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Risk of lymphoid malignancies increased after Puumala virus infection in Finland, 2009-2019: A retrospective register-based cohort study

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ABSTRACT

Objectives: The Puumala virus (PUUV) is a hantavirus that causes hemorrhagic fever with renal syndrome. Studies showing an increased risk of lymphoid malignancies after hantavirus infection, together with the observation that PUUV infects B cells, motivated us to study the risk of lymphoid malignancies after PUUV infection.

Methods: We linked data from the Finnish Cancer Registry and National Infectious Diseases Register for 2009-2019. We used a time-dependent Cox regression model to evaluate the hazard of the lymphoid malignancies grouped according to the HAEMACARE classification.

Results: We identified 68 cases of lymphoid malignancies after PUUV infection among 16,075 PUUV-infected individuals during 61,114,826 person-years of observation. A total of 10 cases occurred within 3-<12 months and 38 within 1-<5 years after PUUV infection, and the risk of lymphoid malignancies increased with hazard ratios (HRs) of 2.0 (95% confidence interval [CI], 1.1-3.7) and 1.6 (95% CI, 1.2-2.3), respectively. The group of mature B cell neoplasms showed an increased risk 3-<12 months and 1-<5 years after PUUV infection, HR 2.2 (95% CI, 1.2-4.3) and HR 1.8 (95% CI, 1.3-2.5), respectively.

Conclusion: PUUV infection is associated with lymphoid malignancies in the Finnish population, supporting the earlier studies. Further research is required to understand the pathophysiological mechanisms behind this association.

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Introduction

The Puumala virus (PUUV), genus *Orthohantavirus*, subfamily *Mammantavirinae*, family *Hantaviridae*, is a zoonotic virus occasionally infecting humans [1–3]. PUUV is mainly transmitted to humans through aerosolized rodent excreta and is one of the five hantaviruses causing hemorrhagic fever with renal syndrome (HFRS) in Eurasia.

The main reservoir for PUUV in Europe is the bank vole (*Myodes glareolus*). The only hantavirus pathogenic to humans in Finland is PUUV. PUUV is a significant public health problem in Finland; although, it primarily causes a mild form of HFRS. The annual incidence is high, 31 per 100,000 population, and the population-based seroprevalence was 12.5% in 2011 [4,5]. Sweden has a similar disease burden, with an average annual incidence of 20 per 100,000 [6,7]. There are major seasonal, periodical, and regional variations in PUUV incidence rates in Finland and Sweden [8,9].

The incubation period of PUUV infection varies from 10 days to 6 weeks [10], and when the patients seek medical care, the virus has often already been cleared. Thus, PUUV infection is mainly diagnosed by serology [11]. The detection of immunoglobulin (Ig)M or low avidity IgG antibodies through methods, such as enzyme immunoassay, immunochromatography, and immunofluorescence, serves to demonstrate acute infection. Rapid immunochromatogra-

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phy tests for IgM detection are also used in PUUV diagnostics, especially in the emergency room setting [4]. The antibodies to PUUV are long-lasting, likely leading to life-long immunity [12].

Being a male and living in rural area are risk factors for PUUV infection, whereas smoking is a risk factor for PUUV infection and clinical severity [5,7]. The course of HFRS is divided into five distinct phases: febrile, hypotensive, oliguric, polyuric, and convalescent. Acute kidney injury, capillary leakage, and thrombocytopenia are typically seen during acute infection [3,13]. In Finland, the 28-day case fatality is 0.14% [4]. Hantaviruses primarily replicate in the endothelium [3]; however, some recent reports indicate that the virus infects naïve B cells [14] directly and induces polyclonal B cell activation, resulting in plasmablast expansion [14,15]. No etiologic treatment or vaccine is currently available for PUUV infection.

Not much is known about the long-term sequelae of PUUV infection on subsequent health outcomes, but a Swedish study reported an increased risk of lymphoma after PUUV infection [16]. Although the Swedish study did not show an increased risk for other types of cancers, a South Korean study showed an association of Hantaan, Seoul, Soocheong, and Muju virus-caused HFRS with both hematologic malignancies and solid cancers compared with the general population [17].

Through a retrospective register-based cohort study, we assessed whether PUUV infection was a risk factor for lymphoid malignancies in the Finnish population.

