Synergistic Effect of Depression and Cerebrovascular Disease in Mid- to Late-life on the Risk for Dementia: A Nationwide Population-based Cohort Study

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Research

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Abstract

Background: Dementia is a progressive neurocognitive disease with a substantial social burden. No apparent breakthroughs in treatment options have evolved so far, suggesting that disease prevention for at-risk populations is essential. Depression and cerebrovascular disease (CVD) are known independent risk factors for dementia, but no studies have examined whether the risk for dementia among people with both illnesses is higher than the sum from each effect individually. This study aims to evaluate the dementia risk among people with depression, CVD, or both, compared to those with neither.

Methods: A population-based cohort study analyzing the Korean National Health Insurance Service-National Sample Cohort database was conducted for all individuals aged over 50 years. This population had not been diagnosed with dementia at baseline, and was followed up from January 1, 2005, to December 31, 2013. The analyses used a time-varying Cox proportional hazard regression model that was adjusted for potential confounding factors. The synergistic effect of depression and CVD was estimated by calculating the attributable proportion (AP) due to interaction.

Results: A total of 242,237 participants were included in the analytical sample, and 12,735 (5.3%) participants developed dementia. Compared with participants without depression or CVD, the adjusted hazard ratio for the incidence of dementia for those with depression alone was 2.35 (95% CI 2.21-2.49); CVD alone, 3.25 (95% CI 3.11-3.39); and comorbid depression and CVD, 5.02 (95% CI 4.66-5.42). The synergistic effect between depression and CVD was statistically significant (AP due to interaction = 0.08, *P*-value = 0.037), whereby 8% of incident dementia among those with comorbid depression and CVD was attributed to the concomitance of the two illnesses.

Conclusions: In this population-based nationwide cohort with a long-term follow-up, depression and CVD were associated with an increased risk of dementia, and their coexistence had a synergistic association.

Introduction

Dementia is a neurodegenerative disease characterized by a progressive cognitive decline. Dementia precludes patients from carrying out their independent daily lives and devastates the lives of not only patients but also their caregivers. Although the prevalence and disease burden of dementia is increasing [1], there have been no apparent breakthroughs in treatment options so far. Therefore, the importance of preventive approaches before the onset of dementia has been emphasized, in order to reduce the disease burden. Identifying at-risk populations and applying tailored care can be helpful in terms of cost-effectiveness as well [2].

Cerebrovascular disease (CVD), including cerebral ischemia and hemorrhage, is a widely known independent risk factor for dementia [3-8]. Vascular dysfunction is known to cause cognitive decline through changes in the blood supply [9, 10], inflammation [11-13], and in the immune system [14], as well as through brain parenchymal damage [3, 7, 15]. Depression has also been suggested as a risk factor for dementia. According to recent meta-analyses of several epidemiological studies [16, 17], late-life

depression is associated with an increased dementia risk. Because depression and CVD share a common pathophysiology, such as hypothalamic-pituitary-adrenal (HPA) axis dysregulation [18], chronic inflammation [19], and endothelial dysfunction [20], depression and CVD may aggravate each other. Depressive patients are at higher risk of stroke morbidity and mortality [21], and the reverse is true as well [22]. The association between depression and microvascular dysfunction has also been described in a recent systemic review and meta-analysis [23].

Despite the relevance between these noteworthy risk factors, the prior studies on dementia risks have not focused on the concurrent effects of depression and cerebrovascular disease (CVD). Therefore, whether concomitant depression and CVD synergistically increase the risk of dementia more than the sum of their individual effects is still undetermined. In the current study, we evaluated the association of depression, CVD, and their relative interactions with subsequent dementia using a nationwide population-based cohort. We also investigated whether the synergistic effect of the two conditions on dementia risk changes with the age or sex of those studied.

Methods

Participants

We used a nationwide population-based cohort database, the South Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) [24]. Among 1,044,097 individuals who were enrolled in the cohort during the baseline period from January 1st, 2002, to December 31st, 2004, we included 244,920 individuals over the age of 50, and then excluded 2,683 cases who had or received a dementia diagnosis during this time period (Fig. 1). The analyses included a total of 242,237 participants. The institutional review board at Samsung Medical Center approved this study. All data were deidentified and kept confidential, therefore, participants' informed consent was exempted.

