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Research Article

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Relationship between shift work and age-related macular degeneration: a cross-sectional analysis of data from the 5th Korea National Health and Nutrition Examination Survey (2010–2012)

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Abbreviations
8-OHdG: 8-hydroxydeoxyguanosine; AMD: age-related macular degeneration; BMI: body mass index; CI: confidence interval; DM: diabetes mellitus; GA: geographic atrophy; IRB: Institutional Review Board;

ABSTRACT

Background: Age-related macular degeneration (AMD) is the leading cause of blindness. Shift work has well-known adverse effects on health. However, few studies have investigated the relationship between shift work and AMD. This study was conducted to investigate the relationship between shift work and AMD.
Methods: This study used aggregated data from the 2010–2012 cycles of the Korea National Health and Nutrition Examination Survey. The work schedules were classified into 2 types: day work and shift work. AMD was determined using fundus photographs. The χ^2 test and multiple logistic regression analysis were used to assess sex-stratified relationship between shift work and AMD.
Results: The odds ratio (OR) of AMD in male shift workers was higher (1.54 [95% confidence interval, CI: 1.01–2.36]) than that in male day workers after adjusting for covariates. After dividing into subgroups of the shift work pattern, the OR of AMD in male night shift workers was higher (1.75 [95% CI: 1.07–2.85]) than that in male day workers after adjusting for covariates. However, results of the female worker group were not significant.
Conclusions: The results of this study provide limited support for the hypothesis that shift work is related to AMD. Further prospective studies are needed to define the relationship between shift work and AMD.

Keywords: Shift work; AMD; KNHANES

INTRODUCTION

Humans normally work during the day and sleep at night. With the development of modern industries, humans work both during the day and night [1]. Consequently, the so-called "shift work," which provides labor at unusual times, has become unavoidable [2]. Despite some differences in literature, the National Institute for Occupational Safety and Health defined

KNHANES: Korea National Health and Nutrition Examination Survey; KOS: Korean Ophthalmological Society; MDA: malondialdehyde; OR: odds ratio; ROS: reactive oxygen species; RPE: retinal pigment epithelium.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Kim K, Yoon S; Data curation: Kim K, Kim J, Woo KH; Formal analysis: Kim K, Cho SY; Investigation: Jo HR; Methodology: Jo HR; Software: Kim K, Yoon S; Validation: Kim J, Jo HR; Writing - original draft: Kim K, Kim J, Yoon S, Woo KH; Writing - review & editing: Kim K, Cho SY, Yoon S, Jo HR.

shift work as all types of work other than that at the regular working time (7 a.m. to 6 p.m.) [3]. At least 15% of workers are engaged in shift work in the European Union [4] and United States [5], and an estimated 10.2%–14.5% of wage earners in Korea (1.27–1.97 million people) perform shift work [6,7].

Shift work disrupts the circadian rhythms of workers and may cause various health problems [8]. Moreover, shift work is associated with chronic diseases such as cardiovascular diseases, diabetes mellitus (DM), metabolic syndrome, and breast cancer [9]. Recent studies have suggested that circadian rhythm changes can lead to oxidant-antioxidant imbalances and cause oxidative stress [10-15]. Sharifian et al. [12] noted that total plasma antioxidant capacities were lower in night-shift workers and suggested that night shift work can act as an oxidative stressor. Night shift work is also associated with high levels of urinary 8-hydroxydeoxyguanosine (8-OHdG) indicating oxidative DNA damage [16]. Previous studies have reported the effects of shift work in hospitals and police offices. Levels of malondialdehyde (MDA), an indicator of lipid peroxidation, were found to be higher in 32 nurses and 52 staff members on night and evening shifts than in 85 age-matched healthy controls [13,14]. Serum levels of 2 oxidative stress markers, oxidized low-density lipoproteins and neutrophil gelatinase lipocalin-2, were found to be higher in 204 police officers working 12/24 shifts (work for 12 hours and then rest for 24 hours) than those measured in the control group [17].

Age-related macular degeneration (AMD) is a progressive neurodegenerative disease of the central retinal area (macula lutea) and is a major cause of loss of vision in people aged ≥ 65 years in Western countries [18]. Furthermore, AMD has been reported as a disease critical in causing reduced visual acuity and vision loss in the ≥ 65-year-old population in Asian countries [19,20]. Owing to the longer life expectancy and westernized diet in South Korea, there is an increasing prevalence of AMD [21]. Loss of vision and blindness cause many health problems, such as falls [22], fractures [23], and loss of independence [24]; these adverse health issues may increase mortality risk among affected individuals compared to unaffected individuals [25]. The aim of treating AMD is to prevent worsening of the disease; however, the complete cure of AMD is difficult even with continuous intervention, though treatment at an early stage of the disease might preserve a certain degree of visual ability in the patient. Therefore, the most important approaches of reducing AMD-induced visual impairment include early discovery and risk factors management [26]. Using frequent screening makes it possible to detect the disease sufficiently early to control the risk factors before the disease progresses further or provide timely treatment before the patient's eyesight deteriorates. Besides, maintaining sufficient visual acuity should have a significant positive impact on daily life to help reduce various personal and social problems caused by the disease [27].