Methods

We linked the data from two national registers, the National Infectious Diseases Register (NIDR) and the Finnish Cancer Registry (FCR). PUUV infections have been reported to the NIDR since 1995, with national identity codes included from 2004 and onward [18]. Laboratories report positive findings primarily through electronic reporting. The laboratory notification in the NIDR includes information on the date and type of laboratory specimen, diagnostic test, date of birth, sex, and municipality of residence. The dates of death were obtained from the Finnish Population Register. If there were multiple notifications for one person, we took the first one into account.

The FCR is a nationwide registry that collects data on all cancer diagnoses in Finland and follows up on the incidences of different types of cancers. Reporting cancers to the registry has been mandatory since 1961 and is done by health care professionals, mainly physicians and pathologists. Since 2008, the FCR has used the HAEMACARE classification of hematologic cancers with the respective International Classification of Diseases, Tenth Revision (ICD-10) codes in the reporting of cancer cases [19].

In the HAEMACARE classification, lymphoid malignancies are categorized into six groups: Hodgkin lymphoma; acute lymphoblastic leukemia/lymphoma; leukemia, other, or unspecified; non-Hodgkin lymphoma, other, or unspecified; mature T and natural killer cell lymphoma/leukemia; and mature B cell neoplasms [19]. Mature B cell neoplasms are divided into nine subgroups: myeloma and other plasma cell tumors, chronic lymphatic leukemia, malignant immunoproliferative diseases, mantle cell lymphoma, follicular B lymphoma, diffuse B lymphoma, Burkitt lymphoma/leukemia, marginal zone lymphoma, and other mature B cell neoplasms.

We obtained data on all lymphoid malignancies diagnosed in Finland during January 01, 2004-December 31, 2019 from the FCR and linked these data through the national identity codes to the PUUV laboratory notifications in the NIDR for the same period.

We defined a PUUV-infected individual as an individual in the NIDR who had a laboratory notification of PUUV infection during 2009-2019.

We defined a lymphoid malignancy case as an individual having their first lymphoid malignancy (based on the HAEMACARE classification) during 2009-2019 reported in the FCR.

We defined the study period as January 1, 2009-December 31, 2019 and obtained data for the whole Finnish population for that period from the Finnish Population Register. These data were combined with the data from the FCR and the NIDR.

We excluded individuals with a lymphoid malignancy diagnosis during 2004-2008 because a previous lymphoid malignancy or its treatment can be a risk factor for a new lymphoid malignancy or relapses of previous lymphoid malignancy may occur [20]. Only the first lymphoid malignancy diagnosis was taken into account for those who developed a lymphoid malignancy during 2009-2019. We kept PUUV-infected individuals in the NIDR during 2004-2008 in the database and followed up for lymphoid malignancy. PUUV infection in 2004-2008 was analyzed as a variable in the Cox regression.

We excluded individuals who had a foreign country of birth in the Finnish Population Register as we did not have the date of immigration and thus could not count the follow-up time for this group.

Statistical methods

We used the chi-square test to determine if there was a significant difference between PUUV-infected and PUUV-uninfected individuals in terms of having a lymphoid malignancy outcome.

We used a time-dependent Cox regression model to evaluate the hazard of lymphoid malignancy after PUUV infection. We calculated the hazard ratios (HRs) for different periods after PUUV infection: under 3 months, 3-<12 months, 1-<5 years, 5-<10 years, and ≥10 years. The main time scale in the model was age. We allowed different baseline hazards and stratified the baseline hazards by 5-year birth cohort. We added sex, region (health care district), and PUUV infection during 2004-2008 to the model. As a sensitivity analysis, we conducted the Cox regression using 6-month and 12-month wash-out periods between the dates of PUUV infection and lymphoid malignancy diagnoses. We also conducted the Cox regression for the data where previous PUUV infection (diagnoses in the year 2004-2008) was an exclusion criterion. In addition to all lymphoid malignancy cases as one group, we conducted Cox regression for the groups of lymphoid malignancies and their subgroups using the HAEMACARE classification. These analyses were done for the categories where there were more than five cases of lymphoid malignancies after PUUV infection for at least one of the periods after PUUV infection. We analyzed the interaction of age with the outcome of lymphoid malignancy after PUUV infection in the Cox regression.

We counted the estimated incidences of lymphoid malignancies for PUUV-infected and uninfected individuals with their 95% confidence intervals (CIs). Furthermore, we calculated age-and sex-standardized incidence ratios (SIRs) and 95% CIs for lymphoid malignancies for PUUV-infected individuals against the expected number of lymphoid malignancy cases in the Finnish population at different time points after PUUV infection.