Exposure variables: depression and CVD

Depression was defined as those having an International Classification of Diseases 10th revision (ICD-10) code of depressive disorder (F32 or F33), and a documented history of taking antidepressant medication (Additional file 1: Table S6) on the first day of their depression diagnosis during the follow-up period [25]. CVD was defined as those with an ICD-10 code of cerebrovascular disease (I60-69) as a primary diagnosis with two or more hospital visits during the follow-up period. Unlike the medications used for depression or dementia patients, medications for patients with CVD are not exclusive to this disease. Therefore, we defined CVD as having the ICD code with multiple hospital visits, and did not include medication criteria.

Outcome of interest: dementia

The primary outcome was overall survival free of dementia. Dementia was defined as having dementia as classified by the ICD-10 code (F00-03, G30-31) and a documented history of taking anti-dementia medication (donepezil, rivastigmine, galantamine, or memantine) during the follow-up period [25, 26]. As mentioned above, we excluded all cases with a dementia diagnosis during the two years of the baseline period, in order to focus on incident cases of dementia. We set secondary outcomes as dementia subtypes, according to the respective ICD-10 codes assigned on their first day of dementia diagnosis; F00 and G30 as Alzheimer's disease (AD); F01 as vascular dementia (VD); and F02-03 and G31 as other dementias (non-AD or non-VD).

Covariates

Analyses were adjusted for the following potential confounding variables: age, sex, residential area, income level, and comorbidities defined during the baseline period from 2002 to 2004. As for residential area, individuals who resided in the capital city of South Korea and the surrounding metropolitan cities (Seoul, Incheon, Gyeonggi-do) were classified as pertaining to a 'capital region'; the others, as residing in a 'non-capital region.' Income levels were defined as low (up to the 30^{th} percentile), middle (40 to 70^{th} percentile), and high (80 to 100^{th} percentile) income group. The ICD-10 disease codes from Charlson's Comorbidity Index were used, which is a widely used method to adjust for the effects of comorbidities [27]. We defined the comorbidities based on the respective ICD-10 codes for each disease (Additional file 1: Table S5) with two or more hospital visits during the baseline period.

Statistical analysis

We used Cox proportional hazards regression models to determine the adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for depression, CVD, or comorbid depression and CVD in terms of dementia incidence. We followed up the participants from the index date (January 1^{st}, 2005) until December 31^{st}, 2013, or until the date of dementia onset within that period, defined as the follow-up period. Patients' death and the end of the follow-up were treated as censoring events in the analysis. During the follow-up period of up to 9 years, individuals were classified into four groups based on their exposure to depression and CVD. These groups included: individuals without depression nor CVD, those with depression alone, those with CVD alone, and those with both depression and CVD. Because a cohort design can cause an immortal-time bias, we used a time-varying Cox regression model to prevent time-related biases [28, 29]. First, we evaluated the individual aHRs and 95% CIs calculated for cases with depression and CVD with dementia risk in two separate regression models, in order to validate the disease diagnoses and assure generalizability of the study sample. Next, we examined the synergistic effect of the two exposure diseases by testing the hypothesis that there is no excess risk due to their interaction. We calculated the attributable proportion (AP) that was due to their interaction as a measure of excess risk to individuals, which could not be explained by the independent effects of each of the two

exposure conditions individually [30]. We also determined any age or sex modification effects that could result in incident dementia.

$$AP_{Interaction} = \frac{HR_{Depression\,\&\,CVD} - HR_{Depression} - HR_{CVD} + 1}{HR_{Depression\,\&\,CVD}}$$

We conducted two additional analyses. First, incident dementia was classified as AD, VD, and non-AD or non-VD according to their initial ICD-10 dementia code. The association between the exposure conditions and each subtype of dementia were examined in the adjusted models. Second, we conducted sensitivity analyses to ensure the robustness of the results using 1:1 and 1:2 propensity score matching methods. The propensity score matching method has been widely used in observational studies to reduce biases caused by different covariates characteristics among groups [31]. We estimated the propensity scores using a logistic regression to match two groups; a group without depression or CVD versus a group with at least one of depression or CVD. Matching covariates were age, sex, residential area, and income level, as well as the presence of 14 comorbidities. Each matching process was conducted based on replacement sampling. There were no significant differences in all covariates between the two groups after matching except for one comorbidity of non-metastatic solid cancer with a 1:1 match (*P*-value =0.03, Additional file 1: Table S4A and B). All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC/USA).

