Associations Between Smoking, Alcohol Consumption, Physical Activity and Depression in Middle-Aged Premenopausal and Postmenopausal Women

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Background: Changes in lifestyle factors are known to affect mood. However, there is insufficient evidence supporting the association between smoking, alcohol consumption, physical activity and depression in middle-aged women who are likely to experience rapid hormonal changes.

Methods: We used a nationwide database of medical records in South Korea. 901,721 premenopausal and 943,710 postmenopausal women aged 40 years or older included in this study. Information on smoking, alcohol consumption, physical activity was identified from health examination data and followed up for the occurrence of depression using claims data.

Results: Compared with never-smokers, ex-smokers and current smokers among premenopausal and postmenopausal women showed an increased risk of depression in a dose-dependent manner (aHR 1.13 for ex-smokers; aHR 1.23 for current smokers). Compared with non-drinkers, mild drinkers showed a decreased risk of depression (aHR 0.98 for premenopausal women; aHR 0.95 for postmenopausal women), and heavy drinkers showed an increased risk of depression both among premenopausal (aHR 1.20) and postmenopausal women (aHR 1.05). The risk of depression due to smoking and heavy alcohol consumption was higher in premenopausal women than in postmenopausal women. Compared with those who had not engaged in regular physical activity, those who had engaged showed a decreased risk of depression both among premenopausal (aHR 0.96) and postmenopausal women (aHR 0.95).
Conclusions: Smoking and heavy alcohol consumption increased the risk of depression, and the increased risk was prominent in premenopausal than in postmenopausal women. Regular physical activity decreased the risk of depression both in premenopausal and postmenopausal women.

Keywords: alcohol consumption, depression, lifestyle factors, physical activity, smoking—adverse effects, middle aged women

INTRODUCTION

Depression is a common mental illness associated with significant morbidity (1). Depression is characterized by symptoms of depressed mood, decreased interest, motivation and cognition, accompanied by vegetative symptoms including changes in appetite or sleeping. Depressive symptoms can significantly impair individual functioning and sometimes lead to suicide attempts, with depression associated with 60–70% of all suicides (2). A previous study using a large representative sample of the South Korean population reported that the overall prevalence of depression was approximately 5.3% with a higher prevalence among females (6.81%) than in males (3.88%) (3).

Globally, the prevalence of depression is higher in women than in men (4–6). The sex-based differences in depression (7) may be attributed to estrogen, a major female sex hormone, although affected by various socioeconomic factors. Unlike men, women experience certain forms of depression such as premenstrual dysphoric disorder, and postpartum depression that occur during periods of rapid changes in estrogen levels (8). In addition, studies have reported that removal of one or both ovaries via oophorectomy increases the risk of depression (9, 10). In animal models, oophorectomy increased depressive behaviors, which were reversed by the administration of estrogen (11, 12). Women’s reproductive aging cycle includes the reproductive stage, menopausal transition stage and postmenopausal stage according to changes in the levels of female sex hormones including estrogen (13). Although the period of menopausal transition varies individually, on average, the level of estrogen rapidly decreases from 2 years before to 2 years after the final menstrual period, and thereafter remains very low (14). Therefore, the risk of depression associated with decreased levels of estrogen may occur in middle-aged women in their 40s and later ages considering the average age of menopause in women (15).

Smoking, alcohol consumption, and physical inactivity are established unhealthy lifestyle factors, which increase the risk of cardiovascular and metabolic diseases (16–19). Evidence demonstrates the association between these lifestyle factors and depression. Smoking is very common in patients with mental disorders (20). Previous studies have reported mixed effects of smoking on mood. A previous study reported antidepressant and anxiolytic effects of smoking (21), and another study suggested that nicotine use by smokers improves adaptation to stressful situations (22). However, despite a temporary increase in mood immediately after smoking, throughout the day, the mood was worse than that of non-smokers, and the diurnal variation was larger in smokers (23). Further, a prospective cohort study showed that smokers had an increased risk of major depressive disorder by about 93% compared with non-smokers (24). A number of studies have shown a positive association between alcohol consumption and depression (25–29). Studies reported that the amount of alcohol consumption affects depression more than the act of drinking, and a strong association with depression was found in heavy drinkers (27, 28). In addition, the association between alcohol consumption and depression was stronger in women than in men (26, 27, 29). Studies have consistently reported a protective effect of physical activity on depression. A case-control study involving older men and women showed that physical activity had a protective effect on depressive disorders with an odds ratio (OR) of 0.55 (30). A cohort study of middle-aged and elderly individuals showed that greater physical activity prevented depression (OR = 0.83) (31). Further, a large-sample British prospective cohort study showed a bidirectional association between physical activity and depression, suggesting that physical activity has a protective effect on depression (OR = 0.72) and individuals with depression are unlikely to meet the recommended levels of physical activity (OR = 1.79) (32).

