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Is retinal vein occlusion associated with depression symptoms?

A nationwide cohort study

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Abstract

Retinal vessels share similar anatomical and physiological characteristics with the cerebral microvasculature, and abnormal cerebral blood flow is reportedly associated with depressive disorder. However, there is limited evidence regarding the relationship between depression and the risk of retinal vein occlusion (RVO). This study aimed to investigate the association between depression and the prospective risk of RVO using nationally representative longitudinal data. This retrospective, nationwide, population-based cohort study included 9,178,222 people aged 20 years or older who underwent the Korean National Health Screening Program examination in 2009. The depression group consisted of subjects whose initial diagnoses were made between 2009 and 2010 (n = 128,700). The predictive value for RVO was analyzed using multivariate Cox proportional hazard regression models.

From the Kaplan–Meier curves, the depression group showed significantly higher RVO incidence probability, relative to the comparison group (P < .0001). After all confounding variables were adjusted, the hazard ratio of RVO in the depression group with or without recurrence was 1.2 (95% confidence interval [CI]: 1.076–1.338) and 1.087 (95% CI: 1.012–1.167), respectively, relative to the comparison group. This is the first nationwide, population-based, epidemiologic study that evaluated the association between depression and the risk of RVO development. The presence of depression was significantly associated with increased risks of RVO, and the recurrence of depression showed a higher RVO incidence probability.

Abbreviations: BP = blood pressure, BMI = body mass index; BRVO = branch retinal vein occlusion, CI = confidence interval, CRVO = central retinal vein occlusion, HR = hazard ratio; KNHIS = Korean National Health Insurance System, NHSP = National Health Screening Program, RVO = retinal vein occlusion.

Keywords: depression, nationwide, retina, retinal vessel, RVO

1. Introduction

The word "depression" has numerous definitions ranging from a transient feeling of a flat mood, to serious clinical syndromes that can be severe, disabling, and recurrent.[1] The World Health

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Organization reported depression as the third of 10 major diseases of humankind and predicted it to become the first in 2030.[2] In Korea, the prevalence of major depressive disorder was 7.5% in males and 10.1% in females, according to the survey of domestic mental disorders conducted in 2011, which is 1.5 times higher than that recorded in 2001 and 19.6% higher than that recorded in 2006. Previous studies showed that abnormal cerebral blood flow is associated with depression.[3] Notably, cerebral and retinal microvasculature vessels share similarities in terms of anatomical and functional characteristics,[4] and a plausible hypothesis may be raised that retinal vasculature abnormality reflects cerebral vasculature condition. In this context, depression has been reported to accompany early retinal microvascular changes;[4] depressed individuals are at an increased risk for developing cardiovascular disease and cerebrovascular disease as well.[5,6] Taken together, there may be an association between retinal vein occlusion (RVO) and depression.

Over 16 million people are affected by RVO globally.[7] RVO is the second most common vision-threatening retinal vascular disease.[7] It is broadly classified into central RVO (CRVO) and branch RVO (BRVO). The true incidence of RVO in a population is difficult to establish, as many RVOs are silent when the condition is mild; the patient is asymptomatic and it is only detected incidentally.[8] Older age is a known risk factor for RVO,[9] and with the increasing life expectancy of the global population, the prevalence of the venous occlusive disease is likely to rise in the coming decades. Personal and societal costs

associated with RVO and depression are estimated to be much higher than costs for normal age-matched controls.[10] Furthermore, despite adequate treatment, RVO does not completely resolve because of secondary complications.[11] For these reasons, there is an urgent need to identify new strategies for the diagnosis and treatment of RVO.

The exact role of microvascular disease and the development of RVO in depression is unknown. Interestingly, RVO and depression share common risk factors.[9,12–14] Emerging evidence suggests that variations in retinal arteriolar and venular caliber reflect early pathophysiological processes linked to small-vessel diseases such as stroke[15] and cognitive impairment.[16] However, to the best of authors' knowledge, there are no studies to date that have evaluated the association between depression and the risk of RVO development. In this nationwide cohort study, the association between depression and the risk of RVO was investigated in a Korean population using the National Health Insurance Service National Sample Cohort.