Results

Participant characteristics and incidence of dementia

Participant characteristics are presented in Table 1. A total of 242,237 participants were included in the analyses (77,587 [68.0%] aged over 65 years at baseline; 131,712 [54.4%] women; 140,415 [58.0%] from non-capital regions). There was a total of 7,006 (2.9%) participants who had histories of depression during the enrollment period from 2002 to 2004. There was a total of 9,680 (4.0%) participants with CVD during the same period. The demographic characteristics of the study participants and the diseases from Charlson's Comorbidity index were set as covariates (Table 1). A total of 12,735 (5.3%) participants were newly diagnosed with dementia (AD, 9,729 [76.4%]; VD, 1,306 [10.3%]; non-AD or non-VD, 1,700 [13.3%], Table S1 in Additional file 1). There were significant differences between the groups in terms of age, sex, income level, and comorbidities (*P*-value < 0.05).

When the patients were classified into the four categories as shown in Fig. 1, the number of patients with newly diagnosed dementia was 7,525 (4.0 %) in the reference group (*N* = 190,255, 78.5%), 1,336 (6.8%) in the depression alone group (*N* = 19,692, 8.1%), 3,099 (11.6%) in the CVD alone group (*N* = 26,798, 11.1%), and 775 (14.1%) in the comorbid depression and CVD group (*N* = 5,492, 2.3%).

	Study Population		With Dementia		Without Dementia	
	N	%	*N*	%	*N*	%
TOTAL	242,237	100.0	12,735	100.0	229,502	100.0
Age						
50 to 64 years	164,650	68.0	3,345	26.3	161,305	70.3
Older than 64 years	77,587	32.0	9,390	73.7	68,197	29.7
Sex						
Men	110,525	45.6	3,982	31.3	106,543	46.4
Women	131,712	54.4	8,753	68.7	122,959	53.6
Residential area [a]						
Capital region	101,822	42.0	4,403	34.6	97,419	42.5
Non-capital region	140,415	58.0	8,332	65.4	132,083	57.6
Income level [b]						
Low	65,730	27.1	3,948	31.0	61,782	26.9
Middle	80,753	33.3	3,683	28.9	77,070	33.6
High	95,754	39.5	5,104	40.1	90,650	39.5
Comorbidities						
Myocardial infarction	2,332	1.0	156	1.2	2,176	1.0
Congestive heart failure	8,904	3.7	814	6.4	8,090	3.5
Peripheral vascular disease	6,661	2.8	575	4.5	6,086	2.7
Chronic pulmonary disease	47,871	19.8	3,232	25.4	44,639	19.5
Connective tissue disorder	11,761	4.9	881	6.9	10,880	4.7
Peptic ulcer	50,849	21.0	2,984	23.4	47,865	20.9
Mild liver disease	22,914	9.5	1,022	8.0	21,892	9.5
Uncomplicated diabetes	29,720	12.3	2,209	17.4	27,511	12.0
Complicated diabetes [c]	11,717	4.8	933	7.3	10,784	4.7
Hemiplegia	1,533	0.6	151	1.2	1,382	0.6
Moderate or severe renal diseases	1,476	0.6	96	0.8	1,380	0.6

Non-metastatic solid cancer [d]	9,382	3.9	435	3.4	8,947	3.9
Moderate or severe liver diseases	754	0.3	17	0.1	737	0.3
Metastatic solid cancer	2,805	1.2	51	0.4	2,754	1.2

Table 1
Table 1 Descriptive characteristics of the study population

[a] Individuals who resided in the capital city of South Korea and surrounding metropolitan cities (Seoul, Incheon, Gyeonggi-do) were classified as pertaining to a “capital region”; the others, to a “non-capital region.”

[b] Income levels were divided into three groups according to low (up to the 30th percentile), middle (40 to 70th percentile), and high (80 to 100th percentile) incomes.