The current pathophysiological understanding of AMD indicates a primary role of age-related, cumulative oxidative damage to the retinal pigment epithelium (RPE) due to oxidant-antioxidant imbalances [28-31]. A huge body of literature supports the involvement of oxidative stress in AMD. Serum samples of AMD patients showed increased levels of oxidative stress indicated by increased levels of MDA, protein carbonyls, and 8-OHdG compared to those of normal non-AMD cohorts, thus suggesting that systemic oxidative stress is related to AMD [29]. Concurrently, studies have shown increased oxidative stress in the retina from donors' eyes with AMD [31,32]. Given that shift work is known to increase the risk of oxidant-antioxidant imbalances and cause oxidative stress [10-15], it may directly or indirectly affect the occurrence of AMD.

Despite the possible association between shift work and AMD, few studies have investigated it. Therefore, this study was conducted to analyze the association between shift work and AMD using data from a nationwide population-based survey, the Korean National Health and Nutrition Examination Survey (KNHANES).

METHODS

Participants

This study used aggregated data from the 2010–2012 cycles of the Korea National Health and Nutrition Examination Survey. The KNHANES is a national cross-sectional survey conducted annually by the Korean Centers for Disease Control and Prevention, and is provided as secondary data designed according to multistage stratified and cluster sampling. The data includes medical history and socioeconomic status using a set of structured questionnaires and anthropometric measurements, blood tests, and ophthalmic surveys. The total number of participants was 25,534. Participants who were at least 40 years old and whose occupational information was available were included in this study. Individuals with missing values for major variables and covariates were excluded. Finally, 18,338 participants were excluded, and a total of 7,196 participants were included in the final analysis data set.

Shift work and day work

In the KNHANES, the work groups were divided based on responses to the following questions: "Do you usually work during the day time (between 6 a.m. and 6 p.m.)?" and "are you working in another time?". Participants who answered "Usually work during the day time (between 6 a.m. and 6 p.m.)" were classified as day workers, and those who answered "fixed-evening shift (between 2 p.m. and 11 p.m.), fixed-night shift (between 9 p.m. and 8 a.m. the next day), regular day and night rotating shift, 24-hour rotating shift, split shift (working 2 shifts in 1 day), and irregular rotating shift" were classified as shift workers [33,34]. The work schedule was subdivided into 3 groups of day work, non-night shift work (fixed-evening shift, split shift, and irregular rotating shift), and night shift work (fixed-night shift, regular day and night rotating shift, and 24-hour rotating shift).

Definition of AMD

Retinal examinations were performed by ophthalmologists assigned by the Korean Ophthalmological Society (KOS) who were periodically trained by the KOS National Epidemiologic Survey Committee. Retinal examinations were performed by obtaining a 45° field-angle nonmydriatic fundus photograph of each eye with a digital fundus camera (TRC-NW6S; Topcon, Tokyo, Japan) that used preinstalled software (IMAGEnet; Topcon) in a dark room to facilitate physiological pupillary dilation. In cases where the nonmydriatic photograph was of unsatisfactory quality owing to media opacity or a small pupil, a mydriatic fundus photograph was taken after achieving maximal pupillary dilation with 1.0% tropicamide and 10% phenylephrine.

Patients were defined as having AMD if the fundus photograph met one of the following 3 criteria: 1) presence of soft indistinct drusen or reticular drusen, 2) presence of hard or soft distinct drusen with pigmentary abnormalities (increased pigmentation or hypopigmentation of the RPE), or 3) presence of signs of wet AMD or geographic atrophy (GA). Wet AMD was defined as RPE detachment or serous detachment of the sensory retina, subretinal or sub-RPE hemorrhages, and subretinal fibrous scars. GA was defined as a

circular discrete area (diameter > 175 μm) of retinal depigmentation with visible choroidal vessels in the absence of signs of wet AMD.

Covariates

Age, sex, smoking status, drinking status, hours of sleep, body mass index (BMI), history of disease (hypertension, DM, and dyslipidemia), education status, and sun exposure status were included as potential confounding variables. Information on demographic and social factors was obtained using a standardized questionnaire in the health interviews. The participants were stratified into 4 groups on the basis of age: 40–49, 50–59, 60–69, and > 70 years. Smoking status was classified as nonsmokers, ex-smokers, and current smokers. Drinking status was defined as nondrinkers, social drinkers, and binge drinkers; social drinkers were categorized as drinking less than 5 units of alcohol each time, and binge drinkers as drinking ≥ 5 units of alcohol per day [35]. Hours of sleep were categorized into 3 groups (< 7, 7–9, and > 9 hours per night) according to the appropriate sleep durations recommended by the National Sleep Foundation [36]. The BMI was calculated by dividing body weight by height squared (kg/m^2). On the basis of education status, the participants were divided into 2 groups: participants with at least high school degree and those who had graduated from middle school or had less than middle school education. On the basis of sun exposure status, the participants were classified into 2 groups: those with an average of < 5 hours/day and those with ≥ 5 hours/day of sun exposure.