2. Materials and methods

2.1. Data source

This study involved the analysis of data culled from the Korean National Health Screening Program (NHSP) examination in 2009. In South Korea, the government has implemented an obligatory National Health Insurance system that covers 97% of the population and requires patients to pay only about 30% of their total healthcare cost. Therefore, the medical information of almost all patients in the healthcare institutions in Korea has prospectively integrated into the Korean National Health Insurance System (KNHIS) claim database.

2.2. Data collection

This study is a retrospective, nationwide, population-based cohort study. From among all individuals (n=10,505,818) who underwent health examinations between January 1, 2009, and December 31, 2009, individuals <20 years of age (n=15,327), those with any missing variables (n=491,449), those with a prior diagnosis of RVO between 2002 and enrollment (n=39,021), and those with a prior diagnosis of depression 1 year before the examination date (n=758,872) were excluded. Additionally, 222,928 subjects were excluded to account for the 1-year lag period (Fig. 1). From the remaining 9,178,221 subjects, we identified patients who were diagnosed with depression (ICD-10 code F32, F33). Finally, 9,049,521 individuals were enrolled in the depression and comparison groups, respectively; all individuals enrolled were monitored for the development of RVO (ICD, 10th revision, clinical modification [ICD-10-CM] code H34.81, CRVO, or H34.83, venous tributary [branch] occlusion). Thus, this study included 9,178,222 people aged 20 years and older who underwent the NHSP examination at least once in 2009 and patients who were diagnosed with RVO during the washout period (2002-before healthcare check-up date). The washout period for depression was from 2002 to 1 year before the examination date and the lag period was 1 year. Follow-up was conducted until 2017. Subjects were classified into 2 groups (depression and comparison groups) based on whether they had depression, which occurred during the first year before the check-up date, or not.
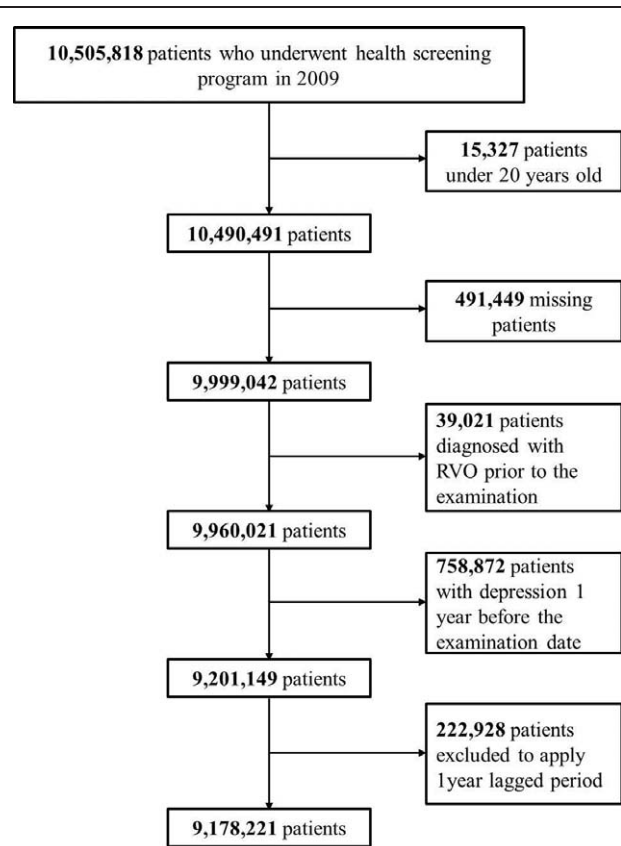

Figure 1. Flow diagram of sample selection for depression and RVO development analysis. RVO = retinal vein occlusion.

2.3. Ethical statement

This study adhered to the tenets of the Declaration of Helsinki, and the study protocol was reviewed and approved by the Institutional Review Board of Catholic University of Medicine, Yeouido St. Mary's Hospital (CMC no. SC19ZESE0044), which waived the requirement for informed consent as well. We have been approved by the Health Insurance Corporation to use data for academic research purposes (NHIS-2019-1-576).

