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Factors related to elevated serum immunoglobulin G4 (IgG4) levels in a Japanese general population

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Abstract

Background Elevated serum immunoglobulin G4 (IgG4) concentrations are one of the characteristic findings in IgG4-related disease (IgG4-RD). This study investigated the frequency of elevated serum IgG4 levels and associated factors in a general Japanese population.

Methods Serum IgG4 concentrations were measured in 1,201 residents of Ishikawa prefecture who underwent general medical examinations. Factors associated with elevated serum IgG4 concentrations were assessed by logistic regression analysis. Participants with elevated serum IgG4 were subjected to secondary examinations.

Results The mean serum IgG4 concentration was 44 mg/dL, with 42 (3.5%) participants having elevated serum IgG4 levels. Age- and sex-adjusted logistic regression analyses showed that male sex, older age, and lower intake of lipids and polyunsaturated fatty acids and higher intake of carbohydrates in daily diet were associated with elevated serum IgG4 concentration. Subgroup analyses in men showed that older age, lower estimated glomerular filtration rates based on serum cystatin C (eGFR-cysC) levels, and higher hemoglobin A1c (HbA1c) levels were associated with elevated serum IgG4 concentration. Analyses in women showed that lower intake of lipids and fatty acids and higher intake of carbohydrates were significantly associated with elevated serum IgG4 concentration. One of the 15 participants who underwent secondary examinations was diagnosed with possible IgG4-related retroperitoneal fibrosis.

Conclusions Elevated serum IgG4 levels in a Japanese general population were significantly associated with older age, male gender, and dietary intake of nutrients, with some of these factors identical to the epidemiological features of IgG4-RD.

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Keywords IgG4-related disease, Resident examinations, Serum IgG4 levels

Background

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is characterized primarily by elevated serum IgG4 levels, relatively latent onset and progression with few symptoms, and swelling of organs and/or nodular lesions, as detected clinically and/or radiologically [1, 2]. Pathologic features common to affected organs include dense lymphoplasmacytic infiltration by abundant numbers IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis [1, 2]. None of these clinical, serological, radiological, or pathological features alone, however, is sufficient for a definitive diagnosis of IgG4-RD, with combinations of all four categories required for diagnostic confirmation [3].

Serum IgG4 levels contribute to the diagnosis of IgG4-RD, although their sensitivity and specificity remain unestablished. The Japanese comprehensive diagnostic criteria for IgG4-RD [4], organ-specific diagnostic criteria [5–12], and the 2019 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for IgG4-RD [13] regard serum IgG4 levels as an important criterion, with studies in Japan, China, the United States, and Europe reporting elevated serum IgG4 levels in 55–97% of patients with IgG4-RD [14–16]. Elevated serum IgG4 levels, however, have been observed in patients with other diseases, such as eosinophilic granulomatosis with polyangiitis (EGPA) and multicentric Castleman's disease. Serum IgG4 levels alone were reported to have a diagnostic specificity for IgG4-RD of 60–93% [17, 18]. One study reported serum IgG4 concentrations > 130 mg/dL in 80 (6.4%) of 1,258 patients, with nine (14.7%) of the 61 patients who underwent further examination diagnosed with for IgG4-RD [19]. Another study found that serum IgG4 levels > 140 mg/dL were present in 390 (6.5%) of 6,014 patients, with 39 (10%) patients having elevated IgG4 being diagnosed with IgG4-RD [20]. These results suggested that 10–15% of patients with elevated serum IgG4 levels had IgG4-RD.

Few studies to date have assessed the prevalence of elevated serum IgG4 levels and/or IgG4-RD in asymptomatic adults. A Spanish study in 413 adults found that five (1.2%) had serum IgG4 levels > 135 mg/dL, but none was diagnosed with IgG4-RD based on the tracking on the database [21]. That study, however, did not report whether those participants had undergone close examination for IgG4-RD, making the true absence of IgG4-RD unclear. Because a considerable proportion of patients with IgG4-RD are asymptomatic, there is a need to assess the prevalence of IgG4-RD in general populations, such as people undergoing general health examinations, not only in patients visiting a medical institution [19, 20]. Analyses of general populations may provide information on the epidemiology of elevated serum IgG4 levels and IgG4-RD.

Although the epidemiology of IgG4-RD remains unclear, several environmental factors and comorbidities have been implicated in its pathogenesis. Patients with IgG4-RD have been reported to be at high risk of malignancy [22–24], suggesting that IgG4-RD has aspects of paraneoplastic syndrome, similar to dermatomyositis [25]. Allergic predispositions, including elevated serum IgE, eosinophilia, and complications of bronchial asthma and/or allergic rhinitis, are frequently observed in IgG4-RD [15, 26, 27]. In addition, serum IgG4 molecules from patients with IgG4-RD have been found to react with various antigens in, for example, rice, wheat, milk, peanuts, cats, and bananas [28], suggesting associations between IgG4-RD and allergic reactions. Moreover, a recent case-control study demonstrating a significant association between smoking and IgG4-RD [29] indicated that lifestyle habits could affect the pathogenesis of IgG4-RD. These environmental factors and comorbidities may also be associated with the enhanced production of IgG4 and/or the onset of IgG4-RD in participants undergoing general health examinations. The present study assessed the frequency of elevated serum IgG4 levels and the prevalence of latent IgG4-RD in Japanese adults undergoing general health examinations by measuring serum IgG4 concentrations and by secondary examination for IgG4-RD in those with elevated IgG4.