[c] Diabetes complicated with retinopathy, neuropathy, renal disease

[d] Non-metastatic solid cancer including leukemia, lymphoma, and multiple myeloma

Independent associations of depression and CVD with increased dementia risk

In an analysis of the time-varying Cox proportional hazard model, depression was found to be associated with a 122 % increased risk of dementia (HR 2.22, 95% CI 2.12-2.33, Table 2, Fig. 2A) after adjusting for age, sex, residential area, income level, and comorbid chronic diseases, compared to participants without depression. The lag-time analyses showed that the effect of depression was significant, even after considering depression as a prodrome of dementia for up to two years (Additional file 1: Table S2). The analyses with CVD showed a similar risk increase, with a higher risk hazard for dementia onset (HR 3.12, 95% CI 3.00-3.25, Table 2, Fig. 2B). Effects which were modified according to age and sex were statistically significant in both the analyses for depression and CVD patients (*P*-value for the interaction was <0.0001). The effect of depression on the development of dementia was outstanding in men and in those under the age of 65, and the same was seen for the effect of CVD.

	No Depression	Depression	No CVD	CVD
Total population	217,053 (89.6%)	25,184 (10.4%)	209,947 (86.7%)	32,290 (13.3%)
Dementia events	10,624 (4.9%)	2,111 (8.4%)	8,861 (4.2%)	3,874 (12.0%)
Person-years	1,777,860	210,499	1,734,836	253,523
Incidence (events/1,000 person-years)	5.98	10.03	5.11	15.28
Unadjusted HR in Model 1 (95% CI)	1 [Reference]	2.40 (2.29-2.51)	1 [Reference]	4.36 (4.20-4.53)
aHR in Model 2 (95% CI) [a]	1 [Reference]	2.35 (2.24-2.46)	1 [Reference]	3.26 (3.14-3.39)
aHR in Model 3 (95% CI) [b]	1 [Reference]	2.22 (2.12-2.33)	1 [Reference]	3.12 (3.00-3.25)
50 to 64 years	147,019 (89.3%)	17,631 (10.7%)	147,069 (89.3%)	17,851 (10.7%)
Dementia events	2,591 (1.8%)	754 (4.3%)	2,150 (1.5%)	1,195 (6.8%)
Person-years	1,271,789	152,534	1,276,238	148,084
Incidence (events/1,000 person-years)	2.04	4.94	1.68	8.07
Unadjusted HR in Model 1 (95% CI)	1 [Reference]	3.43 (3.16-3.72)	1 [Reference]	6.82 (6.35-7.32)
aHR in Model 2 (95% CI) [a]	1 [Reference]	3.24 (2.99-3.52)	1 [Reference]	6.84 (6.37-7.34)
aHR in Model 3 (95% CI) [b]	1 [Reference]	3.11 (2.86-3.37)	1 [Reference]	6.54 (6.09-7.03)
Older than 64 years	70,034 (90.3%)	7,553 (9.7%)	62,878 (81.0%)	14,709 (19.0%)
Dementia events	8,033 (11.5%)	1,357 (18.0%)	6,711 (10.7%)	2,679 (18.2%)
Person-years	506,071	57,965	458,597	105,439
Incidence (events/1,000 person-years)	15.87	23.41	14.63	25.41
Unadjusted HR in Model 1 (95% CI)	1 [Reference]	2.06 (1.95-2.18)	1 [Reference]	2.50 (2.39-2.62)
aHR in Model 2 (95% CI) [a]	1 [Reference]	2.04 (1.93-2.16)	1 [Reference]	2.55 (2.43-2.66)