The statistical analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, TX, USA).

Results

We identified 16,075 PUUV-infected individuals during 2009-2019 in the NIDR; 58% were male, and the median age of PUUV diagnosis was 49 (range, 1-99) years (Table 1). The incidence of PUUV infection varied regionally, with the highest rates in eastern Finland (Figure 1).

Table 1
Characteristics of individuals infected and uninfected by the PUUV in Finland, 2009-2019.

	PUUV-infected n = 16,075	PUUV-uninfected n = 6,134,886	*P*-value
Sex, n (%)			
Male	9391 (58.4)	3,088,641 (50.3)	<0.001[a]
Female	6684 (41.6)	3,046,245 (49.7)	
Median age[b] (range), years	49.0 (1.4-98.6)		
Age group, n (%)			
0-19	719 (4.5)		
20-39	4270 (26.6)		
40-59	6442 (40.1)		
60-79	4302 (26.8)		
≥ 80	342 (2.1)		

PUUV, Puumala virus.
[a] Chi-square test.
[b] Age at the time of PUUV infection.

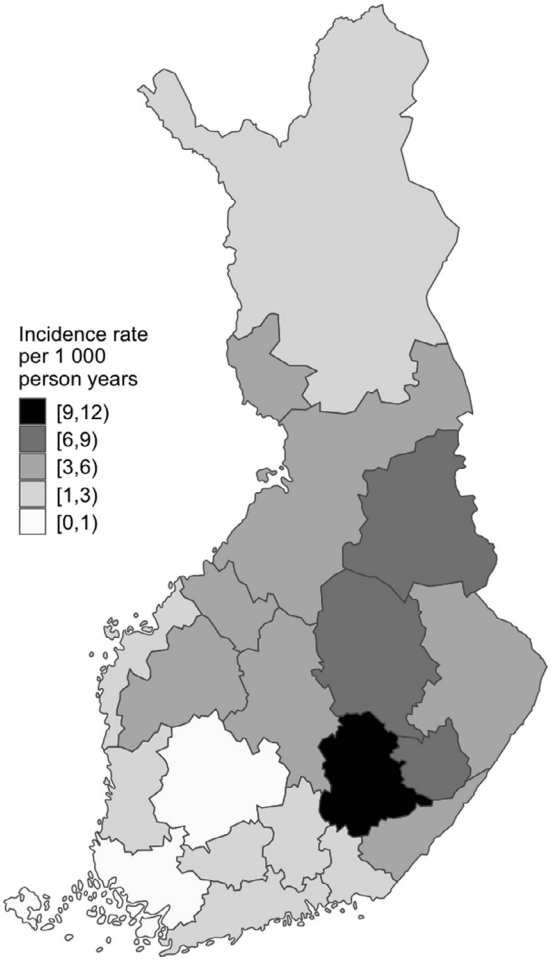

Figure 1. Incidence of Puumala virus infection in 20 health care districts and Åland during 2009-2019 in Finland.

Altogether, there were 24,691 cases of lymphoid malignancies, of which 90 were among the 16,075 PUUV-infected individuals, during a total of 61,144,826 person-years of observation (Table 2). In 68 cases, lymphoid malignancy was diagnosed after PUUV infection, contributing to the analysis. Three lymphoid malignancy cases occurred less than 3 months after the PUUV infection. A total of 10 cases occurred within 3-<12 months after the PUUV infection, and 38 cases within 1-<5 years after the PUUV infection. In addition, 16 lymphoid malignancies occurred within 5-<10 years after the PUUV infection and one case 10 years or more after the PUUV infection. The Cox regression analysis showed an association between the risk of lymphoid malignancy and PUUV infection 3-<12 months and 1-<5 years after the PUUV infection in HR 2.0 (95% CI, 1.1-3.7; $P = 0.029$) and HR 1.6 (95% CI, 1.2-2.3; $P = 0.002$), respectively (Table 3). The risk of lymphoid malignancy was not significantly increased ≥5 years after the PUUV infection. The analysis identified being a male as an independent risk factor for lymphoid malignancy, HR 1.49 (95% CI, 1.45-1.54; P <0.001).

