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Incidence of central serous chorioretinopathy (2011–2018): a nationwide population-based cohort study of Japan

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2021-319403).

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Received 8 April 2021
Accepted 19 June 2021

ABSTRACT

Aims The aim of this study was to elucidate the epidemiological background of central serous chorioretinopathy (CSC), including its incidence and treatment pattern.

Methods This was a population-based longitudinal cohort study using a nationwide health insurance claims database of the Japan Ministry of Health, Labour and Welfare (MHLW). As Japan employs universal health coverage, the database covers more than 95% of claims issued in Japan. We accessed all data stored in the database with permission from the MHLW. We traced all individuals aged 30 years or older and identified individuals with new onset of CSC between January 2011 and December 2018. CSC cases were categorised by age and sex for each year, and incidence rate was calculated. We also identified major treatments for CSC to elucidate the initial treatment pattern.

Results During the 8-year period, 247 930 incidences of CSC were identified, among which 75.9% were men. The crude incidence rate (per 100 000 person-years) in the general population aged 30 years or older was 34.0 (95% CI 33.9 to 34.2), in men was 54.2 (95% CI 53.9 to 54.4) and in women was 15.7 (95% CI 15.5 to 15.8). The mean age of onset was lower in men than in women (50.5±12.5 years vs 54.7±13.5 years). Most of the patients with newly diagnosed CSC (86.8%) did not receive major treatment.

Conclusions The current study provides the nationwide population-based evidence to clarify the detailed epidemiology of CSC. These results could help to understand the pathogenesis and mechanisms of CSC in the future.

INTRODUCTION

Central serous chorioretinopathy (CSC) is a common ocular disease, whose characteristics include serous retinal detachment of the macular regions and damage to the retinal pigment epithelium.[1 2] Although retinal detachments in CSC eyes are generally self-limiting, in some cases, these become chronic, leading to persistent retinal detachment and permanent retinal tissue damage.[3 4]

Historically, CSC has been considered to be a self-limiting benign disease with a good visual prognosis.[5] However, in 2019, Mrejen *et al* investigated the long-term visual outcomes of patients with CSC with subretinal fluid lasting for more than 6 months and reported that 12.8% of these patients had social blindness in both eyes during a mean follow-up of 11.3 years.[6] We have also recently pointed out the possibility that Asian age-related macular degeneration (AMD) includes a considerable number of choroidal neovascularisation (CNV) secondary to CSC cases (recently named pachychoroid neovasculopathy) through a genetic risk score analysis of 200 Asian patients with AMD and a genome-wide association study of 1546 CSC samples and 13 029 controls from Asian and Caucasian participants.[7 8] Based on these findings, CSC is recognised as an important sight-threatening disease that can lead to legal blindness.

Despite the increasing importance of CSC, its epidemiological background has not been well reported, with only three population-based studies evaluating the incidence of the disease.[2 9 10] To understand the pathogenesis and ethnic differences of CSC, more epidemiological fundamental information needs to be reported. Herein, under the permission of the Japan Ministry of Health, Labour and Welfare (MHLW), we accessed and analysed all data stored in the National Database of Health Insurance Claims and Specific Health Check-ups of Japan (NDB,[11 12] covering more than 95% of the claims issued in Japan[13]) managed by the MHLW to evaluate the epidemiological background of CSC.

MATERIALS AND METHODS

The institutional review board and the ethics committee of Kyoto University Hospital and Kyoto University Graduate School of Medicine approved this retrospective, nationwide population-based cohort study (approval number R2035). All investigations adhered to the tenets of the Declaration of Helsinki and its later amendments.

Database

Japan has universal health coverage system covering most of the 127 138 033 individuals that make up the Japanese population as of 2020. The Japanese MHLW gradually made it mandatory to submit medical claims electronically from 2008 to 2011, and all claims are principally submitted electronically from 2011. These data are stored in the NDB after anonymisation. In the current study, we used this database via the NDB Onsite Research Center Kyoto, one of the two NDB onsite remote

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To cite: Kido A, Miyake M, Tamura H, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2021-319403

access centres with access to the whole NDB dataset, under the approval of the MHLW.[11 14] The current study was conducted during the authorised research period between 11 October 2019 and 10 April 2020.

The NDB contains detailed information of more than 95% of medical claims data in Japan, including diagnoses coded by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (ICD-10), drugs, and procedures for both outpatients and inpatients.[15] These are also coded by local claim codes of Japan. Flags for suspicion can be added to the diagnostic codes. At the time of research initiation, a total of >14 billion claims covering the whole Japanese population (n≥127 million) generated between 2009 and 2019 were available. Further, as Japan is known to be a nation of ethnically homogenous people, the NDB provides us with abundant and exhaustive medical information of a single ethnic group.

Onset of CSC

Although the NDB contains personal unique IDs (ID1 and ID2), it is known that they sometimes fail to link the same person due to several reasons.[14 16] Therefore, we created a new personal unique ID, called ID0, according to the previously reported method,[16 17] which allowed us to more accurately link the tens of billions of claims than the predefined personal unique ID. Though the detail is described elsewhere,[16] we have also provided the details of the ID0 creation method in the supplementary note.

After linking as many of the claims of individuals aged ≥30 years as possible using the ID0 method, we identified the unique IDs of individuals who were diagnosed as having CSC at any time between 1 April 2009 and 31 December 2018. When the claim with the diagnosis of CSC was issued for the first time and the date of diagnosis of CSC matched the month of medical care, the date of diagnosis of CSC was defined as the onset of CSC. The incident case of CSC between 1 April 2009 and 31 December 2010 was excluded from the current study to washout the recurrent cases.