2.4. Measurements and definitions

According to the Korean NHSP examination procedures, the personal information of each patient including age, sex, the results of a questionnaire regarding past medical history and health behavior, body mass index (BMI), waist circumference, and blood pressure (BP), and results of laboratory tests such as fasting blood glucose and cholesterol level, were recorded. The diagnosis of depressive disorder was based on the diagnostic ICD-10 codes (F32-F33). Hypertension was defined as systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg or diagnosis based on ICD-10 codes (10–13, I15). Diabetes was defined as a fasting blood glucose level ≥126 mg/dL or diagnosis based on ICD-10 codes (E11–E14). Dyslipidaemia was defined as a fasting total cholesterol ≥240 mg/dL or the use of cholesterol-lowering medications or diagnosis based on ICD-10 codes (E78). BMI was calculated as body weight (kg)/height (m^2), after measuring the height and weight of the patients in the screening test. Obesity was defined as BMI greater than 25 kg/m^2 according to the Clinical Practice Guidelines for

Overweight and Obesity compiled by the Korean Society for the Study of Obesity. Chronic kidney disease was defined as a glomerular filtration rate <60mL/min/1.73m^2. Additionally, the definitions of lifestyle variables were as follows: (1) smoking status was categorized into the 3 groups namely: non-smokers, current smokers who had smoked 100 cigarettes or more in their lifetime, and ex-smokers who had smoked in the past but had quit at least 1 month ago; (2) alcohol consumption status was categorized into 3 groups namely: non-drinkers, those who drank less than 30g of pure alcohol a day on average, and heavy drinkers who drank more than 30g of alcohol per day. Intense exercise was defined as a fraction of 20 minutes of intense physical activity that was challenging and made breathing difficult, performed more than 3 days a week during the past week; moderate exercise was defined as the percentage of physical activity that was a bit tough on the body or made breathing slightly difficult, performed for 30 minutes at a time for more than 5 days or more per week during the past week.

2.5. Statistical analysis

Baseline characteristics were presented as numbers with percentages (%) for categorical variables or mean values with standard deviations for continuous variables. Chi-square test was used to analyze categorical variables and a student *t* test was used to analyze continuous variables. Kaplan–Meier survival analysis was used to draw the cumulative incidence probability of RVO. The log-rank test was used to test for differences in survival curves between the 2 groups. Associations between depression and the risk of RVO were analyzed using multivariable-adjusted Cox proportional-hazards models, and the hazard ratio (HR) and 95% confidence interval (CI) for the severity of depression, relative to the reference group (comparison group), were presented for each of the 3 models. Model 1 was adjusted for age and sex; Model 2 was further adjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption; and Model 3 is an additional application of the number of visits to hospitals in Model 2. Stratified analysis was conducted for determining the association between depression and RVO development according to other characteristics of the subjects. Statistical analysis was performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). *P* values <.05 were considered statistically significant.

3. Results

3.1. Basic characteristics

The baseline characteristics of the study population are shown in Table 1. The subjects with depression were generally older (middle-aged), had higher BMI, larger WC, higher fasting blood glucose levels, diabetes, hypertension, dyslipidemia, were mostly non-smokers and had more females compared with the subjects in the comparison group (all *P* values <.001).

3.2. Longitudinal association between depression and RVO

Kaplan–Meier survival analyses were performed with RVO development as with and without depression. The log-rank test showed statistically significant *P* values <.0001. Therefore, the depression group showed a higher RVO incidence probability than the comparison group (Fig. 2). In Table 2, multivariable-adjusted Cox regression models (Models 1–3) demonstrate the

Table 1		

Characteristics of the study population comparison group (n= 9,049,521) and depression group (n=128,700).