In this study, we investigated the association between smoking, alcohol consumption, physical activity and depression in middle-aged women, with a particular focus on the differences between premenopausal and postmenopausal women. We hypothesized that (1) smoking and alcohol consumption increase the risk of depression; (2) regular physical activity decreases the risk of depression; (3) a discrepancy in these associations exists between premenopausal and postmenopausal women.

METHODS

Data Source

This study used the National Health Insurance Sharing Service (NHISS) database of National Health Insurance Service (NHIS) of South Korea (33, 34). NHIS is a public institution responsible for operating a mandatory universal health insurance program. Nearly 97% of the total South Korean population is enrolled in this service, while the remaining 3% is covered by the Medical Aid Program. The NHISS database contains not only the medical services claims data such as admission, emergency room visits, ambulatory care visits, and pharmaceutical services but also health checkup data. NHISS data are anonymized to protect the privacy of individuals.

We also used the National Cancer Screening Program (NCSP) database (35). The NCSP includes screening of all individuals for stomach, liver, colorectal, breast, and cervical cancers based
on age. In addition, subjects respond to self-questionnaires on lifestyle factors such as smoking, alcohol consumption, and physical activity. All South Korean women aged 40 years or older are recommended screening for breast and cervical cancers. Although the screening program is voluntary, the participation rate is as high as approximately 70% (36).

The NHISS and NCSP data are linked and anonymized to protect individual privacy. The study protocol was approved by the Institutional Review Board of the Samsung Medical Center (No. SMC 2020-10-005).

**Case Identification**

For the case identification, first, we used NCSP data. We identified subjects’ lifestyle factors including smoking, alcohol consumption and physical activity from self-questionnaire in the health examination data, and menopausal status and female reproductive factors from data of screening for breast and cervical cancer data. A total of 3,109,506 female subjects aged 40 years or older underwent health examination and cancer screening in 2009. Among them, 1,059,579 were premenopausal women aged 40–60 years and 1,368,400 were postmenopausal women aged 40–69 years. Then, using NHISS data, we excluded people with a history of depressive disorder before the examination (83,992 and 195,975 cases of premenopausal and postmenopausal women, respectively) to establish the first diagnosis of depressive disorder. Those with incomplete information about variables were also excluded (53,664 and 190,151 cases of premenopausal and postmenopausal women, respectively). We also excluded 20,202 premenopausal and 38,564 postmenopausal women who were diagnosed with depressive disorder within 1 year after the examination to eliminate the effect of a temporary increase in the diagnosis of depression following the examination. Finally, 901,721 premenopausal and 943,710 postmenopausal women were eligible and included in the study. We reviewed their medical records using NHISS data until December 31, 2018 (Figure 1).

**Smoking Status**

We extracted data involving smoking status, duration of smoking, and the level of smoking among subjects from the self-administrated questionnaire conducted on the day of health examination. Based on smoking status, subjects were categorized into never smokers, ex-smokers, and current smokers. The level of smoking was measured in terms of cigarettes smoked per day and pack-years.
Alcohol Consumption
The number of drinking days per week and the amount of daily drinking were determined from the self-administrated questionnaire administered on the day of health examination. We categorized alcohol users according to the amount of alcohol consumption: mild (up to 1.5 drinks a day), moderate (1.5–3 drinks a day) and heavy (more than 3 drinks a day).

Physical Activity
In the self-questionnaire during health examination, subjects' physical activity was measured based on their response indicating the number of days a week of intense physical exercise lasting more than 20 mins, moderate intensity exercise of more than 30 mins and mild intensity workout of more than 30 mins. Regular exercise was operationally defined as moderate physical activity of more than 30 mins at least 5 times a week or intense physical activity of more than 20 mins at least 3 times a week.