Data analysis

The independent t-test and the χ^2 test were used to examine the general characteristics of the study population with regard to AMD. The relationship between shift work and AMD was examined using multiple logistic regression analysis after stratification for sex and age group (participants aged < or ≥ 60 years). The unadjusted model only included whether the subject was engaged in shift work. In the adjusted model, analyses were adjusted for covariates including physical factors (age and BMI), present health status (hypertension, DM, and dyslipidemia), and lifestyle factors (smoking, alcohol consumption, education, and sun exposure). Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) to take into account the sample weights and complex sample design effects.

Ethics statement

All participants of the KNHANES included in this study provided written informed consent. This study was approved by the Institutional Review Board (IRB) of Soonchunhyang University Hospital in Gumi (IRB No. Medicine 2020–08).

RESULTS

General characteristics

The general characteristics of the participants are shown in **Table 1**. Among the 7,196 participants included in the final analysis, there were 3,758 (52.2%) and 3,438 (47.8%) male and female participants, respectively. In terms of mean age, female shift workers were younger than female day workers. Regarding work schedule, the proportion of day workers was higher than shift workers among both male and female workers. Considering the patterns of shift-work schedule, the proportion of individuals with a fixed-evening shift was the highest among both male and female shift workers. The proportion of regular day and night rotating shifts and 24-hour rotating shifts was higher in male shift workers than

Table 1. General characteristics of the subjects

Variable	Male				Female			
	Total	Day work	Shift work	*p*-value	Total	Day work	Shift work	*p*-value
Total[a]	3,758	3,158 (84.0)	600 (16.0)	-	3,438	2,927 (85.1)	511 (14.9)	-
Shift work patterns				-				-
Fixed-evening shift	173 (28.8)	-	173 (28.8)		313 (61.3)	-	313 (61.3)	
Fixed-night shift	76 (12.7)	-	76 (12.7)		67 (13.1)	-	67 (13.1)	
Regular day and night rotating shift	106 (17.7)	-	106 (17.7)		42 (8.2)	-	42 (8.2)	
24-hours rotating shift	152 (25.3)	-	152 (25.3)		12 (2.3)	-	12 (2.3)	
Split shift	36 (6.0)	-	36 (6.0)		38 (7.4)	-	38 (7.4)	
Irregular rotating shift	57 (9.5)	-	57 (9.5)		39 (7.6)	-	39 (7.6)	
Age (years)	52.2 ± 9.05	52.2 ± 9.05	51.9 ± 9.05	0.55[b]	53.1 ± 9.69	53.5 ± 10.01	51.0 ± 7.50	< 0.01[b]
Age group				< 0.01[c]				< 0.01[c]
40–49	1,279 (34.0)	1,049 (33.2)	230 (38.3)		1,148 (33.4)	945 (32.3)	203 (39.7)	
50–59	1,203 (32.0)	1,041 (33.0)	162 (27.0)		1,216 (35.4)	1,000 (34.2)	216 (42.3)	
60–69	874 (23.3)	711 (22.5)	163 (27.2)		671 (19.5)	598 (20.4)	73 (14.3)	
≥ 70	402 (10.7)	357 (11.3)	45 (7.5)		403 (11.7)	384 (13.1)	19 (3.7)	
BMI (kg/m^2)	24.2 ± 2.92	24.2 ± 2.93	24.2 ± 2.84	0.76[b]	23.9 ± 3.25	24.0 ± 3.25	23.8 ± 3.23	0.50[b]
BMI group				0.24[c]				0.24[c]
< 23	1,338 (35.6)	1,142 (36.2)	196 (32.7)		1,433 (41.7)	1,203 (41.1)	230 (45.0)	
23–25	1,034 (27.5)	865 (27.4)	169 (28.2)		869 (25.3)	750 (25.6)	119 (23.3)	
≥ 25	1,386 (36.9)	1,151 (36.4)	235 (39.2)		1,136 (33.0)	974 (33.3)	162 (31.7)	
Smoking status				0.37[c]				< 0.01[c]
Non-smoker	595 (15.8)	502 (15.9)	93 (15.5)		3,189 (92.8)	2,734 (93.4)	455 (89.0)	
Ex-smoker	1,705 (45.4)	1,445 (45.8)	260 (43.3)		111 (3.2)	92 (3.1)	19 (3.7)	
Current smoker	1,458 (38.8)	1,211 (38.3)	247 (41.2)		138 (4.0)	101 (3.5)	37 (7.2)	
Drinking status[d]				0.64[c]				< 0.01[c]
Non-drinker	606 (16.1)	517 (16.4)	89 (14.8)		1,267 (36.9)	1,123 (38.4)	144 (28.2)	
Social-drinker	1,394 (37.1)	1,155 (36.6)	239 (39.8)		1,906 (55.4)	1,607 (54.9)	299 (58.5)	
Binge-drinker	1,758 (46.8)	1,486 (47.1)	272 (45.3)		265 (7.7)	197 (6.7)	68 (13.3)	
Hours of sleep (hours/day)				0.92[c]				< 0.01[c]
< 7	1,577 (42.0)	1,321 (41.8)	256 (42.7)		1,563 (45.5)	1,323 (45.2)	240 (47.0)	
7–9	2,059 (54.8)	1,732 (54.8)	327 (54.5)		1,803 (52.4)	1,552 (53.0)	251 (49.1)	
> 9	122 (3.2)	105 (3.3)	17 (2.8)		72 (2.1)	52 (1.8)	20 (3.9)	
Hypertension				0.29[c]				0.03[c]
No	2,759 (73.4)	2,327 (73.7)	432 (72.0)		2,587 (75.2)	2,175 (74.3)	412 (80.6)	
Yes	999 (26.6)	831 (26.3)	168 (28.0)		851 (24.8)	752 (25.7)	99 (19.4)	
DM				0.18[c]				0.18[c]
No	3,354 (89.2)	2,810 (89.0)	544 (90.7)		3,192 (92.8)	2,701 (92.3)	491 (96.1)	
Yes	404 (10.8)	348 (11.0)	56 (9.3)		246 (7.2)	226 (7.7)	20 (3.9)	
Dyslipidemia				0.51[c]				0.70[c]
No	3,292 (87.6)	2,769 (87.7)	523 (87.2)		2,995 (87.1)	2,549 (87.1)	446 (87.3)	
Yes	466 (12.4)	389 (12.3)	77 (12.8)		443 (12.9)	378 (12.9)	65 (12.7)	
Education				0.28[c]				< 0.01[c]
> Middle school	2,401 (63.9)	2,002 (63.4)	399 (66.5)		1,512 (44.0)	1,218 (41.6)	294 (57.5)	
≤ Middle school	1,357 (36.1)	1,156 (36.6)	201 (33.5)		1,926 (56.0)	1,709 (58.4)	217 (42.5)	
Sun exposure (≥ 5 hours/day)				< 0.01[c]				< 0.01[c]
No	2,897 (77.1)	2,368 (75.0)	529 (88.2)		2,894 (84.2)	2,411 (82.4)	483 (94.5)	
Yes	861 (22.9)	790 (25.0)	71 (11.8)		544 (15.8)	516 (17.6)	28 (5.5)	
AMD				0.10[c]				0.20[c]
No	3,500 (93.1)	2,946 (93.3)	554 (92.3)		3,199 (93.0)	2,708 (92.5)	491 (96.1)	
Yes	258 (6.9)	212 (6.7)	46 (7.7)		239 (7.0)	219 (7.5)	20 (3.9)	