Methods

Patients and materials

The present study included adults who underwent annual general health examinations in Noto district, Ishikawa Prefecture, Japan, between January 1, 2013, and March 31, 2019. Of 1336 consecutive participants, blood samples were collected from 1,201 (90%) for measurement of their serum IgG4 concentrations, which were measured with the nephelometry immunoassay (NIA)-based IgG subclass BS-NIA IgG4 kit (Binding Site, Birmingham, United Kingdom). Participants were asked about their daily diet and history of cancer, allergies, atherosclerotic diseases, alcohol consumption, and smoking. Subject age at the time of examination and sex were recorded; height and body weight were measured; and body mass index (BMI) was calculated. Systolic and diastolic blood pressure (BP) were measured, as were serum concentrations of IgG, IgE, CH50, C-reactive protein (CRP), creatinine, cystatin-C, uric acid, liver enzymes, total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C),

high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Also measured were hemoglobin A1c (HbA1c) levels, peripheral blood counts, and the presence or absence of anti-nuclear antibody (ANA) and rheumatoid factor (RF). Participants with serum IgG4 concentrations ≥ 135 mg/dL were more closely examined for IgG4-RD, with IgG4-RD diagnosed by experts based on Japanese and 2019 ACR/EULAR criteria. Specifically, detailed medical history taking, evaluation of physical findings, and whole-body dynamic CT were performed in all participants with serum IgG4 concentrations ≥ 135 mg/dL who underwent secondary examination.

Allergic diseases included bronchial asthma, allergic rhinitis, atopic dermatitis, and food allergies, and atherosclerotic disease included cerebrovascular and ischemic heart diseases. Estimated glomerular filtration rate (eGFR) based on serum creatinine level (eGFR-creatinine) was calculated using a three-variable Japanese equation [30], whereas eGFR based on serum cystatin-C level (eGFR-cystatin-C) was calculated using a Japanese equation formulate by the Japanese Society of Nephrology [31].

Nutritional status, including the intake of proteins, lipids, carbohydrates, polyunsaturated fatty acids, and saturated fatty acids, was assessed using the brief-type self-administered diet history questionnaire (BDHQ) [32]. The relative amount of each nutrient consumed daily as a percentage of daily energy intake was calculated using the density method [33].

The upper limit of normal (ULN) of serum IgG4 levels in the present study was set at 135 mg/dL because this threshold has been found suitable for the diagnosis of IgG4-RD in Japanese [4–12].

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) and compared using Mann-Whitney U tests. Categorical variables are reported as number (percentage) and compared using the χ^2 test or Fisher's exact probability test, as appropriate. Factors associated with elevated serum IgG4 levels and factors associated with the diagnosis of IgG4-RD were each assessed by unadjusted and age- and sex-adjusted logistic regression analysis. Based on the principle of one variable for every 10 outcomes [34], a multivariate model for elevated serum IgG4 levels could be built within four variables because the 1,201 participants included 42 with elevated serum IgG4 levels. Sub-analyses included identical logistic regression analyses in men and in women. In these logistic regression analyses, the units for increments of continuous variables to calculate odds ratios were set at 1 year for age; 1 kg/m^2 for BMI; 1 mmHg for BP; 1% for fraction of peripheral blood eosinophils, HbA1c levels, and intake of proteins, lipids, carbohydrates, polyunsaturated fatty acids, and saturated fatty acids; 100 IU/mL for serum IgE levels; 1 U/mL for serum CH50 levels; 1 mg/dL for serum CRP, cholesterol, TG, and uric acid levels; and 1 mL/min/1.73m^2 for eGFR. In the logistic regression analysis of each variable, patients with defective data were excluded. All statistical analyses were performed using SPSS V.25 (IBM Corp., Armonk, NY, USA), with $P<0.05$ defined as statistically significant.

Results

Participant profiles

The profiles of the 1,201 participants are listed in Table 1. Their mean age was 62 ± 11 years, 46.5% were male, and their mean BMI was 23.3 ± 3.3 kg/m2. These participants had a mean systolic BP of 138 ± 19 mmHg, a mean diastolic BP of 80 ± 12 mmHg, a mean total-C concentration of 214 ± 36 mg/dL, a mean LDL-C of 130 ± 35 mg/dL, a mean HDL-C of 65 ± 17 mg/dL, a mean TG of 117 ± 81 mg/dL, a mean HbA1c of 5.9 ± 0.6%, and a mean uric acid concentration of 5.1 ± 1.4 mg/dL. Evaluation of renal function showed a mean serum creatinine level of 0.79 ± 0.46 mg/dL, a mean eGFR-creatinine of 71.2 ± 14.2 mL/min/1.73m^2, a mean serum cystatin-C level of 0.91 ± 0.41 mg/dL, and a mean eGFR-cystatin-C of 83.1 ± 19.4 mL/min/1.73m^2. Their mean serum IgG4 level was 44 ± 36 mg/dL, with 42 (3.5%) of the 1,201 participants having serum IgG4 levels > 135 mg/dL (Fig. 1). Their mean serum IgG, IgE, and CH50 levels were 1,319 ± 273 mg/dL, 225 ± 593 IU/mL, and 38 ± 9 U/mL, respectively, with 7.4% and 8.6% being positive for ANA and RF, respectively. Mean intake of proteins, lipids, carbohydrates, polyunsaturated fatty acids, and saturated fatty acids was 15.2 ± 3.2%, 24.7 ± 6.1%, 54.0 ± 8.7%, 6.1 ± 1.5%, and 6.5 ± 2.0%, respectively.