Outcomes
The main outcome was the diagnosis of depressive disorder during the follow-up period identified from NHIS claims data. Depressive disorder (F32 and F33) was defined according to the International Statistical Classification of Disease and Related Health Problems 10th revision (ICD-10) and the diagnostic codes were entered by clinicians when they see a patient.

Subgroup
We performed subgroup analysis to identify the association between lifestyle factors and depression according to the diagnostic history of bipolar disorder. The subgroup with bipolar disorder was defined as those who had diagnosed with bipolar disorder (F30 and F31) as a primary diagnosis during entire research period (from January 1, 2009 to December 31, 2018).

Covariates
We calculated body mass index (BMI) using weight and height information. Comorbid physical illnesses including hypertension, diabetes mellitus, and dyslipidemia were identified from past medical history based on ICD-10 codes. We identified the age at menarche, age at menopause, parity, duration of oral contraceptive (OC) use, duration of breast feeding, and duration of hormone replacement therapy (HRT) as female reproductive factors using the self-administered questionnaire data. The duration of fertility was calculated as the interval between age at menarche and age at menopause.

Statistical Analyses
We presented the baseline characteristics (i.e., personal information, physical status, smoking status, alcohol consumption, regular physical activity, female reproductive factors, comorbid physical illnesses and comorbid psychiatric illnesses) with continuous variables as mean ± standard deviation (SD) and categorical variables as numbers and percentages. Student’s t-tests and chi-square tests were used to compare the differences in baseline factors between depression group and non-depression group. Cox proportional hazards regression analyses were conducted to identify the association between smoking, alcohol consumption, physical activity and diagnosis of depression. Hazard ratios (HR) were presented to show the magnitude of risk of depression according to the variables. Statistical analyses were performed using SAS version 9.4 (SAS institute Inc., Cary, NC, USA).

RESULTS
Baseline Characteristics of the Study Subjects
Table 1 shows the baseline characteristics of the study subjects. The mean age was older in those diagnosed with depression both among premenopausal (depression group: 45.77, SD 3.99 vs. non-depression group: 44.81, SD 3.91) and postmenopausal women (depression group: 59.31, SD 5.81 vs. non-depression group: 57.99, SD 5.78). There were more never-smokers in the non-depression groups, and more ex-smokers and current smokers in the depression group both in premenopausal and postmenopausal women. Regarding alcohol consumption, there were more mild alcohol users in the non-depression group and more heavy alcohol users in the depression group both in premenopausal and postmenopausal women. There were more non-alcohol users in the non-depression group in premenopausal women, and more in the depression group in postmenopausal women. The proportion of those who had engaged in regular physical activity was higher in the non-depression group than in the depression group among postmenopausal women, while there was no significant difference between groups among premenopausal women.

Incidence of Depressive Disorder
Among premenopausal women, the average length of follow-up was 7.54 years (SD, 1.98), 164,146 patients were newly diagnosed with a depressive disorder during the follow-up period, and the incidence rate was 24.1 per 1,000 person-years.
Among postmenopausal women, the average length of follow-up was 7.07 years (SD, 2.45), 269,539 patients were newly diagnosed with a depressive disorder during the follow-up period, and the incidence rate was 40.4 per 1,000 person-years.

Hazard Ratios of Smoking, Alcohol Consumption, and Regular Physical Activity for Occurrence of Depression
Table 2 presents HRs of depression according to the status of smoking, alcohol consumption, and physical activity. Compared with never-smokers, ex-smokers and current smokers showed an increased HR both among premenopausal (aHR 1.28, 95% CI 1.23–1.33 for ex-smokers and aHR 1.40, 95% CI 1.36–1.43 for current smokers) and postmenopausal women (aHR 1.13, 95% CI 1.09–1.17 for ex-smokers and aHR 1.23, 95% CI 1.20–1.26 for current smokers). Compared with non-alcohol users, mild alcohol users showed a decreased risk of depression (aHR 0.98, 95% CI 0.97–0.99), whereas moderate (aHR 1.12, 95% CI 1.09–1.15) and heavy alcohol users (aHR 1.20, 95% CI 1.15–1.25) showed an increased risk of depression among premenopausal women. Among postmenopausal women, heavy alcohol users
### TABLE 1 | Baseline characteristics of study subjects.