Mature B cell neoplasms represented the majority in all lymphoid malignancies and those that developed after the PUUV infection, respectively representing 80% and 88% of all cases (Table 2). There were 60 cases of mature B cell neoplasms after PUUV; nine cases occurred within 3-<12 months after the PUUV infection and 34 cases within 1-<5 years after the PUUV infection (Table 4). The association between the risk of lymphoid malignancy and PUUV infection was significant for these periods, HR 2.2 (95% CI, 1.2-4.3; $P = 0.017$) and HR 1.8 (95% CI, 1.3-2.5; $P = 0.001$), respectively. The small number (<5) of lymphoid malignancy cases after the PUUV infection prevented reliable analyses for the other groups of lymphoid malignancies.

We further analyzed the largest subgroups of mature B cell neoplasms using Cox regression (Supplementary Table 1). The analysis showed an association between PUUV infection and the development of lymphoid malignancy for the subgroups of myeloma and plasma cell neoplasms 1-<5 years after the PUUV infection. We did not see an association for the subgroups of chronic lymphatic leukemia and diffuse B cell lymphoma. Due to the low number of cases in the other subgroups, they could not be reliably tested.

We performed a Cox regression using a 6-month wash-out period instead of 3 months; there were six cases 6-<12 months after the PUUV infection, with HR 1.8 (95% CI, 0.8-4.0; $P = 0.145$). When the first 12 months after the PUUV infection were analyzed as one period (13 cases), the association for the first year was HR 1.9 (95% CI, 1.1-3.3; $P = 0.017$). The exclusion of individuals with earlier PUUV infection (2004-2008) did not change the results (data not shown).

In the SIR analysis, the risk of lymphoid malignancy increased during 3-<12 months and during 1-<5 years after the PUUV infection, SIR 2.0 (95% CI, 1.1-3.7) and SIR 1.6 (95% CI, 1.2-2.3), respectively (Supplementary Table 2).

Discussion

We identified an increased risk of lymphoid malignancies after PUUV infection. Our results align with the earlier findings from Sweden, showing a similar association [16]. We also identified the risk of lymphoid malignancy associated with the group of mature B cell neoplasms specifically. The analyses identified the male sex, a known risk factor for PUUV infection [7], as an independent risk factor for developing lymphoid malignancy, which was described earlier [21].

The Swedish and South Korean studies showing an increased risk of lymphoid malignancies after HFRS provided the rationale for the current study addressing the association of lymphoid malignancies with PUUV infection in Finland [16,17]. In the Swedish study, the authors did not identify an association of a previous PUUV infection with any other cancers, whereas, in a South Korean study, HFRS was associated with both hematologic malignancies and solid organ cancers. The nationwide registers and high PUUV incidence in Finland allowed us to study this topic further. We found the association using two different statistical methods, Cox regression and SIR analysis, the latter of which was also applied in the Swedish study. The results of the two analyses were very similar, and the results were also in line with those of the Swedish study: in our study, the SIR for the development of lymphoid malignancy was 2.0 for 3-<12 months after the PUUV in-

Table 2
Characteristics of all individuals with lymphoid malignancy and those who developed lymphoid malignancy after the PUUV infection in Finland, 2009-2019.

	Cases of lymphoid malignancy, all n = 24,691	%	Lymphoid malignancy cases after the PUUV infection n = 68	%
Sex				
Male	13,393	54.2	32	47.1
Female	11,298	45.8	36	52.9
Age[a], median (range), years	69.8 (0-101)		67.2 (24.0-88.6)	
Age group[a], years				
0-19	826	3.4	0	0
20-39	1256	5.1	1	1.5
40-59	4075	16.5	17	25.0
60-79	13,272	53.8	45	66.2
≥80	5262	21.3	5	7.4
Lymphoid malignancy group and subgroup				
Mature B cell neoplasms	19,637	79.5	60	88.2
Myeloma and other plasma cell tumors	4401	22.4	16	26.7
Chronic lymphatic leukemia	3576	18.2	10	16.7
Malignant immunoproliferative diseases	431	2.2	0	0
Mantle cell lymphoma	990	5.0	7	11.7
Follicular B cell lymphoma	2836	14.4	6	10.0
Diffuse B cell lymphoma	6170	31.4	16	26.7
Burkitt's lymphoma/leukemia	151	0.77	0	0
Marginal zone lymphoma	873	4.4	5	8.3
Other mature B cell neoplasms	209	1.1	0	0
Hodgkin lymphoma	1648	6.7	2	2.9
Mature T and natural killer cell lymphoma/leukemia	1352	5.5	4	5.9
Acute lymphoblastic leukemia/lymphoma	847	3.4	0	0
Non-Hodgkin lymphoma, other or unspecified	810	3.3	0	0
Leukemia, other or unspecified	397	1.6	2	2.9

PUUV, Puumala virus.
[a] Age at diagnosis of lymphoid malignancy.

