: 0.63–0.95). Sensitivity analysis of participants showed that the uptake of PPSV23 was negatively associated with incident dementia in those with ≤ 1,200 follow-up days and in those with > 1,200 follow-up days (HR: 0.79; 95 % CI; 0.63–0.98 and HR: 0.47; 95 % CI: 0.24–0.94, respectively). Second, we calculated the HR and 95 % CI of incident dementia in participants with PPSV23 uptake, excluding those with IIV uptake, which indicated that both groups with and without PPSV23 uptake did not receive IIV. PPSV23 uptake was negatively associated with the incidence of dementia in patients without IIV uptake during the follow-up (HR: 0.44; 95 % CI: 0.24 – 0.81). Sensitivity analysis showed that PPSV23 uptake was negatively associated with incident dementia in participants without IIV uptake in ≤ 1,200 follow-up days (HR: 0.44; 95 % CI: 0.24 – 0.81). We did not show the HR and 95 % CI of the association between incident dementia and PPSV23 uptake among participants with PPSV23 uptake without IIV uptake with > 1,200 follow-up days because the statistical software calculated extreme values (HR: 1.64E-20; 95 % CI: 7.19E-21-3.74E-20). This was likely due to model instability, and we did not consider these appropriate values. Conversely, we did not observe an association between IIV uptake and incident dementia on any follow-up day (HR: 0.86; 95 % CI: 0.63 – 1.16). Participants with or without IIV uptake may have received PPSV23. Furthermore, we did not observe an association between the IIV uptake and incident dementia in the sensitivity analysis (≤1,200 follow-up days: HR: 0.83; 95 % CI: 0.60 – 1.13 and > 1,200 follow-up days: HR: 0.74; 95 % CI: 0.28 − 1.94). We did not observe an association in participants who did not receive PPSV23, regardless of the follow-up duration (participants in all follow-up days: HR: 0.87; 95 % CI: 0.62 − 1.23, participants in ≤ 1200 follow-up days for the sensitivity analysis: HR: 0.82; 95 % CI: 0.57 − 1.18, and participants in > 1,200 follow-up days for the sensitivity analysis: HR: 0.79; 95 % CI: 0.27 − 2.31). Competitive risk analysis of incident dementia and PPSV23 or IIV uptake without SIPW confirmed that the PPSV23 uptake was negatively associated with incident dementia in participants after control for confounders using SIPW. (Supplementary Fig. 1).

Fig. 3 shows the competing risk analysis of incident dementia with PPSV23 or IIV uptake after SIPW among participants over the long-term follow-up period. PPSV23 uptake was negatively associated with