Characteristics of the participants with elevated serum IgG4 levels

Compared with the participants having normal serum IgG4 levels, those with elevated serum IgG4 levels were significantly older (65.8 ± 10.5 vs. 61.9 ± 11.2 years, $P=0.026$), had a greater male predominance (69% vs. 46%, $P=0.004$), and had significantly lower serum HDL-C levels (58.7 ± 12.7 vs. 65.6 ± 17.3 mg/dL, $P=0.018$), and significantly higher serum IgG (1,564 ± 349 vs. 1,310 ± 266 mg/dL, $P<0.001$), IgE (366 ± 439 vs. 219 ± 598 IU/mL, $P<0.001$), and cystatin-C (0.99 ± 0.24 vs. 0.91 ± 0.41 mg/dL, $P=0.015$) concentrations. Participants with elevated IgG4 also had significantly lower eGFR-cystatin-C levels (75.6 ± 20.1 vs. 83.3 ± 19.3 mL/min/1.73m^2, $P=0.045$) and lower intake of lipids (21.8 ± 5.9% vs. 24.9 ± 6.1%, $P=0.007$), polyunsaturated fatty acids (5.4 ± 1.4% vs. 6.2 ± 1.5%, $P=0.011$), and saturated fatty acids (5.8 ± 2.0% vs. 6.6 ± 2.0%, $P=0.044$). The

Table 1 Baseline clinical characteristics of 1,201 participants with/without elevated serum IgG4 level

	All ($n=1,201$)	IgG4 elevation (+) ($n=42$)	IgG4 elevation (-) ($n=1,159$)	*P*-values
Age (years)	62 ± 11	66 ± 11 [b]	62 ± 11	0.026
Gender (male, %)	46	69 [b]	46	0.004
BMI (kg/m^2)	23.3 ± 3.3	23.4 ± 3.4	23.3 ± 3.3	0.771
Systolic BP (mmHg)	138 ± 19	135 ± 20	138 ± 19	0.569
Diastolic BP (mmHg)	80 ± 12	78 ± 11	80 ± 12	0.187
Smoking history (+, %)	46	60	46	0.085
Allergic disease (+, %)	13	18	13	0.248
History of Malignancy (+, %)	7	6	7	0.999
Fraction of Eosinophil (%)	2.7 ± 2.1	3.0 ± 2.4	2.7 ± 2.0	0.539
Serum IgE level (IU/mL)	225 ± 593 ($n=1,001$)	366 ± 439 [b] ($n=39$)	219 ± 598 ($n=962$)	< 0.001
Serum IgG level (mg/dL)	1,319 ± 273 ($n=1,136$)	1,564 ± 349 [b] ($n=40$)	1,310 ± 266 ($n=1,096$)	< 0.001
Serum IgG4 level (mg/dL)	44 ± 36	172 ± 39 [b]	40 ± 26	< 0.001
Serum CH50 level (U/mL)	38 ± 9 ($n=1,126$)	38 ± 8 ($n=40$)	38 ± 9 ($n=1,086$)	0.984
Serum CRP level (mg/dL)	0.12 ± 0.45	0.16 ± 0.32	0.12 ± 0.45	0.248
ANA positivity (+, %)	7.4 ($n=975$)	15.2 ($n=33$)	7.1 ($n=942$)	0.089
RF positivity (+, %)	8.6 ($n=975$)	15.2 ($n=33$)	8.4 ($n=942$)	0.196
Serum creatinine level (mg/dL)[a]	0.79 ± 0.46	0.82 ± 0.27	0.79 ± 0.47	0.849
eGFR-creatinine (mL/min/1.73m^2)	71 ± 14	71 ± 16	71 ± 14	0.924
Serum cystatin-C level (mg/dL)	0.91 ± 0.41 ($n=1,057$)	0.99 ± 0.24 [b] ($n=35$)	0.91 ± 0.41 ($n=1,022$)	0.015
eGFR-cystatin-C (mL/min/1.73m^2)	83 ± 19 ($n=1,057$)	76 ± 20 [b] ($n=35$)	83 ± 19 ($n=1,022$)	0.045
Serum LDL-cholesterol level (mg/dL)	130 ± 35	132 ± 32	130 ± 36	0.736
Serum HDL-cholesterol level (mg/dL)	65 ± 17	59 ± 13 [b]	66 ± 17	0.018
Serum triglyceride level (mg/dL)	117 ± 81	140 ± 189	116 ± 74	0.348
Serum uric acid level (mg/dL)	5.1 ± 1.4	5.4 ± 1.5	5.1 ± 1.4	0.135
HbA1c level (%)	5.9 ± 0.6	6.2 ± 1.0	5.9 ± 0.6	0.176
Protein intake (%)	15.2 ± 3.2 ($n=938$)	14.2 ± 3.1 ($n=36$)	15.2 ± 3.2 ($n=902$)	0.116
Lipid intake (%)	24.7 ± 6.1 ($n=938$)	21.8 ± 5.9 [b] ($n=36$)	24.9 ± 6.1 ($n=902$)	0.007
Carbohydrate intake (%)	54.0 ± 8.7 ($n=938$)	57.1 ± 9.1 ($n=36$)	53.9 ± 8.7 ($n=902$)	0.085
Polyunsaturated fatty acids intake (%)	6.1 ± 1.5 ($n=938$)	5.4 ± 1.4[b] ($n=36$)	6.2 ± 1.5 ($n=902$)	0.011
Saturated fatty acids intake (%)	6.5 ± 2.0 ($n=938$)	5.8 ± 2.0[b] ($n=36$)	6.6 ± 2.0 ($n=902$)	0.044

