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Melatonin and Risk of Age-Related Macular Degeneration

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IMPORTANCE Melatonin has been shown to oppose several processes that are known to mediate age-related macular degeneration (AMD), but whether melatonin can confer benefits against AMD remains unclear.

OBJECTIVE To examine the association between melatonin supplementation and the risk of the development or progression of AMD.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study accessed data from TriNetX, a national database of deidentified electronic medical records from both inpatient and outpatient health care organizations across the US, between December 4, 2023, and March 19, 2024. Patients aged 50 years or older, 60 years or older, and 70 years or older with no history of AMD (AMD-naive group) and with a history of nonexudative AMD (nonexudative AMD group) were queried for instances of melatonin medication codes between November 14, 2008, and November 14, 2023. Patients were then classified into either a melatonin group or a control group based on the presence of medication codes for melatonin. Propensity score matching (PSM) was performed to match the cohorts based on demographic variables, comorbidities, and nonmelatonin hypnotic medication use.

EXPOSURE The presence of at least 4 instances of melatonin records that each occurred at least 3 months apart.

MAIN OUTCOMES AND MEASURES After PSM, the melatonin and the control cohorts were compared to evaluate the risk ratios (RRs) and the 95% CIs of having an outcome. For the AMD-naive group, the outcome was defined as a new diagnosis of any AMD, whereas for the nonexudative AMD group, the outcome was progression to exudative AMD.

RESULTS Among 121 523 patients in the melatonin-naive group aged 50 years or older (4848 in the melatonin cohort [4580 after PSM; mean (SD) age, 68.24 (11.47) years; 2588 female (56.5%)] and 116 675 in the control cohort [4580 after PSM; mean (SD) age, 68.17 (10.63) years; 2681 female (58.5%)]), melatonin use was associated with a reduced risk of developing AMD (RR, 0.42; 95% CI, 0.28-0.62). Among 66 253 patients aged 50 years or older in the nonexudative AMD group (4350 in the melatonin cohort [4064 after PSM; mean (SD) age, 80.21 (8.78) years; 2482 female (61.1%)] and 61 903 in the control cohort [4064 patients after PSM; mean (SD) age, 80.31 (8.03) years; 2531 female (62.3%)]), melatonin was associated with a reduced risk of AMD progression to exudative AMD (RR, 0.44; 95% CI, 0.34-0.56). The results were consistent among subsets of individuals aged 60 years or older (AMD-naive cohort: RR, 0.36 [95% CI, 0.25-0.54]; nonexudative AMD cohort: RR, 0.38 [95% CI, 0.30-0.49]) and 70 years or older (AMD-naive cohort: RR, 0.35 [95% CI, 0.23-0.53]; nonexudative AMD cohort: RR, 0.40 [95% CI, 0.31-0.51]).

CONCLUSIONS AND RELEVANCE Melatonin use was associated with a decreased risk of development and progression of AMD. Although lifestyle factors may have influenced this association, these findings provide a rationale for further research on the efficacy of using melatonin as a preventive therapy against AMD.

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Supplemental content

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Age-related macular degeneration (AMD) is a multifactorial disease characterized by progressive degeneration of the macula and is currently the leading cause of vision loss for adults aged 60 years or older.[1] As its incidence is projected to steadily rise to reach an estimated prevalence of 18 million individuals in the US by 2050,[2] AMD is an important public health concern to address in today's aging population.[3]

Although the exact pathogenesis of AMD remains elusive, oxidative damage, pathologic neovascularization, and loss of the regenerative function of the retinal cells have been implicated as key factors.[4-6] While recent advances in anti–vascular endothelial growth factor (VEGF) therapy have substantially alleviated the adverse consequences of exudative AMD, this therapy requires frequent office visits, as anti-VEGF agents must be administered via intraocular injections.[7] Furthermore, while recent advances have expanded the options for the treatment of late stages of nonexudative (dry) AMD,[8-10] preventive interventions against the development of AMD have largely been limited to lifestyle modifications.[11] These limitations highlight the importance of preventing the development of AMD and the need for noninvasive supplemental therapy.

Melatonin, a hormone known for its role in regulating sleep-wake cycles,[12] is often used for the treatment of sleep disorders, such as insomnia.[13] However, studies in both animal models and humans have suggested that melatonin may also possess potent antioxidant, anti-inflammatory, antiangiogenic, and mitochondrial-protective properties.[4,14-16] As these properties may counteract many of the key pathologic processes that mediate AMD, such as oxidative damage, choroidal neovascularization, and dysregulated apoptosis,[4-6,17] melatonin may be a promising candidate for interventions targeting AMD.

Wang et al[18] showed that, in vitro, melatonin treatment increases the viability of retinal pigmented epithelial (RPE) cells, which are key supporters of the retina that are markedly damaged in AMD.[5,19,20] Subsequent in vivo analysis revealed that melatonin-treated mice had enhanced renewal of retinal cells in response to oxidative stress compared with control.[18] A study conducted in China further corroborated these findings, showcasing that patients with AMD who were treated with 3 mg of melatonin for at least 3 months had fewer pathologic macular changes and less decline in visual acuity than the estimated decline in the natural course of AMD.[21] While these findings support the promising therapeutic potential of melatonin against AMD, this study did not have a control group and may not be generalizable to racially and culturally diverse populations. To address the gaps in current clinical research, our study explored a large cohort of the US population to examine potential associations between melatonin use and the risks of AMD development or progression.

Key Points

Question What is the association between melatonin use and the development and progression of age-related macular degeneration (AMD)?

Findings In this cohort study of 121 523 patients with no history of AMD aged 50 years or older, taking melatonin was associated with a decreased risk of developing AMD. Likewise, among 66 253 patients with preexisting nonexudative AMD, melatonin supplementation was negatively associated with the rate of progression to exudative AMD.

Meaning These findings provide a rationale for expanding clinical research on the potential therapeutic efficacy of melatonin in preventing AMD development or its progression.

Methods

This retrospective cohort study used data from the TriNetX database, a federated health research network that aggregates deidentified electronic health records (EHRs) of more than 95 million patients from more than 60 US health care organizations. These organizations encompass both hospital and ambulatory care settings, allowing for greater patient diversity. As all data displayed on the platform are deidentified per the standard defined in section 164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule, Case Western Reserve University and the MetroHealth institutional review boards determined the study exempt from review and waived the need to obtain informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

All queries used for this study's data analysis were based on the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*), Anatomical Therapeutic Chemical, RxNorm, and Logical Observation Identifier Names and Codes coding systems between November 14, 2008, and November 14, 2023. Any diagnoses occurring prior to 2015 and recorded as *International Classification of Diseases, Ninth Revision* codes were converted to the corresponding *ICD-10* codes based on the Centers for Medicare & Medicaid Services General Equivalence Mappings. The relevant codes used are provided in eTables 1 through 3 in Supplement 1. All data were accessed between December 4, 2023, and March 19, 2024.