|                        | Premenopausal women | Postmenopausal women | p         |
|------------------------|---------------------|----------------------|-----------|
|                        | Depression          |                      |           |
|                        | No (n = 737,757)     | Yes (n = 164,148)    |           |
| Age (years)            | 44.81 ± 3.91        | 45.77 ± 3.99         | <0.0001   |
| BMI (kg/m²)            | 23.2 ± 3.05         | 23.36 ± 3.11         | <0.0001   |
| Systolic BP (mmHg)     | 117.27 ± 14.35      | 117.46 ± 14.35       | <0.0001   |
| Diastolic BP (mmHg)    | 73.14 ± 9.97        | 73.4 ± 9.95          | <0.0001   |
| Fasting glucose (mg/dL)| 93.54 ± 17.42       | 94.15 ± 19.5         | <0.0001   |
| Total cholesterol (mg/dL)| 191.78 ± 38.36   | 193.34 ± 40.82       | <0.0001   |
| HDL (mg/dL)            | 60.45 ± 35.54       | 60.51 ± 36.34        | 0.051     |
| LDL (mg/dL)            | 114.5 ± 71.61       | 115.02 ± 60.57       | 0.006     |
| Smoking status         |                     |                      |           |
| Never                  | 706,116 (95.73)     | 154,513 (94.13)      |           |
| Ex-smoker              | 10,001 (1.38)       | 2,691 (1.64)         |           |
| Current smoker         | 21,458 (2.91)       | 6,942 (4.23)         |           |
| Alcohol consumptiona   |                     |                      | <0.0001   |
| None                   | 528,694 (71.68)     | 117,543 (71.61)      |           |
| Mild                   | 180,131 (24.42)     | 38,390 (23.39)       |           |
| Moderate               | 21,155 (2.67)       | 5,801 (3.53)         |           |
| Heavy                  | 7,595 (1.03)        | 2,412 (1.47)         |           |
| Regular physical activity| 127,624 (17.30)  | 28,096 (17.12)       | 0.070     |
| Hypertension           | 99,390 (13.48)      | 26,068 (15.88)       |           |
| Diabetes mellitus      | 20,963 (2.84)       | 4,798 (3.53)         |           |
| Dyslipidemia           | 78,424 (10.63)      | 21,189 (12.91)       |           |
| Stroke                 | 1,457 (0.40)        | 457 (0.55)           |           |
| Cardiovascular disease | 2,945 (0.80)        | 1,008 (1.21)         | <0.0001   |
| Parity                 |                      |                      |           |
| Nulliparity            | 31,140 (4.22)       | 6,328 (3.86)         |           |
| 1                      | 97,371 (13.2)       | 22,391 (13.64)       |           |
| ≥ 2                    | 609,064 (82.58)     | 135,427 (82.50)      |           |
| Duration of breast feeding (months) | <0.0001 |                      |           |
| Never                  | 183,268 (24.85)     | 36,240 (22.08)       |           |
| < 6                    | 197,576 (26.79)     | 42,563 (25.93)       |           |
| 6–12                   | 221,624 (30.05)     | 57,254 (34.88)       |           |
| ≥ 12                   | 135,107 (18.32)     | 28,089 (17.11)       |           |
| Duration of OC use (years) | <0.0001 |                      |           |
| Never                  | 617,748 (83.75)     | 134,076 (81.68)      |           |
| < 1                    | 66,813 (9.06)       | 16,254 (9.90)        |           |
| ≥ 1                    | 23,155 (3.14)       | 6,342 (3.86)         |           |
| Unknown                | 29,859 (4.05)       | 7,947 (4.55)         |           |
| Age at menarche (years) | 15.05 ± 1.64      | 15.31 ± 1.71         | <0.0001   |
| Age at menopause (years) | –                | –                   |           |
| Duration of fertility (years) | –                | –                   |           |
| Duration of HRT (years) | –                | –                   |           |
| Never                  | –                   | –                   | 560,433 (83.13) |
| < 2                    | –                   | –                   | 216,136 (80.19) |
| 2–5                    | –                   | –                   | 67,186 (8.97) |
| ≥ 5                    | –                   | –                   | 30,489 (11.31) |
| Diagnosis of bipolar disorder | 989 (0.13) | 874 (0.53)         | <0.0001   |
| Substance-related disorders | 3,814 (0.52) | 2,231 (1.36)       | <0.0001   |

Data are expressed as the mean ± standard deviation, SD, or n (%).