In line with previous studies, CSC diagnosis was defined as having the diagnostic code for CSC.[9] The diagnoses with flag for suspicion were excluded. In the NDB, seven-digit local diagnostic codes ('NDB diagnostic codes', hereafter) are employed as diagnostic codes; these are known to be more specific than ICD-10 codes. For example, 'central serous choroidopathy' and 'central serous retinochoriopathy' are represented by the same disease name in ICD-10 as H35.7, whereas they are assigned different codes in the NDB diagnosis codes (online supplemental table). Thus, individuals who had NDB diagnostic codes for CSC and its various synonyms, which reflect a history of CSC described under various names, were diagnosed with CSC in the current study.[18] The online supplemental table presents the correspondence between NDB diagnostic codes and ICD-10 codes.

Incidence and incidence rate of CSC

The number of cases of CSC onset, namely the incidence of CSC, was counted by age and sex categories per year between 2011 and 2018.

Incidence rates stratified by age and sex were determined by dividing the number of CSC cases within each group by the population at risk within the corresponding group. The age-standardised incidence rate of CSC was calculated according to the standard age-structure world population of the WHO for 2000–2025.[19] The current population estimates of each year between 2011 and 2018 provided by the Japanese Ministry of Internal Affairs and Communications were used to define the entire population and each subgroup population as the population at risk (available at https://www.stat.go.jp/english/data/jinsui/2.html, accessed 24 June 2020).

Initial treatments for CSC

Transition of the initial treatment for CSC during 2011–2018 was also evaluated. We focused on three major treatment for CSC,[20 21] namely, laser photocoagulation, photodynamic therapy (PDT) with verteporfin and anti-vascular endothelial growth factor (anti-VEGF) intravitreal injection. PDT uses a laser after infusing the photosensitiser, verteporfin. Anti-VEGF drugs include ocular agents, namely, pegaptanib, ranibizumab and aflibercept. Because the NDB employs local drug codes (NDB drug codes) and local procedure codes (NDB procedure codes), we used them to identify the above-mentioned drugs and procedures. The online supplemental table summarises the correspondence between these local codes and the *Anatomical Therapeutic Chemical Classification System* (ATC)/the *International Classification of Diseases Ninth Revision, Clinical Modification* (ICD-9-CM) codes. The duration from the CSC onset was counted by day.

Geographical, climatic and seasonal variation of incidence rate

The incidence of CSC in 2015 was counted for each of the 47 prefectures in Japan. We divided them into two to eight groups depending on the variables of interest, namely, the eight main Japanese regions, urban area or not, the average annual temperature, the number of snowfall days per year and total daylight hours per year. The eight main Japanese regions comprise Hokkaido, Tohoku, Kanto, Chubu, Kansai (Kinki), Chugoku, Shikoku and Kyushu.[22 23] Classification as an urban area or not was determined by the modified definition from the Organisation for Economic Co-operation and Development (regional typology) with reference to a previous report.[24] The climatological normal of annual temperature, number of snowfall days per year and total daylight hours per year of each prefecture were obtained from publicly available Japanese government statistics (available at https://www.e-stat.go.jp/en/dbview?sid=0000010202, accessed 24 June 2020). Regarding these three variables, the 47 prefectures were divided into three groups by the tertile values.

To evaluate seasonal variation, the incidence of CSC was also counted for each month from 2011 to 2018. Average CSC incidence rates for each month were calculated.

Statistical analyses

All statistical analyses were performed using Oracle R Enterprise V.1.4.1 and R V.3.4.1. All values are presented with 95% CIs based on the Poisson distribution. Between-group differences were tested using the z-test and/or analysis of variance. A two-sided p value of ≤0.05 was considered as statistically significant.

RESULTS

In total, 2 47 930 cases of CSC were identified in the NDB dataset during the 8-year study period, among which 75.9% were men. Online supplemental figure 1 shows a flow diagram of the extraction process. Table 1 shows the number of incident CSC cases, incidence rates of CSC (per 100 000 person-years) and mean age of the patients at CSC onset from 2011 to 2018. The crude incidence rate was 34.0 per 100 000 person-years (95% CI 33.9 to 34.2) for the overall population, which corresponds to 19.4 per 100 000

Table 1 Annual incidence of central serous chorioretinopathy, 2011–2018

	1000 person-years			Incidence			Incidence rate (95% CI)			Age at onset (mean±SD)		
Year	Man	Woman	Total	Man	Woman	Total	Man	Woman	Total	Man	Woman	Total
2011	43 150	47 278	90 428	26 320	7901	34 221	61.0 (60.3 to 61.7)	16.7 (16.3 to 17.1)	37.8 (37.4 to 38.2)	49.9±12.0	54.2±13.2	50.9±12.4
2012	43 244	47 397	90 641	26 214	8061	34 275	60.6 (60.0 to 61.4)	17.0 (16.6 to 17.4)	37.8 (37.4 to 38.2)	50.0±12.0	54.1±13.2	51.0±12.4
2013	43 315	47 493	90 808	24 527	7486	32 013	56.6 (55.9 to 57.3)	15.8 (15.4 to 16.1)	35.3 (34.9 to 35.6)	50.1±12.3	54.6±13.3	51.1±12.7
2014	43 385	47 584	90 969	23 556	7500	31 056	54.3 (53.6 to 55.0)	15.8 (15.4 to 16.1)	34.1 (33.8 to 34.5)	50.7±12.5	54.6±13.5	51.6±12.8
2015	43 641	47 739	91 380	23 543	7879	31 422	54.0 (53.3 to 54.6)	16.5 (16.1 to 16.9)	34.4 (34.0 to 34.8)	51.0±12.7	54.8±13.6	51.9±13.0
2016	43 663	47 771	91 434	22 163	7173	29 336	50.8 (50.1 to 51.4)	15.0 (14.7 to 15.4)	32.1 (31.7 to 32.5)	50.9±12.8	54.8±13.7	51.8±13.2
2017	43 654	47 766	91 420	21 238	6893	28 131	48.7 (48.0 to 49.3)	14.4 (14.1 to 14.8)	30.8 (30.4 to 31.1)	50.9±12.8	54.8±13.9	51.9±13.2
2018	43 609	47 730	91 339	20 719	6757	27 476	47.5 (46.9 to 48.2)	14.2 (13.8 to 14.5)	30.1 (29.7 to 30.4)	51.0±12.9	55.3±13.9	52.1±13.3
Total	347 661	380 758	728 419	188 280	59 650	247 930	54.2 (53.9 to 54.4)	15.7 (15.5 to 15.8)	34.0 (33.9 to 34.2)	50.5±12.5	54.7±13.5	51.5±12.9