Notes [a] Conversion factor for creatinine: mg/dL to μmol/L, ×88.4; [b] $P<0.05$, IgG4 elevation (+) vs. (-). ANA positivity is defined as ANA titer ≥ ×80. RF positivity is defined as RF titer ≥ 15 IU/mL

Abbreviations ANA: anti-nuclear antibody; BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; IgG: immunoglobulin G; IgG4: immunoglobulin G4; IgE: immunoglobulin E; LDL: low-density lipoprotein; RF: rheumatoid factor

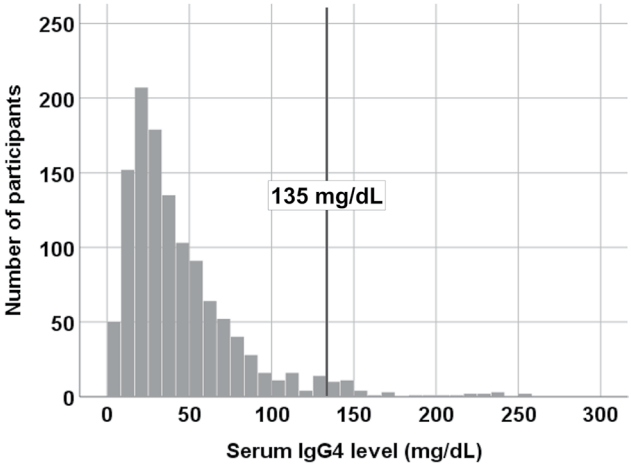

Fig. 1 Histogram of serum IgG4 levels in health examination participants. Elevated serum IgG4 levels were observed in 42 patients (3.5%)

prevalence of smoking history, which has been associated with IgG4-RD [29], tended to be higher in participants with elevated than with normal serum IgG4 levels (60% vs. 46%, $P=0.085$). Other variables, including BMI, BP, HbA1c levels, fraction of peripheral blood eosinophils, and prevalence of cancer, allergic diseases, and atherosclerotic diseases, did not differ in participants with and without elevated serum IgG4 levels (Table 1).

Demographic, laboratory, and nutritional factors significantly associated with elevated serum IgG4 levels

Unadjusted logistic regression analyses showed that male sex [odds ratio (OR) 2.666, 95% confidence interval (CI) 1.372–5.180], older age (OR 1.032, 95% CI 1.003–1.062), lower eGFR-cystatin-C (OR 0.980, 95% CI 0.964–0.997), lower serum HDL-C levels (OR 0.973, 95% CI 0.953–0.994), and higher HbA1c levels (OR 1.513, 95% CI 1.107–2.068) were associated with elevated serum IgG4.

Assessment of nutritional factors showed that greater carbohydrate intake (OR 1.044, 95% CI 1.003–1.086) and lower intake of proteins (OR 0.893, 95% CI 0.798-1.000), lipids (OR 0.919, 95% CI 0.869–0.972), polyunsaturated fatty acids (OR 0.713, 95% CI 0.564–0.901), and saturated fatty acids (OR 0.818, 95% CI 0.683–0.981) was associated with elevated serum IgG4. Following age- and sex-adjusted analyses, male sex (OR 2.683, 95% CI 1.379–5.220), older age (OR 1.033, 95% CI 1.004–1.063), greater intake of carbohydrates (OR 1.043, 95% CI 1.002–1.085), and lower intake of lipids (OR 0.937, 95% CI 0.884–0.994) and polyunsaturated fatty acids (OR 0.769, 95% CI 0.606–0.978) remained significant, whereas the other five factors did not (Table 2).

Subgroup analyses in men showed that older age (OR 1.046, 95% CI 1.009–1.084), lower eGFR-cystatin-C levels (OR 0.981, 95% CI 0.963-1.000), and higher HbA1c levels (OR 1.519, 95% CI 1.077–2.143) were significantly associated with elevated serum IgG4. In contrast, analyses in women found that only nutritional factors, including greater carbohydrate intake (OR 1.116, 95% CI 1.040–1.197) and lower intake of lipids (OR 0.876, 95% CI 0.794–0.966), polyunsaturated fatty acids (OR 0.639, 95% CI 0.419–0.973), and saturated fatty acids (OR 0.718, 95% CI 0.521–0.989), were significantly associated with elevated IgG4 (Table 3).

