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Original article

Association of serum 25-hydroxyvitamin D with influenza in case-control study nested in a cohort of Japanese employees

Akiko Nanri ^{a,*}, Kengo Nakamoto ^b, Nobuaki Sakamoto ^c, Teppei Imai ^d, Shamima Akter ^a, Daisuke Nonaka ^e, Tetsuya Mizoue ^a^a Department of Epidemiology and Prevention, National Center for Global Health and Medicine, Tokyo, Japan^b NGK Insulators, Ltd., Aichi, Japan^c Health Design Inc., Tokyo, Japan^d Azbil Corporation, Tokyo, Japan^e Department of Global Health, School of Health Sciences, University of the Ryukyus, Okinawa, Japan

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SUMMARY

Background & aims: Several intervention studies have examined the effect of vitamin D supplementation on influenza or influenza-like illness, but their results have been inconsistent. We prospectively examined the association of serum 25-hydroxyvitamin D with influenza among Japanese workers.

Methods: We conducted a nested case-control study in a cohort of workers in 4 companies in the Kanto and Tokai areas of Japan. Physician-diagnosed influenza that occurred during the winter season was ascertained using a self-administered questionnaire. Two controls matched by company, sex, and age (and checkup date in 1 company) were selected for each case. Serum 25-hydroxyvitamin D concentrations at baseline were measured using a competitive protein binding assay. Odds ratio of influenza were estimated by conditional logistic regression with adjustment for covariates.

Results: Of 182 cases and 364 controls, 179 cases and 353 controls with complete data were included in the analysis. Serum 25-hydroxyvitamin D concentrations were not associated with a significantly lower risk of influenza; the multivariable-adjusted odds ratio for the highest (≥ 30 ng/mL) versus lowest category (< 20 ng/mL) was 0.77 (95% confidence interval 0.37–1.59) (P for trend = 0.80). In a subgroup of participants without vaccination, vitamin D sufficiency (≥ 30 ng/mL) was associated with a significantly lower risk of influenza (odds ratio 0.14; 95% confidence interval 0.03–0.74).

Conclusions: Overall, circulating 25-hydroxyvitamin D concentrations were not appreciably associated with influenza episodes. However, the lower influenza risk associated with vitamin D sufficiency among unvaccinated participants warrants further investigation.

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1. Introduction

Influenza epidemics occur during the winter season. In some cases, this disease spreads in a pandemic fashion, as did the H1N1 influenza in 2009. Due to its severe symptoms, influenza has a significant impact on daily life and productivity. Although the effect of preventive behaviors against influenza, such as vaccination and hand-washing, has been well investigated, the effect of nutritional factors remains unclear. In particular, vitamin D is known to play a

role in the immune response to infection [1] and may combat influenza.

In a meta-analysis of 11 randomized controlled trials, vitamin D was shown to decrease risk of respiratory tract infections [2]. However, few studies have examined the effect of vitamin D on influenza. One study reported significantly lower risk of cold and influenza among African-American postmenopausal women [3], and another study reported significantly lower incidence of influenza A among Japanese schoolchildren receiving supplemental vitamin D [4]. In contrast, another study failed to find any effect of vitamin D supplementation on influenza among Japanese students [5]. In addition, a pooled analysis of 10 different clinical trials observed that vitamin D supplementation (1111–6800 IU/day) had no effect on influenza-like illness risk in Western countries [6]. This

* Corresponding author. Department of Epidemiology and Prevention, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. Tel.: +81-3-3202-7181; fax: +81 3 3202 7364.

E-mail address: nanri@ri.ncgm.go.jp (A. Nanri).

inconsistency among studies may be partly ascribed to baseline differences in the vitamin D status of the target populations, attained vitamin D status after supplementation, and other influential factors, including vaccination. The knowledge about these issues would be a basis of trials, i.e., in selecting the target for intervention and the dose of vitamin D supplement. However, evidence from observational studies on these issues has been lacking. Here, we prospectively examined the association of circulating 25-hydroxyvitamin D concentrations with influenza episodes among Japanese workers.