The incidence rate is reported per 100 000 person-years.

person-years after age standardisation to WHO's standard world population. The mean incidence rate in men was 54.2 per 100 000 person-years (53.9–54.4) and that in women was 15.7 per 100 000 person-years (15.5–15.8), which represents decreasing trends, especially in men. The mean age of onset was younger in men than in women (50.5±12.5 years vs 54.7±13.5 years, p<0.001).

Table 2 and figure 1 show the age-stratified and sex-stratified average annual incidence and incidence rates of CSC. The distributions were different between men and women. The incidence rate of CSC was higher in men than that in women for every age group. The highest incidence rate was observed in men and women aged 40–44 years and 50–54 years, respectively. Figure 2 shows the age-stratified and sex-stratified incidence rates of CSC across the study period. While the incidence rate was nearly stable in the youngest age group (30–34 years group) and the higher age groups (65 years or more) between 2011 and 2018, incidence rate in individuals aged 35–64 years was not; the incidence rates in this age bracket were high between 2011 and 2013 and showed a decreasing trend thereafter.

Table 3 shows the initial treatments and their timings among 181 501 cases (73.2%) who could be observed for more than 1 year. In the first 12 months since diagnosis, 157 513 patients (86.8%) did not receive PDT, laser photocoagulation or anti-VEGF treatment. The proportion of treatment cases steadily increased over the research period, with an increasing trend for PDT and anti-VEGF therapy. The duration from onset to treatment was 110.0±94.8 days, 60.0±82.2 days and 96.0±92.4 days for PDT, laser photocoagulation and anti-VEGF, respectively. Online supplemental figure 2 shows the days from diagnosis to the initial PDT.

Online supplemental figure 3 summarises the descriptive statistics regarding geographical and climatic variations in the CSC incidence rate. The CSC incidence rate was significantly higher in predominantly urban prefectures than in rural prefectures (36.1 (95% CI 35.6 to 36.6) vs 32.0 (95% CI 31.4 to 32.6) per 100 000 person-years, 3A). We observed high regional variation in the CSC incidence rates, ranging from 43.1 per 100 000 person-years (95% CI 40.7 to 45.5) in Shikoku to 28.8 per 100 000 person-years (95% CI 27.5 to 30.1) in Tohoku (3B). The CSC incidence rate increased in line with the rise in average temperatures (3C). Regarding the snowfall days and the total daylight hours per year, the CSC incidence rate was low in places with the highest snowfall days per year and those with the lowest total daylight hours per year (3D and 3E). Online supplemental figure 4, illustrated by HT, one of the authors, shows a geographical heatmap of the incidence rate of CSC by prefecture. Online supplemental figure 5 shows the seasonal variation of the incidence of CSC. The incidence of CSC was significantly different among months (p<0.001). Incidence from March

Table 2 Age-stratified and sex-stratified incidence of central serous chorioretinopathy, 2011–2018

	Average annual incidence			Incidence rate (95% CI)		
Age group (yrs)	Man	Woman	Total	Man	Woman	Total
30–34	1333	394.8	1727.8	36.1 (35.4–36.8)	11.1 (10.7 to 11.5)	23.8 (23.4 to 24.4)
35–39	3285.4	639.8	3925.1	76.5 (75.6–77.4)	15.4 (15.0 to 15.8)	46.5 (46.0 to 47.0)
40–44	4513.5	919.9	5433.4	94.7 (93.7–95.7)	19.9 (19.5 to 20.4)	57.9 (57.4 to 58.4)
45–49	3849	1010.6	4859.6	88.0 (87.0–88.9)	23.6 (23.1 to 24.1)	56.2 (55.6 to 56.7)
50–54	2816.9	974.6	3791.5	71.8 (70.9–72.8)	25.1 (24.6 to 25.7)	48.6 (48.1 to 49.2)
55–59	2124.5	855.1	2979.6	55.6 (54.7–56.4)	22.2 (21.7 to 22.7)	38.8 (38.3 to 39.3)
60–64	1903.4	812.1	2715.5	43.5 (42.8–44.2)	18.0 (17.5 to 18.4)	30.5 (30.1 to 31.0)
65–69	1509.5	696.1	2205.6	34.4 (33.8–35.0)	14.8 (14.4 to 15.2)	24.2 (23.9 to 24.6)
70–74	1025.1	495.3	1520.4	28.8 (28.2–29.5)	12.2 (11.8 to 12.6)	19.9 (19.6 to 20.3)
75–79	662	339.9	1001.9	23.3 (22.7–24.0)	9.5 (9.2 to 9.9)	15.6 (15.3 to 16.0)
80–84	351.6	199.5	551.1	17.8 (17.1–18.4)	6.8 (6.4 to 7.1)	11.2 (10.8 to 11.5)
85–89	130.4	89.1	219.5	12.6 (11.8–13.3)	4.4 (4.0 to 4.7)	7.1 (6.8 to 7.5)
90 and above	30.8	29.5	60.3	7.5 (6.6–8.5)	2.2 (1.9 to 2.4)	3.4 (3.1 to 3.7)
All participants	23 535	7456.3	30 991.3	54.2 (53.9–54.4)	15.7 (15.5 to 15.8)	34.0 (33.9 to 34.2)

The incidence rate is reported per 100 000 person-years.