In addition, we conducted a sub-analysis excluding one case of IgG4-RD. Unadjusted logistic regression analyses showed that male sex (OR 2.574, 95% CI 1.320–5.020), older age (OR 1.030, 95% CI 1.001–1.060), lower eGFR-cystatin-C (OR 0.980, 95% CI 0.964–0.997), lower serum HDL-C levels (OR 0.975, 95% CI 0.955–0.996), and higher HbA1c levels (OR 1.526, 95% CI 1.116–2.086) were associated with elevated serum IgG4. Assessment of nutritional factors showed that lower intake of lipids (OR 0.924, 95% CI 0.874–0.978), polyunsaturated fatty acids (OR 0.731, 95% CI 0.577–0.926), and saturated fatty acids (OR 0.833, 95% CI 0.693-1.000) was associated with elevated serum IgG4. Following age- and sex-adjusted analyses, male sex (OR 2.590, 95% CI 1.326–5.056), older age (OR 1.031, 95% CI 1.001–1.061), and lower intake of lipids (OR 0.942, 95% CI 0.888–0.999) remained significant, whereas the other five factors did not (Table S1). Subgroup analyses in men showed that older age (OR 1.043, 95% CI 1.006–1.081), lower eGFR-cystatin-C levels (OR 0.981, 95% CI 0.963-1.000), and higher HbA1c levels (OR 1.540, 95% CI 1.090–2.174) were significantly associated with elevated serum IgG4. Analyses in women was the same as those in Table 3 (Table S2).

Diagnosis of IgG4-RD in participants with elevated serum IgG4 levels

Fifteen participants with elevated serum IgG4 agreed to undergo secondary examinations for IgG4-RD (Table 4). Their mean age was 67.9±9.0 years (range 56–93 years). One subject had chronic kidney disease with hydronephrosis and a retroperitoneal lesion (periaortitis/periarteritis) and was diagnosed with possible IgG4-RD based on the 2020 revised Japanese comprehensive diagnostic criteria. According to the 2019 ACR/EULAR classification criteria for IgG4-RD, this participant had an inclusion score of 8 points, but did not meet the threshold for inclusion due to involvement of a single organ and lack of biopsy of the affected organ. This subject was a male in his 70s with a serum IgG4 concentration of 254 mg/dL. His previous medical history included hypertension, renal insufficiency, and right hydronephrosis. Laboratory findings included serum creatinine 2.04 mg/dL; eGFR-creatinine 25.7 mL/min/1.73m^2; serum IgG 2,419 mg/dL, serum IgE 464 IU/mL, serum CH50 43 U/mL, and urinary β2-microglobulin 1033 μg/L. Contrast-enhanced computed tomography (CT) showed periaortic/periarterial wall thickening of the abdominal aorta and its major branch and right hydroureteronephrosis (Fig. 2) but involvement of no other organs, such as the salivary and lacrimal glands, pancreas, bile duct, and kidneys.

Discussion

The present study, which included a large number of participants undergoing general health examinations, analyzed the prevalence of elevated serum IgG4 levels in a Japanese general adult population. Of the 1,201 participants analyzed, 42 (3.5%) had serum IgG4 concentrations>135 mg/dL, a higher percentage than the 1.2% reported in a study from Spain [21]. In addition, the present study found that male gender, older age, renal dysfunction, metabolic disturbance, and nutrition intake status were associated with elevated serum IgG4 levels. In men, older age, renal dysfunction, and glucose intolerance were associated with elevated serum IgG4, whereas, in women, nutrition intake status was associated with elevated serum IgG4, suggesting that factors associated with elevated serum IgG4 differed by gender. Moreover, one of the 15 symptom-free participants with elevated serum IgG4 who underwent a more comprehensive examination was found to have clinical features of IgG4-RD. These results suggested that, in addition to allergic diseases and IgG4-RD, other factors are associated with elevated serum IgG4, including age, gender, metabolism, and nutrition and may partly explain the reasons that elevated serum IgG4 is not always specific for the diagnosis of IgG4-RD. Some of the epidemiological factors frequently associated with IgG4-RD, such as older age and male gender, were observed in the study participants with elevated serum IgG4, whereas others, such as malignancies, were not. Additional studies are needed to determine whether and how these factors are related to the pathogenesis of IgG4-RD.

Table 2 Odds ratios for elevated serum IgG4 levels in the 1,201 participants

Variable	Unadjusted		Age- and sex-adjusted	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.032 (1.003 to 1.062)	0.028	1.033 (1.004 to 1.063)	0.027
Male gender	2.666 (1.372 to 5.180)	0.004	2.683 (1.379 to 5.220)	0.004
BMI (kg/m^2)	1.011 (0.921 to 1.110)	0.814		
Systolic BP (mmHg)	0.993 (0.976 to 1.010)	0.399		
Diastolic BP (mmHg)	0.983 (0.956 to 1.010)	0.223		
Smoking history	1.742 (0.931 to 3.261)	0.083		
Allergic disease	1.483 (0.601 to 3.661)	0.393		
History of Malignancy	0.777 (0.182 to 3.316)	0.734		
Fraction of Eosinophil (%)	1.067 (0.943 to 1.207)	0.304		
Serum IgE level (per100 IU/mL)	1.021 (0.991 to 1.051)	0.171		
Serum CH50 level (U/mL)	0.999 (0.965 to 1.033)	0.940		
Serum CRP level (mg/dL)	1.149 (0.732 to 1.803)	0.546		
ANA	2.332 (0.872 to 6.235)	0.092		
RF	1.951 (0.733 to 5.193)	0.181		
eGFR-creatinine ($mL/min/1.73m^2$)	0.999 (0.977 to 1.021)	0.902		
eGFR-cystatin-C ($mL/min/1.73m^2$)	0.980 (0.964 to 0.997)	0.019	0.986 (0.965 to 1.007)	0.191
LDL-cholesterol (mg/dL)	1.002 (0.988 to 1.016)	0.802		
HDL-cholesterol (mg/dL)	0.973 (0.953 to 0.994)	0.012	0.982 (0.961 to 1.003)	0.100
Triglyceride (mg/dL)	1.002 (1.000 to 1.005)	0.079		
Uric acid (mg/dL)	1.189 (0.961 to 1.471)	0.111		
HbA1c (%)	1.513 (1.107 to 2.068)	0.009	1.370 (0.980 to 1.916)	0.065
Protein intake (%)	0.893 (0.798 to 1.000)	0.049	0.898 (0.801 to 1.007)	0.066
Lipid intake (%)	0.919 (0.869 to 0.972)	0.003	0.937 (0.884 to 0.994)	0.030
Carbohydrate intake (%)	1.044 (1.003 to 1.086)	0.033	1.043 (1.002 to 1.085)	0.040
Polyunsaturated fatty acids intake (%)	0.713 (0.564 to 0.901)	0.005	0.769 (0.606 to 0.978)	0.032
Saturated fatty acids intake (%)	0.818 (0.683 to 0.981)	0.030	0.875 (0.724 to 1.057)	0.166