2. Methods

2.1. Study procedure

We conducted a nested case-control study among employees in 4 companies in the Kanto and Tokai areas of Japan. During the periodic health checkup, which was conducted from September through December 2011, we collected anthropometric data and information on lifestyle, including smoking, alcohol drinking, and exercise, and asked participants to donate surplus serum samples, which were cryopreserved until analysis. In the follow-up survey, which was conducted from May through July 2012, we asked participants to fill out a survey questionnaire about influenza diagnosis from November 2011 to April 2012 and related factors, including vaccination, living with schoolchild(ren), and commuting from home to work. Written informed consent was obtained from each participant at either baseline or follow-up. This study was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan.

2.2. Participants

Figure 1 shows the flow chart of study protocol. Of 4522 employees who attended the health checkup (including blood testing), 220 did not agree to participate in the study at baseline. In the follow-up survey, we distributed a survey questionnaire among the remaining participants ($n = 4302$); of these, 3681 participants (86%) returned the questionnaire. After exclusion of participants with missing health checkup data or no serum sample, 3327 participants formed the study cohort. Of these, after exclusion of 30 participants with missing data on influenza diagnosis, 182 participants (5.5%) reported influenza diagnosis by a doctor during the period from November 2011 through April 2012 and were defined as study cases (Fig. 1). Of the remaining participants, we excluded those with an episode of fever of ≥ 37.8 °C ($n = 438$) or with missing data on fever ($n = 18$), leaving 2659 participants as potential controls. For each case, we randomly selected two controls matched by company, sex, and age (± 2 years). In one company, where the checkup lasted for 3 months, we also matched by the date of health checkup (± 1 week). Of the 182 cases and 364 matched controls, we excluded 2 case-control sets due to matching error, 1 case-control set due to missing covariate of the case, and 5 controls with missing covariates, leaving 179 cases and 353 controls (174 sets of 1 case and 2 matched controls and 5 sets of 1 case and 1 matched control) in the analysis.

2.3. Measurements

We measured serum 25-hydroxyvitamin D concentrations at an external laboratory (LSI Medience Corporation, Tokyo, Japan) using a competitive protein binding assay. Intra-assay coefficients of variation was 10.3% at 13.3 ng/mL and 8.4% at 21.3 ng/mL.

2.4. Outcome

The outcome of the present study was defined as participants who were reportedly diagnosed with influenza either using rapid diagnostic testing or assessment of clinical symptoms by a physician during the period from November 2011 through April 2012 at the follow-up survey. In the questionnaire, we used the following question: “have you been diagnosed with influenza by a doctor from November 2011 to the end of April 2012?” We regarded participants who responded “yes” to this question as influenza diagnosis cases. Moreover, we asked participants who reported influenza diagnosis by a doctor whether a diagnostic kit was used.

2.5. Other variables

At the follow-up survey, participants who reported influenza diagnosis by a doctor were asked about the time of the diagnosis and the type of influenza (A, B, or unknown). To avoid confusion with the terms influenza, influenza-like illness, and upper respiratory infection among participants, we asked all participants whether they experienced fever of 37.8 °C or more without an influenza diagnosis or cold symptoms, such as mild fever, nasal stuffiness, runny nose, sneeze, cough, and sore throat without an influenza diagnosis; fever of 37.8 °C or more; or allergy disease from November 2011 through April 2012. Moreover, participants were asked whether they received influenza vaccination from November 2011 through April 2012. We also asked about living with a child or children who attend school, commuting to work (walk, bicycle, bus, train, and car), and green tea intake (from almost null to ≥ 1 cup/day). We retrieved data on height and weight, smoking status, and exercise from a health checkup database.

2.6. Statistical analysis

Differences in baseline characteristics between cases and controls were assessed using the chi-squared test for categorical variables and the Student *t*-test for continuous variables. Participants were classified according to serum 25-hydroxyvitamin D concentration. Vitamin D deficiency, insufficiency, and sufficiency were defined as a serum 25-hydroxyvitamin D concentration of <20 ng/mL, 20 to <30 ng/mL, and ≥ 30 ng/mL, respectively [7].