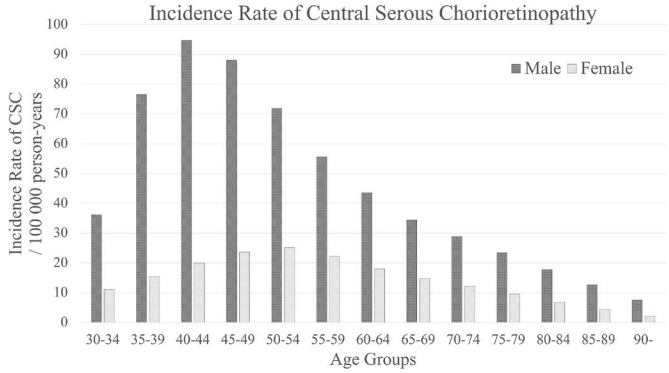

Figure 1 Age-stratified and sex-stratified incidence rate of central serous chorioretinopathy (CSC) per 100 000 person-years. The overall distribution was skewed to the right in both men and women. The incidence rate of CSC in men was higher than women in every age group. The highest incidence rate was observed in the 40–44 years group in men and the 50–54 years group in women.

to June and from October to November was higher than the annual average monthly incidence.

DISCUSSION

We conducted a nationwide retrospective cohort study to elucidate the epidemiology of CSC. To the best of our knowledge, this is the largest population-based cohort study of CSC to date. This analysis revealed a relatively higher incidence of CSC compared with that reported in Caucasians, clear sex differences and seasonal variation.

Thus far, three population-based studies have been conducted regarding CSC: the first from Olmsted County, Minnesota, USA,[2] conducted between 1980 and 2002; the second from Taiwan between 2001 and 2006[9]; and the third from South Korea between 2011 and 2015.[10] The CSC incidence rate of the current study (34 per 100 000 person-years) was more similar to those of South Korea (35 per 100 000 person-years) and Taiwan (21 per 100 000 person-years) compared with that of Olmsted County, Minnesota (5.8 per 100 000 person-years). Even considering that the estimates of the two previous reports may not have been as precise as the current study due to the small number of incident cases (784 per 6 years in Taiwan and 74 per 22 years

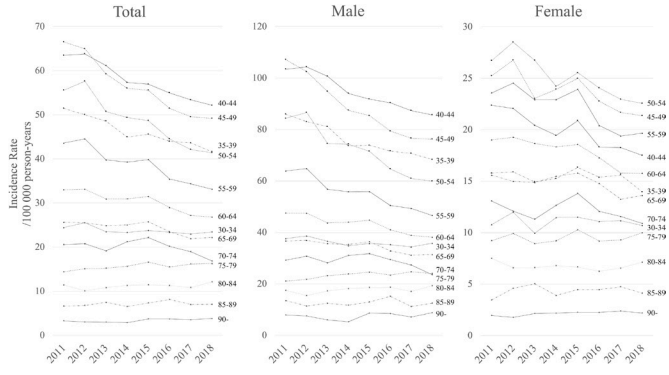

Figure 2 Transition of age-stratified and sex-stratified incidence rate of central serous chorioretinopathy (CSC) per 100 000 person-years. While the incidence rate of CSC was nearly stable in the youngest age group (30–34 years group) and higher age groups (65 years or more) between 2011 and 2018, incidence rate in individuals aged 35–64 years was high in 2011–2013 and decreased thereafter both in men and women.

in Olmsted Country, Minnesota, compared with 247 930 per 8 years in the current study), we can state that the incidence rate of CSC is higher in Asians compared with Caucasians. This is compatible with the recent findings that pachychoroid neovasculopathy, a CNV secondary to CSC spectrum masquerading as AMD, is more prevalent in Asians than Caucasians.[8]

The annual incidence rate of CSC in men was 3.46 times higher than that in women, and the peak age of onset was higher in women than in men, which were consistent with the known epidemiology of CSC and the results of previous reports.[2 9 10] However, our results enabled a more precise evaluation of distribution of onset age; the highest incidence rate was observed in men aged 40–44 years and women aged 50–55 years. The peak shift of onset age in women may be related to hormonal balance changes due to menopause.[25]

The reason the incidence rate of CSC in people aged 35–64 years was higher from 2011 to 2013 than that thereafter is unknown. However, this declining trend may be associated with a decrease in stress, which is a major risk factor of CSC. In fact, the number of suicides, especially among men, has also declined significantly (available at https://www.mhlw.go.jp/wp/hakusyo/jisatsu/16/dl/1-01.pdf, accessed 7 October 2020), which would be related to the global economic recovery. Another possible reason is the insufficient exclusion of recurrent cases. However, the incident case of CSC prior to 2010 was excluded from the current study, which allowed us to secure the washout period of up to about 2 years, even for those with the onset in 2011. Considering most of the recurrences are reportedly observed within 2 years,[26 27] the overestimation due to the insufficient exclusion of recurrent cases would be limited.