The eMethods in Supplement 1 provide a detailed description of the study methods. In brief, the overall aim of this study was to compare patients who were taking melatonin (melatonin cohort) with those who had no melatonin prescription record (control cohort) on the risks of 2 primary outcomes: the development of AMD and the progression of nonexudative AMD to exudative AMD. The analysis on the development of AMD included patients with no history of AMD (AMD-naive group), whereas the analysis on the progression of AMD included patients with a history of nonexudative AMD but no history of exudative AMD (nonexudative AMD group) (eTable 1 in Supplement 1). Each of these 2 groups was further divided into 3 subgroups of patients aged 50 years or older, 60 years or older, and 70 years or older, yielding a total of 6 subgroups for comparative analysis. The comparative analysis performed within each of these subgroups involved the following steps: (1) querying the EHRs for instances of melatonin records and assigning patients to the melatonin cohort or the control cohort; (2) matching the cohorts via propensity score matching (PSM) analysis; (3) reevaluating the matched cohorts to exclude patients who developed the outcome measure prior to the observation period (eTable 1 in Supple-

ment 1); and (4) comparing the melatonin cohort and control cohort to evaluate the risk ratios (RRs) of developing AMD during the observation period.

The observation period was between 1 year after the index event to the date of data collection. For the control cohort in the AMD-naive group, the index event was defined as the patient's first record of receiving an eye examination. For the melatonin cohort in the AMD-naive group, the index event was defined as the first instance when the requirements for an eye examination record and having a record of melatonin were both satisfied. Similarly, the index event for the control cohort in the nonexudative AMD group was defined as the patient's first nonexudative AMD diagnosis record, while for the melatonin cohort, it was defined as the first instance when the requirements for a nonexudative AMD diagnosis code and melatonin were both satisfied.

Sensitivity and Negative Control Analyses

After completing the primary analysis, 5 sensitivity analyses were performed to ensure the reliability of the results and to address potential confounders. First, to address the possibility that 1 year after the index date may not be sufficient for the development or the progression of AMD, the comparative analyses described above were repeated with the index date set as at least 2 years after the index event. Second, to ensure that the results were reproducible even when the melatonin cohort was more rigorously defined, patients in the melatonin cohort whose dosage information was not specified were excluded from the cohort, and the analysis was again repeated. Third, since the existence of other retinal disorders—or the treatments that patients may have been receiving for such disorders—may contribute to AMD development and progression, the analysis was performed again after excluding patients with proliferative diabetic retinopathy, diabetic macular edema, retinal vascular occlusions, retinal edema, or a record of receiving an anti-VEGF injection before AMD development or progression (relevant codes corresponding to these exclusions are listed in eTable 1C in Supplement 1). Fourth, because melatonin is most commonly used for sleep disorders, any associations observed in our primary analyses could potentially be attributed to the outcomes of sleep disorder treatment. To minimize this confounding effect, an additional sensitivity analysis was performed by selecting patients with a history of a sleep disorder (eTable 1C in Supplement 1) and comparing the risks of AMD development and progression between the melatonin and the control cohorts in this subpopulation. Fifth, to show that any significant associations observed in the primary analysis were not artifacts of residual bias, the analysis was repeated, with head trauma serving as a negative control (eTable 1C in Supplement 1). Head trauma was chosen as the negative outcome variable because melatonin has been implicated in several ocular[22,23] and systemic diseases.[24-27]

Statistical Analysis

To balance differences in confounding variables between subgroups, PSM analysis was performed before each comparative analysis using a 1-to-1 greedy matching algorithm with a caliper of 0.25 pooled SDs. Cohorts were matched on demographic characteristics (including sex, race [Asian, Black or African American, White, or other], and ethnicity [Hispanic or Latino]), socioeconomic status, nonmelatonin hypnotic medication use, and the presence of selected comorbidities. Other race included any known race besides American Indian or Alaska Native, Asian, Black, Native Hawaiian or Pacific Islander, or White. Cohorts were not matched on American Indian or Alaska Native and Native Hawaiian or Pacific Islander race because of the low prevalence in the cohorts (<1%). Race and ethnicity were obtained from the patients' structured electronic health records and were included as covariates because of the racial and ethnic differences in the prevalence of AMD.[28] The RRs of having the outcome and corresponding 95% CIs were calculated through logistic regression. A 2-sided $P < .05$ was considered statistically significant. The analyses were performed using the analysis tool built into the platform.

Results

Risks of Developing AMD

Our final analysis included 121 523 patients aged 50 years or older in the AMD-naive group at baseline, including 4848 in the melatonin cohort (4580 patients after PSM; mean [SD] age, 68.24 [11.47] years; 2588 female [56.5%] and 1992 male [43.5%]; 106 Asian [2.3%], 721 Black [15.7%], 3131 White [68.4%], 219 other [4.8%], 671 unknown or missing [8.8%] race; and 284 Hispanic or Latino ethnicity [6.2%]) and 116 675 in the control group (4580 patients after PSM; mean [SD] age, 68.17 [10.63] years; 2681 female [58.5%] and 1899 male [41.5%]; 102 Asian [2.2%], 721 Black [15.7%], 3160 White [69.0%], 203 other [4.4%], and 394 missing or unknown [8.6%] race; and 252 Hispanic or Latino ethnicity [5.5%]). The PSM analysis results are shown in eTable 4A in Supplement 1, and the results of the comparative analyses are summarized in the **Table** and **Figure 1**.

Among patients aged 50 years or older, those in the melatonin cohort had a reduced risk of receiving an AMD diagnosis compared with the control cohort (RR, 0.42; 95% CI, 0.28-0.62). The analysis of the older subsets of patients revealed similar findings (aged ≥60 years: RR, 0.36 [95% CI, 0.25-0.54]; aged ≥70 years old: RR, 0.35 [95% CI, 0.23-0.53]). Such associations persisted even when patients were monitored for AMD development at least 2 years after the index event (aged ≥50 years: RR, 0.22 [95% CI, 0.12-0.39]; aged ≥60 years: RR, 0.40 [95% CI, 0.19-0.83]; aged ≥70 years: RR, 0.22 [95% CI, 0.12-0.43]). Likewise, our sensitivity analyses revealed consistent results with that of the primary analysis (eTables 6-8 in Supplement 1). The negative control outcome analysis showed that melatonin treatment was not associated with the risk of head injuries (eTable 9 in Supplement 1).