We calculated odds ratios (ORs) and their 95% confidence intervals (CIs) for influenza diagnosis using conditional logistic regression, taking the category of 25-hydroxyvitamin D <20 ng/mL as reference. We adjusted for influenza vaccination (yes or no), body mass index (continuous, kg/m²), exercise (<2 times/week or ≥ 2 times/week), current smoking (yes or no), living with schoolchild(ren) (yes or no), green tea consumption (0, 1–6 cups/week, or ≥ 1 cup/day), and use of public transport for commuting to work (bus and/or train: yes or no), which are known or suspected risk/protective factors associated with influenza [8,9]. Trend association was assessed by assigning ordinal numbers to the increasing category of serum 25-hydroxyvitamin D and treating them as continuous. We conducted a series of sensitivity analyses among the case-controls sets of participants who: 1) were not vaccinated for influenza, 2) were diagnosed using a diagnostic kit (case only), 3) had type A influenza (case only), and 4) received their health checkup between November and December (lower vitamin D status). In each analysis, a case-control set was excluded if no case or no matched control remained after applying the restriction criteria. We also performed restricted cubic spline regression to evaluate the shape of the relation between 25-hydroxyvitamin D and the odds of influenza, by assigning 16.2 ng/mL to the reference value of 25-hydroxyvitamin D and 16.2, 21.9, and 29.7 ng/mL (10th, 50th,