Variables	Comparison group No. (%)	Depression group No. (%)
Age (yrs)		
20–39	3,017,726 (33.35%)	17,719 (13.77%)
40–64	4,976,247 (54.99%)	76,926 (59.77%)
≥65	1,055,548 (11.66%)	34,055 (26.46%)
Sex		
Male	5,133,840 (56.73%)	49,527 (38.48%)
Female	3,915,681 (43.27%)	79,173 (61.52%)
Current smoker	2,471,434 (27.31%)	20,907 (16.24%)
Drinker		
Non	8,402,821 (92.85%)	123,023 (95.59%)
Heavy	646,700 (7.15%)	5677 (4.41%)
Low income	2,382,107 (26.32%)	35,218 (27.36%)
Diabetes	742,967 (8.21%)	16,851 (13.09%)
Hypertension	2,209,781 (24.42%)	48,200 (37.45%)
Dyslipidemia	1,558,919 (17.23%)	35,618 (27.68%)
Age (years)	46.31±13.91	54.59±13.88
Fasting blood glucose (mg/dL)	96.9±22.68	98.92±24.26
BMI (kg/m^2)	23.69±3.21	23.72±3.19
WC (waist circumference) (cm)	80.18±9.08	80.44±8.98
Systolic BP (mmHg)	122.31±14.88	123.15±15.46
Diastolic BP (mmHg)	76.29±9.97	76.23±10
GFR (mL/min/1.73m^2)	88.7±44.73	85.48±37.17
LOG (triglyceride)	113.34 (113.29–113.38)	116.35 (116–116.7)

Continuous data are presented in the format of mean±standard deviation.

BP=blood pressure, GFR=glomerular filtration rate.

influence of depression on the development of RVO in the Korean population. The adjusted HRs of RVO were 1.159 (95% CI: 1.096–1.226 for Model 1), 1.128 (95% CI: 1.066–1.193 for Model 2), and 1.118 (95% CI: 1.053–1.188 for Model 3) in the depression group compared with those in the comparison group. We further divided the severity of depression based on recurrence 1 to 2 years after the onset of depression (no recurrence group: no recurrence after 1 year from the date of onset, recurrence group: recurrence within 1 to 2 years after the date of onset; both groups had a history of depression 1 year before the examination). The adjusted HRs of RVO were 1.127 (95% CI: 1.055–1.205 for Model 1), 1.104 (95% CI: 1.033–1.18 for Model 2), and 1.087 (95% CI: 1.012–1.167 for Model 3) in the mild depression subgroup. The adjusted HRs of RVO were 1.247 (95% CI: 1.126–1.382 for Model 1), 1.192 (95% CI: 1.077–1.321 for Model 2), and 1.2(95% CI: 1.076–1.338 for Model 3) in the severe depression subgroup. In addition, the incidence of RVO was also 2 times higher in the depression group (comparison group: 0.8415, depression group: 1.56996). Table 2 shows that the greater the severity of depression, the higher the incidence rate of RVO (comparison group: 0.84155, no recurrence group: 1.43179, and recurrence group: 2.04357).

3.3. Subgroup analysis on the association between depression and RVO

Stratified analysis showed the association between depression and RVO development based on various baseline characteristics of the subjects. When we evaluated the effects of several confounding factors on RVO development according to depres-
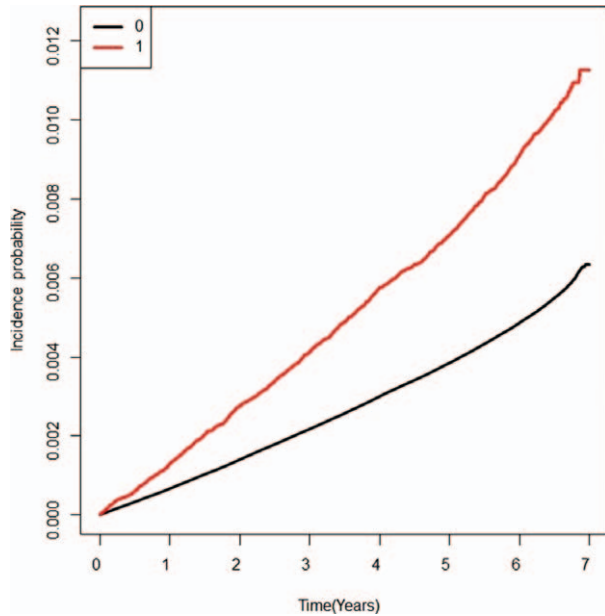
Figure 2. Kaplan–Meier curves showing the incidence of RVO in the depression and comparison groups. The group with depression showed a higher incidence probability than the group without depression. RVO = retinal vein occlusion.

sion, diabetes and hypertension affected the association of depression with RVO development (diabetes P = .0329, hypertension P = .0036 respectively) adjusted variable for a number of visits to hospital (Table 3).