Risk of AMD Progression

Our final analysis included 66 253 patients aged 50 years or older in the nonexudative AMD group at baseline, including 4350 in the melatonin cohort (4064 patients after PSM; mean [SD] age, 80.21 [8.78] years; 2482 female [61.1%] and 1582 male

Table. Risks of AMD Development and Progression at Least 1 Year After the Index Event

Outcome and age group	Melatonin		Control		RR (95% CI)	*P* value
	Total	Events, No. (%)	Total	Events, No. (%)		
Development of AMD among patients with no history of AMD						
≥50 y	4150	35 (0.84)	4112	83 (2.02)	0.42 (0.28-0.62)	<.001
≥60 y	3410	33 (0.97)	3349	89 (2.66)	0.36 (0.25-0.54)	<.001
≥70 y	2195	31 (1.41)	2131	86 (4.04)	0.35 (0.23-0.53)	<.001
Progression to exudative AMD among patients with preexisting nonexudative AMD						
≥50 y	3140	88 (2.80)	3273	211 (6.45)	0.44 (0.34-0.56)	<.001
≥60 y	3094	87 (2.81)	3219	237 (7.36)	0.38 (0.30-0.49)	<.001
≥70 y	2885	86 (2.98)	2979	224 (7.52)	0.40 (0.31-0.51)	<.001

Abbreviations: AMD, age-related macular degeneration; RR, risk ratio.

Figure 1. Risk of Age-Related Macular Degeneration (AMD) Diagnosis in Patients Without a History of AMD

Age, y	Melatonin Total, No.	Melatonin Events, No. (%)	Control Total, No.	Control Events, No. (%)	Risk ratio (95% CI)
≥50	4150	35 (0.84)	4112	83 (2.02)	0.42 (0.28-0.62)
≥60	3410	33 (0.97)	3349	89 (2.66)	0.36 (0.25-0.54)
≥70	2195	31 (1.41)	2131	86 (4.04)	0.35 (0.23-0.53)

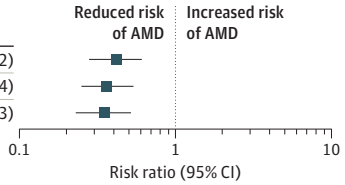
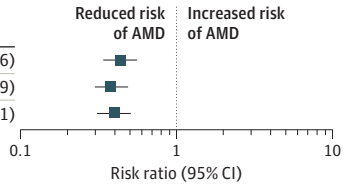


Figure 2. Risk of Exudative Age-Related Macular Degeneration (AMD) Diagnosis in Patients With a History of Nonexudative AMD

Age, y	Melatonin Total, No.	Melatonin Events, No. (%)	Control Total, No.	Control Events, No. (%)	Risk ratio (95% CI)
≥50	3140	88 (2.80)	3273	211 (6.45)	0.44 (0.34-0.56)
≥60	3094	87 (2.81)	3219	237 (7.36)	0.38 (0.30-0.49)
≥70	2885	86 (2.98)	2979	224 (7.52)	0.40 (0.31-0.51)



[38.9%]; 64 Asian [1.6%], 129 Black [3.2%], 3576 White [88.0%], 75 other [1.9%], and 220 missing or unknown [5.4%] race; and 109 Hispanic or Latino ethnicity [2.7%]), and 61 903 in the control group (4064 patients after PSM; mean [SD] age, 80.31 [8.03] years; 2531 female [62.3%] and 1533 male [37.7%]; 65 Asian [1.6%], 125 Black [3.1%], 3580 White [88.1%], 72 other [1.8%], and 222 missing or unknown [5.5%] race; and 107 Hispanic or Latino ethnicity [2.6%]). The PSM analysis results are shown in eTable 4B in Supplement 1, and the results of the comparative analyses are summarized in the Table and **Figure 2**.

Across all 3 age subsets, the melatonin cohort had reduced risks of progression to exudative AMD compared with the control cohort (aged ≥50 years, RR, 0.44 [95% CI, 0.34-0.56]; aged ≥60 years: RR, 0.38 [95% CI, 0.30-0.49]; aged ≥70 years: RR, 0.40 [95% CI, 0.31-0.51]). The sensitivity analysis on the 2-year outcomes and various subsets of patients revealed consistent findings, supporting the negative association between melatonin use and the risk of nonexudative AMD progression to the exudative form (eTables 5-8 in Supplement 1). While the negative control outcome analysis revealed no significant associations between melatonin use and the risk of head injuries among patients aged 70 years or older (RR, 0.87; 95% CI, 0.74-1.02), significant associations were observed for the analyses comparing the melatonin cohort with the control cohort among patients aged 50 years or older (RR, 0.84; 95% CI, 0.71-0.98) and 60 years or older (RR, 0.83; 95% CI, 0.71-0.98) (eTable 9 in Supplement 1).

Discussion

In this cohort study, melatonin use was associated with a reduced risk of both diagnosis and progression of AMD. Although variances in such confounding factors as lifestyle and health care access must be considered when interpreting these results, the consistency of these findings across different age groups lends support for the potential benefits of melatonin against AMD, even among older populations.

These findings align with those of previous experimental studies using animal models that showed that melatonin

treatment may delay or reverse the known pathologic processes observed in AMD.[29,30] Such potential protective outcomes of melatonin are further reinforced by the established knowledge from earlier research studies that nocturnal melatonin levels naturally decline with age, reaching markedly low levels after the age of 60 years.[31-33] As this natural decline coincides with the age group most susceptible to AMD,[34] melatonin may play a protective role against the age-related changes that can predispose older individuals to macular degeneration. Considering today's aging population trends and increasing prevalence of AMD, expanding research in this area could bear substantial public health value.

As a natural antioxidant and anti-inflammatory agent, melatonin possesses several properties that can oppose the processes detrimental to visual function. For instance, melatonin plays a crucial role in cell survival and regeneration, and these effects have been shown to protect RPE cells, which are particularly vulnerable to damage induced by reactive oxygen species in the retina.[19,20,35] The RPE cells play a critical role in maintaining the homeostasis of the retinal microenvironment by preserving the blood-retinal barrier, reducing photooxidative stress through the absorption of excess light, and clearing debris produced by photoreceptor cells during continuous regeneration.[19,36-38] Since the loss of RPE cells is a hallmark of AMD even in the early stages of the disease,[35,39,40] the protective effects of melatonin on RPE cells provide encouraging insight into the clinical use of melatonin in preventing AMD.