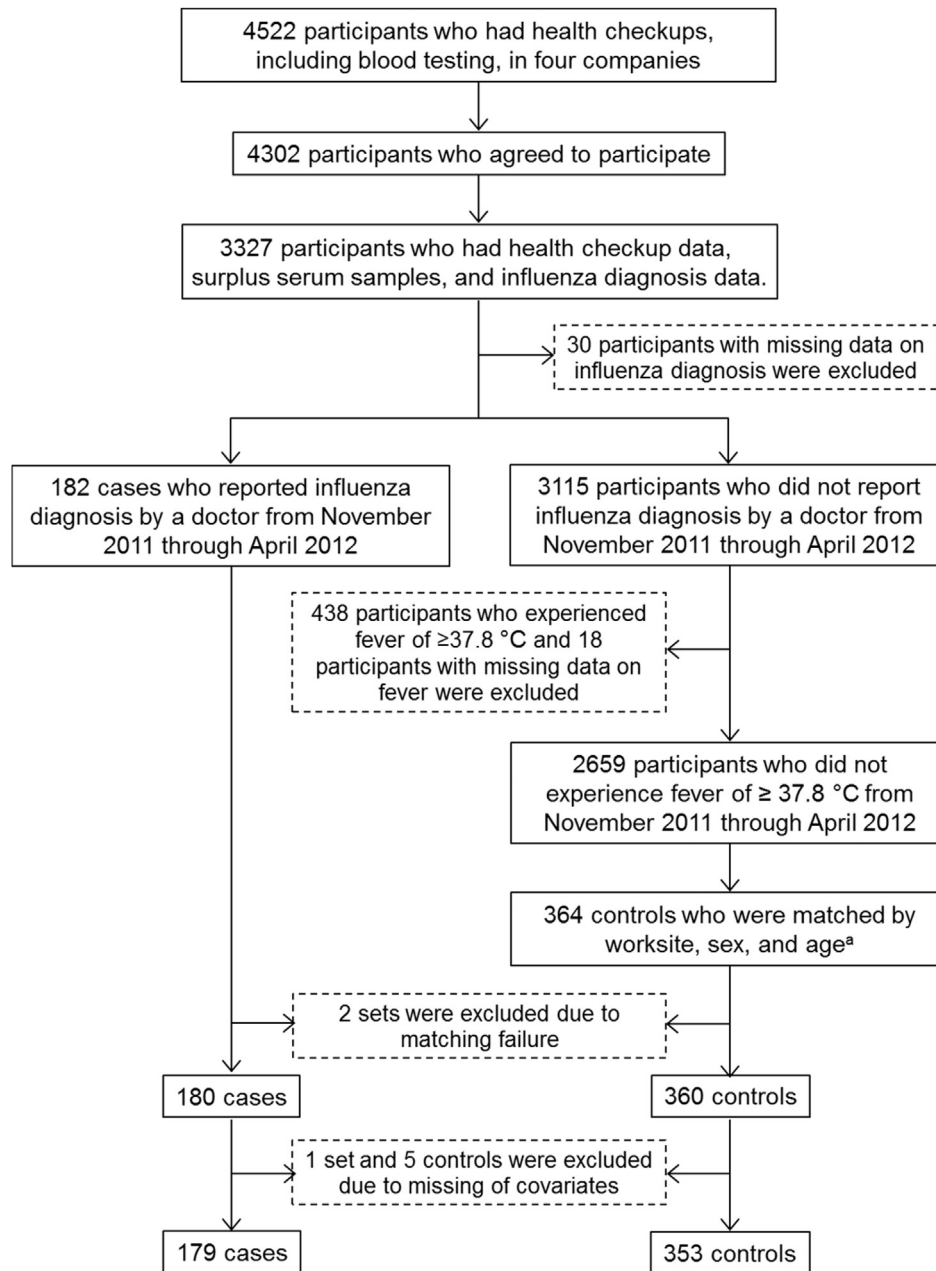


Fig. 1. Flow chart of study protocol. ^a In one company, health checkup date was used as an additional matching factor.

and 90th percentiles, respectively) to the 3 knots. Two-side P values <0.05 were regarded as statistically significant. Analyses were performed using Statistical Analysis System (SAS) software version 9.3 (SAS Institute, Cary, NC, USA) and Stata version 13.1 (StataCorp, College Station, TX, USA).

3. Results

The mean serum 25-hydroxyvitamin D concentrations was 22.5 (standard deviation 5.2; range 11.0–41.2) ng/mL. The characteristics of case and control subjects are shown in Table 1. The mean age was 37.6 years for both cases and controls. The proportion of participants who lived with schoolchildren was higher in cases than controls. Green tea consumption was lower in cases than controls. For other characteristics, there were no significant differences

between the two groups. Of 179 case subjects who reported influenza diagnosis by a doctor, 116 cases (65%) reported having been diagnosed using a diagnostic kit.

The ORs of influenza according to serum 25-hydroxyvitamin D concentration are shown in Table 2. Overall, there was no significant association; the multivariable-adjusted OR of influenza was 0.77 (95% CI 0.37–1.59) in the highest (≥ 30 ng/mL) versus lowest (<20 ng/mL) category of serum 25-hydroxyvitamin D concentration (P for trend = 0.80).

Among those who were not vaccinated for influenza, serum 25-hydroxyvitamin D concentrations were statistically significantly associated with a decreased risk of influenza; the multivariable-adjusted OR of influenza for the highest (≥ 30 ng/mL) versus the lowest (<20 ng/mL) category of 25-hydroxyvitamin D concentration was 0.14 (95% CI 0.03–0.74). Among participants who attended

Table 1
Baseline characteristics of cases and controls.

	Cases	Controls	P value ^a
Number of participants	179	353	
Age (years)	37.6 ± 11.6 ^b	37.6 ± 11.6	0.99
Women (%)	16.8	17.0	0.95
Body mass index (kg/m ²)	22.2 ± 3.1	22.5 ± 3.5	0.38
Current smoker (%)	30.7	27.8	0.48
Exercise ^c (≥2 times/week, %)	17.3	22.1	0.20
Influenza vaccination (%)	26.3	27.5	0.76
Living with schoolchildren (%)	46.9	36.8	0.03
Commuting to work (%)			
Walk	57.5	51.3	0.17
Bicycle	26.3	24.1	0.58
Bus	28.5	28.3	0.97
Train	59.8	53.5	0.17
Car	22.9	26.6	0.35
Green tea (≥1 cup/week, %)	64.8	73.7	0.03
Serum 25-hydroxyvitamin D (ng/mL)	22.52 ± 5.13	22.44 ± 5.22	0.88

^a Based on chi-squared test for categorical variables and Student t-test for continuous variables.

^b Mean ± SD (all such values).

^c Exercise with sweating of ≥30 min/time.

the health checkup in the late autumn or early winter (November and December), the risk of influenza was non-significantly decreased in the highest category of 25-hydroxyvitamin D concentration (OR 0.62; 95% CI 0.21–1.90). 25-hydroxyvitamin D concentration was not associated with the risk of influenza among case-control sets in which influenza infection was confirmed using a diagnostic kit or in which the influenza was type A.

