



Sleep Disturbance as a Risk Factor for Retinal Neurodegeneration and Subsequent Glaucoma

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- **PURPOSE:** To determine whether insufficient sleep, insomnia, and sleep-apnea syndrome (SAS) are associated with retinal nerve fiber layer (RNFL) thinning and incident glaucoma in adults.
- **DESIGN:** Community-based cross-sectional analysis and nationwide population-based retrospective cohort study.
- **PARTICIPANTS:** The regional cohort included 5958 adults aged 40-80 years who underwent wrist actigraphy and optical coherence tomography. The nationwide cohort, comprised adults aged ≥ 40 years, totaling 985,136 patients with insomnia and 72,075 with sleep apnea syndrome, along with respective control groups without these disorders.
- **METHODS:** In the regional cohort, we conducted a cross-sectional analysis to assess the association between objectively measured sleep parameters and retinal nerve fiber layer (RNFL) thickness, using multivariable linear models. In the nationwide cohort, we performed a longitudinal analysis with up to 7.5 years of follow-up, estimating adjusted hazard ratios (aHR) for incident glaucoma using Cox proportional hazards models.
- **RESULTS:** In the regional cohort, RNFL thickness peaked at 6-7 h of actual sleep and declined with shorter duration; sleeping < 6 h remained independently associated with thinner RNFL after adjustment for age, sex, intraocular pressure, and systemic factors. In the nationwide cohort, glaucoma risk was higher in patients with

insomnia (aHR 1.30, 95% CI 1.28-1.32) and SAS (aHR 1.43, 95% CI 1.35-1.51) compared with controls.

• **CONCLUSIONS:** Objective sleep insufficiency and clinically diagnosed sleep disorders correlate with retinal neurodegeneration and confer a higher risk of developing glaucoma. Integrating sleep evaluation and management into ophthalmic care may aid glaucoma prevention. (Am J Ophthalmol 2025;280: 193-202. © 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>))

INTRODUCTION

GLAUCOMA IS A LEADING CAUSE OF SEVERE VISUAL impairment and blindness among the older adults population worldwide.¹ It is recognized as a neurodegenerative disease that shares common features with other neurodegenerative disorders, such as progressive neuronal loss and irreversible functional decline.² Open-angle glaucoma is the most common form of glaucoma, accounting for approximately 80-90% of all glaucoma cases in North America and Asia.³⁻⁵ It is characterized by progressive optic neuropathy with an open anterior chamber angle, leading to gradual and irreversible loss of vision. Although aging remains the primary risk factor for glaucoma, its pathogenesis is multifactorial, involving both ocular and systemic factors.⁶ Among the systemic factors, recent studies have increasingly implicated aberrant sleep patterns as potential contributors to glaucoma development.⁷⁻¹³

Sleep duration, sleep quality, and clinically diagnosed sleep disorders such as insomnia and sleep apnea syndrome (SAS), are increasingly recognized for their broad systemic effects; they influence cardiovascular, metabolic, and neurovascular health and contribute to neuroinflammatory and neurodegenerative conditions such as Alzheimer's

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disease.¹⁴⁻¹⁷ Insomnia is characterized by difficulty initiating or maintaining sleep, whereas SAS involves recurrent episodes of airway obstruction during sleep, leading to intermittent hypoxia.^{18,19} Despite growing interest in the systemic consequences of poor sleep, its potential role in ocular health—particularly in relation to glaucoma—remains poorly understood. Our previous findings from the Nagahama study suggest an association between SAS and thinner retinal nerve fiber layer (RNFL), which is a critical indicator of glaucoma progression.²⁰ However, large-scale, nationwide investigations on this relationship are lacking. Moreover, the influence of sleep duration on RNFL thickness has not been thoroughly investigated.

In this study, we aimed to elucidate the potential impact of sleep-related factors, including sleep duration and quality, as well as diagnosed sleep disorders, on glaucoma incidence through a 2-stage, population-based approach. First, we conducted a cross-sectional analysis using the Nagahama study to investigate associations between sleep duration and RNFL thickness. Second, we employed the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), a nationwide claims database that covers almost all insured citizens in Japan,^{21,22} to examine the association between diagnosed sleep disorders, specifically insomnia and SAS, and glaucoma incidence in a broader population.

METHODS

• **DATA SOURCE:** This study utilized 2 primary data sources. The first was the Nagahama Prospective Cohort for Comprehensive Bioscience (the Nagahama Study), a community-based prospective cohort conducted in Nagahama City, Shiga Prefecture, Japan.^{20,23} Participants were enrolled between July 2013 and February 2017 based on the following inclusion criteria: age 40-80 years, ability to live independently, and absence of current serious diseases or physical impairments, allowing them to attend the baseline survey independently. The participants underwent comprehensive examinations, including physical and lung function tests, blood tests, ophthalmic assessments (optical coherence tomography [OCT], intraocular pressure [IOP], and axial length measurements), sleep tests, and self-report questionnaires. The exclusion criteria were missing essential data on mean RNFL thickness or sleep-disordered breathing measures, current glaucoma treatment, or poor-quality retinal images.

The study adhered to the Declaration of Helsinki, and approval was granted by the Ethics Committee of the Graduate School of Medicine at Kyoto University (Registry ID G0278) and the Nagahama Municipal Review Board. Written informed consent was obtained from all participants.

The second primary data source used was the NDB, spanning the period from September 2013 to March 2023. Over-

seen by the Ministry of Health, Labor, and Welfare, the NDB compiles the health information from over 126 million individuals, covering 99% of Japan's hospital facilities and receiving approximately 1.6 billion electronic claims annually.^{24,25} This database includes unique patient identifiers, demographic information, such as age and sex, as well as diagnostic data categorized according to the International Classification of Diseases, Tenth Revision (ICD-10), and additional Japanese-specific diagnostic codes. It also captures medical procedures and pharmaceutical prescriptions based on Japan's unique coding system.

Since the NDB data were fully anonymized, individual informed consent was not required. Ethical clearance for their use was obtained from the institutional review board at Kyoto University (No. R3987) and in line with the principles of the Declaration of Helsinki.

• **PATIENTS AND EXPOSURES:** In the Nagahama Study, participants first underwent mean RNFL thickness measurements and within 1 week of that assessment they completed objective sleep monitoring. The participants wore an actigraphy device (Actiwatch 2 or Actiwatch Spectrum Plus; Philips Respironics, Murrysville, Pennsylvania, USA) continuously for 7 consecutive days, and a pulse oximeter (PULSOX-Me300; Konica Minolta Inc, Tokyo, Japan) was used simultaneously for 4 days to record sleep variables, using an algorithm that has been validated against polysomnography.²⁶⁻²⁹ When incomplete or unreadable signals were encountered, those data were excluded. For inclusion in the analyses, participants were required to have at least 5 valid days of actigraphy data, including at least 1 weekend day, and a minimum of 2 valid days of pulse oximetry recordings. Sleep onset and wake-up times were determined by integrating actigraphy recordings with participant sleep diaries, which included bed-in and bed-out times verified by well-trained staff using the actigraph light sensor. Total sleep duration (interval from sleep onset to wake-up) and actual sleep duration (total sleep duration minus any wake-time after sleep onset) were then automatically calculated using the manufacturer's default algorithm. Sleep efficiency was defined as the ratio of actual sleep duration to time spent in bed, as measured by actigraphy. During sleep the wrist-worn pulse oximeter recorded percutaneous arterial blood oxygen saturation (SpO₂) as 3-second moving averages, stored at 1-second intervals. We measured the actigraphy-modified cumulative percentage of sleep actigraphy-modified cumulative time with SpO₂ < 90% as a surrogate marker for hypoxic burden, as in our previous report.²⁰

For the NDB analyses, we employed 2 types of patient identifiers to link insurance claims data, following established methods.³⁰ We then extracted records for individuals aged 40 years or older during the baseline period from September 2013 to August 2014. To ensure a washout period and improve the accuracy of identifying incident cases, individuals with a prior insomnia or SAS diagnosis during