In our analysis of patients with a history of nonexudative AMD, melatonin use was also associated with a lower risk of progression to exudative AMD, even after excluding patients who were receiving anti-VEGF injection therapy (eTable 7 in Supplement 1). In line with this finding, both ex vivo[41] and in vivo[42,43] studies have shown that melatonin may reduce reactive oxygen species–induced overexpression of VEGF, which is the main mediator of the pathologic neovascularization that marks the onset of the exudative form of AMD.[6,44] It is important to acknowledge that these findings cannot necessarily be extrapolated to draw the same conclusion in humans until confirmed in controlled clinical trials, especially as the dosage of melatonin administered in these previous studies was much higher than the typical dosages of melatonin supplements.[42,43] Nevertheless, given the consistency of our results in a national cohort of patients with nonexudative AMD across various age groups, such evidence suggests that exploration of melatonin as a potential therapeutic supplement for individuals with nonexudative AMD may be a promising direction for future research.

Limitations

As this study was primarily exploratory, it has several important limitations. First, variations in coding practices among clinicians and institutions should be considered when interpreting our results. For instance, some physicians may have entered the unspecified macular degeneration diagnosis code for patients with exudative AMD instead of specifying the code for exudative AMD. Such instances of miscoding may have limited the accuracy of our results on the progression of nonexudative AMD, as our analysis of the nonexudative AMD group did not explicitly exclude patients with unspecified macular degeneration prior to the index date. Relying solely on diagnostic codes could have also limited the accuracy of the PSM analysis, as certain conditions, such as tobacco use[45] and socioeconomic deprivation,[46] may be underreported and not accurately reflected in the EHR data. Similarly, inaccuracies that are often associated with the reporting of over-the-counter medications[47] such as melatonin in the EHR could have biased our results.

Additional covariates that could not be controlled by PSM analysis, such as the use of Age-Related Eye Disease Study formula multivitamins, could have confounded the results. Furthermore, as the modifiable risk factors of AMD extend beyond cigarette smoking and use of Age-Related Eye Disease Study vitamins,[48,49] the reduced risks of AMD observed in the melatonin groups may be attributed to healthy user bias, as individuals regularly taking supplements such as melatonin may be more proactive about maintaining a healthy lifestyle. Likewise, because we could not control for variances in the frequency of contact with medical professionals after the index date, our results may be limited by surveillance bias, as patients with fewer visits to ophthalmologists or who have less health care access may be less likely to be diagnosed with AMD or exudative AMD.

To select patients with long-term melatonin use when constructing our melatonin cohorts, we established a requirement for multiple instances of melatonin records; however, the duration of melatonin therapy during the observation period could not be standardized. As differences in this duration could have further confounded our study, controlled clinical trials are needed to confirm our results and clarify the minimum effective duration of melatonin therapy for the prevention of AMD development or progression. The dose and the frequency of melatonin also could not be standardized in this study. Because melatonin is only regulated as a supplement by the US Food and Drug Administration,[50,51] the frequency and dose of the drug is often empirically determined based on the patient's clinical response to the initial dose. In addition, because the bioavailability of melatonin is highly variable,[52-54] the resulting variations in serum levels of melatonin among patients could have increased the uncertainty of our results.

Finally, while the consistency of the results observed in our sensitivity analyses strengthened the reliability of our primary findings, it must be acknowledged that these analyses themselves were also limited by various factors. For instance, reporting bias of melatonin could have particularly limited the sensitivity analysis of patients with sleep disorders (eTable 8 in Supplement 1). Furthermore, our negative control analyses showed significant associations in 2 of the analyses in the nonexudative AMD group (eTable 6 in Supplement 1). Although the degree of these associations was marginal compared with those observed in our primary analyses and may be associated with the variances in coding practices across institutions or uncontrolled confounders, confirmation of our conclusions in future clinical trials in different populations is necessary to ensure the reliability and generalizability of the therapeutic potential of melatonin against AMD.

Conclusions

The findings of this cohort study highlight that melatonin use is associated with a reduced risk of AMD development or progression. The protective influence of melatonin on RPE cells and its ability to reduce oxidative stress and resulting VEGF overexpression may contribute to its promising role in AMD management. This study was primarily exploratory, and overall differences in lifestyle habits and engagement with the health care system between melatonin users and nonusers could have influenced the associations observed; however, the results provide a rationale for further exploration of the use of melatonin in AMD prevention and management. Given the convenient availability in oral form and generally benign safety profile of melatonin,[13] confirmation of this study's results in future clinical trials and longitudinal studies could contribute to advancing the current treatment options for AMD.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Jeong, Shaia, Markle, Talcott.
Drafting of the manuscript: Jeong, Markle.
Critical review of the manuscript for important intellectual content: All authors.
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Supplemental Online Content

Jeong H, Shaia JK, Markle JC, Talcott KE, Singh RP. Melatonin and risk of age-related macular degeneration. *JAMA Ophthalmol*. Published online June 6, 2024. doi:10.1001/jamaophthalmol.2024.1822

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Investigating the associations between melatonin and the risks of developing age-related macular degeneration (AMD)

In order to determine how melatonin use may be associated with the risk of developing AMD in patients without a prior history AMD ("AMD-naïve"), we performed the following steps: 1) defining the initial AMD-naïve group; 2) assigning patients in this initial group into cohorts based on their melatonin usage; 3) matching the cohorts via propensity score matching (PSM) analysis; 4) reevaluating the matched cohorts to exclude patients who developed AMD prior to the index date, which will be defined later in this section; 5) comparing the cohorts to evaluate the risk ratios (RR) of developing AMD.

Defining the initial AMD-naïve group

Patients included in the AMD-naïve group were identified by querying the database for patient records between November 2008 and November 2023. This group comprised patients who had at least one record of body mass index (BMI), had at least one record of receiving an eye examination or screening for ocular disorders, and were aged 50 years or above (eTable 1A in the Supplement). The requirement for a record of receiving an eye examination or screening was added to minimize the number of patients with undiagnosed AMD that may otherwise have confounded the results. The age restriction was used because AMD is most prevalent in middle-aged and elderly populations[1].

In addition to this analysis on patients aged ≥50 years, a secondary aim of this study was to explore whether the association between melatonin and AMD may differ in subgroups of patients aged ≥60 years and ≥70 years, as the risk of AMD has been known to increase with age even within this population[1]. Therefore, prior to the outcome analysis, subgroups of patients aged ≥60 years and ≥70 years were created to allow for age-stratified analysis. These age groups were selected because the prevalence of AMD and vision-threatening AMD sharply rises after 60 and 70 years of age, respectively[1].