aHR in Model 3 (95% CI) [b]	1 [Reference]	1.92 (1.81-2.04)	1 [Reference]	2.44 (2.33-2.56)
Men	102,043 (92.3%)	8,482 (7.7%)	95,637 (86.5%)	14,888 (13.5%)
Dementia events	3,388 (3.3%)	594 (7.0%)	2,531 (2.7%)	1,451 (9.6%)
Person-years	831,452	69,492	784,992	115,952
Incidence (events/1,000 person-years)	4.07	8.55	3.22	12.51
Unadjusted HR in Model 1 (95% CI)	1 [Reference]	3.13 (2.87-3.42)	1 [Reference]	5.69 (5.33-6.07)
aHR in Model 2 (95% CI) [a]	1 [Reference]	2.83 (2.60-3.09)	1 [Reference]	4.15 (3.88-4.42)
aHR in Model 3 (95% CI) [b]	1 [Reference]	2.69 (2.46-2.93)	1 [Reference]	3.99 (3.74-4.26)
Women	115,010 (87.3%)	16,702 (12.7%)	114,310 (86.8%)	17,402 (13.2%)
Dementia events	7,236 (6.3%)	1,517 (9.1%)	6,330 (5.5%)	2,423 (13.9%)
Person-years	946,408	141,007	949,844	137,571
Incidence (events/1,000 person-years)	7.65	10.76	6.66	17.61
Unadjusted HR in Model 1 (95% CI)	1 [Reference]	1.97 (1.87-2.09)	1 [Reference]	3.84 (3.67-4.03)
aHR in Model 2 (95% CI) [a]	1 [Reference]	2.19 (2.07-2.32)	1 [Reference]	2.89 (2.76-3.03)
aHR in Model 3 (95% CI) [b]	1 [Reference]	2.07 (1.96-2.19)	1 [Reference]	2.77 (2.64-2.91)

Table 2

Table 2 Cox regression analysis for the association between the exposure diseases and dementia

Abbreviations: HR hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval

[a] Adjusted for demographic characteristics (age, sex, residential area, and income level)

[b] Adjusted for demographic characteristics (age, sex, residential area, and income level), other exposure diseases, and 14 comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, connective tissue disorder, peptic ulcer, mild liver disease, uncomplicated diabetes, complicated diabetes, hemiplegia, moderate or severe renal diseases, non-metastatic solid cancer, moderate or severe liver diseases, and metastatic solid cancer)

Synergistic interaction of depression and CVD on dementia risk

Compared to the participants without depression or CVD, the depression alone group (aHR 2.35, 95% CI 2.21-2.49), CVD alone group (aHR 3.25, 95% CI 3.11-3.39), and comorbid depression and CVD group (aHR 5.02, 95% CI 4.66-5.42) were significantly associated with an increased risk of dementia (Table 3). The AP due to the interaction between depression and CVD was 0.08, which was statistically significant (*P*-value = 0.037, Table 3 and Fig. 2C). The coexistence of the two diseases added 8% to the subsequent dementia risk determined with the sum of the individual conditions. When participants were distinguished according to their dementia subtypes, the AP due to interaction with each dementia subtype were statistically insignificant. Nevertheless, there was evidence of a synergistic effect on AD in the sensitivity analyses that used 1:2 propensity score matching (AP due to interaction 0.10, 95% CI 0.01-0.20, *P*-value = 0.056, Table S3). The synergistic effect between depression and CVD changed with sex, which was significant only in women. AP due to interaction among women with comorbid depression and CVD was 0.12 (*P*-value = 0.010, Table 3). The sensitivity analyses that used 1:1 or 1:2 propensity score matching further supported the results (Additional file 1: Table S3).

	Risk of dementia, HR (95% CI)				AP due to Interaction	
	No Depression or CVD	Depression	CVD	Depression and CVD	AP (95% CI)	*P*-value[a]
Model 1[b]	1 [Reference]	2.41 (2.27-2.55)	4.51 (4.32-4.70)	6.54 (6.08-7.05)	0.10 (0.02-0.17)	0.016
Model 2[c]	1 [Reference]	2.39 (2.26-2.54)	3.33 (3.19-3.47)	5.16 (4.79-5.56)	0.09 (0.01-0.16)	0.035
Model 3[d]	**1 [Reference]**	**2.35 (2.21-2.49)**	**3.25 (3.11-3.39)**	**5.02 (4.66-5.42)**	**0.08 (0.01-0.16)**	**0.037**
Dementia subtypes[e]						
AD	1 [Reference]	2.36 (2.21-2.52)	2.77 (2.63-2.91)	4.54 (4.15-4.95)	0.09 (0.00-0.18)	0.056
VD	1 [Reference]	2.13 (1.68-2.70)	9.75 (8.64-11.02)	11.98 (9.74-14.75)	0.09 (-0.14-0.32)	0.431
Non-AD or non-VD[f]	1 [Reference]	2.37 (2.02-2.78)	2.97 (2.64-3.35)	4.55 (3.68-5.62)	0.05 (-0.18-0.28)	0.696
Age[e]						
50 to 64 years	1 [Reference]	3.46 (3.12-3.83)	6.93 (6.38-7.53)	10.10 (8.85-11.53)	0.07 (-0.07-0.21)	0.316
Older than 64 years	1 [Reference]	2.01 (1.87-2.16)	2.53 (2.41-2.66)	3.83 (3.50-4.21)	0.08 (-0.02-0.18)	0.126
Sex[e]						
Men	1 [Reference]	3.16 (2.82-3.54)	4.31 (4.01-4.64)	6.71 (5.85-7.69)	0.04 (-0.12-0.19)	0.649
Women	1 [Reference]	2.11 (1.97-2.26)	2.82 (2.67-2.97)	4.46 (4.07-4.88)	0.12 (0.03-0.21)	0.010

