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

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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 neovascularopathy) 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 Japan13) 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
access centres with access to the whole NDB dataset, under the approval of the MHLW. 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. 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. Therefore, we created a new personal unique ID, called ID0, according to the previously reported method, 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, 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. 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 retinopathy’ are represented by the same disease name in ICD-10 as H35.7, whereas they are assigned different codes in the NDB diagnostic codes (online supplemental table). Thus, individuals who had NDB diagnostic codes for CSC and its various synonyms, which reflect a history of CSC described 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.

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. The current population estimates of each year as of 2000–2025 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, 2,479,300 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 men.
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 1 815 011 cases (73.2%) who could be observed for more than 1 year. In the first 12 months since diagnosis, 1 575 131 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, 60.2±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 (31.1 (95% CI 30.5 to 31.6) vs 21.9 (95% CI 21.6 to 22.2) 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 to August was higher than from September to February (3F).
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 neovascularopathy, 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.23

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 serious detachment associated with CSC are known to be self-limiting,3 8 90–90% 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;
this may have led to an underestimation of CSC incidence. However, such cases would be minimal because CSC causes obvious subjective symptoms such as blurred vision, relative central scotoma, metamorphopsia, micropsia and/or reduced contrast sensitivity. 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. 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 pachychoroidal 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.

Table 3  Chronological changes of treatment for central serous chorioretinopathy

| Year | Incidence* | Not treated |  | Treated |  | Anti-VEGF |  |
|------|------------|-------------|---|---------|---|-----------|---|
|      | Cases (%)  | Cases (%)   |   | Cases (%) |   | Cases (%) |   |
| 2011 | 28075      | 25667 (91.42) |   | 2408 (8.58) |   | 458        |   |
| 2012 | 29407      | 26113 (88.80) |   | 3294 (11.20) |   | 535        |   |
| 2013 | 27831      | 24327 (87.41) |   | 3504 (12.59) |   | 517        |   |
| 2014 | 26776      | 23182 (86.61) |   | 3594 (13.39) |   | 560        |   |
| 2015 | 26668      | 22867 (85.75) |   | 3801 (14.25) |   | 574        |   |
| 2016 | 24332      | 20653 (84.88) |   | 3679 (15.12) |   | 569        |   |
| 2017 | 18422      | 14704 (79.82) |   | 3718 (20.18) |   | 622        |   |
| Total| 181501     | 157513 (86.78) |   | 23988 (13.22) |   | 3835       |   |

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.

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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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REFERENCES
1. Gemenetzis M, De Salvo G, Lotery AJ. Central serous chorioretinopathy: an update on pathogenesis and treatment. *Eye* 2010;24:1743–56.
2. Kitzmann AS, Pulido JS, Diehl NN, et al. The incidence of central serous chorioretinopathy in Olmsted County, Minnesota, 1980-2002. *Ophthalmology* 2008;115:169–73.
3. Jalkhi AE, Jabbour N, Avila MP, et al. Retinal pigment epithelial decompensation I: clinical features and natural course. *Ophthalmology* 1984;91:1544–8.
4. Nicholson B, Noble J, Foroughian F, et al. Central serous chorioretinopathy: update on pathophysiology and treatment. *Surv Ophthalmol* 2013;58:103–26.
5. Klein ML, Van Buskirk EM, Friedman E, et al. Experience with nontreatment of central serous choroidopathy. *Arch Ophthalmal* 1974;91:247–50.
6. Mrejen S, Okumura K, Matsuda S, et al. History of the secondary use of national database of health insurance claims and specific health checkups of Japan (NDB). *J Epidemiol* 2019;29:353–8.
7. Salah M, Kim HS, Kwak J, et al. Nationwide incidence of central retinal artery occlusion in Japan: there are no significant differences in incidence among eight areas of Japan. *Prog Retin Eye Res* 2019;73:100770.
8. Sie-Boen-Lian. The etiological agent of serous central chorioretinitis. *Ophthalmologica* 1964;148:263–70.
9. Ahmad OB, Boschi Pinto C, Lopez AD. Age standardization of rates: a new who standard. *GPE Discussion Paper Series* 2001;3:10–12.
10. Salehi M, Wenick AS, Law HA, et al. Interventions for central serous chorioretinopathy: a network meta-analysis. *Cochrane Database Syst Rev* 2015;12:CD011841. doi:10.1002/14651858.CD011841.pub2
11. Lu HQ, Wang EQ, Zhang T, et al. Photodynamic therapy and anti-vascular endothelial growth factor for acute central serous chorioretinopathy: a systematic review and meta-analysis. *Eyes* 2016;10:19–22. doi:10.1088/1566-9768/10/1/208
12. Kono S, Ikeda M, Ogata M. Salt and geographical mortality of gastric cancer and stroke in Japan. *J Epidemiol Community Health* 1983;37:43–46.
13. Hayama K, Sugiyama M, Tanaka S, et al. High-Incidence of C9 deficiency throughout Japan: there are no significant differences in incidence among eight areas of Japan. *Int Arch Allergy Immunol* 1989;90:400–4.
14. Sakai R, Wang W, Yamaguchi N, et al. The impact of Japan’s 2004 postgraduate training program on intra-prefectural distribution of pediatricians in Japan. *PLoS One* 2013;8:e77045.
15. Conway MD, Noble JA, Peyman GA. Central serous chorioretinopathy in postmenopausal women receiving exogenous testosterone. *Retin Cases Brief Rep* 2017;11:95–9.
16. Matet A, Daruich A, Zola M, et al. Risk factors for recurrences of central serous chorioretinopathy. *Retina* 2018;38:1403–14.
17. Kim Y-K, Ryoo N-K, Woo SJ, et al. Choroidal thickness changes after photodynamic therapy and recurrence of chronic central serous chorioretinopathy. *Am J Ophthalmol* 2015;160:72–84.
18. van Rijssen TJ, van Dijk EHC, Yzer S, et al. Central serous chorioretinopathy: towards an evidence-based treatment guideline. *Prog Retin Eye Res* 2019;73:100770.
19. Fung AT, Yannuzzi LA, Freund KB. Type 1 (sub-retinal pigment epithelial) neovascularization in central serous chorioretinopathy masquerading as neovascular age-related macular degeneration. *Retina* 2012;32:1829–37.
20. Subbacher F, Schütze C, Burmüller M, et al. Clinical evaluation of neovascular and non-neovascular chronic central serous chorioretinopathy (CSC) diagnosed by swept source optical coherence tomography angiography (SS OCTA). *Graefes Arch Clin Exp Ophthalmol* 2019;257:1381–90.
21. Wu J-S, Chen S-H. Optical coherence tomography angiography for diagnosis of choroidal neovascularization in chronic central serous chorioretinopathy after photodynamic therapy. *Sci Rep* 2019;9:9404.
22. Cassel GH, Brown GC, Annesley WH. Central serous chorioretinopathy: a seasonal variation? *Br J Ophthalmol* 1984;68:724–6.
23. Kida T, Kobayashi T, Sato T, et al. Seasonal variation in Japanese central serous chorioretinopathy. *Ophthalmologica* 2018;240:150–6.
24. Kaya R, Chandra S, Sheht J, et al. Central serous chorioretinopathy: an update on risk factors, pathophysiology and imaging modalities. *Prog Retin Eye Res* 2020;79:100865.
25. Hayashi S, Noda T, Kubo S, et al. Variation in fracture risk by season and weather: a comprehensive analysis across age and fracture site using a national database of health insurance claims in Japan. *Bone* 2019;120:512–8.