Cohort assignment

Then, patients within each age subset were assigned to either the "control" cohort or the "melatonin" cohort based on their history of receiving melatonin (RxNorm code: 6711). The control cohort comprised eligible patients with no recorded instances of a melatonin code during the study period. Conversely, eligible patients were assigned to the melatonin cohort if they had at least four instances of melatonin records that each occurred at least 3 months apart from one another. However, if a patient had received melatonin treatment consistently enough and for a sufficient amount of time to be assigned to the melatonin cohort, but subsequently discontinued melatonin well before their outcome was assessed, it is unlikely that their remote history of melatonin use had a substantial impact on their outcome. Therefore, patients who initially qualified for inclusion in the melatonin cohort based on the melatonin prescription requirements were excluded from the melatonin cohort if their last melatonin record occurred two or more years before they developed AMD.

Then, for each age subset, the risks of developing AMD (eTable 3) were compared between the melatonin cohort and the control.

Propensity Score Matching

In order to balance differences in confounding variables between the subgroups, PSM analysis was performed prior to each comparative analysis. This was performed using a one-to-one greedy matching algorithm with a caliper of 0.25 pooled standard deviations. Cohorts were matched on demographic characteristics, socioeconomic status, non-melatonin hypnotic medication use, and the presence of selected comorbidities (a full list of covariates and their ICD-10 codes are shown in eTable 2 in the Supplement).

Evaluating the risk ratios

After PSM, the cohorts were examined for the occurrence of an AMD diagnosis code between the index date and this study's data collection date. The index date at which this observation period began was defined as at least one year after the first date of the index event. For the control cohort, the index event was defined as the first eye examination record. For the melatonin cohort, the index event was defined as the first instance when the requirements for an eye examination record and melatonin prescription were both satisfied.

Investigating the associations between melatonin and the risks of AMD progression

Another objective of this study was to investigate how melatonin use may be associated with the risk of adverse progression of AMD from nonexudative to exudative AMD. A "nonexudative-AMD" group was established for similar analyses performed on the AMD-naïve group. The nonexudative-AMD group comprised patients aged 50

years or above who had a history of nonexudative AMD at baseline and at least one record of BMI (eTable 1B in the Supplement).

Using the same criteria as those used in the AMD-naïve group, controls were compared to the melatonin cohort in patients aged ≥50, ≥60, and ≥70 years. The cohorts were matched (eTable 2 in the Supplement) and compared to calculate the RR of developing exudative AMD (eTable 3) at least one year after the index event. The index event for the control cohort was defined as the nonexudative AMD diagnosis record, while for the melatonin cohort, it was defined as the first instance when the requirements for a nonexudative AMD diagnosis code and melatonin prescription were both satisfied.

eTable 1. Relevant Codes Used to Define the AMD Groups for the Primary Analysis and the Additional Inclusion and Exclusion Criteria for the Sensitivity and the Negative Control Analyses

eTable 1A: Relevant codes used to define the AMD-naïve group for the primary analysis

Inclusion criteria	**Code System**	**Relevant code**
Eye examination	ICD-10	Z01.0, Z13.5
Body Mass Index	LOINC	39156-5
Age: ≥50, ≥60, and ≥70 years old		
Exclusion criteria: patients with a history of any of the following before the index date were excluded from the final analysis**.**	**Code System**	**Relevant code**
Unspecified macular degeneration	ICD-10	H35.30
Nonexudative AMD	ICD-10	H35.31
Exudative AMD	ICD-10	H35.32

AMD: age-related macular degeneration; ICD-10: International Classification of Diseases, 10th Revision; LOINC: Logical Observation Identifiers Names and Codes

eTable 1B: Relevant codes used to define the nonexudative-AMD group for the primary analysis

Inclusion criteria	**Code System**	**Relevant code**
Nonexudative AMD	ICD-10	H35.31
Body Mass Index	LOINC	39156-5
Age: ≥50 years old		
Exclusion criteria: patients with a history of any of the following before the index date were excluded from the final analysis**.**	**Code System**	**Relevant code**
Exudative AMD	ICD-10	H35.32

AMD: age-related macular degeneration; ICD-10: International Classification of Diseases, 10th Revision; LOINC: Logical Observation Identifiers Names and Codes

eTable 1C: Relevant codes used to define the additional inclusion and exclusion criteria for the sensitivity and the negative control analyses

Variable	Code System	Relevant code
Ophthalmic anti-VEGF agents	RxNorm	1232150, 2204915, 253337, 2591519, 498509, 595060
Ocular comorbidities		
Proliferative diabetic retinopathy	ICD-10	E10.35, E11.35
Diabetic macular edema	ICD-10	E10.37, E10.311, E10.321, E10.331, E10.341, E10.351, E11.37, E11.311, E11.321, E11.331, E11.341, E11.351
Retinal vascular occlusions	ICD-10	H34
Retinal edema	ICD-10	H35.81
Sleep disorder	ICD-10	G27
Injuries to the head	ICD-10	S00-S09

AMD: age-related macular degeneration; ICD-10: International Classification of Diseases, 10th Revision

eTable 2. Covariates and Their Relevant Codes for Propensity Score Matching

Covariate	Code System	Relevant code
Age at Index		
Female		
Race		
White		
Black or African American		
Asian		
Unknown Race		
Ethnicity: Hispanic		
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	ICD-10	Z55-Z65
Body Mass Index	LOINC	39156-5
< 18.5		
18.5-24.9		
25-29.9		
30-39.9		
> 40.0		
Nicotine dependence	ICD-10	F17
Tobacco use	ICD-10	Z72.0
Alcohol related disorders	ICD-10	F10
Diseases of the circulatory system	ICD-10	I00-I99
Hypertensive diseases	ICD-10	I10-I16
Ischemic heart diseases	ICD-10	I20-I25
Diseases of arteries, arterioles and capillaries	ICD-10	I70-I79
Cerebrovascular diseases	ICD-10	I60-I69
Alzheimer's Disease	ICD-10	G30
Parkinson's Disease	ICD-10	G20
Sleep disorders	ICD-10	G47
Insomnia	ICD-10	G47.0
Sleep disorders not due to a substance or known physiological condition	ICD-10	F51
Diabetes Mellitus	ICD-10	E08-E13
Type 2 diabetes mellitus with ophthalmic complications	ICD-10	E11.3
Type 2 diabetes mellitus with unspecified diabetic retinopathy	ICD-10	E11.31
Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy	ICD-10	E11.32
Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy	ICD-10	E11.33
Type 2 diabetes mellitus with proliferative diabetic retinopathy	ICD-10	E11.35
Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy	ICD-10	E11.34
Retinal edema	ICD-10	H35.80
Medications		
Benzodiazepine derivatives	ATC	N05CD
Benzodiazepine related drugs	ATC	N05CF
Other hypnotics and sedatives	ATC	N05CM