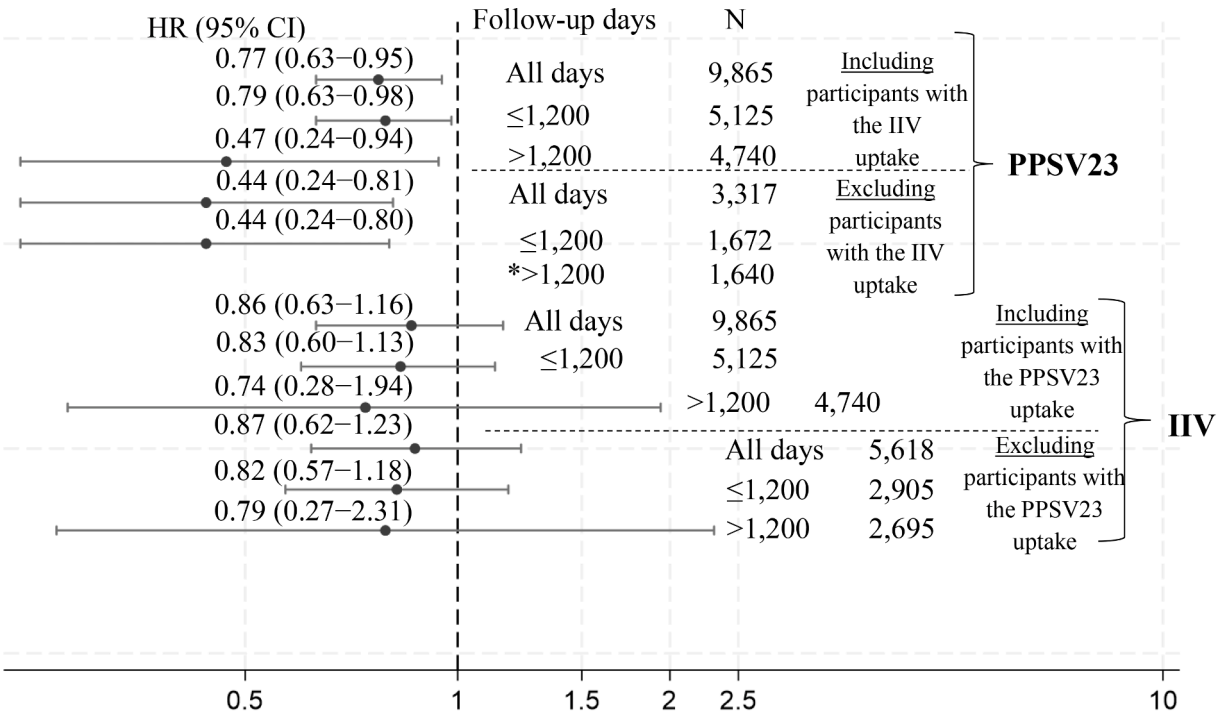

Fig. 2. Competing risk analysis with death as the competing event: the HRs and 95 % confidence intervals of the associations of incident dementia with the PPSV23 or IIV with SIPW among older adults in the short-term follow-up. HR: hazard ratio: 95 % CI: 95 % confidence interval; PPSV23:23-valent pneumococcal polysaccharides vaccination; IIV: inactivated influenza vaccination; SIPW: stabilized inverse proportional weighting; the short-term follow-up: 3.5 years follow-up periods; N: number of the participants; We used the competitive risk model to obtain HRs with SIPW adjusted for the following variables: age, sex, educational years, equalized income, marital status, household structure, smoking status, alcohol consumption, BMI ≥ 30, medical checkup, self-rate health, frequency of intense, moderate, and mild physical activities, heart disease, stroke, high blood pressure, diabetes, ear disease, respiratory disease, frailty, pneumococcal and influenza history, pneumococcal and influenza vaccination status, social participation, social cohesion, and reciprocity. For the sensitivity analysis, we used extended models to obtain separate HRs according to follow-up duration (≤1,200 or > 1,200 days). We did not show the HR and 95 % CI of the association among those with the PPSV23 uptake, but without the IIV uptake with > 1,200 follow-up days (*) because the statistical software calculated extreme values (HR: 4.46E-17, 95 % CI: 6.96E-32 − 0.03) likely due to instability of the model. Therefore, we did not consider the appropriate values. The HR of incident dementia without vaccination was set at 1.00 as the reference.

incident dementia in participants with all follow-up days (HR: 0.83; 95 % CI: 0.70–0.97). Sensitivity analysis revealed that PPSV23 uptake was negatively associated with incident dementia among participants with ≤ 2,200 follow-up days, but not in those with > 2,200 follow-up days (HR: 0.81; 95 % CI: 0.68–0.96 and HR: 0.56; 95 % CI: 0.26–1.19, respectively). PPSV23 uptake was negatively associated with incident dementia in participants without IIV uptake on all follow-up days (HR: 0.47; 95 % CI: 0.29–0.76). Sensitivity analysis revealed that PPSV23 uptake was negatively associated with incident dementia in participants without the IIV uptake in ≤ 2,200 follow-up days, but not in those without IIV uptake in > 2,200 follow-up days (HR: 0.48; 95 % CI: 0.29–0.77 and HR: 0.41; 95 % CI: 0.05–3.17). IIV uptake was not associated with incident dementia in the participants on any follow-up day (HR: 0.99; 95 % CI: 0.76 − 1.29). Sensitivity analysis revealed that IIV uptake was not associated with incident dementia (≤2,200 follow-up days: HR: 0.96; 95 % CI: 0.74 − 1.25 and > 2,200 follow-up days: HR: 1.23; 95 % CI: 0.42 − 3.60). IIV uptake was not associated with incident dementia in participants without the PPSV23 uptake (participants with all follow-up days: HR: 1.00; 95 % CI: 0.74 − 1.35, participants with ≤ 2,200 follow-up days for the sensitivity analysis: HR: 1.01; 95 % CI: 0.75 − 1.36, and participants with > 2,200 follow-up days for the sensitivity analysis: HR: 1.41; 95 % CI: 0.43 − 4.58). Analysis without SIPW confirmed that the negative association between incident dementia and PPSV23 uptake was dependent on SIPW (Supplementary Fig. 2).