The present study was the first to disclose the actual treatment practice for CSC. As many cases of serous detachment associated with CSC are known to be self-limiting,[5] 80%–90% of patients with CSC did not receive any of the intervention of interest within a year from onset. However, in line with the accumulating evidence of the efficacy of PDT to treat CSC,[28] PDT was more likely to be selected as a first-line treatment for CSC from 2011 to 2017, as shown in table 3. From 2013, the year after when Fung *et al* reported a case series of CNV in CSC masquerading as neovascular AMD,[29] the use of anti-VEGF therapy also increased. Although there is no sufficient evidence to support the efficacy of anti-VEGF therapy for CSC without CNV, current evidence indicates that it can be recommended for CSC if CNV is present.[28] Recent further increases in the use of anti-VEGF therapy might be accelerated by the popularisation of optical coherence tomography angiography, which can non-invasively detect CNV.[30 31]

Geographical, climatic and seasonal variations in the incidence rate of CSC offer us interesting implications. Especially, the current study successfully replicated the results of previous small-sized studies from the UK and Japan that reported CSC incidence was higher in spring and autumn.[32 33] The lowest incidence of CSC in winter might be related to the observation that the CSC incidence rate was low in prefectures with low temperatures, high number of snowfall days and low total daylight hours (online supplemental figure 3). The reason for the relatively low incidence in summer is unknown. However, because the CSC incidence rate in prefectures with the highest total daylight hours was lower than that in those with middle total daylight hours, daylight hours might have some causal effect on CSC.

While this nationwide population-based study has strengths in its large sample size and its representativeness, there are still certain limitations. First, we were not able to identify patients with CSC who had not visited a hospital;

Table 3 Chronological changes of treatment for central serous chorioretinopathy

				Treated		
		Not treated	Treated	PDT	Laser photocoagulation	Anti-VEGF
Year	Incidence*	Cases (%)	Cases (%)	Cases	Cases	Cases
2011	28075	25667 (91.42)	2408 (8.58)	458	1423	531
2012	29407	26113 (88.80)	3294 (11.20)	535	2136	632
2013	27831	24327 (87.41)	3504 (12.59)	517	2070	925
2014	26776	23182 (86.61)	3594 (13.39)	560	1976	1060
2015	26668	22867 (85.75)	3801 (14.25)	574	2040	1195
2016	24332	20653 (84.88)	3679 (15.12)	569	1826	1301
2017	18422	14704 (79.82)	3718 (20.18)	622	1723	1384
Total	181501	157513 (86.78)	23988 (13.22)	3835	13194	7028

The duration from onset to the initial treatment (±SD) was 110.0±94.8 days, 60.0±82.2 days and 96.0±92.4 days for PDT, laser photocoagulation and anti-VEGF, respectively.
*Incidence of central serous chorioretinopathy with at least 1 year of follow-up.
PDT, photodynamic therapy; Anti-VEGF, anti-vascular endothelial growth factor

this may have led to an underestimation of CSC incidence. However, such cases would be minimum because CSC causes obvious subjective symptoms such as blurred vision, relative central scotoma, metamorphopsia, micropsia and/or reduced contrast sensitivity.[34] Second, CSC diagnosis was based on NDB diagnostic codes. Because CSC diagnosis based on NDB diagnostic codes has not yet been fully validated, some caution is required, and the issue needs to be addressed. Nevertheless, this limitation may not have had a great impact on the present study, because the NDB diagnostic codes for CSC are more specific than the ICD-10 codes, and CSC is less likely to be misdiagnosed since its presentation is typical. Third, there is a possibility that ophthalmologists initially coded a rule-out diagnosis and corrected it after examinations, which might lead to an overestimation of the incidence. However, such effect was minimised because we excluded the diagnostic codes with flags for suspicion. Finally, although the NDB is a comprehensive administrative database that covers most of medical care for the entire Japanese population, medical care not covered by health insurance, for example, medical care paid by welfare and medical care paid by industrial accident compensation insurance, is not included in the NDB.[12 35] Thus, it is likely that we missed some CSC cases under such conditions. However, because such cases are not common, we believe its influence was also minimal.

In summary, the current study provides the largest population-based evidence to clarify the detailed epidemiology of CSC. The incidence rate of CSC is higher in Asians compared with Caucasians, which supports the importance of pachychoroid diseases, especially in Asians. Although clear sex differences in age-stratified incidence rate, climatic variation and seasonal variation need to be validated in future studies, these factors might be associated with the pathogenesis of CSC. Epidemiological, genetic and clinical studies of CSC will help to further elucidate the pathogenesis and mechanisms of CSC in the future.

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Funding This work was partly supported by JSPS KAKENHI Grant Number 20H03841.

Disclaimer The funding organisations had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data availability: The permission to access NDB expired after the authorised research period; therefore, we can no longer access the raw data without obtaining another access permission. The raw data can be accessed only after obtaining permission from the MHLW. Those who want to access raw data need to apply to the MHLW. The program codes used during the current study are available from the corresponding author on reasonable request.

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Supplemental Material

Supplemental Note

Two types of personal identification numbers: ID1 and ID2

Because Japan has not deployed unique personal identification numbers in the healthcare system, unlike the U.S.[1] or Taiwan, [2] the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) includes two types of personal identification number to link the insurance claims of individual patients: ID1 and ID2.[3] ID1 is a hash value generated from the insurer's ID, and the beneficiary's ID, date of birth, and sex; ID2 is a hash value generated from the beneficiary's name, date of birth, and sex.[3, 4] Because these IDs can change by some life events such as marriage, career change, retirement, etc., more robust personal identification number is preferable.

ID0

To improve personal identification, the improved personal identification number named ID0 has been proposed and is commonly used in NDB analysis. While the original method was described by Kubo et al.,[4] their method was limited in that it could link only claims of 2 years due to computer recourse.

In this study, we were able to link claims of over 8 years by modifying the original ID0 methods. Briefly, our modified method generates a number of chunks, and processes them one by one to effectively utilize the computer recourse. The details are described hereafter.

ID0 creation

ID1, ID2, the date of medical care, and medical care outcomes were extracted from the following 5 NDB categories: "medical inpatient claims," "medical outpatient claims," "medical inpatient claims subjected to bundled payment during diagnosis procedure combination (DPC) hospitalization," "DPC claims during DPC hospitalization," and "DPC claims subjected to bundled payment during DPC hospitalization".