Abbreviations ANA: anti-nuclear antibody; BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; IgG: immunoglobulin G; IgG4: immunoglobulin G4; IgE: immunoglobulin E; LDL: low-density lipoprotein; RF: rheumatoid factor

Table 3 Odds ratios for elevated serum IgG4 levels in the male and female participants

Variable	Male ($n=557$)		Female ($n=644$)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (years)	1.046 (1.009 to 1.084)	0.014	1.008 (0.960 to 1.058)	0.745
BMI (kg/m^2)	0.974 (0.861 to 1.103)	0.683	0.986 (0.830 to 1.172)	0.875
Systolic BP (mmHg)	0.989 (0.968 to 1.011)	0.322	0.983 (0.952 to 1.016)	0.313
Diastolic BP (mmHg)	0.969 (0.939 to 1.001)	0.060	0.987 (0.936 to 1.042)	0.641
Smoking history	0.830 (0.329 to 2.095)	0.694	1.001 (0.218 to 4.586)	0.999
Allergic disease	2.174 (0.770 to 6.134)	0.142	0.624 (0.079 to 4.957)	0.656
History of Malignancy	0.514 (0.067 to 3.933)	0.521	1.348 (0.167 to 10.857)	0.779
Fraction of Eosinophil (%)	1.030 (0.888 to 1.195)	0.698	1.073 (0.813 to 1.418)	0.617
Serum IgE level (per100 IU/mL)	1.016 (0.985 to 1.049)	0.318	1.016 (0.893 to 1.156)	0.810
Serum CH50 level (U/mL)	1.028 (0.988 to 1.073)	0.205	0.953 (0.899 to 1.010)	0.107
Serum CRP level (mg/dL)	0.960 (0.457 to 2.018)	0.914	1.674 (0.789 to 3.553)	0.180
ANA	4.894 (1.507 to 15.895)	0.008	0.882 (0.111 to 6.983)	0.905
RF	2.339 (0.651 to 8.404)	0.193	1.812 (0.386 to 8.503)	0.451
eGFR-creatinine (mL/min/1.73m^2)	0.998 (0.973 to 1.024)	0.882	1.010 (0.971 to 1.050)	0.618
eGFR-cystatin-C (mL/min/1.73m^2)	0.981 (0.963 to 1.000)	0.048	0.985 (0.952 to 1.018)	0.365
LDL-cholesterol (mg/dL)	1.012 (0.992 to 1.032)	0.239	0.992 (0.957 to 1.027)	0.642
HDL-cholesterol (mg/dL)	0.979 (0.952 to 1.006)	0.127	0.981 (0.947 to 1.015)	0.269
Triglyceride (mg/dL)	1.002 (1.000 to 1.004)	0.101	0.991 (0.978 to 1.005)	0.219
Uric acid (mg/dL)	1.032 (0.781 to 1.364)	0.823	0.912 (0.526 to 1.580)	0.742
HbA1c (%)	1.519 (1.077 to 2.143)	0.017	1.008 (0.367 to 2.771)	0.987
Protein intake (%)	0.954 (0.828 to 1.099)	0.515	0.856 (0.702 to 1.044)	0.124
Lipid intake (%)	0.963 (0.897 to 1.035)	0.306	0.876 (0.794 to 0.966)	0.008
Carbohydrate intake (%)	1.018 (0.972 to 1.067)	0.451	1.116 (1.040 to 1.197)	0.002
Polyunsaturated fatty acids intake (%)	0.816 (0.609 to 1.092)	0.171	0.639 (0.419 to 0.973)	0.037
Saturated fatty acids intake (%)	0.955 (0.756 to 1.205)	0.695	0.718 (0.521 to 0.989)	0.043

Abbreviations ANA: anti-nuclear antibody; BMI: body mass index; BP: blood pressure; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; IgG: immunoglobulin G; IgG4: immunoglobulin G4; IgE: immunoglobulin E; LDL: low-density lipoprotein; RF: rheumatoid factor

. Characteristics and results of secondary examination in the 15 participants with elevated serum IgG4 levels