According to the results of cubic spline regression analysis (Fig. 2), the association between serum 25-hydroxyvitamin D concentration and influenza appeared to be linear (from 21.9 ng/mL of serum 25-hydroxyvitamin D) among participants who were not vaccinated for influenza, with the odds of influenza steadily decreasing with increasing 25-hydroxyvitamin D concentration.

4. Discussion

In this nested case-control study among Japanese workers, circulating 25-hydroxyvitamin D concentrations at baseline were not appreciably associated with influenza risk. Among participants

who did not receive vaccination, however, we found a significantly decreased risk of influenza in the highest category of 25-hydroxyvitamin D concentration. To our knowledge, this was the first prospective study to exclusively examine the association of blood 25-hydroxyvitamin D concentration with the risk of influenza.

Previously, several studies reported an association between a circulating form of vitamin D and respiratory infection among adult populations. Of 3 prospective studies so far, 2 observed that participants with lower 25-hydroxyvitamin D concentrations (<16 ng/mL in one study [10] and <38 ng/mL in the other [11]) had a longer period of absence due to respiratory infection [10] and higher incidence of acute viral respiratory tract infections [11] compared to those with higher concentrations (≥16 ng/mL in one study [10] and ≥38 ng/mL in the other [11]). Another study reported an inverse, albeit statistically non-significant, association between 25-hydroxyvitamin D concentrations and respiratory infection [12]. Of 3 cross-sectional studies, lower serum 25-hydroxyvitamin D concentrations (<30 ng/mL [13,14]) were associated with higher prevalence of upper respiratory tract infections [13], respiratory infections [15], or acute respiratory infection [14]. In contrast with these data consistently supporting a protective role of vitamin D against respiratory infections, the present study, which was specifically designed to explore the vitamin D-influenza association, did not find a clear link between them.

Few intervention studies have exclusively examined the effect of vitamin D on influenza. In a study of 430 Japanese schoolchildren (aged 6–15 years) [4], incidence of influenza A was significantly decreased in the vitamin D3 supplementation group (1200 IU/day for 4 months) compared with the placebo group. In contrast, in another study of 247 Japanese high school students [5], an effect of vitamin D3 supplementation (2000 IU/day for 2 months) on influenza A during the 2009 H1N1 pandemic was not observed. In addition, in a pooled analysis of 10 different clinical trials among 569 participants (aged 32–84 years), vitamin D supplementation (1111–6800 IU/day) had no effect on influenza-like illness risk (intervention period: at least 12 weeks) [6]. The inconsistency in these previous findings might be attributable to differences in the age of the participants, the intervention period, and the prevalent influenza subtype.

Vaccination may confound the association between 25-hydroxyvitamin D concentration and influenza. However, few

Table 2
Odds ratio and 95% confidence intervals of influenza according to serum 25-hydroxyvitamin D concentration.

	Predefined category of serum 25-hydroxyvitamin D			P for trend ^a
	<20 ng/mL	20 to <30 ng/mL	≥30 ng/mL	
Number of cases/controls	59/121	106/197	14/35	
Crude model	1.00 (reference)	1.09 (0.73, 1.63)	0.83 (0.40, 1.68)	0.87
Multivariable model ^b	1.00 (reference)	1.11 (0.74, 1.68)	0.77 (0.37, 1.59)	0.80
No influenza vaccination (n = 217)				
No of cases/controls	32/57	40/70	2/18	
Multivariable model ^c	1.00 (reference)	1.12 (0.59, 2.11)	0.14 (0.03, 0.74)	0.15
Influenza confirmed by using diagnostic kit (n = 344)				
No of cases/controls	34/80	71/121	11/27	
Multivariable model ^b	1.00 (reference)	1.43 (0.84, 2.45)	0.99 (0.41, 2.38)	0.61
Type A influenza (n = 271)				
No of cases/controls	28/60	54/96	9/24	
Multivariable model ^b	1.00 (reference)	1.20 (0.64, 2.24)	0.79 (0.29, 2.15)	0.88
Blood drawn in November and December (n = 296)				
No of cases/controls	42/77	52/105	6/14	
Multivariable model ^b	1.00 (reference)	0.83 (0.48, 1.41)	0.62 (0.21, 1.90)	0.35

^a Based on conditional logistic regression analysis with the assignment of ordinal numbers (treated as continuous) to each category of serum 25-hydroxyvitamin D concentration.