Data are shown as number (%) for categorical variables and as mean ± standard error for continuous variables.
BMI: body mass index; DM: diabetes mellitus; AMD: age-related macular degeneration.
[a]Unweighted count; [b]The *p*-value by independent 2 sample t-test; [c]The *p*-value by χ^2 test; [d]Categorized as drinking units of alcohol per time (social drinkers < 5 units, binge drinkers ≥ 5 units).

in female shift workers. Among lifestyle factors, the proportion of sun exposure < 5 hours/day was higher among shift workers. The proportion of current smokers, binge drinkers, and sleeping < 7 hours was higher in female shift workers than in female day workers.

Prevalence of AMD according to the work schedule and associated variables

The participants were divided into 2 groups: normal and AMD groups. The prevalence of AMD for each variable is shown in **Table 2**. When the work schedule was subdivided into 3

Table 2. Prevalence of AMD according to work schedule and associated variables in subjects

Variable	Male				Female			
	Total	Non-AMD	AMD	*p*-value	Total	Non-AMD	AMD	*p*-value
Total[a]	3,758	3,500 (93.1)	258 (6.9)	-	3,438	3,199 (93.0)	239 (7.0)	-
Work schedule				0.02[c]				0.40[c]
Day work	3,158 (84.0)	2,946 (93.3)	212 (6.7)		2,927 (85.1)	2,708 (92.5)	219 (7.5)	
Non-night shift work	266 (7.1)	252 (94.7)	14 (5.3)		390 (11.3)	376 (96.4)	14 (3.6)	
Night Shift work	334 (8.9)	302 (90.4)	32 (9.6)		121 (3.6)	115 (95.0)	6 (5.0)	
Shift work patterns				0.12[c]				0.84[c]
Fixed-evening shift	173 (28.8)	161 (93.1)	12 (6.9)		313 (52.1)	302 (96.5)	11 (3.5)	
Fixed-night shift	76 (12.6)	70 (92.1)	6 (7.9)		67 (11.1)	64 (95.5)	3 (4.5)	
Regular day and night rotating shift	106 (17.6)	101 (95.3)	5 (4.7)		42 (7.0)	40 (95.2)	2 (4.8)	
24-hours rotating shift	153 (25.5)	131 (86.2)	21 (13.8)		12 (2.0)	11 (91.7)	1 (8.3)	
Split shift	36 (6.0)	35 (97.2)	1 (2.8)		38 (6.3)	36 (94.7)	2 (5.3)	
Irregular rotating shift	57 (9.5)	56 (98.2)	1 (1.8)		39 (6.5)	38 (97.4)	1 (2.6)	
Age (years)	52.2 ± 9.05	51.7 ± 8.80	61.4 ± 8.79	< 0.01[b]	53.1 ± 9.69	52.4 ± 9.26	63.5 ± 10.30	< 0.01[b]
Age group				< 0.01[c]				< 0.01[c]
40–49	1,279 (34.0)	1,268 (99.1)	11 (0.9)		1,148 (33.4)	1,134 (98.8)	14 (1.2)	
50–59	1,203 (32.0)	1,133 (94.2)	70 (5.8)		1,216 (35.4)	1,157 (95.1)	59 (4.9)	
60–69	874 (23.3)	772 (88.3)	102 (11.7)		671 (19.5)	588 (87.6)	83 (12.4)	
≥ 70	402 (10.7)	327 (81.3)	75 (18.7)		403 (11.7)	320 (79.4)	83 (20.6)	
BMI (kg/m^2)	24.2 ± 2.92	24.2 ± 2.91	23.7 ± 2.93	0.02[b]	23.9 ± 3.25	24.0 ± 3.25	23.6 ± 3.23	0.15[b]