	Gender	IgG (mg/dL)	IgG4 (mg/dL)	IgE (IU/mL)	Hypocomple-mentemia	Cre-atinine (mg/dL)	ANA	RF (IU/mL)	IGRA for TB infection	Imaging findings on CT
1	Male	1,207	137	429	-	0.92	NA	-	NA	No significant finding
2	Female	1,517	140	7.9	-	0.56	NA	5	-	No significant finding
3	Male	1,150	142	674	-	0.79	NA	-	NA	No significant finding
4	Male	1,699	142	431	-	1.13	NA	5	-	No significant finding
5	Male	1,654	151	NA	-	0.63	NA	NA	-	Inflammatory scarring in the middle lobe and tongue area of the lung
6	Female	1,774	154	144	-	0.71	×40	NA	NA	No significant finding
7	Female	1,520	156	70	-	0.91	NA	NA	-	No significant finding
8	Male	1,531	197	1,460	-	0.92	NA	4	+	No significant finding
9	Female	1,612	205	95	-	0.60	NA	4	NA	No significant finding
10	Male	2,292	206	1,410	-	0.80	NA	37	-	No significant finding
11	Male	1,270	211	29	+	0.89	NA	NA	NA	No significant finding
12	Male	892	217	NA	-	0.79	NA	5	NA	No significant finding
13	Female	1,631	231	19	-	0.69	NA	NA	NA	No significant finding
14	Male	1,464	236	412	-	0.53	NA	NA	NA	No significant finding
15	Male	2,419	254	465	-	2.04	×40	14	NA	Hydronephrosis and retroperitoneal lesion (periaortitis/periarteritis)

Note Hypocomplementemia is defined as serum CH50 levels less than reference range (32–47 U/mL)

Abbreviations ANA: anti-nuclear antibody; IgG: immunoglobulin G; IgG4: immunoglobulin G4; IgE: immunoglobulin E; IGRA: interferon-gamma release assays; NA: not available; RF: rheumatoid factor; TB: tuberculosis

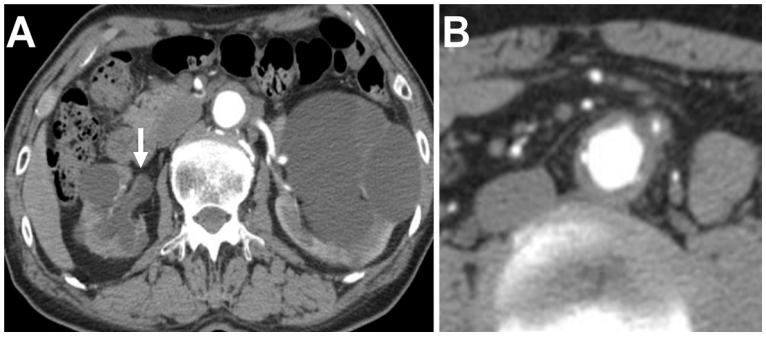

Fig. 2 Hydronephrosis and periaortic/periarterial lesion in one participant with elevated serum IgG4 level. Contrast-enhanced computed tomography (CT) imaging showed right hydroureteronephrosis (**A**, arrow) and periaortic/periarterial wall thickening of the abdominal aorta and its major branch (**B**)

Our findings, that male gender and older age were significantly associated with elevated serum IgG4, were in agreement with findings in a Spanish population [21]. Interestingly, these factors are also associated with IgG4-RD, indicating that elevated serum IgG4 levels and the pathogenesis of IgG4-RD have common features. Metabolic syndrome-related factors, such as low serum HDL-C levels and higher HbA1c concentrations, also tended to be associated with elevated serum IgG4. One unique aspect of the present study was the determination of nutrition intake based on the BDHQ, with results suggesting that elevated serum IgG4 levels were associated with factors such as higher carbohydrate intake and lower intake of lipids and fatty acids. Because few participants in this study developed IgG4-RD, the association between nutrition intake and the development of IgG4-RD remains to be clarified.

Interestingly, the factors associated with elevated serum IgG4 differed by gender. In men, age, HbA1c, and renal function were associated with elevated serum IgG4, whereas nutrition intake was not. In women, however, nutrition intake was associated with elevated serum IgG4. This difference may have been due to the influence of sex hormones, but their concentrations were not evaluated in the present study. Moreover, this study included many elderly participants, in whom sex hormones were likely less influential. Further studies are needed to analyze the influence of sex hormones and other factors on the differences between genders.

Although the mechanisms linking dietary intake and elevated IgG4 levels have not been fully elucidated, a hypothesis worth considering is that the intestinal microbiota may mediate this relationship. In humans, a low intake of saturated fatty acids, independent of fiber intake, has been reported to result in increased diversity of intestinal microorganisms [35], suggesting a relationship between dietary intake and the state of intestinal microorganisms. On the other hand, Karashima et al. investigated the relationship between the intestinal flora and serum IgG4 levels in participants undergoing general health examinations and found that the bacteria associated with elevated serum IgG4 levels differed between men and women [36]. This may partially explain the results of the present study, where the impact of dietary intake on serum IgG4 levels varied by sex. Furthermore, changes in the composition of the intestinal flora (characterized by a decrease in beneficial bacteria and an increase in potentially pathogenic bacterial species) have been reported in individuals with IgG4-RD [37]. In a mouse model, autoimmune pancreatitis-like lesions developed in response to the induction of innate immune responses against the intestinal flora [38]. These findings suggest that both the intestinal flora and the intake of certain nutrients that can influence the flora may be involved in the elevation of serum IgG4 levels and potentially in the development of IgG4-RD.