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OC, oral contraceptives; HRT, hormone replacement therapy.

a Alcohol consumption: mild = up to 15g (equivalent to 1.5 drinks) a day; moderate = 15g to 30g a day; heavy = more than 30g (equivalent to 3 drinks) a day.
### TABLE 2 | Hazard ratios of lifestyle factors associated with the occurrence of depression.

| Smoking status | Premenopausal women | Postmenopausal women |
|----------------|---------------------|----------------------|
|                | Crude Model         | Model 1              | Model 2              |
| **Never**      | 1 (Ref.)            | 1.06 (1.02, 1.10)    | 1.13 (1.09, 1.17)    |
| **Ex-smoker**  | 1.21 (1.16, 1.26)   | 1.01 (0.97, 1.04)    | 1.07 (1.02, 1.13)    |
| **Current smoker** | 1.43 (1.39, 1.46) | 1.16 (1.14, 1.19)    | 1.23 (1.20, 1.26)    |

| Alcohol consumption | Premenopausal women | Postmenopausal women |
|---------------------|---------------------|----------------------|
| **None**            | 1 (Ref.)            | 1 (Ref.)             |
| **Mild**            | 0.96 (0.95, 0.97)   | 0.90 (0.89, 0.91)    |
| **Moderate**        | 1.21 (1.18, 1.24)   | 0.97 (0.94, 1.00)    |
| **Heavy**           | 1.38 (1.32, 1.43)   | 1.02 (0.97, 1.07)    |

| Regular physical activity | Premenopausal women | Postmenopausal women |
|---------------------------|---------------------|----------------------|
| **No**                    | 1 (Ref.)            | 1 (Ref.)             |
| **Yes**                   | 0.99 (0.97, 1.00)   | 0.95 (0.95, 0.96)    |

Model: adjusted for age at menarche, parity, duration of breast feeding, history of oral contraceptive use, age, smoking status, alcohol consumption, regular exercise, body mass index, diabetes mellitus, hypertension, and dyslipidemia.

Model 1: adjusted for age at menarche, age at menopause, parity, duration of breast feeding, history of oral contraceptive use, duration of hormone replacement therapy, age, smoking status, alcohol consumption, regular exercise, body mass index, diabetes mellitus, hypertension, and dyslipidemia.

Model 2: adjusted for duration of fertility instead of age at menarche and menopause in Model 1.

### TABLE 3 | Hazard ratios of combinations of lifestyle factors associated with the occurrence of depression.

| Ever smoking | Heavy drinking | Regular physical activity | Hazard ratio (95% confidence interval) |
|--------------|----------------|---------------------------|----------------------------------------|
| No           | No             | Yes                       | 1 (Ref.)                               |
| No           | No             | No                        | 1.16 (0.97, 1.40)                      |
| No           | Yes            | Yes                       | 1.22 (1.11, 1.35)                      |
| Yes          | No             | No                        | 0.74 (0.69, 0.79)                      |
| Yes          | No             | Yes                       | 0.92 (0.81, 1.04)                      |
| Yes          | Yes            | No                        | 0.99 (0.91, 1.08)                      |

Model: adjusted for age at menarche, parity, duration of breast feeding, history of oral contraceptive use, age, smoking status, alcohol consumption, regular exercise, body mass index, diabetes mellitus, hypertension, and dyslipidemia.

Model 1: adjusted for age at menarche, age at menopause, parity, duration of breast feeding, history of oral contraceptive use, duration of hormone replacement therapy, age, smoking status, alcohol consumption, regular exercise, body mass index, diabetes mellitus, hypertension, and dyslipidemia.

Model 2: adjusted for duration of fertility instead of age at menarche and menopause in Model 1.

Supplementary Table 1 shows the associations between lifestyle factors and risk of depression in the subgroup without history of bipolar disorder, and the results were similar with the main outcome. While, **Supplementary Table 2** shows the associations between lifestyle factors and risk of depression in the subgroup with history of bipolar disorder. Compared with never-smokers, current smokers showed an increased HR both among premenopausal (aHR 1.44, 95% CI 1.12–1.86) and postmenopausal women (aHR 1.46, 95% CI 1.06–2.00).