^b Adjusted for influenza vaccination (yes or no), body mass index (continuous, kg/m²), exercise (<2 times/week or ≥2 times/week), current smoking (yes or no), living with schoolchildren (yes or no), green tea (0, 1–6 cups/week, or ≥1 cup/day), and use of public transport (bus or train) for commuting (yes or no).

^c Adjusted for the same variables as in footnote b with the exception of influenza vaccination.

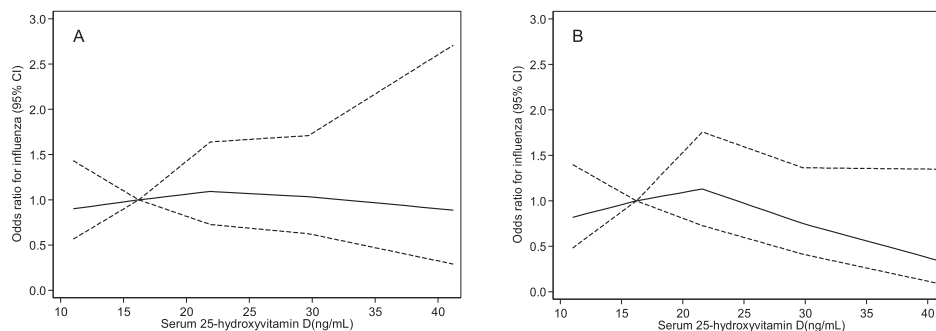


Fig. 2. Restricted cubic spline regression for the association between serum 25-hydroxyvitamin D concentration and influenza. Solid line represents odds ratio; dashed line represents 95% confidence interval. Knots were placed at the 10th, 50th, and 90th percentiles (16.2, 21.9, and 29.7 ng/mL) of serum 25-hydroxyvitamin D. The reference value was 16.2 ng/mL. Figure A for total population ($n = 532$), B for those who did not vaccinate for influenza ($n = 388$). The model was adjusted for influenza vaccination (yes or no), body mass index (continuous, kg/m²), exercise (<2 times/week or ≥ 2 times/week), current smoker (yes or no), living with schoolchildren (yes or no), green tea (0, 1–6 cups/week, or ≥ 1 cup/day), and use of public transport (bus or train) for commuting (yes or no). Figure B adjusted for all variables except influenza vaccination.

studies have conducted stratified analysis by vaccination status. In the present study, among participants without vaccination, we found a significantly lower risk in the highest category of serum 25-hydroxyvitamin D concentration (≥ 30 ng/mL) compared to the lowest category (<20 ng/mL). This finding, based on a small subgroup, may be solely due to chance. Alternatively, it could be that the protective effect of vitamin D against influenza, which may be masked in the presence of influenza vaccination, is evident only among unvaccinated individuals, who should rely on innate immunity, a hypothesized mechanism by which vitamin D prevents influenza infection. More research is needed to confirm the association of 25-hydroxyvitamin D concentration with influenza risk among unvaccinated individuals.

The present finding of no association between 25-hydroxyvitamin D concentration and influenza might be explained by the fact that the cutoff of vitamin D deficiency that we used (<20 ng/mL) differed from that based on the guideline by the Institute of Medicine (<12 ng/mL) [16]. However, we were unable to this definition because only two of our participants met it. When we defined deficiency as serum 25-hydroxyvitamin D of <15 ng/mL ($n = 32$), we observed no association between serum 25-hydroxyvitamin D concentration and influenza (Fig. 2A); the multivariable-adjusted ORs (95% CI) of influenza were 1.00 (reference), 1.28 (0.52–3.15), and 1.31 (0.56–3.10) for the serum 25-hydroxyvitamin D categories of <15, 15 to <20, and ≥ 20 ng/mL, respectively (P for trend = 0.62).