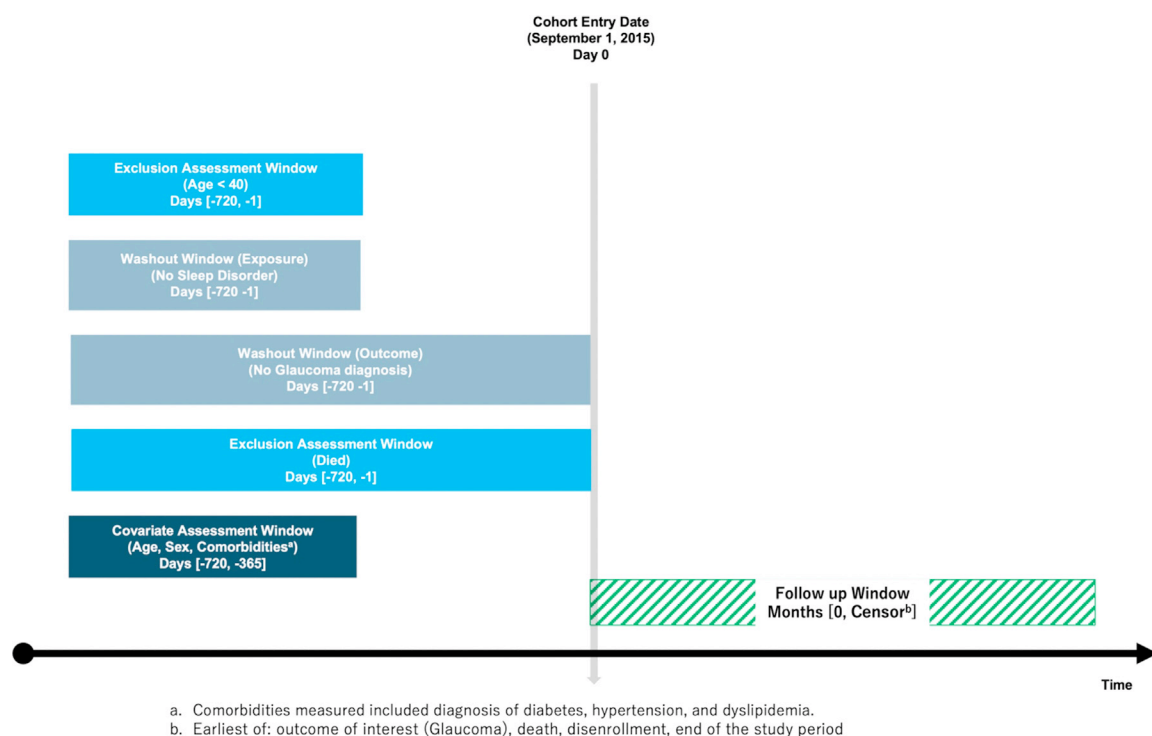


FIGURE 1. Overview of study design using the national database (NDB). For individuals aged 40 years or older, data were extracted from September 2013 to August 2014. A washout period was applied by excluding those diagnosed with insomnia or sleep apnea syndrome during this time frame to ensure accurate ascertainment of incident cases in subsequent analyses.

this period were excluded. To assess the potential for selection bias introduced by this exclusion, we conducted a sensitivity analysis in which patients diagnosed with insomnia or SAS during the baseline period were retained.

Given the potential limitations of relying on disease names alone, we classified patients with insomnia as (1) those newly diagnosed with insomnia between September 2015 and August 2023 and (2) those who subsequently received prescriptions for sleep medications. Similarly, patients with SAS were defined as (1) those newly diagnosed with sleep apnea during the same interval and (2) those who underwent home continuous positive airway pressure therapy. Diagnoses were determined using NDB-specific diagnostic codes, which provide more precise identification than the ICD-10 codes (Supplemental Table 1 lists code correspondence). The table also includes a list of sleep medications used in the study. Although over-the-counter (OTC) medications are not captured in the NDB, Japan permits only limited OTC options;³¹ therefore, sleep medication users were identified based on prescription records. From September 2014 to August 2015, we identified individuals who met the criteria for new-onset insomnia or SAS and excluded any who died in the interim. An overview of the NDB study design is illustrated in Figure 1.

• **OUTCOMES:** For the Nagahama Prospective Cohort, the primary outcome was RNFL thickness, measured via cir-

cumpapillary OCT (RS-3000 advance2; Nidek). An adequate Signal Strength Index (SSI) was required; scans with an SSI below 6 were considered low quality and were excluded, in accordance with prior literature.³² As described previously,²⁰ retinal layers were automatically segmented by the OCT software and manually verified by 2 ophthalmologists, with RNFL thickness defined as the distance between the outer border of the inner limiting membrane and the inner border of the ganglion cell layer.

For the nationwide cohort derived from the NDB, open-angle glaucoma onset was determined using a validated definition with high sensitivity and specificity.³³ Specifically, it was defined as the presence of both a diagnostic code for glaucoma—including unspecified glaucoma—and a prescription for glaucoma eye drops. To improve diagnostic precision, we used detailed Japanese diagnostic codes instead of the broader ICD-10 categories, as summarized in Supplemental Table 1. Although this definition may include a small number of angle-closure or secondary glaucoma cases, the glaucoma cases identified by this definition are likely to represent open-angle glaucoma in most instances.⁵ We adopted this definition because restricting to specific codes for open-angle glaucoma would substantially reduce sensitivity.³³

• **COVARIATES:** For the Nagahama Study, the following variables were used as covariates: age (years), female sex,

body mass index (BMI; kg/m²), IOP, hypertension, dyslipidemia, diabetes mellitus, and sleep medication use. IOP was measured once using a noncontact tonometer (TX-20P, Canon) during daytime as part of the ophthalmic examination. Hypertension was defined as the use of antihypertensive medications, and a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Dyslipidemia was defined as either a high-density lipoprotein cholesterol level of <40 mg/dL, low-density lipoprotein cholesterol level of ≥ 140 mg/dL, or taking lipid-lowering drugs. Diabetes mellitus was defined as the use of oral antihyperglycemic agents and/or insulin or having a hemoglobin A1c level $>6.5\%$. BMI was calculated based on measured height and weight. Ischemic heart disease history and sleep medications use were also recorded as a potential confounding factor.

For the NDB dataset, the covariates evaluated included (1) age, (2) sex, and (3) comorbid conditions, such as diabetes, dyslipidemia, and hypertension. Each comorbid condition was defined using diagnostic codes from the medical records, with disease definitions validated by prior studies^{34,35} to ensure robust and reliable identification of factors that could influence study outcomes.

- **STATISTICAL ANALYSES:** Two distinct analytical approaches were employed to address the differences in study design between the Nagahama Study and the NDB.

In the Nagahama Study, we investigated the association between mean RNFL thickness and actigraphy-measured sleep duration and sleep efficiency. To assess whether RNFL thickness differed across categories of sleep duration and sleep efficiency, we first conducted 1-way analysis of variance (ANOVA). To further account for potential confounding factors, we then performed multivariable linear regression analyses adjusting for relevant covariates. In the linear regression analyses, continuous variables with skewed distributions were log transformed. Sleep duration was categorized into 3 groups: <6 hours, 6-8 hours (reference), and >8 hours, whereas sleep efficiency was categorized as $<65\%$, 65-85%, and $>85\%$ (reference), based on previous studies.^{36,37} Confounders were selected based on prior literature demonstrating their associations with both sleep parameters and RNFL thickness.²⁰ To assess the robustness of the findings, a sensitivity analysis excluding current users of sleep medications was performed.

For the nationwide analysis using the NDB, we utilized survival analysis to examine the hazard ratios for glaucoma development between different sleep disorder groups: individuals with insomnia versus those without, and individuals with SAS versus those without. We estimated Kaplan-Meier survival curves for each group to depict the time until the onset of glaucoma, providing insights into the probability of remaining free from glaucoma throughout the study period.

Further, after confirming that the proportional hazards assumption was reasonable using the Schoenfeld residuals method,^{38,39} we applied Cox proportional hazards regres-

sion models to calculate the hazard ratios for the onset of glaucoma among participants with insomnia and SAS compared to their respective control groups without these conditions. Adjustments were made for potential confounding factors, such as age, sex, and comorbidities. This methodological approach was selected for its effectiveness in managing censored data and its capacity to assess the impact of specific sleep disorders on glaucoma risk for the study duration.

We used R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and PostgreSQL EnterpriseDB version 14.1 for the statistical analyses. Statistical significance was set at $P < .05$ for all analyses.

RESULTS

After applying all exclusion criteria, such as poor-quality or missing sleep data due to refusal to wear the devices, a total of 5958 participants from the Nagahama Study were included in the final analyses (Table 1 and Supplemental Figure 1). The mean RNFL thickness was 100.8 ± 11.9 μm , IOP was 14.3 ± 2.9 mmHg, and the average axial length was 24.1 ± 1.4 mm. Based on actigraphy data, the mean actual sleep time was 359.8 ± 57.9 minutes. Regarding sleep duration categories, 14.0% of participants slept < 5 hours, whereas 2.0% exceeded 8 hours. The mean sleep efficiency was $84.8 \pm 6.4\%$, with 3.0% of participants showing $<70\%$ sleep efficiency and 20.2% achieving $>90\%$. Further baseline characteristics stratified by actual sleep time and sleep efficiency categories are provided in Supplemental Tables 2 and 3.