Table 3 shows the HRs stratified according to ever smoking, heavy alcohol use, and regular physical activity. Compared with never-smoking, non-heavy alcohol use, and regular physical activity, the lowest risk of depression was found.
| TABLE 4 | The dose-response relationships between lifestyle factors and the risk of depression. |
|----------------------------------------------------------|
| Hazard ratio (95% confidence interval)                    |
|                                                           |
| **Hazard ratio (95% confidence interval)**                |
|                                                           |
| **Premenopausal women**                                  |
|                                                           |
| Crude Model                                              |
| Model                                                    |
|                                                           |
| **Postmenopausal women**                                 |
|                                                           |
| Crude Model                                              |
| Model 1                                                  |
| Model 2                                                  |
|                                                           |
| **Smoking**                                              |
| Level of smoking (cigarettes/day)                        |
|                                                           |
| Never smoker                                             |
| 1 (Ref.)                                                 |
| Ex-smoker / < 10                                         |
| 1.14 (1.08, 1.20)                                        |
| Ex-smoker / < 20                                         |
| 1.26 (1.18, 1.34)                                        |
| Ex-smoker / ≥ 20                                         |
| 1.45 (1.30, 1.61)                                        |
| Current smoker / < 10                                    |
| 1.24 (1.20, 1.29)                                        |
| Current smoker / < 20                                    |
| 1.46 (1.42, 1.51)                                        |
| Current smoker / ≥ 20                                    |
| 1.81 (1.72, 1.91)                                        |
| **Duration of smoking (years)**                          |
|                                                           |
| Never smoker                                             |
| 1 (Ref.)                                                 |
| Ex-smoker / < 10                                         |
| 1.17 (1.11, 1.23)                                        |
| Ex-smoker / < 20                                         |
| 1.26 (1.17, 1.34)                                        |
| Ex-smoker / ≥ 20                                         |
| 1.36 (1.19, 1.55)                                        |
| Current smoker / < 10                                    |
| 1.38 (1.32, 1.44)                                        |
| Current smoker / ≥ 20                                    |
| 1.39 (1.34, 1.44)                                        |
| **Pack-years of smoking**                                |
|                                                           |
| Never smoker                                             |
| 1 (Ref.)                                                 |
| Ex-smoker / < 20                                         |
| 1.20 (1.15, 1.25)                                        |
| Ex-smoker / ≥ 20                                         |
| 1.54 (1.24, 1.90)                                        |
| Current smoker / < 20                                    |
| 1.39 (1.36, 1.43)                                        |
| Current smoker / ≥ 20                                    |
| 1.88 (1.74, 2.04)                                        |
| **Alcohol consumption**                                  |
| Drinking days per week                                   |
|                                                           |
| Non-drinker                                              |
| 1 (Ref.)                                                 |
| < 3                                                     |
| 0.97 (0.96, 0.98)                                        |
| < 5                                                     |
| 1.16 (1.13, 1.19)                                        |
| ≥ 5                                                     |
| 1.32 (1.27, 1.37)                                        |
| Amount of daily alcohol consumption (drinks)              |
|                                                           |
| Non-drinker                                              |
| 1 (Ref.)                                                 |
| ≤4                                                      |
| 0.95 (0.94, 0.96)                                        |
| 5–7                                                     |
| 1.11 (1.09, 1.13)                                        |
| 8–14                                                    |
| 1.24 (1.20, 1.29)                                        |
| >14                                                     |
| 1.36 (1.22, 1.50)                                        |
| **Physical activity**                                    |
| Days of walking per week                                 |
|                                                           |
| 0                                                       |
| 1.11 (1.09, 1.13)                                        |
| 1                                                       |
| 0.96 (0.94, 0.96)                                        |
| 2                                                       |
| 0.96 (0.96, 1.00)                                        |
| 3                                                       |
| 0.98 (0.95, 1.00)                                        |
| 4                                                       |
| 0.98 (0.95, 1.00)                                        |
| 5                                                       |
| 0.90 (0.88, 0.92)                                        |
| 6                                                       |
| 0.96 (0.94, 0.99)                                        |
| 7                                                       |
| 1.02 (1.00, 1.05)                                        |
| Days of moderate intensity physical activities per week   |
|                                                           |
| 0                                                       |
| 1.10 (1.09, 1.12)                                        |
| 1                                                       |

(Continued)
Both in premenopausal (aHR 0.74, 95% CI 0.69–0.79) and postmenopausal women (aHR 0.85, 95% CI 0.80–0.90) who ever smoked, and engaged in non-heavy alcohol use and regular physical activity, while those who never smoked, indulged in heavy alcohol use and not engaged in regular physical activity showed the highest risk of depression among premenopausal (aHR 1.23, 95% CI 1.11–1.36) and postmenopausal women (aHR 1.16, 95% CI 1.03–1.30).