Factors reported to be associated with IgG4-RD were not associated with elevated serum IgG4 levels in these participants. For example, a study from Taiwan reported that 13 (41.9%) of the 31 non-IgG4-RD participants with allergic disease had serum IgG4 concentrations > 135 mg/dL [39], and a Japanese study found that one (14.3%) of seven patients with bronchial asthma, but none of the healthy controls, had a serum IgG4 level > 144 mg/dL [40]. In the present study, however, the prevalence of elevated serum IgG4 levels did not differ in participants with and without allergic disease, and logistic regression analysis did not show a significant association between allergic disease and elevated serum IgG4. Similarly, a Spanish study found that patients with an atopic predisposition had a median serum IgG4 level of 38.4 mg/dL (IQR 21.7–56.6 mg/mL), suggesting that few had serum IgG4 concentrations > 135 mg/dL [21]. Although malignancy has been associated with IgG4-RD [22–24], the prevalence of elevated serum IgG4 did not differ in our study participants with and without a history of malignancy. These results suggest that factors related to IgG4-RD may not be responsible for enhancing IgG4 production.

This study also provided data on the rates of elevated serum IgG4 and IgG4-RD in a general population of adults undergoing regular health examinations, not in patients visiting a medical institution. Previous studies found that 10–15% of patients with elevated serum IgG4 levels had IgG4-RD. In the present study, although few participants underwent close secondary examination, more than 0.08% of all participants or more than 2.4% of those with elevated serum IgG4 levels had IgG4-RD, a higher prevalence than previously reported [2, 41]. In the Spanish study of adults undergoing health examinations [21], none of those with elevated serum IgG4 levels was diagnosed with IgG4-RD. This was likely due to the small number of participants and/or the low percentage who underwent close secondary examination. Studies that include much higher numbers of participants are needed to estimate the prevalence of IgG4-RD more accurately.

The results of the present study also suggest the likelihood of regional and racial differences in the prevalence of elevated serum IgG4 levels. Although comparisons are limited, the prevalence of elevated serum IgG4 was three times higher in one Japanese region than in one Spanish region. To determine whether there are regional differences in Japan, we are now evaluating the prevalence of elevated serum IgG4 levels in health examination participants in another Japanese region. Further evaluations in more countries and regions will be necessary to determine the prevalence rates of elevated serum IgG4 and IgG4-RD and the factors related to them in general populations.

This study had several limitations. First, although this study included more participants than did a comparable study [21], the number of participants was insufficient to analyze factors affecting the epidemiology of IgG4-RD. In addition, a very low rate (35.7%) of undergoing close secondary examination in patients with elevated serum IgG4 concentrations was an important limitation of the present study. Second, serum IgG4 concentrations were not measured in 10% of the consecutive participants, leading to a potential for selection bias in this study. Some missing values could also potentially affect the results. Third, because this study was limited to a single region in Japan, the associations of regional and racial factor with elevated serum IgG4 or the onset of IgG4-RD could not be sufficiently evaluated. Finally, because this study was a cross-sectional survey, the time courses of serum IgG4 elevation and IgG4-RD onset could not be analyzed longitudinally. These analyses would require nationwide multi-center and/or multi-national studies analyzing multi-year results of health examinations.

Conclusions

Elevated serum IgG4 levels are significantly associated with older age, male gender, and nutrition intake status. Although some of these factors are identical to the epidemiological features of IgG4-RD, they rarely lead to a diagnosis of IgG4-RD in the general Japanese population. Nevertheless, the prevalence of IgG4-RD may be higher than expected. Although larger-scale multi-national and

multi-center studies are needed to confirm these results and clarify regional and racial differences, the present results can help determine the prevalence and clinical significance of elevated serum IgG4 levels in a general population.

Abbreviations

ACR	American College of Rheumatology
ANA	Anti-nuclear antibody
BP	Blood pressure
BMI	Body mass index
BDHQ	Brief-type self-administered diet history questionnaire
CT	Computed tomography
CI	Confidence interval
CRP	C-reactive protein
eGFR	Estimated glomerular filtration rate
EULAR	European League Against Rheumatism
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
IgG4	Immunoglobulin G4
IgG4-RD	Immunoglobulin G4-related disease
LDL-C	Low-density lipoprotein cholesterol
OR	Odds ratio
RF	Rheumatoid factor
SD	Standard deviation
Total-C	Total cholesterol
TG	Triglycerides
ULN	Upper limit of normal

Supplementary Information

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Supplementary Material 1

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Author contributions
ST, HF, IM, MK: conception and design, data collection and analysis, manuscript writing and final approval of the manuscript. HT, MY, NS, YT, AT, SHorita, YF, TM, TZ, RN, HNuka, SHara, YT, YS, KI, KY, SN: data collection and analysis, critical revision and final approval of the manuscript. MT, AH, AK, HNakamura, YI: conception and design, critical revision and final approval of the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the institutional ethics boards of the Medical Ethics Committee of Kanazawa University, Nagasaki University, and Johoku Hospital, and informed consent for the use of all data was obtained from each participant. This study was conducted in compliance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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