Figure 2 illustrates the mean RNFL thickness and intraocular pressure across sleep duration categories (<5 h, 5-6 h, 6-7 h, 7-8 h, >8 h) and sleep efficiency groups ($<70\%$, 70-80%, 80-90%, $>90\%$). The 1-way ANOVA revealed significant differences in RNFL thickness across both sleep duration ($P = .021$) and sleep efficiency categories ($P < .001$). The highest RNFL thickness was observed in the 6-7 hour sleep duration group. Notably, greater RNFL thickness was associated with increasing sleep efficiency. A significant difference was observed in IOP across sleep duration categories ($P = .0089$), with the highest IOP noted in the 7-8 hour sleep duration group. In contrast, no significant differences in IOP were found across sleep efficiency categories ($P = .18$). The multivariable linear regression analyses were performed to examine the association between sleep parameters and RNFL thickness, adjusting for potential confounders (Table 2). Short sleep duration (<6 h) was significantly associated with thinner RNFL compared to the reference category (6-8 h) ($\beta = -0.76$, 95% CI: -1.33 to -0.19 , $P = .008$), whereas long sleep duration (>8 h) was not significantly associated with RNFL thickness ($\beta = -1.01$, 95% CI: -2.45 to 0.43 , $P = .474$). Sleep efficiency was not significantly associated with RNFL thickness. The estimates and

TABLE 1. Baseline Demographic and Clinical Characteristics in the Nagahama Cohort.

	All (n = 5958)
Age in years	59.1 ± 10.7
Sex, women/men	3970/1988
Body mass index (kg/m ²)	22.4 ± 3.2
Presence of hypertension, %	29.7
Presence of dyslipidemia, %	23.8
Presence of diabetes mellitus, %	7.0
History of ischemic heart disease, %	3.7
Use of sleep medication, %	7.4
Retinal nerve fiber layer thickness (μm)	100.8 ± 11.9
Intraocular pressure (mmHg)	14.3 ± 2.9
Axial length, mm	24.1 ± 1.4
Acti-CT90, %	0.19 (0.05, 0.79)
Mean actual sleep time (minutes)	359.8 ± 57.9
Mean actual sleep time, <5 h / 5-6 h / 6-7 h / 7-8 h / >8 h, %	14.0 / 34.7 / 37.8 / 11.6 / 2.0
Mean sleep efficiency (%)	84.8 ± 6.4
Mean sleep efficiency, <70%/70-80%/80-90%/>90%, %	3.0 / 15.9 / 60.9 / 20.2

Results are presented as mean ± standard deviation or median (interquartile range).

Categories of actual sleep time and sleep efficiency are expressed as proportions of total participants.

Acti-CT90, actigraphy-modified cumulative time with SpO₂ <90%.

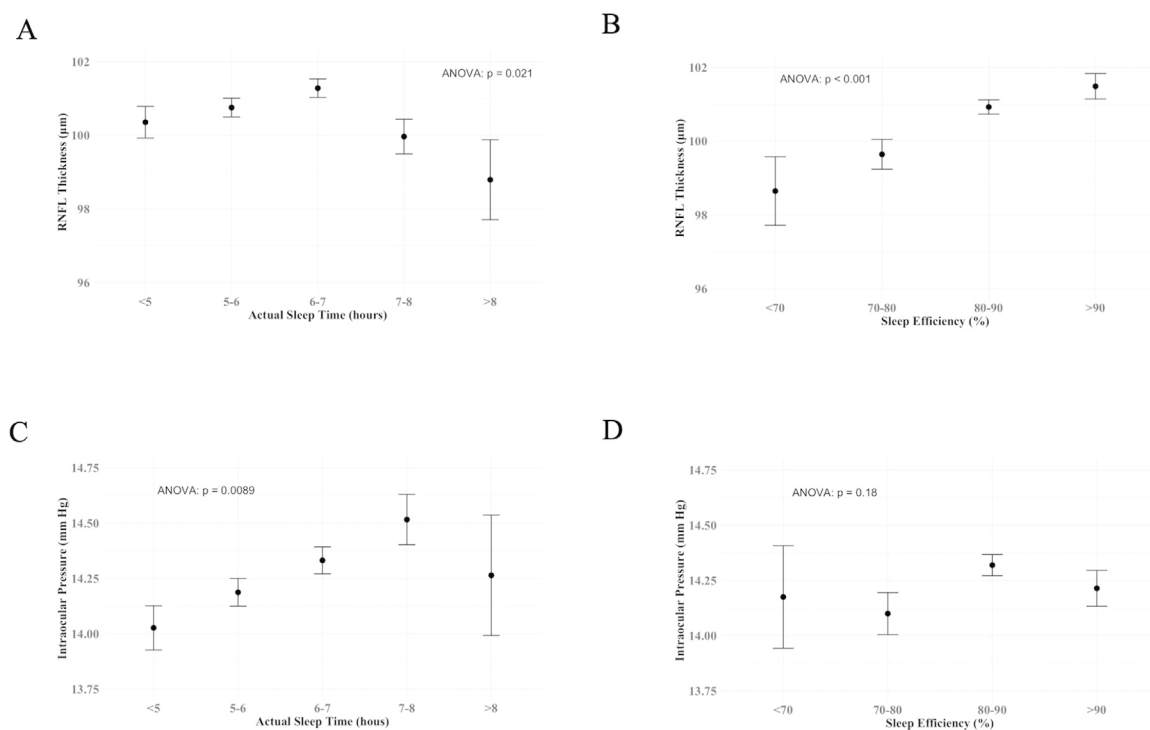


FIGURE 2. Association between sleep parameters and RNFL thickness and intraocular pressure. (A) Relationship between actual sleep duration (minutes) and RNFL thickness (μm). (B) Relationship between sleep efficiency (%) and RNFL thickness (μm). (C) Relationship between actual sleep duration (minutes) and intraocular pressure (mmHg). (D) Relationship between sleep efficiency (%) and intraocular pressure (mmHg). ANOVA = analysis of variance; RNFL = retinal nerve fiber layer.

TABLE 2. Multivariable Linear Regression of Sleep Variables and RNFL Thickness.

Variable	β (95% CI)	P-value
Sleep Duration (reference: 6-8 h)		
Short (<6 h)	−0.76 (−1.33 to −0.19)	.008
Long (>8 h)	−1.01 (−2.45 to 0.43)	.474
Sleep Efficiency (reference: >85%)		
<65%	−2.50 (−3.70 to −1.30)	.422
65-85%	−1.20 (−2.20 to −0.20)	.495
Models were adjusted for age, sex, intraocular pressure, axial length, log-transformed CT90, body mass index, hypertension, dyslipidemia, diabetes mellitus, history of ischemic heart disease, and use of sleep medication. CI = confidence interval; RNFL = retinal nerve fiber layer.		

TABLE 3. Baseline Demographic and Clinical Characteristics by Sleep Disorder Status in the NDB Dataset.

	Insomnia	Control (No Insomnia)	SAS	Control (no SAS)
Number (%)	985,136 (100)	6,318,0432 (100)	72,075 (100)	66,573,036
Men (%)	388,456 (39.4)	28,599,497 (45.3)	58,379 (81.0)	29,684,582 (44.6)
Age in years	69.34 ± 13.40	61.41 ± 13.54	58.97 ± 11.79	61.87 ± 13.65
Comorbidities				
Diabetes (%)	200,349 (20.3)	6,349,199 (10.0)	13,425 (18.6)	7,256,786 (10.9)
Hypertension (%)	393,350 (39.9)	12,285,009 (19.4)	22,531 (31.3)	141,731,34 (21.3)
Hyperlipidemia (%)	216,777 (22.0)	7,186,168 (11.4)	13,464 (18.7)	8,250,359 (12.4)
Age is presented as mean ± standard deviation; categorical variables are expressed as number (%). Control groups comprise individuals without a diagnosis of insomnia or SAS. NDB, National Database of Health Insurance Claims and Specific Health Checkups of Japan; SAS, Sleep Apnea Syndrome.				

P-values for other covariates included in the model are provided in the Supplemental Table 4. In the sensitivity analysis excluding participants using sleep medications, the associations between sleep duration and RNFL thickness remained consistent with the primary analysis (Supplemental Table 5).

For the NDB, a flowchart of the patient selection is displayed in Supplemental Figure 2. A total of 985,136 patients (39.4% men) newly diagnosed with insomnia and 72,075 patients (81.0 % men) diagnosed with SAS were enrolled in the respective case groups. The mean age at enrollment was 69.34 years for the insomnia group and 58.97 years for the SAS group. Separate control cohorts were established, with 63,180,432 individuals for insomnia and 66,573,036 individuals for SAS. Demographic features and pre-existing comorbidities for these cohorts are delineated in Table 3.

During the follow-up period, among the 985,136 patients sampled for insomnia and 72,075 patients sampled for SAS, 18,954 and 1276 were newly diagnosed with glaucoma, respectively. The Kaplan–Meier analysis revealed that patients with insomnia and SAS exhibited an increased risk of developing glaucoma (Figure 3).