BMI group				< 0.01[c]				0.43[c]
< 23	1,338 (35.6)	1,223 (91.4)	115 (8.6)		1,433 (41.7)	1,329 (92.7)	104 (7.3)	
23–25	1,034 (27.5)	967 (93.5)	67 (6.5)		869 (25.3)	804 (92.5)	65 (7.5)	
≥ 25	1,386 (36.9)	1,310 (94.5)	76 (5.5)		1,136 (33.0)	1,066 (93.8)	70 (6.2)	
Smoking status				0.71[c]				0.87[c]
Non-smoker	595 (15.8)	546 (91.8)	49 (8.2)		3,189 (92.8)	2,967 (93.0)	222 (7.0)	
Ex-smoker	1,705 (45.4)	1,594 (93.5)	111 (6.5)		111 (3.2)	105 (94.6)	6 (5.4)	
Current smoker	1,458 (38.8)	1,360 (93.3)	98 (6.7)		138 (4.0)	127 (92.0)	11 (8.0)	
Drinking status[d]				< 0.01[c]				< 0.01[c]
Non-drinker	606 (16.1)	550 (90.8)	56 (9.2)		1,267 (36.9)	1,149 (90.7)	118 (9.3)	
Social-drinker	1,394 (37.1)	1,282 (92.0)	112 (8.0)		1,906 (55.4)	1,795 (94.2)	111 (5.8)	
Binge-drinker	1,758 (46.8)	1,668 (94.9)	90 (5.1)		265 (7.7)	255 (96.2)	10 (3.8)	
Hours of sleep (hours/day)				0.89[c]				0.11[c]
< 7	1,577 (42.0)	1,462 (92.7)	115 (7.3)		1,563 (45.5)	1,445 (92.5)	118 (7.5)	
7–9	2,059 (54.8)	1,927 (93.6)	132 (6.4)		1,803 (52.4)	1,688 (93.6)	115 (6.4)	
> 9	122 (3.2)	111 (91.0)	11 (9.0)		72 (2.1)	66 (91.7)	6 (8.3)	
Hypertension				< 0.01[c]				< 0.01[c]
No	2,759 (73.4)	2,601 (94.3)	158 (5.7)		2,587 (75.2)	2,441 (94.4)	146 (5.6)	
Yes	999 (26.6)	899 (90.0)	100 (10.0)		851 (24.8)	758 (89.1)	93 (10.9)	
DM				0.11[c]				0.32[c]
No	3,354 (89.2)	3,128 (93.3)	226 (6.7)		3,192 (92.8)	2,971 (93.1)	221 (6.9)	
Yes	404 (10.8)	372 (92.1)	32 (7.9)		246 (7.2)	228 (92.7)	18 (7.3)	
Dyslipidemia				0.96[c]				0.54[c]
No	3,292 (87.6)	3,063 (93.0)	229 (7.0)		2,995 (87.1)	2,788 (93.1)	207 (6.9)	
Yes	466 (12.4)	437 (93.8)	29 (6.2)		443 (12.9)	411 (92.8)	32 (7.2)	
Education				< 0.01[c]				< 0.01[c]
> Middle school	2,401 (63.9)	2,290 (95.4)	111 (4.6)		1,512 (44.0)	1,476 (97.6)	36 (2.4)	
≤ Middle school	1,357 (36.1)	1,210 (89.2)	147 (10.8)		1,926 (56.0)	1,723 (89.5)	203 (10.5)	
Sun exposure (≥ 5 hours/day)				< 0.01[c]				< 0.01[c]
No	2,897 (77.1)	2,725 (94.1)	172 (5.9)		2,894 (84.2)	2,730 (94.3)	164 (5.7)	
Yes	861 (22.9)	775 (90.0)	86 (10.0)		544 (15.8)	469 (86.2)	75 (13.8)	

Data are shown as number (%) for categorical variables and as mean ± standard error for continuous variables.
BMI: body mass index; DM: diabetes mellitus; AMD: age-related macular degeneration.
[a]Unweighted count; [b]The *p*-value by independent 2 sample t-test; [c]The *p*-value by χ^2 test; [d]Categorized as drinking units of alcohol per time (social drinkers < 5 units, binge drinkers ≥ 5 units).