4. Discussion

In this study, we found that depression was associated with a risk of RVO development after adjusting for confounding factors including age, sex, current smoking status, alcohol consumption, exercise, income, BMI, hypertension, dyslipidaemia, diabetes, and a number of visits to the hospital in sample population drawn from a nationwide population database in Korea. Our finding, therefore, adds to a small but growing body of literature that suggests that there is an association between depression and RVO disease, possibly at the level of the microvasculature. The risk of RVO was nearly doubled with more severe depression. Additionally, most subgroups, except for those with diabetes

Table 3

Multivariable-adjusted Cox regression analysis showing the association between depression and RVO development according to other characteristics of the subjects.

Variables	HR (95% CI)	Interaction P value
Age (yrs)		.3382
20–39	0.801 (0.443–1.450)	
40–64	1.121 (1.029–1.22)	
≥65	1.123 (1.046–1.243)	
Sex		.408
Male	1.065 (0.959–1.182)	
Female	1.152 (1.070–1.24)	
Drinker		.2577
Non	1.125 (1.058–1.196)	
Heavy	0.906 (0.619–1.325)	
Exercise		.5717
Non	1.114 (1.030–1.205)	
Yes	1.128 (1.026–1.24)	
Smoking		.7293
No	1.126 (1.057–1.2)	
Current	1.081 (0.897–1.302)	
Obesity		.3023
No	1.125 (1.042–1.214)	
Yes	1.104 (1.100–1.218)	
Abdominal obesity		.2338
No	1.124 (1.045–1.209)	
Yes	1.103 (0.991–1.228)	
Diabetes		.0329
No	1.127 (1.052–1.207)	
Yes	1.1 (0.968–1.249)	
Dyslipidemia		.0997
No	1.14 (1.057–1.23)	
Yes	1.089 (0.985–1.204)	
Hypertension		.0036
No	1.151 (1.051–1.261)	
Yes	1.093 (1.013–1.191)	

CI = confidence interval, HR = hazard ratio, RVO = retinal vein occlusion.

and hypertension, did not show significant associations between depression and the development of RVO. To the best of our knowledge, this is the first study to demonstrate the direct association between depression and risk of developing RVO using nationwide, population-based cohort study data in monoethnic Korea.

Previous studies have found an association between depression and cardiovascular and cerebrovascular diseases.[1,17,18] Interestingly, several studies have also shown that depression causes

Table 2

Multivariable-adjusted Cox regression analysis of the association between RVO incidence and depression.

Depression	N	RVO development	RATE	HR (95% CI) MODEL 1[*]	MODEL 2[†]	MODEL 3[‡]
No	9,049,521	47,938	0.84155	1 (reference)	1 (reference)	1 (reference)
Yes	128,700	1262	1.56996	1.159 (1.096–1.226)	1.128 (1.066–1.193)	1.118 (1.053–1.188)
Severity						
No depression	9,049,521	47,938	0.84155	1 (reference)	1 (reference)	1 (reference)
No recurrence	99,420	891	1.43179	1.127 (1.055–1.205)	1.104 (1.033–1.18)	1.087 (1.012–1.167)
Recurrence	29,280	371	2.04357	1.247 (1.126–1.382)	1.192 (1.077–1.321)	1.2 (1.076–1.338)

BMI = body mass index, CI = confidence interval (95% confidence interval), HR = hazard ratio, RVO = retinal vein occlusion.

[*] Adjusted for age and sex.

[†] Adjusted for age, sex, current smoking, alcohol consumption, exercise, income, BMI, hypertension, dyslipidemia, and diabetes.