The Cox proportional hazard regression analyses, adjusting for age, sex, and pre-existing comorbidities, independently correlated both insomnia and SAS with increased

glaucoma risk. Insomnia was associated with a higher likelihood of developing glaucoma (adjusted hazard ratio [aHR], 1.30; 95% confidence interval [CI], 1.28-1.32; $P < .001$; Table 4). SAS showed even stronger associations with glaucoma (adjusted HR, 1.43; 95% CI, 1.35-1.51; $P < .001$; Table 4).

The sensitivity analysis supported these findings; a comprehensive results overview is presented in Supplemental Figures 3 and 4 and Supplemental Tables 6 and 7.

DISCUSSION

The present study integrated both region-based and nationwide population-based cohorts, which indicate the potential role of sleep duration and sleep disorders—particularly insomnia and SAS—in increasing the risk of RNFL thinning and open-angle glaucoma development. A cross-sectional assessment of sleep time in the Nagahama study showed significant associations with RNFL thickness in an adjusted analysis. Although sleep medications could potentially mask underlying sleep disturbances and confound associations, the sensitivity analysis excluding sleep medication users yielded consistent results, supporting the robustness of our findings. Furthermore, in the analysis for ac-

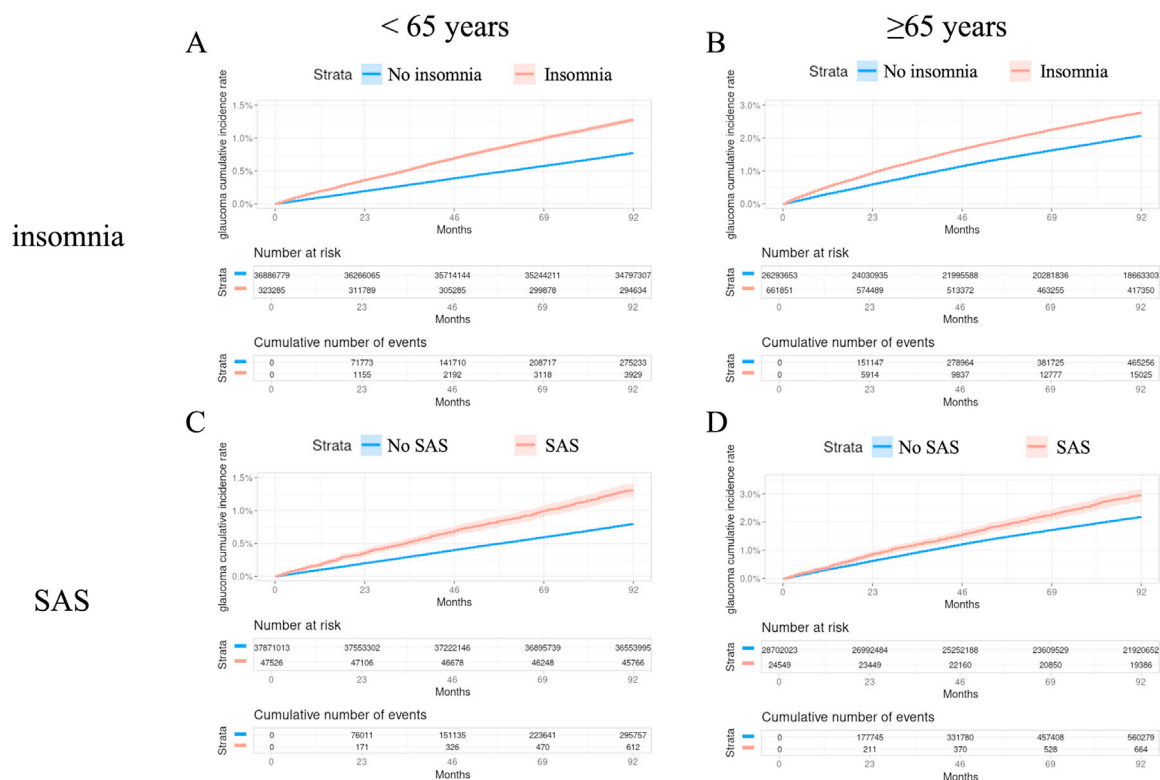


FIGURE 3. Kaplan–Meier Estimates for Incident Glaucoma by Sleep Disorder Status. Kaplan–Meier curves showing cumulative incidence of glaucoma among patients with insomnia and sleep apnea syndrome (SAS), compared to their respective control groups. This analysis excluded individuals diagnosed with sleep disorders during the washout period to minimize potential biases. Cumulative incidence of glaucoma shown by sleep disorder status and age group. (A) Aged <65 years, insomnia. (B) Aged ≥65 years, insomnia. (C) Aged <65 years, SAS. (D) Aged ≥65 years, SAS.

TABLE 4. Glaucoma Incidence Unadjusted and Adjusted Hazard Ratios Regarding Insomnia and Sleep Apnea Syndrome.

Comparison	Unadjusted HR (95% CI)	P-value	Model 1 Adjusted HR (95% CI)	P-value	Model 2 Adjusted HR (95% CI)	P-value
Control vs. Insomnia	1.79 (1.76-1.81)	<.001	1.36 (1.34-1.38)	<.001	1.30 (1.28-1.32)	<.001
Control vs. SAS	1.36 (1.28-1.43)	<.001	1.50 (1.42-1.58)	<.001	1.43 (1.35-1.51)	<.001

Model 1: Cox proportional hazards model adjusted for age and sex only.
Model 2: Cox proportional hazards model fully adjusted for all relevant covariates, including age, sex, and comorbidities.
CI = confidence interval; HR = hazard ratio.

tual sleep time and IOP, IOP was highest among participants sleeping 7–8 hours—a duration typically considered optimal—and tended to increase with longer sleep durations. This finding indicates that a thinner RNFL observed in the short-sleep group may be attributable to factors other than elevated IOP.

Several prior studies have contributed to our understanding of the relationship between sleep disturbances and glaucoma.⁷⁻¹³ For instance, Sun et al.¹¹ reported a potential link between insomnia and glaucoma using the UK Biobank, whereas Han et al.⁸ examined SAS and glaucoma in a clinical population. These studies underscore the importance of

evaluating sleep-related factors for glaucoma risk. However, limitations such as reliance on self-reported data, lack of objective sleep metrics, and absence of treatment information also have to be noted. Notably, a recent actigraphy-based study did not observe clear differences in objective sleep metrics between individuals with and without glaucoma.⁴⁰ This may be due to the limited power for subgroup analyses, or algorithms, or residual confounding in a clinic-based cross-sectional sample. In the present study, we sought to address these gaps by integrating 2 complementary datasets. The Nagahama cohort offered objectively measured sleep parameters alongside RNFL thickness, whereas the nation-

wide insurance database provided longitudinal, population-based data on clinically diagnosed insomnia and SAS. Our findings reinforce and expand upon earlier reports by combining objective measurements, large-scale cohort data, and consideration of treatment status, thereby providing more comprehensive evidence that sleep disturbance may contribute to glaucomatous neurodegeneration.

Insomnia and SAS are common among older adults, often leading to various negative physical and mental health outcomes. Insomnia, along with its associated stress response, can trigger the secretion of neurotransmitters and activate the autonomic nervous system, potentially affecting the regulation of IOP and blood flow.⁴¹ Chronically reduced ocular blood flow is a well-known risk factor for both onset and progression of glaucoma.⁴²

Regarding insomnia, studies in neurodegenerative diseases, such as Alzheimer's disease, have associated sleep disturbances with dysfunction of the brain's glymphatic system and subsequent accumulation of amyloid- β ($A\beta$).^{43,44} The glymphatic system is more active during sleep and facilitates waste product clearance from the brain.⁴³ Therefore, impaired sleep may reduce this clearance capacity and thereby promote $A\beta$ aggregation.⁴⁴ Recent research has proposed a retinal glymphatic-like system, which functions similarly to the brain's glymphatic system by clearing metabolic waste from the retina.⁴⁵ As $A\beta$ pathology is implicated in the pathogenesis of glaucoma,⁴⁶ insomnia-related glymphatic dysfunction may lead to waste accumulation at the retinal level, ultimately causing retinal ganglion cell degeneration.

In contrast, SAS introduces additional factors that further increase glaucoma risk. Sleep apnea induces hypoxia and oxidative stress, both of which trigger inflammatory responses.⁴⁷ This inflammation is considered to play a significant role in glaucoma development.⁴⁸ As a result, patients with SAS may experience not only the $A\beta$ -related risk associated with insomnia-induced glymphatic dysfunction but also the compounded effects of hypoxia, oxidative stress, and systemic inflammation. Collectively, these factors may intensify the likelihood of glaucoma development and progression.