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groups, the prevalence of AMD was the highest in the night shift work for male participants. In terms of patterns of shift work, the prevalence of AMD was the highest in the 24-hour rotating shift workers regardless of sex, although this difference was not significant. The prevalence of AMD increased with age regardless of sex. When the participants were divided into 3 groups as per alcohol consumption (nondrinker, social drinker, and binge drinker), the prevalence of AMD was the highest in the nondrinker group for both males and females, and this difference was statistically significant in both the sexes. When the participants were divided into 2 groups, namely normal and hypertension groups, the prevalence of AMD was significantly higher in the hypertension groups for both male and female participants. When the participants were stratified by the education level, the prevalence of AMD was significantly higher in those who had graduated from middle school or less for both male and female participants. In the analysis stratified by sun exposure, the prevalence of AMD was significantly higher in those with ≥ 5 hours/day sun exposure for both male and female participants. There were no statistically significant differences in the prevalence of AMD according to smoking status, hours of sleep, DM, and dyslipidemia (**Table 2**).

AMD prevalence according to work patterns in male and female subjects stratified by age group

Table 3 illustrates the participants and AMD prevalence by age group according to work patterns in male and female subjects. For male participants, night shift work (12.1%) was more prevalent compared to non-night shift work (4.2%) among those aged ≥ 60 years. For female participants, the proportion of non-night shift work was 13.5% for those aged < 60 years and 6.5% for those aged ≥ 60 years, which was higher than that of night shift work (4.2% and 2.1%, respectively). The number of night shift workers aged ≥ 60 years was only 22 (2.1%). For male participants, among those aged < 60 years, AMD prevalence was 3.3%, 3.3%, and 3.3% in day work, non-night shift work, and night shift work, respectively, and 13.5%, 13.0%, and 16.9%, respectively, among those aged ≥ 60 years. For female participants, among those aged < 60 years, AMD prevalence was 3.1%, 1.9%, and 6.1%, and among those aged ≥ 60 years, it was 16.1%, 11.4%, and 0.0% in day work, non-night shift work, and night shift work, respectively.

Crude and adjusted odds ratio (OR) for AMD by shift work and shift work patterns in male and female subjects

The association between shift work and AMD identified by multiple logistic regression analysis is shown in **Table 4**. For male participants, the crude OR of AMD in shift work was 1.42 (95% confidence interval [CI]: 0.94–2.15). After adjusting for age, BMI, hypertension, DM, dyslipidemia, smoking, alcohol consumption, education, and sun exposure, the OR of AMD was 1.54 (95% CI: 1.01–2.36). For female participants, the crude OR of AMD in shift work was 0.69 (95% CI: 0.39–1.23) and the adjusted OR was 1.09 (95% CI: 0.60–1.98).

Table 3. AMD prevalence according to work patterns in male and female subjects stratified by age group

Sex	Age (years)	Total[a]		Day work		Non-night shift work		Night shift work		*p*-value[b]
		No.	AMD	No.	AMD	No.	AMD	No.	AMD	
Male	< 60	2,482 (66.0)	81 (3.3)	2,090 (84.2)	68 (3.3)	212 (8.5)	7 (3.3)	180 (7.3)	6 (3.3)	0.89
	≥ 60	1,276 (34.0)	177 (13.9)	1,068 (83.7)	144 (13.5)	54 (4.2)	7 (13.0)	154 (12.1)	26 (16.9)	0.22
Female	< 60	2,364 (68.8)	73 (3.1)	1,945 (82.3)	61 (3.1)	320 (13.5)	6 (1.9)	99 (4.2)	6 (6.1)	0.28
	≥ 60	1,074 (31.2)	166 (15.5)	982 (91.4)	158 (16.1)	70 (6.5)	8 (11.4)	22 (2.1)	0 (0.0)	0.14

Data are shown as number (%) for categorical variables.
AMD: age-related macular degeneration.
[a]Unweighted count; [b]The *p*-value by χ^2 test.