Dose-Response Relationships Between Smoking, Alcohol Consumption, and Regular Physical Activity With Depression

Table 4 shows the dose-response relationships between lifestyle factors and the risk of depression. We found a strong positive dose-response relationship between smoking and depression. Compared with never smokers, current smokers who smoked more than 20 cigarettes a day showed the highest HRs (aHR 1.65, 95% CI 1.57–1.75 for premenopausal women; aHR 1.34, 95% CI 1.28–1.41 for postmenopausal women). Among premenopausal women, compared with never smokers, current smokers who had been smoking for over 20 years showed the highest risk of depression (aHR 1.45, 95% CI 1.38–1.53). While among postmenopausal women, current smokers who smoked for 10–20 years showed the highest risk of depression (aHR 1.27, 95% CI 1.22–1.32). Compared with never smokers, current smokers who had smoked 20 pack-years or more showed the highest risk of depression both among premenopausal (aHR 1.66, 95% CI 1.53–1.80) and postmenopausal women (aHR 1.32, 95% CI 1.25–1.38).

Regarding alcohol consumption, compared with non-drinkers, those who consumed alcohol during fewer than 3 days a week showed a decreased risk of depression (aHR 0.98, 95% CI 0.97–0.99 for premenopausal women; aHR 0.95, 95% CI 0.94–0.96 for postmenopausal women), and those who consumed alcohol on 5 days or more a week showed the highest risk of depression (aHR 1.16, 95% CI 1.12–1.21 for premenopausal women and aHR 1.05, 95% CI 1.01–1.09 for postmenopausal women). Compared with non-drinkers, those who consumed four or fewer drinks a day showed a decreased risk of depression (aHR 0.97, 95% CI 0.96–0.98 for postmenopausal women; aHR 0.95, 95% CI 0.93–0.96 for premenopausal women). On the other hand, premenopausal women who consumed more than 14 drinks a day (aHR 1.19, 95% CI 1.07–1.32) and postmenopausal women who had 8–14 drinks a day (aHR 1.06, 95% CI 1.01–1.11) showed the highest risk of depression.

Regarding physical activity, compared with those who had walked 1 day a week, those who had not walked at least 1 day a week showed an increased risk of depression (aHR 1.05, 95% CI 1.02–1.08 for premenopausal women; aHR 1.03, 95% CI 1.02–1.05 for postmenopausal women), while those who had walked 5 days a week showed the least risk of depression (aHR 0.89, 95% CI 0.87–0.91 for premenopausal women; aHR 0.91, 95% CI 0.90–0.93 for postmenopausal women).

DISCUSSION

In this study, we investigated the association between smoking, alcohol consumption, and physical activity with the risk of depression. The three major findings of the study include: first,
smoking increased the risk of depression in a dose-dependent manner, and the increased risk was higher among premenopausal women compared with postmenopausal women; second, while mild alcohol consumption decreased the risk of depression, heavy alcohol consumption increased the risk of depression, and the association between alcohol consumption and depression was stronger among premenopausal than among postmenopausal women; third, regular physical activity decreased the risk of depression in premenopausal and postmenopausal women. Our results suggest that lifestyle risk factors including smoking, heavy alcohol consumption and physical inactivity are associated with increased risk of depression. The findings were consistent with those of previous studies mentioned in the Introduction.

Cardiovascular changes associated with smoking, heavy alcohol consumption and physical inactivity may affect the occurrence of depression. Smoking is associated with adverse lipid and lipoprotein profiles (37, 38), and alcohol consumption and physical inactivity are associated with increase in blood pressure and levels of fasting glucose (39). Adverse cardiovascular changes can affect the brain, causing focal vascular damage and white matter lesions, which can alter neural connectivity (40, 41). In addition, cardiovascular changes can cause brain dysfunction via inflammation and hypoperfusion that affect the development of depression (41–44). Conversely, symptoms of depression (e.g., decreased motivation or interest) may increase cardiovascular risk factors. The reciprocal relationship between smoking, heavy alcohol consumption, physical activity and depression may lead to the significant results of our study.