This study has some limitations. First, the Nagahama study employed a cross-sectional design, precluding any definitive conclusions about causal relationships. Second, because the Nagahama cohort enrollment was restricted to apparently healthy community-dwelling adults who were able to live independently, this may limit generalizability to populations with significant illness or functional impairment. Third, participants under glaucoma treatment were excluded to avoid confounding from medication effects and advanced RNFL thinning, which may obscure associations between sleep-related factors and glaucoma. While this exclusion allowed us to focus on untreated or subclinical cases, it also limits the applicability of our findings to individuals already receiving treatment. Fourth, the NDB data lacked direct clinical measurements and relied on diagnostic and prescription codes, which may have affected the precision

of disease classification. In particular, our definition of incident glaucoma required both a diagnostic code and initiation of topical medication, potentially missing rare cases managed solely with procedures or surgery. Although such cases are uncommon, a small degree of under-ascertainment is possible. Finally, the NDB dataset lacks detailed information on visual acuity and visual fields.

In summary, our findings support a significant association between clinically diagnosed insomnia and SAS and glaucoma incidence. These findings suggest that sleep-related factors could be taken into account when managing glaucoma. Further studies are required to confirm these associations and explore how interventions for sleep disorders might modify glaucoma progression.

DATA SHARING STATEMENT

The data from the Nagahama Prospective Cohort Study and the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) are not publicly available due to legal and ethical restrictions. These data were obtained under data use agreements that prohibit public sharing of individual-level data. Researchers interested in accessing the Nagahama Study data may contact the study investigators to discuss potential collaboration, subject to approval by the relevant institutional review boards. Access to the NDB data requires approval from the Ministry of Health, Labour and Welfare of Japan and cannot be shared by the authors. The statistical analysis code used in this study is available from the corresponding author upon reasonable request.

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Supplemental Table 1. Correspondence Table of Codes Used in the Current Study

A. NDB diagnostic codes for insomnia

NDB diagnostic code	Disease Name	ICD-10 code
7805009	Sleep disorder	G47.9
8839209	Nonorganic sleep disorder	F51.9
8839792	Insomnia	G47.0
8839210	Nonorganic insomnia	F51.0

B. NDB diagnostic codes for sleep apnea syndrome

NDB diagnostic code	Disease Name	ICD-10 code
8839944	Obstructive Sleep Apnea	G47.3
7805017	Sleep Apnea Syndrome	G47.3
8837607	Central Sleep Apnea	G47.3

C. NDB diagnostic codes for glaucoma

NDB diagnostic code	Disease Name	ICD-10 code
3659003	Glaucoma	H40.9
3659005	Primary glaucoma	H40.9
8831041	Open-angle glaucoma	H40.1
3651011	Normal-tension glaucoma	H40.1
8850700	Glaucomatous optic neuropathy	H40.9

8850699	Glaucomatous optic atrophy	H40.9
8846067	Glaucomatous cupping	H40.9
3651010	Primary open-angle glaucoma	H40.1
3651007	Chronic open-angle glaucoma	H40.1
8840371	Chronic simple glaucoma	H40.1

D. NDB Drug Codes for Sleep Medications

NDB drug code (representative)	Active ingredient	ATC code
622322200	brotizolam	N05CD09
610453022	estazolam	N05CD04
611120088	flunitrazepam	N05CD03
611120118	lormetazepam	N05CD06
622129302	nitrazepam	N05CD02
620008008	quazepam	N05CD10
622706000	triazolam	N05CD05
622707200	alprazolam	N05BA12
620046803	bromazepam	N05BA08
611170781	chlordiazepoxide	N05BA02
611170160	cloxazolam	N05BA22
620045001	diazepam	N05BA01
611170672	flutazolam	—
611170471	lorazepam	N05BA06

611170443	medazepam	N05BA03
611170545	mexazolam	N05BA25
611170183	oxazolam	—
611120113	rilmazafone	—
622933600	eszopiclone	N05CF04
622139903	zolpidem	N05CF02
622317500	zopiclone	N05CF01
611120122	bromisoval	N05CM03
620006049	triclofos	N05CM07
620003966	tandospirone	—
611120002	amobarbital	N05CA02
611120058	barbital	N05CA04
610441004	phenobarbital	N03AA02

Owing to the large number of marketed products, sleep medications are summarized at the active-ingredient level; for each ingredient, one representative NDB drug code and the corresponding

WHO ATC code are presented. Ingredients without a WHO ATC assignment are denoted by an em dash (—).

E. NDB Drug Codes for Glaucoma Ophthalmic Solutions

NDB drug code	Drug Name	ATC code
660432022	Rizmon TG Ophthalmic Solution 0.5%	S01ED01
620003858	Timoptol XE Ophthalmic Solution 0.5%	S01ED01
621972901	Latanoprost Ophthalmic Solution 0.005% "Kissel"	S01EE01
621933101	Lumigan Ophthalmic Solution 0.03%	S01EE03
621978101	Latanoprost Ophthalmic Solution 0.005% "Mylan"	S01EE01
620007742	Pivalephrine Ophthalmic Solution 0.04%	S01EA01
620003860	Timoptol Ophthalmic Solution 0.5%	S01ED01
620004892	Mikelan LA Ophthalmic Solution 2%	S01ED51
621980502	Latanoprost Ophthalmic Solution 0.005% "SEC"	S01EE01
620007743	Pivalephrine Ophthalmic Solution 0.1%	S01EA01
660432002	Trusopt Ophthalmic Solution 0.5%	S01EC04
622278801	Azorga Combination Suspension Ophthalmic Solution	S01EC54
660432003	Trusopt Ophthalmic Solution 1%	S01EC04
621979601	Latanoprost Ophthalmic Solution 0.005% "Towa"	S01EE01
622017801	Latanoprost Ophthalmic Solution 0.005% "NP"	S01EE01
621984601	Latanoprost Ophthalmic Solution 0.005% "Senju"	S01EE01
621978104	Latanoprost Ophthalmic Solution 0.005% "Sandoz"	S01EE01
620008568	Tapros Ophthalmic Solution 0.0015%	S01EE04
622418901	Cosopt Mini Combination Ophthalmic Solution 0.4mL	S01ED51

661310208	Mikelan Ophthalmic Solution 1%	S01ED51
660443013	Mirol Ophthalmic Solution 0.5%	S01ED01
620198601	Sanpilo Ophthalmic Solution 1% 5 mL	S01EB01
622509901	Mikelna Combination Ophthalmic Solution	S01ED51
661310333	Sanpilo Ophthalmic Solution 2% 5 mL	S01EB01
622795101	Ailamide Combination Suspension Ophthalmic Solution	S01EC54
620224801	Xalatan Ophthalmic Solution 0.005%	S01EE01
620198201	Sanpilo Ophthalmic Solution 0.5% 5 mL	S01EB01
621987101	Latanoprost Ophthalmic Solution 0.005% "Nichii"	S01EE01
620005257	Azopt Suspension Ophthalmic Solution 1%	S01EC04
661310317	Rizmon Ophthalmic Solution 0.25%	S01ED01
621984501	Latanoprost Ophthalmic Solution 0.005% "Kaken"	S01EE01
621985001	Duotrav Combination Ophthalmic Solution	S01EE51
621983501	Latanoprost Ophthalmic Solution 0.005% "Kowa"	S01EE01
621975001	Latanoprost Ophthalmic Solution 0.005% "NS"	S01EE01
620003178	Mikelan LA Capsules 15mg	C07AA15
621990401	Latanoprost Ophthalmic Solution 0.005% "Nitto"	S01EE01
622248201	Tapros Mini Ophthalmic Solution 0.0015% 0.3 mL	S01EE04
661310209	Mikelan Ophthalmic Solution 2%	S01ED51
660432021	Rizmon TG Ophthalmic Solution 0.25%	S01ED01
621996001	Latanoprost Ophthalmic Solution 0.005% "AA"	S01EE01
622095801	Latanoprost Ophthalmic Solution 0.005% "CH"	S01EE01

622698001	Albeta Combination Ophthalmic Solution	S01ED51
621983505	Latanoprost Ophthalmic Solution 0.005% "NIG"	S01EE01
622279101	Tapcom Combination Ophthalmic Solution	S01EE51
621983503	Latanoprost Ophthalmic Solution 0.005% "TYK"	S01EE01
661310239	Pivalephrine 0.1%	S01EA01
620003862	Nipranol Ophthalmic Solution 0.25%	S01ED01
620003857	Timoptol XE Ophthalmic Solution 0.25%	S01ED01
621996101	Latanoprost Ophthalmic Solution 0.005% "Sawai"	S01EE01
620003859	Timoptol Ophthalmic Solution 0.25%	S01ED01
622374601	Glanatec Ophthalmic Solution 0.4%	S01EA51
621984801	Cosopt Combination Ophthalmic Solution	S01ED51
620004891	Mikelan LA Ophthalmic Solution 1%	S01ED51
620006449	Timolol Maleate Ophthalmic Solution	S01ED01
620008252	Timolol Maleate Ophthalmic Solution	S01ED01
620006450	Timolol Maleate Ophthalmic Solution	S01ED01
620008251	Timolol Maleate Ophthalmic Solution	S01ED01

ICD-10, International Classification of Diseases, Tenth Revision; NDB, The National Database of Health Insurance Claims and Specific Health Checkups of Japan.