The major strengths of this study were its measurement of blood 25-hydroxyvitamin D concentration, prospective design in a well-defined population, high participation rate, and adjustment for potentially important confounding variables. Our study also had some limitations. First, we used self-reported information about physician-diagnosed influenza for our outcome. Misclassification of cases might have occurred because only 65% of cases were objectively diagnosed using a diagnostic kit. However, when the analysis was restricted to objectively confirmed cases, results were materially unchanged. Second, we excluded participants who experienced fever of ≥ 37.8 °C when selecting controls because we could not rule out the possibility of influenza in these participants. If serum vitamin D levels differ between participants who experienced high fever and those who did not, the association between vitamin D and influenza might be biased. Third, our study is not sufficiently powered to detect an association. Specifically, given the small number of participants with sufficient 25-hydroxyvitamin D of ≥ 30 ng/mL (only 9% of participants) in the present population, we cannot rule out the possibility of risk reduction associated with those levels. Fourth, the results of our subgroup analyses, especially

that among participants without vaccination, should be interpreted cautiously due to the small subgroup sizes. Fifth, although we adjusted for multiple potential confounders, bias due to unmeasured confounders or residual confounding may remain. Finally, as study participants were apparently healthy workers, the present findings may not be applicable to vulnerable populations, such as children and the elderly.

In conclusion, the present study did not detect a significant association between a circulating form of vitamin D and the risk of influenza in a Japanese working population. In a subgroup of unvaccinated participants, however, sufficient serum vitamin D concentration was associated with a significantly lower risk of influenza, a finding warranting further investigation.

Statement of authorship

AN and TM designed the research; AN, KN, NS, and TI conducted research; KN, NS, and TI provided databases for the research; AN analyzed data or performed statistical analysis; SA and TM provided statistical expertise; AN drafted the manuscript; AN and TM had primary responsibility for final content. All authors have read and approved the final manuscript.

Conflict of interest

All the authors declared no conflict of interest.

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References

- [1] Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, et al. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006;134:1129–40.
- [2] Bergman P, Lindh AU, Bjorkhem-Bergman L, Lindh JD. Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials. *PLoS One* 2013;8:e65835.
- [3] Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of vitamin D3 supplementation in African American women. *Arch Intern Med* 2005;165:1618–23.

- [4] Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010;91:1255–60.
- [5] Urashima M, Mezawa H, Noya M, Camargo CA. Effects of vitamin D supplements on influenza A illness during the 2009 H1N1 pandemic: a randomized controlled trial. *Food Funct* 2014;5:2365–70.
- [6] Jorde R, Witham M, Janssens W, Rolighed L, Borchhardt K, de Boer IH, et al. Vitamin D supplementation did not prevent influenza-like illness as diagnosed retrospectively by questionnaires in subjects participating in randomized clinical trials. *Scand J Infect Dis* 2012;44:126–32.
- [7] Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266–81.
- [8] Adler AJ, Eames KT, Funk S, Edmunds WJ. Incidence and risk factors for influenza-like-illness in the UK: online surveillance using Flusurvey. *BMC Infect Dis* 2014;14:232.
- [9] Matsumoto K, Yamada H, Takuma N, Niino H, Sagesaka YM. Effects of green tea catechins and theanine on preventing influenza infection among health-care workers: a randomized controlled trial. *BMC Complement Altern Med* 2011;11:15.
- [10] Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamaki H, et al. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 2007;86:714–7.
- [11] Sabetta JR, DePetrillo P, Cipriani RJ, Smardin J, Burns LA, Landry ML. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 2010;5:e11088.
- [12] Porojnicu AC, Moroti-Constantinescu R, Laslau A, Lagunova Z, Dahlback A, Hristea A, et al. Vitamin D status in healthy Romanian caregivers and risk of respiratory infections. *Public Health Nutr* 2012;15:2157–62.
- [13] Ginde AA, Mansbach JM, Camargo Jr CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2009;169:384–90.
- [14] Monlezun DJ, Bittner EA, Christopher KB, Camargo CA, Quraishi SA. Vitamin D status and acute respiratory infection: cross sectional results from the United States National Health and Nutrition Examination Survey, 2001-2006. *Nutrients* 2015;7:1933–44.
- [15] Berry DJ, Hesketh K, Power C, Hypponen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr* 2011;106:1433–40.
- [16] Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. *Dietary reference intakes for calcium and vitamin D*. Washington, DC: National Academies Press; 2011.