Table 3
Hazard ratios for developing lymphoid malignancy after the PUUV infection in Cox regression in Finland, 2009-2019.

	Number of cases N = 68	Hazard ratio	95% confidence interval	*P*-value
Lymphoid malignancy after PUUV infection				
No PUUV infection		ref.		
<3 months[a]	3	1.78	0.57-5.52	0.317
3-<12 months	10	2.00	1.07-3.71	0.029
1-<5 years	38	1.64	1.19-2.26	0.002
5-<10 years	16	1.16	0.71-1.89	0.563
≥10 years	1	1.34	0.19-9.53	0.769
Sex				
Female	36	ref.		
Male	32	1.49	1.45-1.53	<0.001
Geographical area				
1	10	ref.		
2	0	0.92	0.88-0.97	0.001
3	4	0.90	0.84-0.96	0.001
4	2	0.94	0.87-1.00	0.062
5	7	0.88	0.84-0.92	<0.001
6	3	0.99	0.93-1.05	0.751
7	2	0.97	0.91-1.04	0.440
8	3	0.84	0.78-0.91	<0.001
9	4	0.83	0.76-0.91	<0.001
10	2	0.84	0.74-0.95	0.008
11	3	0.88	0.82-0.95	0.001
12	8	0.83	0.78-0.89	<0.001
13	3	0.83	0.78-0.89	<0.001
14	4	0.93	0.87-0.99	0.024
15	2	0.82	0.76-0.89	<0.001
16	2	0.93	0.83-1.03	0.146
17	8	0.89	0.84-0.94	<0.001
18	1	0.87	0.79-0.97	0.009
19	0	0.88	0.78-0.98	0.025
20	0	0.87	0.79-0.95	0.001
21	0	0.96	0.81-1.14	0.676

PUUV, Puumala virus; ref., reference.
[a] Wash-out period

Table 4
Hazard ratios for developing mature B cell neoplasms after the PUUV infection in Cox regression[a] in Finland, 2009-2019.

	Cases after PUUV N	Hazard ratio	95% confidence interval	*P*-value
Mature B cell neoplasms				
<3 months[b]	2	1.47	0.37-5.87	0.587
3-<12 months	9	2.22	1.15-4.26	0.017
1-<5 years	34	1.80	1.29-2.52	0.001
5-<10 years	14	1.23	0.73-2.07	0.445
≥10 years	1	1.60	0.23-11.38	0.637

PUUV, Puumala virus.
[a] Adjusted for sex and region.
[b] Wash-out period.

fection and 1.6 for 1-<5 years after the PUUV infection; in the Swedish study, the SIR was 2.1 for <1 year and 1.8 for 1-<5 years after the PUUV infection [16]. Unlike in the Swedish study, we used a 3-month wash-out period between the PUUV infection and lymphoid malignancy to exclude the cases of lymphoid malignancies that already existed at the time of the PUUV infection.

In our study, the risk of lymphoid malignancy increased relatively soon after the PUUV infection and was elevated up to 5 years.

The association was the strongest with mature B cell neoplasms among the lymphoid malignancies. However, the small numbers of other groups of lymphoid malignancies among PUUV-infected individuals did not allow a reliable estimation of the association. Earlier studies have associated the risk of malignancies after HFRS with leukemia and non-Hodgkin lymphoma when the cancer reporting was based on ICD-10 codes [17]. In the HAEMACARE classification, the group of mature B cell neoplasms partly overlaps with the ICD-10 group of non-Hodgkin lymphomas [19], but comparing our results to those of the South Korean study is difficult because the categories of the lymphoid malignancies differ. Also, HFRS in South Korea is caused by four different orthohantaviruses, Hantaan, Seoul, Soocheong, and Muju [17], all of which cause more severe clinical manifestation than PUUV; thus, there might be underlying differences in the pathogenesis of human infection [3]. In the South Korean study, the occurrence of both hematologic malignancies and solid cancers increased after HFRS [17].