Supplemental Table 2. Demographic and Clinical Characteristics Stratified by Actual Sleep Time (<5 h, 5–6 h, 6–7 h, 7–8 h, >8 h)

Actual Sleep Time	<5 h	5–6 h	6–7 h	7–8 h	>8 h
n	832	2067	2252	689	118
Age in years, mean (SD)	56.07 (10.01)	57.71 (10.37)	59.85 (10.65)	63.40 (10.52)	67.46 (10.18)
Sex, women (%)	539 (64.8)	1398 (67.6)	1547 (68.7)	434 (63.0)	52 (44.1)
Body mass index (kg/m ²)	22.95 (3.57)	22.48 (3.30)	22.14 (3.14)	22.02 (2.87)	22.11 (3.04)
Presence of hypertension, %	222 (26.7)	566 (27.4)	665 (29.5)	266 (38.6)	48 (40.7)
Presence of dyslipidemia, %	171 (20.6)	475 (23.0)	575 (25.5)	171 (24.8)	27 (22.9)
Presence of diabetes mellitus, %	53 (6.4)	152 (7.4)	145 (6.4)	59 (8.6)	7 (5.9)
History of ischemic heart disease, %	21 (2.5)	52 (2.5)	104 (4.6)	34 (4.9)	7 (5.9)
Use of sleep medication, %	25 (3.0)	104 (5.0)	191 (8.5)	96 (13.9)	24 (20.3)
Retinal nerve fiber layer thickness (μm), mean (SD)	100.36 (12.42)	100.76 (11.60)	101.28 (11.92)	99.97 (12.39)	98.79 (11.82)
Intraocular pressure (mmHg), mean (SD)	14.03 (2.88)	14.19 (2.85)	14.33 (2.89)	14.52 (2.97)	14.26 (2.96)
Axial length, mm, mean (SD)	24.31 (1.48)	24.12 (1.39)	23.99 (1.34)	23.89 (1.40)	23.80 (1.14)
Acti-CT90, % (median [IQR])	0.25 [0.06, 1.26]	0.20 [0.05, 0.78]	0.17 [0.04, 0.75]	0.17 [0.05, 0.65]	0.22 [0.06, 0.77]
Mean actual sleep time (minutes), mean (SD)	264.98 (30.16)	333.18 (17.07)	386.84 (16.63)	440.20 (15.95)	509.46 (29.62)
Mean sleep efficiency (%), mean (SD)	81.44 (8.80)	84.24 (6.37)	85.93 (5.33)	86.69 (4.71)	87.50 (4.66)
Mean sleep efficiency (%)					
<70%	89 (10.7)	65 (3.1)	21 (0.9)	3 (0.4)	0 (0.0)
70–80%	204 (24.5)	392 (19.0)	291 (12.9)	51 (7.4)	8 (6.8)
80–90%	425 (51.1)	1254 (60.7)	1426 (63.3)	455 (66.0)	69 (58.5)
>90%	114 (13.7)	356 (17.2)	514 (22.8)	180 (26.1)	41 (34.7)

Results are presented as mean (standard deviation [SD]) or median as interquartile range [IQR].

Supplemental Table 3. Demographic and Clinical Characteristics Stratified by Sleep Efficiency (<70%, 70–80%, 80–90%, >90%)

Sleep Efficiency	<70%	70–80%	80–90%	>90%
n	178	946	3629	1205
Age in years, mean (SD)	64.83 (9.69)	61.83 (11.00)	58.86 (10.71)	57.03 (9.87)
Sex, women (%)	42 (23.6)	403 (42.6)	2524 (69.6)	1001 (83.1)
Body mass index (kg/m ²)	24.03 (3.78)	23.21 (3.30)	22.32 (3.16)	21.57 (3.09)
Presence of hypertension, %	85 (47.8)	372 (39.3)	1045 (28.8)	265 (22.0)
Presence of dyslipidemia, %	46 (25.8)	230 (24.3)	868 (23.9)	275 (22.8)
Presence of diabetes mellitus, %	33 (18.5)	93 (9.8)	237 (6.5)	53 (4.4)
History of ischemic heart disease, %	12 (6.7)	50 (5.3)	121 (3.3)	35 (2.9)
Use of sleep medication, %	18 (10.1)	71 (7.5)	265 (7.3)	86 (7.1)
Retinal nerve fiber layer thickness (μm), mean (SD)	98.65 (12.41)	99.64 (12.47)	100.93 (11.75)	101.49 (11.95)
Intraocular pressure (mmHg), mean (SD)	14.18 (3.09)	14.10 (2.93)	14.32 (2.89)	14.21 (2.81)
Axial length, mm, mean (SD)	24.15 (1.30)	24.04 (1.38)	24.06 (1.39)	24.06 (1.39)
Acti-CT90, % (median [IQR])	1.06 [0.20, 4.24]	0.38 [0.11, 1.43]	0.19 [0.05, 0.73]	0.09 [0.03, 0.42]
Mean actual sleep time (minutes), mean (SD)	296.23 (57.38)	340.18 (54.27)	363.55 (55.66)	373.32 (57.53)
Mean sleep efficiency (%), mean (SD)	64.40 (5.41)	76.39 (2.69)	85.68 (2.70)	91.92 (1.47)
Actual sleep time (%)				
<5 h	89 (50.0)	204 (21.6)	425 (11.7)	114 (9.5)
5–6 h	65 (36.5)	392 (41.4)	1254 (34.6)	356 (29.5)
6–7 h	21 (11.8)	291 (30.8)	1426 (39.3)	514 (42.7)
7–8 h	3 (1.7)	51 (5.4)	455 (12.5)	180 (14.9)
>8 h	0 (0.0)	8 (0.8)	69 (1.9)	41 (3.4)

Results are presented as mean (standard deviation [SD]) or median as interquartile range [IQR].

Supplemental Table 4. Multivariable Linear Regression of Sleep Parameters and RNFL Thickness

Variable	β (95% CI)	P value
Sleep Duration (reference: 6–8 h)		
Short (<6 h)	-0.80 (-1.38 to -0.21)	0.008
Long (>8 h)	-0.74 (-2.76 to 1.28)	0.474
Sleep Efficiency (reference: >85%)		
Low (<65%)	-2.50 (-3.70 to -1.30)	0.422
Middle (65–85%)	-1.20 (-2.20 to -0.20)	0.495
Age in years	-0.25 (-0.28 to -0.22)	<0.001
Sex, women	0.13 (-0.53 to 0.79)	0.694
Intraocular pressure, mmHg	-0.50 (-0.60 to -0.40)	<0.001
Axial length, mm	-3.07 (-3.28 to -2.86)	<0.001
Log-transformed Acti-CT90, %	-0.16 (-0.32 to 0.01)	0.065
Body mass index (kg/m ²)	0.10 (0.00 to 0.20)	0.044
Presence of hypertension	-1.06 (-1.74 to -0.37)	0.002
Presence of dyslipidemia	0.25 (-0.43 to 0.93)	0.471
Presence of diabetes mellitus	-0.66 (-1.79 to 0.47)	0.254
History of ischemic heart disease	-2.19 (-3.71 to -0.67)	0.005
Sleep medication use	-0.86 (-1.95 to 0.23)	0.122

Supplemental Table 5. Multivariable Linear Regression of Sleep Parameters and RNFL Thickness Excluding Sleep Medication Users (Sensitivity Analysis)

Variable	β (95% CI)	P value
Sleep Duration (reference: 6–8 h)		
Short (<6 h)	-0.94 (-1.55 to -0.34)	0.002
Long (>8 h)	-1.45 (-3.69 to 0.78)	0.203
Sleep Efficiency (reference: >85%)		
Low (<65%)	0.94 (-1.99 to 3.88)	0.53
Middle (65–85%)	-0.33 (-0.95 to 0.29)	0.30
Age in years	-0.26 (-0.29 to -0.22)	<0.001
Sex, women	0.13 (-0.55 to 0.81)	0.708
Intraocular pressure, mmHg	-0.52 (-0.62 to -0.42)	<0.001
Axial length, mm	-3.05 (-3.27 to -2.83)	<0.001
Log-transformed Acti-CT90, %	-0.21 (-0.38 to -0.04)	0.017
Body mass index (kg/m ²)	0.12 (0.02 to 0.22)	0.019
Presence of hypertension	-1.04 (-1.75 to -0.33)	0.0046
Presence of dyslipidemia	0.30 (-0.41 to 0.99)	0.409
Presence of diabetes mellitus	-0.89 (-2.07 to 0.29)	0.144
History of ischemic heart disease	-1.34 (-2.99 to 0.32)	0.115