ICD-10: International Classification of Diseases, 10th Revision; LOINC: Logical Observation Identifiers Names and Codes; ATC: Anatomical Therapeutic Chemical

eTable 3. *ICD-10* Codes for the Outcome Measures

Purpose of the outcome measure in the study	Outcome measure	ICD-10 codes
Evaluation of the risks of developing AMD in AMD-naïve patients	AMD	H35.30, H35.31, H35.32
Evaluation of the risks of progression of AMD in patients with a history of nonexudative AMD	Exudative AMD	H35.32

AMD: age-related macular degeneration; ICD-10: International Classification of Diseases, 10th Revision

eTable 4. Baseline Characteristics of Patients Aged 50 Years or Older by AMD Group

eTable 4A: Baseline characteristics of patients aged 50 years or above in the AMD-naïve group

Characteristic	Before Matching			After Matching		
	Melatonin	Control	SMD	Melatonin	Control	SMD
Number of Patients	4,848	116,675		4,580	4,580	
Age at Index	68.51 (11.45)	68.24 (11.47)	0.522	68.24 (11.47)	68.17 (10.63)	0.006
Female	2,734 (56.39%)	67,407 (57.77%)	0.028	2,588 (56.51%)	2,681 (58.54%)	0.041
Race						
White	3,319 (68.46%)	74,414 (63.78%)	0.099	3,131 (68.36%)	3,160 (69.00%)	0.014
Black or African American	767 (15.82%)	15,671 (13.43%)	0.068	721 (15.74%)	721 (15.74%)	0.000
Asian	107 (2.21%)	4,021 (3.45%)	0.075	106 (2.31%)	102 (2.23%)	0.006
Other	227 (4.68%)	5,940 (5.09%)	0.019	219 (4.78%)	203 (4.43%)	0.017
Hispanic or Latino	299 (6.17%)	8,869 (7.60%)	0.057	284 (6.20%)	252 (5.50%)	0.030
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	747 (15.41%)	4,459 (3.82%)	0.401	656 (14.32%)	627 (13.69%)	0.018
Body Mass Index (kg/m^2)						
< 18.5	613 (12.64%)	3,795 (3.25%)	0.353	532 (11.62%)	515 (11.24%)	0.012
18.5-24.9	2,184 (45.05%)	35,064 (30.05%)	0.313	2,005 (43.78%)	1,963 (42.86%)	0.019
25-29.9	3,121 (64.38%)	51,163 (43.85%)	0.421	2,902 (63.36%)	2,958 (64.59%)	0.025
30-39.9	3,128 (64.52%)	48,511 (41.58%)	0.472	2,909 (63.52%)	2,972 (64.89%)	0.029
> 40.0	1,193 (24.61%)	13,097 (11.23%)	0.354	1,082 (23.62%)	1,097 (23.95%)	0.008
Nicotine dependence	1,437 (29.64%)	15,086 (12.93%)	0.417	1,318 (28.78%)	1,260 (27.51%)	0.028

Tobacco use	490	(10.11%)	3,237	(2.77%)	0.302	436	(9.52%)	420	(9.17%)	0.012
Alcohol related disorders	753	(15.53%)	5,276	(4.52%)	0.373	672	(14.67%)	672	(14.67%)	0.000
Diseases of the circulatory system	4,649	(95.90%)	77,982	(66.84%)	0.804	4,381	(95.66%)	4,391	(95.87%)	0.011
Hypertensive diseases	4,248	(87.62%)	64,692	(55.45%)	0.763	3,983	(86.97%)	3,993	(87.18%)	0.007
Ischemic heart diseases	2,523	(52.04%)	18,004	(15.43%)	0.840	2,295	(50.11%)	2,288	(49.96%)	0.003
Diseases of arteries, arterioles and capillaries	2,275	(46.93%)	16,235	(13.91%)	0.769	2,052	(44.80%)	2,058	(44.93%)	0.003
Cerebrovascular diseases	1,803	(37.19%)	10,667	(9.14%)	0.705	1,592	(34.76%)	1,521	(33.21%)	0.033
Alzheimer's Disease	194	(4.00%)	675	(0.58%)	0.230	162	(3.54%)	162	(3.54%)	0.000
Parkinson's Disease	197	(4.06%)	883	(0.76%)	0.217	160	(3.49%)	156	(3.41%)	0.005
Insomnia	2,349	(48.45%)	12,837	(11.00%)	0.898	2,117	(46.22%)	2,087	(45.57%)	0.013
Sleep disorders	3,483	(71.84%)	28,519	(24.44%)	1.078	3,221	(70.33%)	3,269	(71.38%)	0.023
Sleep disorders not due to a substance or known physiological condition	763	(15.74%)	4,409	(3.78%)	0.411	669	(14.61%)	682	(14.89%)	0.008
Diabetes Mellitus	2,980	(61.47%)	41,789	(35.82%)	0.531	2,763	(60.33%)	2,742	(59.87%)	0.009
Type 2 diabetes mellitus with ophthalmic complications	1,019	(21.02%)	7,449	(6.38%)	0.436	886	(19.34%)	888	(19.39%)	0.001
Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy	422	(8.70%)	2,450	(2.10%)	0.295	361	(7.88%)	360	(7.86%)	0.001
Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy	176	(3.63%)	1,157	(0.99%)	0.176	148	(3.23%)	163	(3.56%)	0.018
Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy	75	(1.55%)	296	(0.25%)	0.137	56	(1.22%)	54	(1.18%)	0.004
Type 2 diabetes mellitus with proliferative diabetic retinopathy	195	(4.02%)	1,200	(1.03%)	0.192	166	(3.62%)	172	(3.76%)	0.007
Type 2 diabetes mellitus with unspecified diabetic retinopathy	656	(13.53%)	4,770	(4.09%)	0.338	566	(12.36%)	570	(12.45%)	0.003
Retinal edema	144	(2.97%)	1,211	(1.04%)	0.138	126	(2.75%)	124	(2.71%)	0.003
Medications										
Benzodiazepine derivatives	3,350	(69.10%)	33,407	(28.63%)	0.885	3,096	(67.60%)	3,126	(68.25%)	0.014
Benzodiazepine related drugs	1,498	(30.90%)	10,643	(9.12%)	0.566	1,345	(29.37%)	1,368	(29.87%)	0.011
Other hypnotics and sedatives	1,016	(20.96%)	5,364	(4.60%)	0.505	881	(19.24%)	871	(19.02%)	0.006