Table 3

Table 3 Interaction analysis for depression and CVD

Abbreviations: AP attributable proportion, *CVD* cerebrovascular disease, *AD* Alzheimer's disease, *VD* vascular dementia, *HR* hazard ratio

[a] *P* value for the test of the null hypothesis that the AP = 0

[b] Unadjusted model

[c] Adjusted for demographic characteristics (age, sex, residential area, and income level)

[d] Adjusted for demographic characteristics (age, sex, residential area, and income level) and 14 comorbidities(myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, connective tissue disorder, peptic ulcer, mild liver disease, uncomplicated diabetes, complicated diabetes, hemiplegia, moderate or severe renal diseases, non-metastatic solid cancer, moderate or severe liver diseases and metastatic solid cancer)

[e] Subgroup analyses that are based on Model 3 (adjusted for demographic characteristics and 14 comorbidities). Age or sex was not entered as a covariate in each subgroup analysis.

[f] Includes dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), and other degenerative diseases of the nervous system, which are not classified elsewhere (G31)

Discussion

In this analysis of a nationwide population-based cohort with 242,237 participants aged over 50, depression and CVD was independently associated with a more than doubled risk of subsequent dementia. The coincidence of the two illnesses modified the associated hazard for dementia in a synergistic way. After adjusting for demographic factors and comorbidities, 8% of participants' incident dementia among those with comorbid depression and CVD may be attributed to the concomitance of the two conditions. The synergistic interaction existed only in women, where 12% of the incident dementia among women with depression and CVD might be due to the concurrence of the diseases.

Our results reinforce the claim that individuals with depression or CVD are more vulnerable to subsequent dementia, with the same hazards seen in previous research that examined the association between depression [16, 22, 32, 33] or CVD [4, 7, 34, 35] with cognitive declines. We replicated prior findings with a large population-based sample, and also tested the generalizability of our results. In our sample, the synergistic interaction between depression and CVD was statistically significant after adjusting for demographical factors and chronic comorbidities. Although we cannot clarify the underlying mechanisms for the results in this study, one possible explanation is that each illness exacerbates the other condition through biological and psychosocial changes. Strokes damage patients' activities of daily living, social functioning, and cognitive function, which can lead to depression as a psychosocial reaction [14]. Vascular damages in specific brain regions that are related to mood regulation could make patients susceptible to depressive disorders [36]. Depression might affect patients' health behaviors and vascular risk factors, and could share a pathophysiology with CVD, such as HPA axis dysregulation or chronic inflammatory status [20].

Another explanation is that the synergistic effect may be related to AD pathology. The synergistic effect of depression and CVD in our study was more remarkable in women, whose population is at risk of AD [1]. Although it requires cautious interpretation, we can establish the hypothesis that the concurrence of vascular damage and AD pathology that is triggered by depression initiates clinically significant cognitive declines. Researchers suggest that chronic stress and hypercortisolemia can induce beta-amyloid accumulation, hyperphosphorylation of Tau proteins, and neurotoxicity [37]. A prior study reported that depressed patients have more beta-amyloid aggregation than healthy individuals [38]. Our findings are also in line with an animal study, which reported chronic stress resulting in increased amyloid plaques in the hippocampus of female mice only, without changes in the cerebral cortices of both male and female mice [39]. A recent clinical study on CVD and AD pathology with 218 participants found that comorbidity of CVD and amyloid plaques was associated with cognitive declines, but CVD was not associated with the rate of the beta-amyloid accumulation [40]. The synergistic interaction between depression and CVD and its relevance to AD pathology should be investigated in further research.