We first searched for the same ID1 and determined that it corresponded to the same individual. The data linkage process ended when death was noted in the outcome section. When a series of claims tracked by ID1 was interrupted at a certain point, the corresponding ID2 at that point was used for further tracking. If more than one candidate ID2 was found, the data linking process was terminated to avoid linking data corresponding to different individuals.

Originally, data for all ages were extracted and linked simultaneously at this stage. However, the data volume was too large to use all the data of the 8 years from 2011 to 2018. Therefore, to deal with this problem, we extracted the data of the 8 years in small sections separated by age. To track individuals by ID1 or ID2, the same person's data must be extracted as a set of data; thus, we did so with great care.

Claims associated with an individual whose eligibility is under question are re-reviewed by the insurer through the Health Insurance Claims Review and Reimbursement Services. Such claims for re-review are not included in the NDB, and the old ID1 and a newly assigned ID1 can co-exist for approximately 3 months. To address this problem, the ID2 corresponding to the old ID1 was used to search data in the following month, the first preceding month, and the second preceding month to obtain an intermediate dataset table (medical and DPC).

The new ID1 was replaced by the old ID1 within a row so that a single ID1 was assigned (provisional ID0). When the replaced ID1 was the old ID1 of a different pair, it was replaced by the new ID1. This process was repeated until all second ID1s were replaced. The remaining ID1 was defined as a new variable ID0. In other words, a new data linkage variable ID0 was obtained by sequentially replacing an old ID1 with a new ID1. When there were no linkable claims because of only one medical visit (and thus no one-to-one ID1 pairing), the ID1 of the single claim served as ID0.

The ID0 generated in this way was used to follow up by connecting claims data across multiple months for the same patient. We identified the first and last month of claims data stored in the NDB for each identical ID0 of the target patient. Months for which no claims data occurred within that period were considered "periods for which insurance was not required."

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Supplemental Table

Supplementary Table. Correspondence Table of Codes used in the current study

A. NDB diagnostic codes

NDB diagnostic code	Disease Name	ICD-10 code
3624004	Central Serous Choriopathy	H35.7
3630002	Central Serous Retinochoriopathy	H35.7
8837586	Central Chorioretinopathy	H30.0
8837587	Central Retinopathy *	H30.0
3624006	Central Chorioretinitis *	H30.0
3630004	Central Retinitis *	H30.0
8837585	Central Choroiditis *	H30.0

*These disease names are historical synonyms for Central Serous Chorioretinopathy.

The ICD-10 code H35.7 and H30.0 correspond to six and eleven NDB diagnostic codes, respectively. We employed only two of six and five of eleven NDB diagnostic codes which correspond to CSC.

B. NDB drug codes

NDB drug code	Drug Name	ATC code
620001909	Verteporfin	S01LA01
620008448	Pegaptanib	S01LA03
620009103	Ranibizumab	S01LA04
621894901	Ranibizumab	S01LA04

622352001	Ranibizumab	S01LA04
622199401	Aflibercept	S01LA05

C. NDB procedure codes

NDB procedure code	Procedure Name	ICD-9-CM code
150244110	Laser photocoagulation	14.55

Supplemental Figure

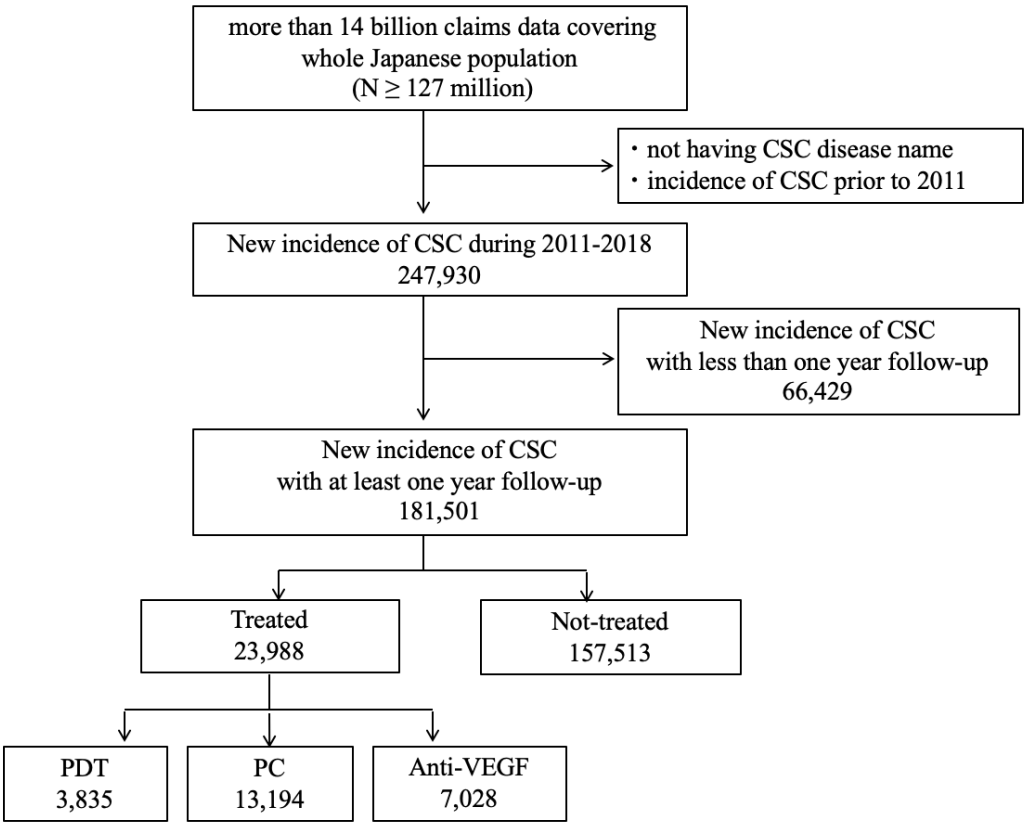
Supplementary Figure 1. Flow-diagram.