4. Discussion

PPSV23 uptake was negatively associated with incident dementia in older Japanese adults aged ≥ 65 years after adjusting for covariates using the SIPW. However, no association was observed between the IIV and dementia incidence.

This study analyzed questionnaire-based health-related data containing social and geriatric factors that are different from medical claims-based data; our results confirmed previously reported findings, namely, that incident dementia has a negative association with routine vaccinations (Lophatananon et al., 2021; Scherrer et al., 2021a; Scherrer et al., 2021b; Wiemken et al., 2021b). Most of the previous studies used medical claims-based data, which included ubiquitous information on dementia-related diagnosis, medication, and high-risk chronic diseases, but provided little information on social and geriatric factors including social relationships and frailty. Years of education, social capital, household composition, and frailty, which have not been adjusted for in previous studies, are potential confounders of the association between vaccinations and dementia. These social and gerontological factors were associated with both vaccination and dementia. (see Methods section) Thus, previous studies cannot exclude potential confounding factors in the association between vaccination and dementia prevention. Previous research has been conducted primarily in the United States, the United Kingdom, and Taiwan, which are economically wealthy countries with high levels of education and government subsidies for vaccination. The potential confounders that have been adjusted for in previous studies are similar and primarily include sex, race, marital status, region of

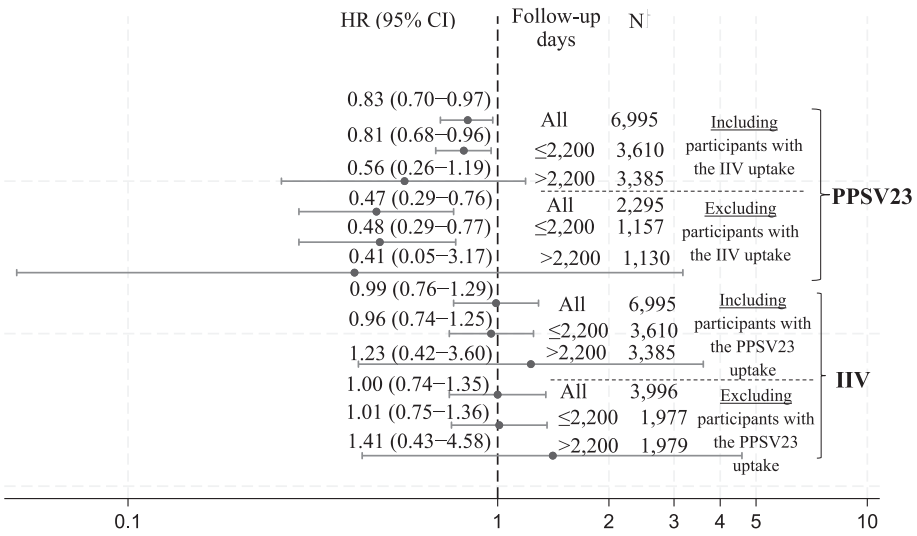

Fig. 3. Competing risk analysis with death as the competing event: the HRs and 95 % confidence intervals of the associations of incident dementia with the PPSV23 or IIV with SIPW among older adults in the long-term follow-up. HR: hazard ratio: 95 % CI: 95 % confidence interval; PPSV23:23-valent pneumococcal polysaccharides vaccination; IIV: inactivated influenza vaccination; SIPW: stabilized inverse proportional weighting; the long-term follow-up: 6 years and 5 months follow-up periods; N: number of the participants; We used the competitive risk model to obtain HRs with SIPW adjusted for the following variables: age, sex, educational years, equalized income, marital status, household structure, smoking status, alcohol consumption, BMI ≥ 30, medical checkup, self-rate health, frequency of intense, moderate, and mild physical activities, heart disease, stroke, high blood pressure, diabetes, ear disease, respiratory disease, frailty, pneumococcal and influenza history, pneumococcal and influenza vaccination status, social participation, social cohesion, and reciprocity. For the sensitivity analysis, we used extended models to obtain separate HRs according to the follow-up duration (≤2,200 or > 2,200 days). The HR of incident dementia without vaccination was set at 1.00 as the reference.