Our findings indicate that individuals with depression or CVD require thorough preventive approaches to avoid another illness. Although treating depressive disorder might not change the course of patients' cognitive decline [32], managing vascular risk factors and preventing CVD in individuals with depression would reduce the incidence of dementia, as well reduce personal and socioeconomic disease burdens. Women are primarily known to have a higher risk of depression, therefore, targeting this at-risk population can help dementia prevention policies work effectively.

Limitations

This study has some limitations. The NHIS-NSC database is not diagnostic data, rather health insurance claims [20]. Therefore, there is a probability that the diagnoses of the diseases of focus in this research, including dementia subtypes, are inaccurate. To make the diagnoses reliable, we set up strict operational definitions using ICD codes based on multiple hospital visits and drug prescription data. Even if using the ICD-10 code can lead to accidentally excluding patients with early or exiguous symptoms of the diseases, our results showed a prevalence similar to the actual prevalence of the conditions, and the hazard ratios of depression and CVD were equivalent to those previously reported. The identification of dementia etiologies is complicated without biopsies or autopsies of brain pathologies. We had no choice but to determine the dementia subtypes according to the initial codes of the main diagnoses for our analyses. Unfortunately, this method cannot be used to separate clinically noteworthy dementia etiologies which are not specified in the ICD-10 code, for example, "mixed dementia." Another limitation is that there was an insufficient consideration of possible confounding factors. Health behaviors, such as drinking and smoking, are known to affect depression, CVD, and dementia. They might depend on age and sex; therefore, our findings in effect modification by age and sex should be interpreted with caution. Finally, there are residual confounders, as in any observational study.

Conclusions

This nationwide, population-based cohort study demonstrates that both depression and CVD are associated with an increased dementia risk, with a synergistic interaction between them. To the best of our knowledge, this is the first study examining the coexistence effect of depression and CVD on subsequent dementia risk. Among those with comorbid depression and CVD, 8% of incident dementia was attributed to the concomitance of the two illnesses. This finding suggests that individuals with depression or CVD need approaches to prevent other conditions.

Abbreviations

AD: Alzheimer's disease

aHR: adjusted hazard ratio

AP: attributable proportion

CI: confidence interval

CVD: cerebrovascular disease

HPA: hypothalamic-pituitary-adrenal

PET: positron emission tomography

HR: hazard ratio

ICD: International Classification of Diseases

NHIS-NSC: National Health Insurance Service-National Sample Cohort

VD: Vascular dementia

Declarations

Ethics approval and consent to participate

The ethics review board of the Samsung Medical Center approved our access to the anonymized data sets used for these analyses (IRB no. 2019-03-105). All data were de-identified and kept confidential, therefore, participants' informed consent was not required.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the Korean National Health Insurance Service (NHIS), but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission from the NHIS.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Drs DK Kim and H Kim had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: YJ Jang, C Kang, SW Lim, and W Myung

Statistical analysis: C Kang, YJ Jang, and W Myung

Interpretation of data: All authors

Drafting of the manuscript: YJ Jang, C Kang

Critical revision of the manuscript for important intellectual content: H Kim and DK Kim

Study supervision: DK Kim and H Kim

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Additional information

Not applicable.

References

1. Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimers Dement. 2016;12:459-509.
2. Pouryamout L, Dams J, Wasem J, Dodel R, Neumann A. Economic evaluation of treatment options in patients with Alzheimer's disease: a systematic review of cost-effectiveness analyses. Drugs.