This is a flow-diagram showing the process of selecting central serous chorioretinopathy patients in the current study.

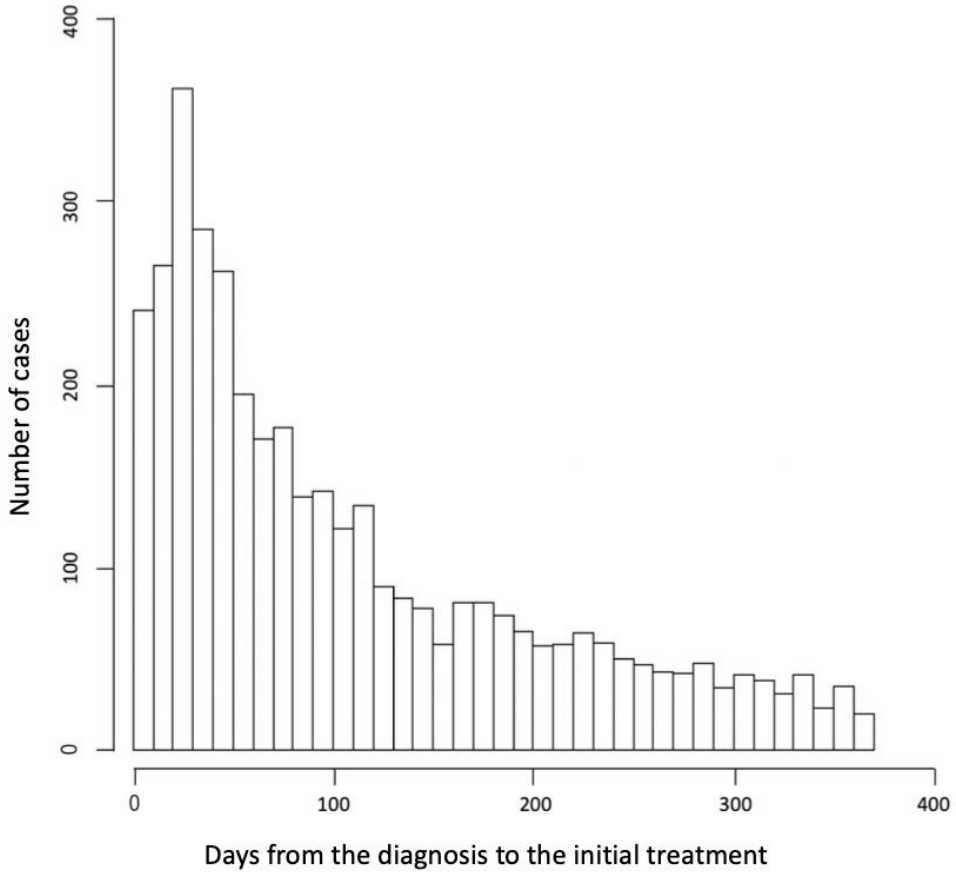
PDT: photodynamic therapy

PC: laser photocoagulation

Anti-VEGF: anti-vascular endothelial growth factor

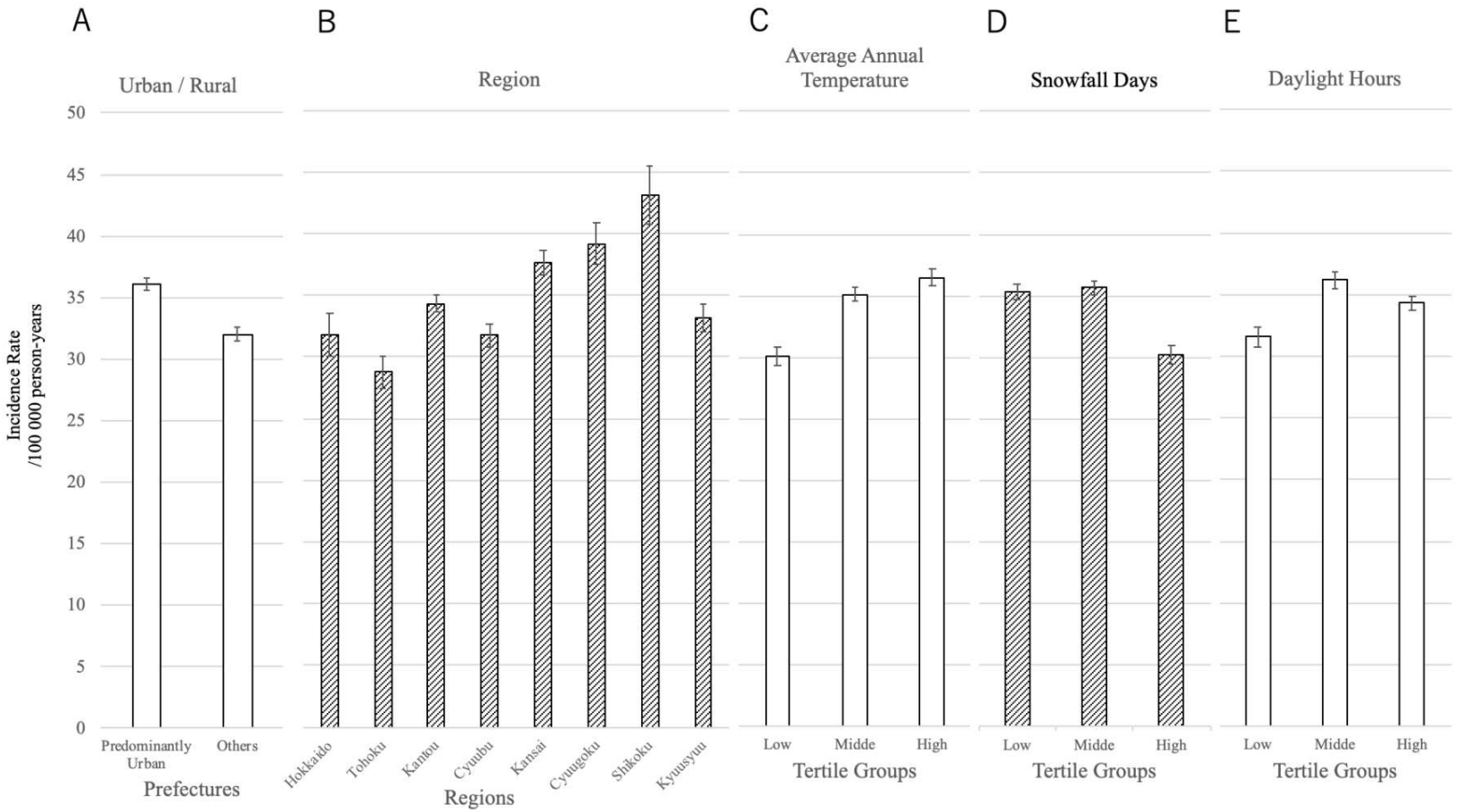


Supplementary Figure 2. Days from the diagnosis of central serous chorioretinopathy to the initial treatment with photodynamic therapy.
The histogram shows the number of cases per 10-days group from the diagnosis of central serous chorioretinopathy to the initial treatment with photodynamic therapy with verteporfin. The peak period of initial treatment 30-40 days from the diagnosis. The overall distribution was skewed to the right.



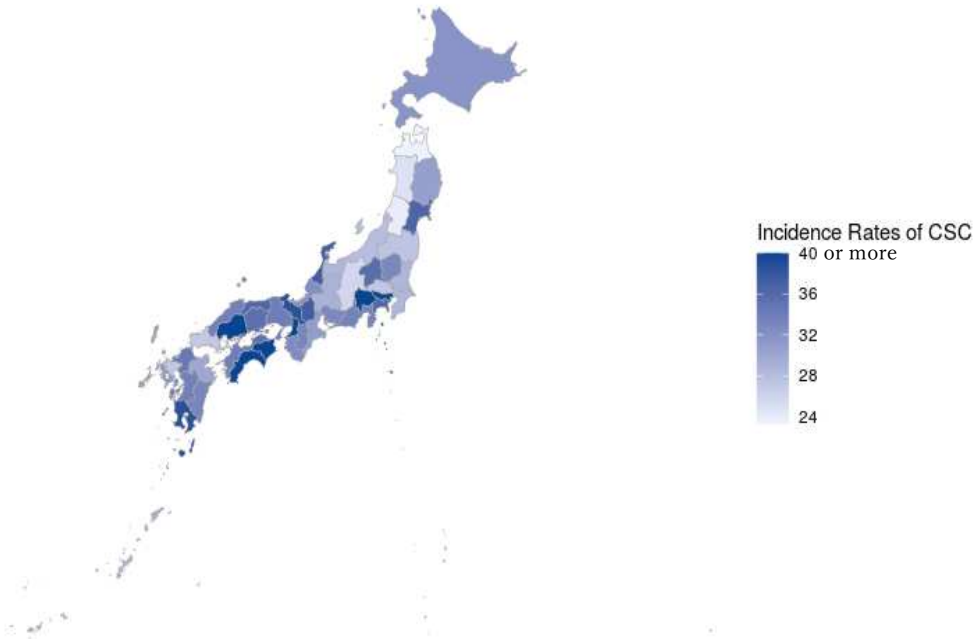
Supplementary Figure 3. Geographical and climatic variation of the incidence rate of central serous chorioretinopathy (CSC) per 100,000 person-years.

A: Comparison between predominantly urban or rural prefectures. The incidence rate of CSC was significantly higher in predominantly urban prefectures than in rural prefectures. **B:** Comparison among the eight main Japanese regions. Regional variation of incidence rate of CSC was apparent. The lowest and highest incidence rates were observed in Tohoku and in Shikoku, respectively. **C:** Comparison among tertile groups of the average annual temperature. The incidence rate of CSC increased in line with the rise in average temperatures. **D:** Comparison among tertile groups of snowfall days in a year. The incidence