residence, diseases at risk for dementia, and medications associated with dementia. Thus, confounding adjusted social and gerontological factors could have produced similar results. Vaccinators may engage in non-vaccination health-promoting behaviors to prevent dementia; this is called healthy patient bias. However, we showed that PPSV23 uptake, but not IIV uptake, was negatively associated with incident dementia, suggesting that healthy patient bias is unlikely to be a confounder of the negative association between PPSV23 uptake and dementia in this study. Our study validated the findings of previous studies by adjusting for these potential confounding factors, thereby contributing to research on the association between vaccination and dementia prevention.

Certain innate immune mechanisms protect against dementia. For example, microglia are the resident immune cells of the brain that are involved in innate immunity. Microglia, such as beta-amyloid plaques and tau protein aggregates, eliminate neurotoxic proteins implicated in dementia. Recent studies have suggested a link between microbial infections and dementia. The innate immunity plays a role in the detection and elimination of microbial infections in the brain, thereby reducing the risk of infection-related dementia (Chen, 2022). Our results showed that the PPSV23, which contains bacterial polysaccharides that are ligands of toll-like receptors 2 and 4, was negatively associated with incident dementia. Ligands are known to activate the innate immune system through receptor-ligand binding (Sen et al., 2005). Our results showed that IIV, which contains inactivated hemagglutinin proteins of influenza viruses without adjuvants, was not associated with incident dementia. IIV without adjuvants does not activate the innate immune system as efficiently as does IIV with adjuvants (Wimmers et al., 2021). Therefore, ligands or adjuvants that activate innate immunity by binding to pattern recognition receptors, including toll-like receptors, may be necessary for the negative association between incident dementia and routine vaccinations. Further research is required to determine whether activation of innate immunity is necessary for the negative association between incident dementia and routine vaccination.

The observational periods for evaluating the negative associations between vaccinations and incident dementia varied in previous studies (Bukhbinder et al., 2022: 4 years; Wiemken et al., 2021a: 7.5 years; Luo et al., 2020: 11 years; Liu et al., 2016: 7 years.). We showed that a maximum of 5 years and 10 months was sufficient to observe a negative association between incident dementia and PPSV23 uptake as follows: the maximum 5 years and 10 months was the sum of the maximum 2 years and 4 months from October 2014 after the implementation of the national PPSV23 program to January 2017 in the second wave due to balancing with SIPW at baseline plus the short-term follow-up (3.5 years). The negative association between PPSV23 uptake and incident dementia likely depends on the activation of the immune system by PPSV23, as previously suggested (Bukhbinder et al., 2023). Our findings suggest that activation of immunity by PPSV23 over the 5 years and 10 months or shorter preceding dementia onset may be sufficient to prevent dementia. Ochoa-Gondar et al. showed that the effectiveness of PPSV23 in preventing community-associated pneumonia declined in older adults five years after vaccination (Ochoa-Gondar et al., 2014). Therefore, the dementia-preventive effect of PPSV23 may diminish beyond 5 years after vaccination.