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Table 4. Crude and adjusted OR for AMD by shift work and shift work patterns in male and female subjects

Variable	AMD	
	Male	Female
Crude OR (95% CI)		
Day work	Reference	Reference
Shift work	1.42 (0.94–2.15)	0.69 (0.39–1.23)
Adjusted[a]		
Day work	Reference	Reference
Shift work	1.54 (1.01–2.36)	1.09 (0.60–1.98)
Crude OR (95% CI)		
Day work	Reference	Reference
Non-night shift work	0.89 (0.44–1.79)	0.63 (0.32–1.24)
Night shift work	1.94 (1.19–3.17)	0.87 (0.31–2.41)
Adjusted[a]		
Day work	Reference	Reference
Non-night shift work	1.43 (0.70–2.92)	1.03 (0.52–2.03)
Night shift work	1.75 (1.07–2.85)	1.25 (0.41–3.81)

Calculated by multiple logistic regression analysis.
OR: odds ratio; AMD: age-related macular degeneration; CI: confidence interval.
[a]Adjusted by age, body mass index, smoking status, drinking status, hypertension, diabetes mellitus, dyslipidemia, education, and sun exposure.

The shift work patterns were divided into 2 groups of non-night shift work and night shift work. For male participants, the crude OR of AMD was 1.94 (95% CI: 1.19–3.17) in night shift work and 0.89 (95% CI: 0.44–1.79) in non-night shift work. The adjusted ORs of AMD in night and non-night shift work were 1.75 (95% CI: 1.07–2.85) and 1.43 (95% CI: 0.70–2.92), respectively. For female participants, the ORs of AMD in night - and non-night shift work were not statistically significant.

Crude and adjusted OR for AMD according to work patterns in male and female subjects stratified by age group

The association between shift work patterns and AMD stratified by age group was analyzed via multiple logistic regression analysis and is shown in **Table 5**. For male participants aged ≥ 60 years, the crude OR of AMD was 1.63 (95% CI: 0.91–2.94) in night shift work and 1.29 (95% CI: 0.47–3.54) in non-night shift work. The adjusted ORs of AMD in night and non-night shift work were 1.88 (95% CI: 1.10–3.24) and 1.93 (95% CI: 0.67–5.54), respectively.

For male participants aged < 60 years, the crude OR of AMD was 1.27 (95% CI: 0.47–3.47) in night shift work and 1.04 (95% CI: 0.39–2.77) in non-night shift work. The adjusted ORs

Table 5. Crude and adjusted OR for AMD according to work patterns in male and female subjects stratified by age group

Variable	AMD			
	Male		Female	
	< 60	≥ 60	< 60	≥ 60
Crude OR (95% CI)				
Day work	Reference	Reference	Reference	Reference
Non-night shift work	1.04 (0.39–2.77)	1.29 (0.47–3.54)	1.00 (0.38–2.67)	0.71 (0.31–1.65)
Night shift work	1.27 (0.47–3.47)	1.63 (0.91–2.94)	2.38 (0.81–6.94)	-
Adjusted[a]				
Day work	Reference	Reference	Reference	Reference
Non-night shift work	1.40 (0.51–3.82)	1.93 (0.67–5.54)	1.04 (0.38–2.91)	0.98 (0.43–2.24)
Night shift work	1.55 (0.60–3.98)	1.88 (1.10–3.24)	2.32 (0.76–7.05)	-

Calculated by multiple logistic regression analysis.
OR: odds ratio; AMD: age-related macular degeneration; CI: confidence interval.
[a]Adjusted by age, body mass index, smoking status, drinking status, hypertension, diabetes mellitus, dyslipidemia, education, and sun exposure.

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of AMD in night and non-night shift work were 1.55 (95% CI: 0.60–3.98) and 1.40 (95% CI: 0.51–3.82), respectively. For female participants, the ORs of AMD in night and non-night shift work were not statistically significant.

DISCUSSION

This study analyzed the relationship between shift work and AMD in Koreans using data from a large-scale survey. Sex differences in the association between shift work and AMD were identified in this study. The results of this study showed that shift work was associated with AMD only in male workers. When patterns of shift work were divided into subgroups, night shift work was associated with AMD in male workers. When stratified by age, there was a significant association between AMD and night shift work among male participants aged ≥ 60 years while no significant association among those aged < 60 years. This is presumed to be due to the low prevalence of AMD in subjects under the age of 60 years. However, for female participants, the proportion of shift work over the age of 60 years was relatively low; in particular, there were 22 female night shift workers aged ≥ 60 years, and among them, none had AMD, making it difficult to determine statistical significance. To the best of our knowledge, the present study is the first to report a significant association between shift work and AMD.

Although the exact cause of AMD is unknown, there have been many studies that have elucidated the risk factors for AMD. Several large-scale studies have been conducted to identify the potential risk factors of AMD, although the results vary slightly among different groups [37]. Genetic and environmental risk factors for AMD have been investigated in different countries and demographic groups. Most of the studies have reported that AMD is associated with smoking and has high incidence in heavy smokers [38]. However, the association between AMD and smoking could not be confirmed in Asian populations [20]. In addition to smoking, other risk factors of AMD, including age, family history, sun exposure, antioxidant intake [39], education [40], BMI [41], and alcohol consumption [42], had been investigated previously. The recent results of a study focusing on the Korean health examination centers [21,43] suggested that age, male sex, smoking status, history of hyperlipidemia, working outdoors, and high blood pressure are all associated positively with AMD. A meta-analysis suggested that cigarette smoking in particular is a strong and consistent risk factor for AMD. According to an analysis of prospective cohort studies, the relative risk was 1.86 (95% CI: 1.27–2.73) [44]. One study provided clear evidence that smoking results in oxidative stress and complement activation, further suggesting that these 2 act synergistically in the pathogenesis of AMD [45].