rate of CSC was lowest in the group with the highest snowfall days per year. **E:** Comparison among tertile groups of daylights hours in a year. The incidence rate of CSC was lowest in group with the lowest total daylight hours per year. Incidence rate of CSC is calculated as incidence / total population at risk in each group. Error bars represent 95% confidence intervals.


A
Urban / Rural
B
Region
C
Average Annual Temperature
D
Snowfall Days
E
Daylight Hours
Incidence Rate /100 000 person-years
50
45
40
35
30
25
20
15
10
5
0
Predominantly Urban
Others
Prefectures
Hokkaido
Tohoku
Kantou
Cyuubu
Kansai
Cyuugoku
Shikoku
Kyuusyuu
Regions
Low
Midde
High
Tertile Groups
Low
Midde
High
Tertile Groups
Low
Midde
High
Tertile Groups

Supplementary Figure 4. Geographical distribution of incidence rates of central serous chorioretinopathy by the Japanese 47 prefectures.

The incidence rates of central serous chorioretinopathy across the 47 Japanese prefectures are presented as a heat map. The incidence rates ranged from 23.9 to 69.7 per 100,000 person-years in Aomori and Kochi, respectively. High incidence rates were observed in urban or western prefectures.



Supplementary Figure 5. Seasonal variation in incidence of central serous chorioretinopathy (CSC). Dashed lines represent average annual monthly incidence of CSC for the entire year. The distribution of CSC in a year was significantly different ($P < 0.001$, analysis of variance). Incidence from March to June and from October to November were higher than the annual average monthly incidence.