In the late 1980s, studies already showed HFRS-causing Hantaan virus to infect human lymphoblastoid cells [22] and to induce a persistent infection in marmoset B-lymphoblastoid cells [23]. Furthermore, reports have shown the presence of the Hantaan virus in the B cells of patients with an acute HFRS [24] and PUUV in the plasmablasts (activated B cells) of patients [14]. In addition to HFRS, studies show that plasmablast expansion also occurs during the other clinical hantavirus disease, hantavirus cardiopulmonary syndrome caused by the Andes virus [15], suggesting that B cell activation is common to both hantavirus diseases. PUUV can directly infect B lymphocytes and induce polyclonal B cell activation in vitro [14]. These reports support the hypothesis that hantavirus infection could contribute to B cell neoplasms by promoting proliferation and, together with antiapoptotic effects of hantavirus proteins [25,26], could directly enhance the development of mature B cell neoplasms.

There are some limitations in our study. We only had data on the laboratory-confirmed cases of PUUV infections reported to the NIDR. However, there may be individuals infected with PUUV who were not diagnosed and thus were misclassified as noninfected. In light of the high population-based seroprevalence of 12.5% determined using a nationwide health survey in 2011 [5], underdiagnosis is likely and might have diminished the association between PUUV infection and lymphoid malignancies in our study. This may be especially true in the nonendemic areas in Finland, where mild PUUV cases are most likely underdiagnosed [4,27]. We also lacked data on PUUV infections diagnosed before 2004.

Our study found an association between PUUV infection and lymphoid malignancies, in which 0.3% of all lymphoid malignancies occurred in patients with a history of a PUUV infection. In this number, other possible causative factors are not considered; thus, this is likely an overestimation of lymphoid malignancy cases related to PUUV infection. Due to the nature of a register-based study, we lacked data on potential confounders, such as smoking, chronic diseases, and socioeconomic factors [5,17]. The correct definition of lymphoid malignancy in the FCR was critical for finding all the cases among those who have had a PUUV infection and in the whole Finnish population. The same definitions were used for both groups. The cancer classification in the FCR was renewed in 2008 and was in place at the start of the study period in 2009. We chose the HAEMACARE classification instead of the ICD-10 classification because it is used in reporting cancers in Europe [19].

More studies are needed to assess whether lymphomas potentially caused by PUUV infection result in a significant public health burden in terms of absolute risks. Nevertheless, our data can inform disease burden estimates, which may be relevant in, *e.g.*, potential vaccine development and targeting of risk groups.

Conclusion

We found a significant association between the incidence of lymphoid malignancies and PUUV infection during the first 5 years after infection in the Finnish population in this register-based study. The association was the strongest for the mature B cell neoplasms. Further research is needed in the field of biological mechanisms behind this association and on the preventive measures of PUUV infection.

Declaration of competing interest

TD works in Monitoring Outbreaks for Disease surveillance in a data science context (MOOD)/Horizon 2020 project, for which funding is received from the Finnish Institute for Health and Welfare and is a member of the executive board of MOOD Horizon 20202. TD also works on a project for vector-borne diseases and climate change in Finland (VECLIMIT), for which funding is received by the Finnish Institute for Health and Welfare from the Academy of Finland. JS owns stocks in a company (Genmab) that is involved in lymphoma drug development. EK reports a grant paid for their institution from the Finnish Society of Sciences and Letters for PUUV research outside of the submitted work.

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Ethical approval

The names and personal ID numbers were used only in the linkage of the NIDR and the FCR to identify the study population. They were not used in data analysis or when reporting the results. The permission to use register data from the NIDR and the FCR was given in the internal process within the Finnish Institute for Health and Welfare (decision number: THL/2253/6.02.00/2021). Ethical approval was not required for this register-based study.

Author contributions

Sohvi Kääriäinen, Jukka Ollgren, Timothee Dub, Outi Laine, Marjatta Sinisalo, Jussi Sane and Outi Lyytikäinen contributed to the conception and design of the study. Sohvi Kääriäinen, Jukka Ollgren and Outi Lyytikäinen did the analyses and graphics. Sohvi Kääriäinen drafted the first version of the manuscript, and together with Jussi Hepojoki, Tomas Strandin, Eliisa Kekäläinen and Outi Lyytikäinen drafted the revisions. All authors contributed to the interpretation of the data and the critical revision of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.03.026.

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