Supplemental Table 6. Baseline Demographic and Clinical Characteristics by Sleep Disorder Status in the NDB Dataset (Sensitivity Analysis)

	Insomnia	Control (no insomnia)	SAS	Control (no SAS)
Number (%)	2699794 (100)	64325294 (100)	396725 (100)	66628363 (100)
Men (%)	1023996 (37.9)	29043223 (45.2)	336685 (84.9)	29730534 (44.6)
Age in years	69.24 ± 13.03	61.54 ± 13.58	58.85 ± 11.59	61.87 ± 13.65
Comorbidities				
Diabetes (%)	682163 (25.3)	6663078 (10.4)	78053 (19.7)	7267188 (10.9)
Hypertension (%)	1402989 (52.0)	12912218 (20.1)	125228 (31.6)	14189979 (21.3)
Hyperlipidemia (%)	813268 (30.1)	7522861 (11.7)	75903 (19.1)	8260226 (12.4)

SAS, sleep apnea syndrome.

Supplemental Table 7. Unadjusted and Adjusted Hazard Ratios for Glaucoma Incidence Based on Insomnia and Sleep Apnea Syndrome (Sensitivity Analysis)

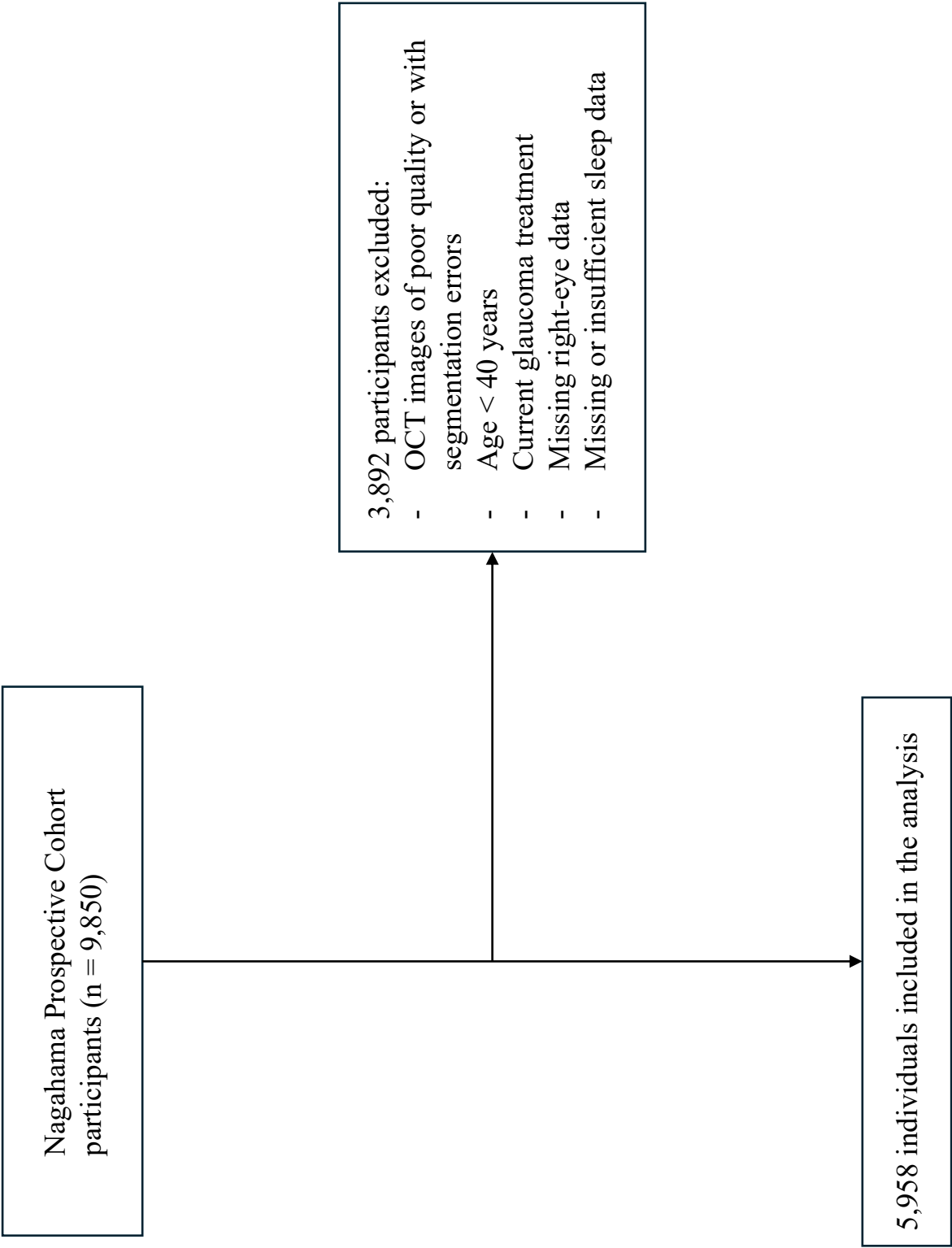
Comparison	Unadjusted HR (95% CI)	P-value	Model 1 Adjusted HR (95% CI)	P-value	Model 2 Adjusted HR (95% CI)	P-value
Control vs. Insomnia	1.84 (1.83–1.86)	<0.001	1.41 (1.40–1.42)	<0.001	1.31 (1.29–1.32)	<0.001
Control vs. SAS	1.31 (1.28–1.34)	<0.001	1.45 (1.42–1.49)	<0.001	1.38 (1.35–1.41)	<0.001

Model 1: Cox proportional hazards model adjusted for age and sex only.

Model 2: Cox proportional hazards model fully adjusted for all relevant covariates, including age, sex, and comorbidities.

SAS, sleep apnea syndrome.

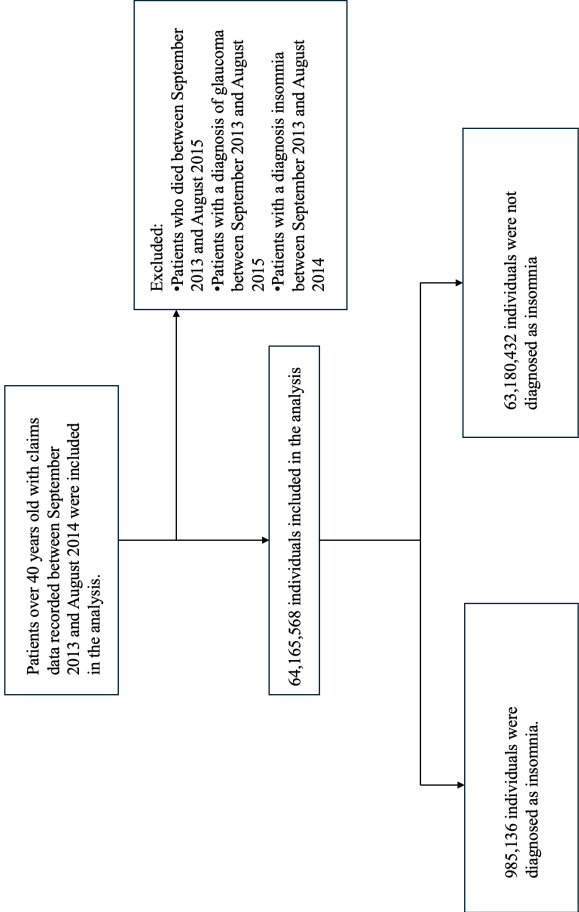
Supplemental Figure 1. Flow diagram of participant selection in the Nagahama Prospective Cohort Study.