Data represents mean (standard deviation) for continuous variables or number (%) for categorical variables
SMD = standardized mean difference

Table 4B: Baseline characteristics of patients aged 50 years or above in the nonexudative-AMD group

Characteristic	Before Matching			After Matching		
	Melatonin	Control	SMD	Melatonin	Control	SMD
Number of Patients	4,350	61,903		4,064	4,064	
Age at Index	80.36 (8.75)	75.92 (9.53)	0.486	80.21 (8.78)	80.31 (8.03)	0.012
Female	2,645 (60.80%)	37,738 (60.96%)	0.003	2,482 (61.07%)	2,531 (62.28%)	0.025
Race						
White	3,825 (87.93%)	50,967 (82.33%)	0.158	3,576 (87.99%)	3,580 (88.09%)	0.003
Black or African American	148 (3.40%)	2,053 (3.32%)	0.005	129 (3.17%)	125 (3.08%)	0.006
Asian	66 (1.52%)	1,458 (2.36%)	0.061	64 (1.57%)	65 (1.60%)	0.002
Other	80 (1.84%)	1,716 (2.77%)	0.062	75 (1.85%)	72 (1.77%)	0.006
Hispanic or Latino	118 (2.71%)	2,154 (3.48%)	0.044	109 (2.68%)	107 (2.63%)	0.003
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	417 (9.59%)	1,109 (1.79%)	0.341	335 (8.24%)	316 (7.78%)	0.017
Body Mass Index (kg/m^2)						
< 18.5	530 (12.18%)	2,523 (4.08%)	0.300	458 (11.27%)	455 (11.20%)	0.002
18.5-24.9	2,246 (51.63%)	19,397 (31.33%)	0.421	2,032 (50.00%)	2,071 (50.96%)	0.019
25-29.9	3,066 (70.48%)	26,363 (42.59%)	0.586	2,811 (69.17%)	2,866 (70.52%)	0.029
30-39.9	2,378 (54.67%)	20,112 (32.49%)	0.459	2,172 (53.44%)	2,155 (53.03%)	0.008
> 40.0	567 (13.03%)	3,923 (6.34%)	0.228	520 (12.80%)	480 (11.81%)	0.030
Nicotine dependence	836 (19.22%)	5,741 (9.27%)	0.287	749 (18.43%)	725 (17.84%)	0.015
Tobacco use	172 (3.95%)	571 (0.92%)	0.198	140 (3.44%)	127 (3.13%)	0.018
Alcohol related disorders	446 (10.25%)	2,038 (3.29%)	0.280	385 (9.47%)	384 (9.45%)	0.001

Diseases of the circulatory system	4,263	(98.00%)	44,170	(71.35%)	0.796	3,977	(97.86%)	3,990	(98.18%)	0.023
Hypertensive diseases	3,960	(91.03%)	37,529	(60.63%)	0.760	3,681	(90.58%)	3,705	(91.17%)	0.021
Ischemic heart diseases	2,471	(56.80%)	14,336	(23.16%)	0.731	2,244	(55.22%)	2,233	(54.95%)	0.005
Diseases of arteries, arterioles and capillaries	2,315	(53.22%)	12,281	(19.84%)	0.739	2,084	(51.28%)	2,117	(52.09%)	0.016
Cerebrovascular diseases	1,856	(42.67%)	9,282	(14.99%)	0.642	1,659	(40.82%)	1,658	(40.80%)	0.001
Alzheimer's Disease	359	(8.25%)	926	(1.50%)	0.318	296	(7.28%)	289	(7.11%)	0.007
Parkinson's Disease	237	(5.45%)	902	(1.46%)	0.220	193	(4.75%)	201	(4.95%)	0.009
Insomnia	1,907	(43.84%)	5,332	(8.61%)	0.874	1,662	(40.90%)	1,676	(41.24%)	0.007
Sleep disorders	2,836	(65.20%)	11,922	(19.26%)	1.051	2,558	(62.94%)	2,578	(63.44%)	0.010
Sleep disorders not due to a substance or known physiological condition	509	(11.70%)	1,233	(1.99%)	0.392	423	(10.41%)	414	(10.19%)	0.007
Diabetes Mellitus	1,770	(40.69%)	15,386	(24.86%)	0.342	1,613	(39.69%)	1,569	(38.61%)	0.022
Type 2 diabetes mellitus with ophthalmic complications	621	(14.28%)	3,973	(6.42%)	0.260	550	(13.53%)	517	(12.72%)	0.024
Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy	288	(6.62%)	1,445	(2.33%)	0.208	253	(6.23%)	230	(5.66%)	0.024
Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy	81	(1.86%)	426	(0.69%)	0.105	71	(1.75%)	63	(1.55%)	0.015
Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy	21	(0.48%)	91	(0.15%)	0.060	14	(0.34%)	12	(0.30%)	0.009
Type 2 diabetes mellitus with proliferative diabetic retinopathy	70	(1.61%)	496	(0.80%)	0.074	61	(1.50%)	54	(1.33%)	0.015
Type 2 diabetes mellitus with unspecified diabetic retinopathy	405	(9.31%)	2,743	(4.43%)	0.194	366	(9.01%)	327	(8.05%)	0.034
Retinal edema	265	(6.09%)	1,980	(3.20%)	0.138	236	(5.81%)	215	(5.29%)	0.023
Medications										
Benzodiazepine derivatives	2,650	(60.92%)	18,211	(29.42%)	0.667	2,407	(59.23%)	2,355	(57.95%)	0.026
Benzodiazepine related drugs	1,353	(31.10%)	5,690	(9.19%)	0.568	1,183	(29.11%)	1,210	(29.77%)	0.015
Other hypnotics and sedatives	673	(15.47%)	2,190	(3.54%)	0.416	553	(13.61%)	518	(12.75%)	0.025

Data represents mean (standard deviation) for continuous variables or number (%) for categorical variables
SMD = standardized mean difference

eTable 5. Risks of AMD Development and Progression at Least 2 Years After the Index Event