The etiopathological mechanism of how shift work leads to AMD has not been identified, although previous studies have shown the association between shift work and oxidative stress [10-15], which is a known risk factor for AMD [28-31]. ROS are highly reactive molecules owing to their unpaired electrons, and ROS overproduction beyond an acceptable range of endogenous antioxidants is called oxidative stress [46]. The retina is very prone to the generation of ROS compared with other tissues. Moreover, the retinal structure comprises a photosensitive tissue with high oxygen levels in the choroid and a high metabolic rate, besides being exposed to light. Furthermore, the retina contains a higher concentration of polyunsaturated fatty acids than other body tissues [47]. Lipids in the outer segment membranes of photoreceptors can be oxidized by the radicals produced during photonic activation, and the endogenous oxygen species that are generated in the eyes via this process

can induce ROS-related acute or chronic retinal damage [48], thus suggesting an association between shift work and AMD.

Furthermore, it is generally well accepted that exposure to light during the night decreases melatonin synthesis [49]. Therefore, shift workers are at a risk of lower melatonin levels [50], which may promote atherosclerosis, because melatonin deficiency may result in a relatively hypercoagulable state [51]. Also, melatonin is known to be a direct radical scavenger and has antioxidant effects [52]. Melatonin, which is an important circadian hormone, protects cultured RPE cells from oxidative stress and ischemia-induced cell death [53,54]. Several studies have reported that melatonin is involved in the pathogenesis of AMD. In 2005, Yi et al. [55] reported that the daily administration of melatonin (3 mg) may protect the retina and delay AMD progression. Further, Rosen et al. [56] reported that the production of melatonin is lower in AMD patients than in age-matched controls, suggesting that a deficiency in melatonin may play a role in the development of AMD. Given that atherosclerosis may be implicated in the etiology of AMD [57], there are several possible explanations for pathways linking shift work and AMD.

Night shift workers may experience a disruption in the synchronization of photoreceptor outer segment disk shedding with light. There is a strong link between ocular physiology and circadian rhythms. The renewal and elimination of aged photoreceptor outer segment tips by cells from the RPE are daily rhythmic processes that are crucial for long-term maintenance of vision. Photoreceptors indefinitely renew their light-sensitive outer segments by disk shedding and subsequent formation of new disks from the cilium of the inner segment [58,59]. This shedding occurs once a day. To maintain the constant length of photoreceptors, the outer segment needs to be shed, and the formation of new outer segments must be coordinated [60,61]. The task of the adjacent RPE is to absorb the discarded photoreceptor outer segment fragments by phagocytosis and to recycle or digest their components [58,62]. Photoreceptor disk shedding and subsequent phagocytosis by the RPE must be precisely regulated [63]. This outer segment renewal and RPE phagocytosis are synchronized under circadian control and are triggered by the dark/light periods of the daily rhythm [64]. Rod shedding mainly occurs in the morning, within the first 2 hours after light onset, whereas cone shedding is more variable and mainly occurs either during the night or during the first 2 hours after light onset [63,64]. Any disruption in this process causes photoreceptor dysfunction and retinal disease [65]. The synchronization of shedding with light seems to be crucial to photoreceptor physiology and survival because the accumulation of undigested material is detrimental to the RPE and retina and may contribute to the development or progression of AMD [66,67].

In our study, we expected that shift work, which interferes with circadian rhythms, would be related to AMD. The results showed a significant association between shift work and AMD among male workers. However, there was no significant association among female workers. Among the patterns of shift work, night shift work was proportionally more common for male shift workers than for female shift workers. Therefore, it can be assumed that differences in the shift work pattern by sex may have affected the sex differences in AMD prevalence.

This study has some limitations. First, given that the KNHANES is a cross-sectional study, only an association between shift work and AMD could be established but not causal relationships. Second, there was no information about the duration of the shift work; therefore, we could not investigate the dose-response relationship with shift work and AMD.

Third, we could not obtain detailed information on the possible differences between shift patterns. Fourth, among female workers, there were limitations in analyzing the association between shift work and AMD because the number of analyzed subjects who were night shift work aged ≥ 60 years was extremely small. Despite these limitations, the strengths of this study include the use of a national, large-scale survey. Moreover, data were analyzed after sex stratification and consideration of multiple variables, such as age, BMI, smoking status, drinking status, hypertension, DM, dyslipidemia, education, and sun exposure.

CONCLUSIONS

This study demonstrated a correlation between shift work and AMD in male workers. Although this study has limitations, it provides basic evidence on the relationship between shift work and AMD. A well-designed cohort study should be undertaken to identify the causal relationship between shift work and AMD and to contribute to the establishment of policies to improve the health and welfare of shift workers.

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