Two recent reports observed that PPSV23 uptake was negatively associated with incident dementia in adults ≥ 65 years in the U.S. (Harris et al., 2023; Ukraintseva et al., 2023), consistent with our results. Ukraintseva et al. showed a negative association between PPSV23 uptake and AD, but this association was only observed in subjects with the rs6859 A gene polymorphism (Ukraintseva et al., 2023). The rs6859 polymorphism is located in the nectin cell adhesion molecule 2 (NECTIN2, also known as herpes virus entry mediator B) gene which is involved in the function of adherens junctions that control the permeability of the brain blood–brain barrier and protects the brain from infection. The rs6859 polymorphism is an established genetic risk factor for AD (Yashin et al., 2018). These results suggest that the negative association between PPSV23 uptake and dementia onset in Japanese older adults may be influenced by the genetic background of the subjects. Harris et al. recently reported that both PPSV23 and 13-valent polysaccharide pneumococcal conjugate vaccine (PCV13) were negatively associated with incident AD (Harris et al., 2023). The authors showed that vaccinations for tetanus, diphtheria, pertussis (Tdap), and HZ were negatively associated with incident AD. These results suggest

that the activation of immunity by several types of vaccines against viruses and bacteria may prevent dementia through similar mechanisms. However, the study by Harris et al. did not establish whether pneumococcal vaccination was negatively associated with AD incidence, independent of the uptake of the other two vaccinations (Tdap and HZ). (Harris et al., 2023). In a footnote, the authors mention the possibility that participants with either PPSV23 or PCV13 uptake may have been with either Tdap or HZ vaccination. (Harris et al., 2023) Bukhbinder et al. reported previously that IIV was negatively associated with AD; however, their recent study did not exclude participants with IIV uptake to observe the negative association of AD with the uptake of PPSSV23 or PCV13. (Bukhbinder et al., 2022; Harris et al., 2023).

We observed that IIV uptake was not associated with the incidence of dementia in older Japanese adults. In contrast, previous studies have shown that the IIV is negatively associated with dementia onset in older adults. At least two possible explanations exist for this discrepancy. First, we detected only dementia requiring LTC (grade IIa or higher dementia based on the MHLW manual), whereas other studies would probably have included relatively mild dementia. Thus, the difference in dementia severity between studies may have influenced the results. Second, we investigated the negative association between IIV and dementia in the Japanese population, whereas other studies have investigated this negative association in countries other than Japan, such as the U.K., the U.S., and Taiwan. (Lophatananon et al., 2023; Bukhbinder et al., 2022; Wiemken et. al., 2021; Luo et al., 2020; Liu et al., 2020; Lee et al., 2016) Differences in the genetic backgrounds of the subjects may alter the effect of the vaccination on dementia onset. Future studies in Japan and other countries are required to establish a negative association between the IIV and the onset of dementia.

Consistent with the findings of previous studies, this study showed a negative association between dementia and PPSV23 in older adults. However, all previous studies, including ours, were observational and only investigated the association between vaccination and dementia onset and not their causal relationship because of unobserved confounders (Lee et al., 2021). Randomized controlled trials are necessary to determine whether routine vaccination effectively prevents dementia. Furthermore, a replication of our study and a *meta*-analysis are needed to establish whether there is an association between routine vaccination and incident dementia (Ukraintseva et al., 2023; Harris et al., 2023; Lophatananon et al., 2023; Bukhbinder et al., 2022; Wiemken et al., 2021a,b; Luo et al., 2020; Liu et al., 2020; Lee et al., 2016).