[‡] Adjusted for age, sex, current smoking, alcohol consumption, exercise, income, BMI, hypertension, dyslipidemia, diabetes, and a number of visits to the hospital.

early microvascular changes and retinal vessel change.[3,19,20] Retinal vessels share similar anatomical, physiological, and embryological characteristics with the cerebral microvasculature. Therefore, we can assume that the strong association between RVO and depression is related to retinal vascular changes. In addition, the risk factors for depression and RVO may be similar to those that connect depression and cardiovascular and cerebral vascular disease. Nguyen and Wong showed that retinal vascular caliber is associated with different pathophysiological processes of retinopathy, and predicts the incidence of cardiovascular disease independent of standard risk factors.[21] The specific pathophysiological mechanisms of the relationship between depression and RVO are not entirely understood. However, there are some plausible explanations; these include alterations in the autonomic nervous system,[22] platelet receptors and function,[23] coagulopathic factors such as plasminogen activator inhibitor-1 and fibrinogen, pro-inflammatory cytokines,[24] endothelial function, neurohormonal factors, and genetic linkages such as with the serotonin transporter mechanism.[25,26]

Some population-based and case-control studies identified all the components of metabolic syndrome, including hypertension,[27–31] diabetes,[32,33] and dyslipidemia, as risk factors for BRVO,[30,34] after adjusting for multiple potential confounding factors. However, there has been much controversy in the available literature as to whether metabolic syndrome components affect the risk of BRVO. Intriguingly, the association between depression and RVO development was statistically significant only in hypertension and diabetes groups in our study. However, we could not confirm the relationship between dyslipidemia, abdominal obesity, obesity, sex, and age, and the RVO in depression patients (Table 3). Previous studies reported that mild forms of depression are found in up to two-thirds of patients after acute myocardial infarction,[35] with the major depressive disorder being found in up to 15% of CVD patients.[17] It is over 2 or 3 times than general population.[36] It is clear that depression is a risk marker for the increased incidence of cardiovascular disease. The patients with depression disorder has potential behavioral risk factor such as smoking, obesity, poor diet, and poor medication adherence.[37] Therefore, these factors may interact with the biological factors described above, causing cardiovascular disease and affecting vascular disease of the retina. The mechanism is not fully understood about the direct relationship between depression and RVO, but the increased RVO incidence in the presence of depression may indicate that both diseases have a common pathogenic mechanism or that there may be other pathways in the RVO etiology than previously known.

Our study has several limitations. The most noteworthy limitation is that the diagnoses of RVO, depression, or any other comorbidity were defined on the basis of ICD codes. The depression incidence may be underestimated because of some patients not seeking medical care. And there was possible under-reporting of asymptomatic RVO or of a delayed diagnosis of RVO. Second, selection bias is present. We selected medical claim-based controls who were more likely to have comorbidities compared with controls based on the general population who neither received medical care nor had a specific diagnosis. Third, there may be reverse causality, although a washout period was considered when RVO was defined. Finally, this study did not include participants of other ethnicities.

In spite of these limitations, this study is the first extremely large-scale cohort study that evaluated the influence of depression on RVO, especially among a study population of only Koreans. Our study provides the first evidence that depression is a risk factor for RVO in almost the entire Korean population, because the KNHIS database, which includes the NHSP examination records, covers the whole population of South Korean adults. It is noteworthy that because Korea is a mono-ethnic nation, there was no need to consider racial differences. Furthermore, we comprehensively analyzed coexisting illnesses and other factors, enabling adjustment for potential confounders. Therefore, we can generalize the results of this study for Koreans because the KNHIS database that was used for this study represents the majority of the Korean adult population. Additionally, for the first time, the relationship between RVO and depressive disorder can be analyzed and used as an important basic research result for future research direction.

5. Conclusion

In conclusion, patients with depression exhibit a significantly higher risk for RVO after adjusting for the following confounding variables: age, sex, current smoking, alcohol consumption, exercise, income, BMI, hypertension, dyslipidemia, diabetes, and the number of hospital visits. A team-based approach, including ophthalmologists, is recommended especially if the patients are experiencing a recurrence of depressive disorder.

Author contributions

Conceptualization: Kyungdo Han.
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Investigation: Younhea Jung.
Methodology: Kyungdo Han.
Resources: Daran Kim, Ji-Sun Paik.
Supervision: Kyung-sun Na.
Writing – original draft: Minji Ha.
Writing – review & editing: Minji Ha, Kyung-sun Na.

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