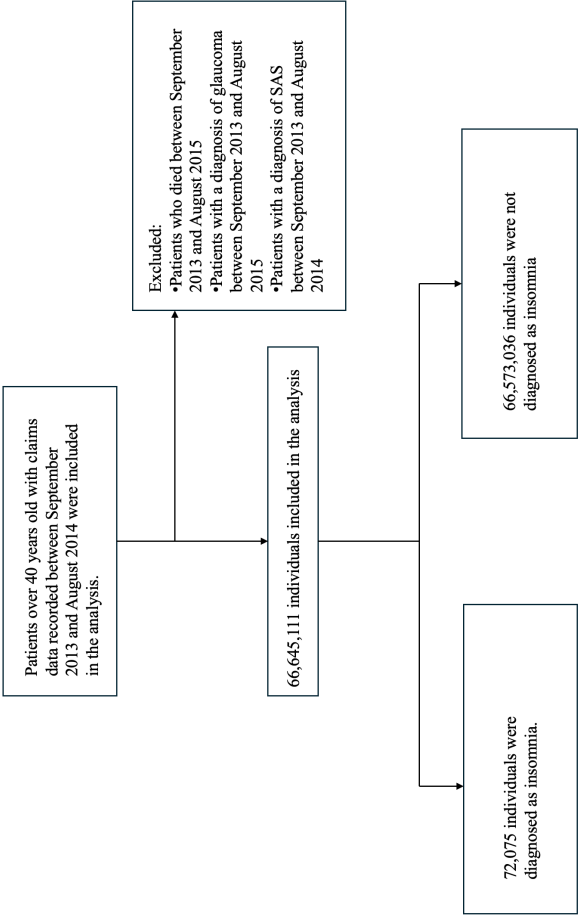
This flowchart illustrates the selection process for the cross-sectional analysis of the Nagahama Prospective Cohort. Among 9,850 participants, 3,892 were excluded due to factors such as poor-quality OCT images, age under 40 years, current glaucoma, missing right-eye data, or missing sleep measurements. Recordings with no signals or incomprehensible traces were excluded from the sleep data. A total of 2,733 (27.7%) participants did not meet the inclusion criteria for sleep measurements, including 741 (7.5%) who declined to wear the devices. The final analytic sample included 5,958 individuals.

Supplemental Figure 2. Flowchart of Patient Selection from the National Database (NDB)

A

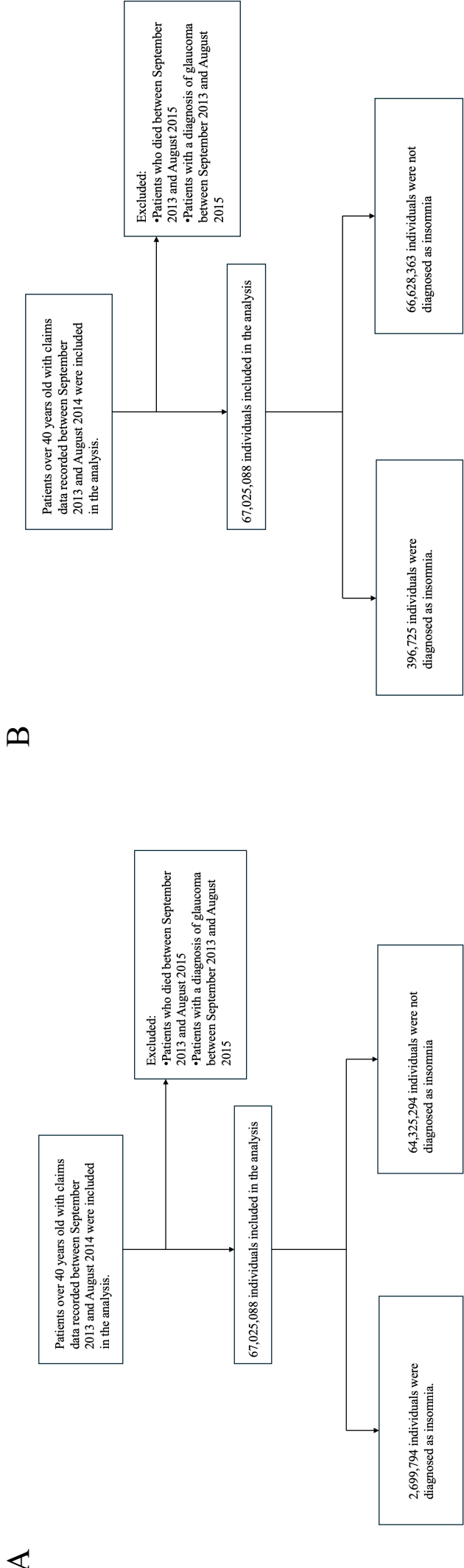


B



(A) Insomnia cohort. Individuals aged 40 years and older were initially identified from September 2013 to August 2014. Patients diagnosed with insomnia during this period were excluded to implement a washout period. From September 2014 to August 2015, eligible patients were identified, excluding those who had died during the interim. Insomnia cases were defined based on both diagnostic codes and prescription of sleep medications. (B) Sleep apnea syndrome (SAS) cohort. The same approach was used to identify and define SAS cases, based on both diagnostic codes and continuous positive airway pressure treatment records.

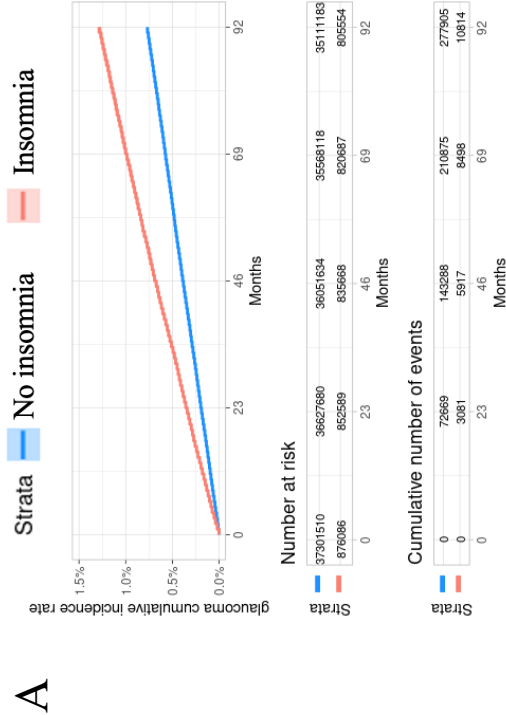
Supplemental figure 3. Flowchart Showing Patient Selection of Sensitivity Analysis.



Flow diagrams illustrating the selection of patients aged ≥ 40 years for sensitivity analyses of insomnia (A) and sleep apnea syndrome (B), without applying a washout period. Individuals with prior diagnoses of the respective sleep disorders during the baseline period (September 2013 to August 2014) were retained to assess the robustness of the main findings.

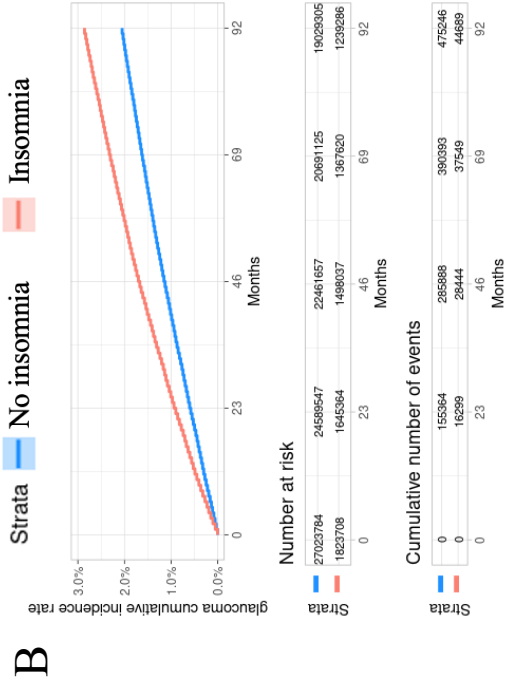
Supplemental figure 4. Kaplan–Meier Estimates for Incident Glaucoma by Sleep Disorder Status of Sensitivity Analysis

< 65 years

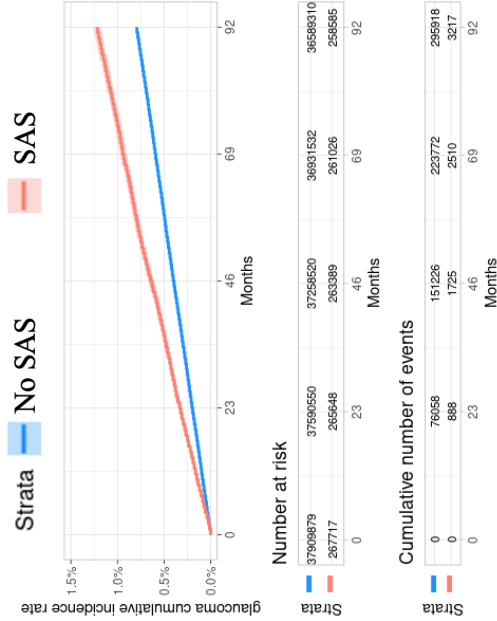


Insomnia

≥65 years



C



SAS

D



Kaplan–Meier curves showing cumulative incidence of glaucoma among individuals with insomnia and sleep apnea syndrome (SAS), compared to their respective control groups. The sensitivity analysis did not exclude individuals diagnosed with sleep disorders during the baseline period, allowing for inclusion of both preexisting and newly diagnosed cases. (A) Aged <65 years, insomnia. (B) Aged ≥65 years, insomnia. (C) Aged <65 years, SAS. (D) Aged ≥65 years, SAS.