Our study had several limitations. First, the observational nature of the study did not clarify the causality because of unmeasured confounders. However, we adjusted for major confounding variables in individuals with dementia. Second, PPSV23 and IIV were assessed by self-reporting. Participants were asked questions about their vaccination status in the previous year for IIV and over the previous five years for PPSV23; however, there is a possibility that participants may not have remembered receiving vaccinations several years or months before the survey. This potential bias may have affected the relationship between incident dementia, PPSV23, and IIV, although the extent of the impact remains unclear. Baseline differences in cognitive impairment between the vaccinated and control groups were unlikely because we adjusted for frailty, including subjective cognitive complaints associated with dementia at baseline (Tomata et al., 2017). Third, we could not determine whether PPSV23 uptake was a confounder in the negative association of IIV because our study did not replicate the negative association of dementia with IIV uptake. Future studies should confirm whether the uptake of one or more IIV is negatively associated with incident dementia in participants without pneumococcal vaccination or other vaccinations recommended for older adults. Fourth, HZ vaccination, which was negatively associated with incident dementia, may have introduced a bias in the negative association between incident dementia and PPSV23 (Harris et al., 2023; Lophatananon et al., 2021; Scherrer et al., 2021a). However, we estimated that vaccination coverage was minimal during this study because HZ vaccination was a voluntary (optional) vaccination for adults aged $\geq$ 50 years, and is currently not provided as a routine vaccination (Hoshi et al., 2019). Only two municipalities started providing subsidies for HZ vaccination in 2019 when tracking of incident dementia commenced in this study (Japanese National Federation of Insurance Doctors' Association, 2023). However, these two municipalities did not participate in this study. Tdap vaccination is available to older adults voluntarily, although, to date, no municipality provides a subsidy for older residents (Ministry of Health, 2023). Fifth, we conducted imputation under the assumption of MAR. However, missing data may have both MAR and missing not at random (MNAR). With MNAR, there is no conditioning in the observed information that can mitigate the missing bias. Therefore, biases caused by missing due to NMAR may not be handled by the imputation. Finally, there may be concerns regarding multiple testing because several subgroup analyses were conducted. However, the results were consistent across different follow-up durations and vaccination statuses.

5. Conclusion

Previous reports have shown that the IIV, which is recommended for older adults to prevent severe respiratory illnesses, is negatively associated with incident dementia. However, these studies did not adjust for pneumococcal vaccination, which is recommended to prevent severe respiratory illnesses. Our results showed that the uptake of PPSV23, but not the IIV, was negatively associated with incident dementia. PPSV23 uptake was negatively associated with incident dementia in participants during the follow-up period and in those without IIV uptake. In contrast, IIV uptake was not associated with incident dementia, regardless of the follow-up period and the uptake of PPSV23. Our results suggest that pneumococcal vaccination uptake is negatively associated with dementia, whereas IIV uptake is not associated with dementia. This study contributes to the generation of robust evidence in this research field and the verification of negative associations between routine vaccinations and incident dementia using data that are not derived from medical claims. Future studies, including randomized controlled trials, are necessary to clarify the causal relationships and investigate the neuroimmunological mechanisms underlying the negative associations between incident dementia and routine vaccination.

Ethical approval

Informed consent was obtained from all participants. A questionnaire was sent via mail, along with an explanation of the study. Participants read the written explanation of the purpose of the study and either consented to participate in the study or did not. The 2013 JAGES protocol was approved by the ethics committee of the National Center for Geriatrics and Gerontology (approval no. 13–14). The 2016 JAGES protocol was approved by the Ethics Committees of the National Center for Geriatrics and Gerontology (approval number: 992) and Chiba University (approval number: 2493). The 2019 JAGES protocol was approved by the JAGES Committee (approval number, 2019–01), the National Center for Geriatrics and Gerontology (approval number, 1274–2), and the Chiba University Ethics Committee (approval number: 3442). This study was conducted following the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants. The STROBE statement was used to report this observational study.

CRediT authorship contribution statement

Kousuke Iwai-Saito: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Koryu Sato:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Funding acquisition. **Masahiro Fujii:** Writing –

review & editing, Writing – original draft, Validation, Supervision. **Katsunori Kondo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Data availability.

The data are available upon request. The JAGES datasets used in this study are available from the corresponding author upon request. All inquiries were addressed to the data management committee via e-mail: dataadmin.ml@jages.net. All JAGES datasets have ethical or legal restrictions for public deposition owing to the inclusion of sensitive information from human participants. Following the regulations of the local governments that cooperated in the survey, the JAGES Data Management Committee imposed restrictions on the data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.06.020.

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