Analyzed Outcome	Age Groups	Melatonin		Control		Risk Ratio	95% Confidence Interval	*p*-value
		Total	Event	Total	Event			
AMD development among patients with no history of AMD (AMD-naïve)	≥50 years old	4,150	14 (0.34%)	4,092	63 (1.54%)	**0.22**	**0.12-0.39**	**<0.001**
	≥60 years old	3,720	10 (0.27%)	2,721	25 (0.92%)	**0.40**	**0.19-0.83**	**0.011**
	≥70 years old	2,173	11 (0.51%)	2,110	48 (2.27%)	**0.22**	**0.12-0.43**	**<0.001**
Progression to exudative AMD among patients with preexisting nonexudative AMD	≥50 years old	3,112	46 (1.48%)	3,263	142 (4.35%)	**0.34**	**0.24-0.47**	**<0.001**
	≥60 years old	3,060	46 (1.50%)	3,180	159 (5.00%)	**0.30**	**0.22-0.42**	**<0.001**
	≥70 years old	2,851	46 (1.61%)	2,945	140 (4.75%)	**0.34**	**0.24-0.47**	**<0.001**

AMD = age-related macular degeneration

eTable 6. Risks of AMD Development and Progression at Least 1 Year After the Index Event, Excluding Patients Whose Melatonin Dosage Was Not Specified

Analyzed Outcome	Age Groups	Melatonin (Known Dose)		Control		Risk Ratio	95% Confidence Interval	*p*-value
		Total	Event	Total	Event			
AMD development among patients with no history of AMD (AMD-naïve)	≥50 years old	1,873	17 (0.91%)	1,922	37 (1.93%)	**0.47**	**0.27-0.83**	**0.008**
	≥60 years old	1,552	17 (1.10%)	1,552	38 (2.45%)	**0.45**	**0.25-0.78**	**0.004**
	≥70 years old	1,011	16 (1.58%)	1,031	52 (5.04%)	**0.31**	**0.18-0.54**	**<0.001**
Progression to exudative AMD among patients with preexisting nonexudative AMD	≥50 years old	1,781	50 (2.81%)	1,843	126 (6.84%)	**0.41**	**0.30-0.57**	**<0.001**
	≥60 years old	1,752	51 (2.91%)	1,787	129 (7.22%)	**0.40**	**0.29-0.55**	**<0.001**
	≥70 years old	1,651	50 (4.95%)	1,708	132 (7.73%)	**0.39**	**0.29-0.54**	**<0.001**

AMD = age-related macular degeneration

eTable 7. Risks of AMD Development and Progression at Least 1 Year After the Index Event, Excluding Patients With a Retinal Comorbidity[a] or a History of Receiving an Ophthalmic Anti-VEGF Injection Therapy Before AMD Development or Progression

Analyzed Outcome	Age Groups	Melatonin		Control		Risk Ratio	95% Confidence Interval	*p*-value
		Total	Event	Total	Event			
AMD development among patients with no history of AMD (AMD-naïve)	≥50 years old	3,958	37 (0.93%)	3,927	86 (2.19%)	**0.43**	**0.29-0.63**	**<0.001**
	≥60 years old	3,254	37 (1.14%)	3,194	78 (2.44%)	**0.47**	**0.32-0.69**	**<0.001**
	≥70 years old	2,066	33 (1.60%)	2,005	64 (3.19%)	**0.50**	**0.33-0.76**	**<0.001**
Progression to exudative AMD among patients with preexisting nonexudative AMD	≥50 years old	2,869	72 (2.51%)	2,954	158 (5.35%)	**0.47**	**0.36-0.62**	**<0.001**
	≥60 years old	2,828	72 (2.55%)	2,829	158 (5.59%)	**0.47**	**0.36-0.61**	**<0.001**
	≥70 years old	2,641	70 (2.65%)	2,719	129 (4.74%)	**0.56**	**0.42-0.74**	**<0.001**

AMD = age-related macular degeneration; VEGF = vascular endothelial growth factor
[a]Retinal comorbidities were defined as proliferative diabetic retinopathy, diabetic macular edema, retinal vascular occlusions, and retinal edema (detailed list of relevant codes are shown in eTable 1C)

eTable 8. Risks of AMD Development and Progression at Least 1 Year After the Index Event Among Patients With a History of Sleep Disorders

Analyzed Outcome	Age Groups	Melatonin		Control		Risk Ratio	95% Confidence Interval	*p*-value
		Total	Event	Total	Event			
AMD development among patients with no history of AMD (AMD-naïve)	≥50 years old	3,518	35 (0.99%)	3,473	86 (2.48%)	**0.40**	**0.27-0.59**	**<0.001**
	≥60 years old	2,945	32 (1.09%)	2,898	67 (2.31%)	**0.47**	**0.31-0.71**	**<0.001**
	≥70 years old	1,896	29 (1.53%)	1,839	51 (2.77%)	**0.55**	**0.35-0.87**	**0.009**
Progression to exudative AMD among patients with preexisting nonexudative AMD	≥50 years old	2,458	71 (2.89%)	2,447	157 (6.42%)	**0.45**	**0.34-0.59**	**<0.001**
	≥60 years old	2,426	71 (2.93%)	2,461	171 (6.95%)	**0.42**	**0.32-0.55**	**<0.001**
	≥70 years old	2,254	69 (3.06%)	2,260	136 (6.02%)	**0.51**	**0.38-0.68**	**<0.001**

AMD = age-related macular degeneration

eTable 9. Risks of a Head Trauma (Negative Control) Diagnosis at Least 1 Year After the Index Event

Patient Group	Age Groups	Melatonin			Control			Risk Ratio	95% Confidence Interval	*p*-value
		Total	Event		Total	Event				
Patients with no history of AMD (AMD-naïve)	≥50 years old	2,682	226	(8.43%)	3,216	273	(8.49%)	0.99	0.84-1.18	0.932
	≥60 years old	2,189	200	(9.14%)	2,636	230	(8.73%)	1.05	0.87-1.26	0.618
	≥70 years old	1,397	127	(9.09%)	1,733	171	(9.87%)	0.92	0.74-1.15	0.462
Patients with preexisting nonexudative AMD	≥50 years old	2,142	224	(10.46%)	2,636	329	(12.48%)	**0.84**	**0.71-0.98**	**0.030**
	≥60 years old	2,112	219	(10.37%)	2,498	312	(12.49%)	**0.83**	**0.71-0.98**	**0.025**
	≥70 years old	1,969	214	(10.87%)	2,376	298	(12.54%)	0.87	0.74-1.02	0.089

AMD = age-related macular degeneration

eReferences

1. Prevalence of Age-Related Macular Degeneration (AMD). Centers for Disease Control and Prevention. Published May 2, 2023. Accessed June 17, 2023. https://www.cdc.gov/visionhealth/vehss/estimates/amd-prevalence.html

Data Sharing Statement

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Data
Data available: No