The association between lifestyle risk factors and depression is known to be stronger in females than in males (29), and estrogen may play an important role in this association. Estrogen decreases the levels of low-density lipoprotein (LDL) cholesterol and fibrinogen, increases high density lipoprotein (HDL) cholesterol and blood flow, and prevents atherosclerotic changes (38, 45–47). A rapid decline in estrogen levels of perimenopausal and postmenopausal women exacerbates cardiovascular adverse effects, which increases the risk of vascular depression (48). In addition, estrogen has neuroprotective effects mediated via modulation of neuroplasticity and inhibition of neurodegeneration (49, 50).

Along with changes resulting from reduced levels of estrogen, age-related changes in the brain such as decreased expression of brain-derived neurotrophic factor (BDNF) (51, 52) and hippocampal atrophy (53) may be important mechanisms that predispose middle-aged women to depression. However, previous studies have reported that physical activity including aerobic exercise may reverse the risk of aging-related depression by promoting BDNF production and increasing hippocampal volume (53, 54). In addition, other mechanisms may explain the association between lifestyle factors and depression. Nicotine is a psychoactive substance that affects the regulation of monoamine neurotransmitters including dopamine (55). Exercise increases the levels of monoamine neurotransmitters and endorphins (56, 57). Further, physical activity may play a role in preventing depression by enhancing physical fitness and increasing self-esteem (58).

One of major findings is that the risk of smoking and heavy alcohol consumption on depression was higher in premenopausal women than in postmenopausal women. Although this study could not explain the underlying mechanism, longer exposure to unhealthy lifestyle factors may increase the risk of depression and the interaction between estrogen and unhealthy lifestyle factors may increase the risk of depression more than the effect of unhealthy lifestyle factors alone. However, the association is not necessarily causation, and temporal association between them should be examined in the future studies including prospective animal models.

This study demonstrates associations between smoking, alcohol consumption, physical activity and depression in middle-aged women based on real-world data. However, this work has several limitations. First, since the information on lifestyle factors is based on a single health questionnaire conducted at a specific time point, the variables do not necessarily reflect long-term habits. Second, menopausal status was identified only once during the health examination and whether or not menopause was attained during the follow-up was not determined. Therefore, it is difficult to conclude that the interaction between hormones and lifestyle factors persisted until the reported outcome or the end of the observation period. Third, the diagnosis of depression was based on patients’ medical records and not clinical evaluation. Clinical information about depression including symptom presentation or severity was lacking. Fourth, the use of medications such as psychotropic medications including antipsychotics, mood stabilizers and antidepressants or other medications for physical illnesses was not included in the analyses. Fifth, since this study was conducted using representative data of South Korea, it is difficult to extrapolate the results directly to other populations worldwide. We identified depression among subjects using medical services records under a diagnosis of depressive disorders. However, it is possible that additional subjects experienced depressive symptoms without using medical services. The use of psychiatric services is affected by attitudes or acceptance of psychiatric illnesses. In Asian countries including South Korea, a negative perception or stigma of psychiatric illnesses is prevalent (59–61), which may lead to insufficient use of psychiatric services and under-reporting of depression.

In conclusion, smoking and heavy alcohol consumption were associated with an increased risk of depression, and the risk is higher in premenopausal women than in postmenopausal women. Regular physical activity was associated with a decreased risk of depression both in premenopausal and postmenopausal women. The results of this study are expected support strategies to correct lifestyle risk factors for the prevention of depression in middle-aged women.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://nhiss.nhis.or.kr/.

ETHICS STATEMENT

The study involving human subjects was reviewed and approved by the Institutional Review Board of the Samsung Medical Center. Written informed consent for subjects was not required.
for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HK contributed to the search for background literature, to writing the original draft of the manuscript, and to reviewing. JY and KH contributed to formal analysis. HJJ contributed to conceptualization, project administration, and supervision. All authors contributed to writing and editing the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.761761/full#supplementary-material

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