2012;72:789-802.
3. Cao L, Tan L, Wang HF, Jiang T, Zhu XC, Yu JT. Cerebral Microinfarcts and Dementia: A Systematic Review and Metaanalysis. Curr Alzheimer Res. 2017;14:802-8.
4. Corraini P, Henderson VW, Ording AG, Pedersen L, Horvath-Puho E, Sorensen HT. Long-Term Risk of Dementia Among Survivors of Ischemic or Hemorrhagic Stroke. Stroke. 2017;48:180-6.
5. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2011;42:2672-713.
6. Kling MA, Trojanowski JQ, Wolk DA, Lee VM, Arnold SE. Vascular disease and dementias: paradigm shifts to drive research in new directions. Alzheimers Dement. 2013;9:76-92.
7. Liu W, Wong A, Law AC, Mok VC. Cerebrovascular disease, amyloid plaques, and dementia. Stroke. 2015;46:1402-7.
8. Love S, Miners JS. Cerebrovascular disease in ageing and Alzheimer's disease. Acta Neuropathol. 2016;131:645-58.
9. Hughes TM, Craft S, Lopez OL. Review of 'the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease'. Neurodegener Dis Manag. 2015;5:121-35.
10. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat Rev Neurosci. 2017;18:419-34.
11. Gorelick PB. Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. Ann N Y Acad Sci. 2010;1207:155-62.
12. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. J Cereb Blood Flow Metab. 2016;36:172-86.
13. Villa RF, Ferrari F, Moretti A. Post-stroke depression: Mechanisms and pharmacological treatment. Pharmacol Ther. 2018;184:131-44.
14. Mijajlovic MD, Pavlovic A, Brainin M, Heiss WD, Quinn TJ, Ihle-Hansen HB, et al. Post-stroke dementia - a comprehensive review. BMC Med. 2017;15:11.
15. Kapasi A, DeCarli C, Schneider JA. Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol. 2017;134:171-86.
16. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF, 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. 2013;202:329-35.
17. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006;63:530-8.
18. Du X, Pang TY. Is Dysregulation of the HPA-Axis a Core Pathophysiology Mediating Co-Morbid Depression in Neurodegenerative Diseases? Front Psychiatry. 2015;6:32.
19. Halaris A. Inflammation-Associated Co-morbidity Between Depression and Cardiovascular Disease. Curr Top Behav Neurosci. 2017;31:45-70.

20. Zhang Y, Chen Y, Ma L. Depression and cardiovascular disease in elderly: Current understanding. J Clin Neurosci. 2018;47:1-5.
21. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB. Depression and risk of stroke morbidity and mortality: a meta-analysis and systematic review. JAMA. 2011;306:1241-9.
22. Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, et al. Vascular depression consensus report - a critical update. BMC Med. 2016;14:161.
23. van Agtmaal MJM, Houben A, Pouwer F, Stehouwer CDA, Schram MT. Association of Microvascular Dysfunction With Late-Life Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017;74:729-39.
24. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort Profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol. 2017;46:e15.
25. Katon W, Pedersen HS, Ribe AR, Fenger-Gron M, Davydow D, Waldorff FB, et al. Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study. JAMA Psychiatry. 2015;72:612-9.
26. Kim CT, Myung W, Lewis M, Lee H, Kim SE, Lee K, et al. Exposure to General Anesthesia and Risk of Dementia: A Nationwide Population-Based Cohort Study. J Alzheimers Dis. 2018;63:395-405.
27. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005;43:1130-9.
28. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087.
29. Shintani AK, Girard TD, Eden SK, Arbogast PG, Moons KG, Ely EW. Immortal time bias in critical care research: application of time-varying Cox regression for observational cohort studies. Crit Care Med. 2009;37:2939-45.
30. Li R, Chambless L. Test for additive interaction in proportional hazards models. Ann Epidemiol. 2007;17:227-36.
31. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat. 1985;39:33-8.
32. Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L. Depression as a modifiable factor to decrease the risk of dementia. Transl Psychiatry. 2017;7:e1117.
33. Byers AL, Yaffe K. Depression and risk of developing dementia. Nat Rev Neurol. 2011;7:323-31.
34. Cai W, Zhang K, Li P, Zhu L, Xu J, Yang B, et al. Dysfunction of the neurovascular unit in ischemic stroke and neurodegenerative diseases: An aging effect. Ageing Res Rev. 2017;34:77-87.
35. Goldwaser EL, Acharya NK, Sarkar A, Godsey G, Nagele RG. Breakdown of the Cerebrovasculature and Blood-Brain Barrier: A Mechanistic Link Between Diabetes Mellitus and Alzheimer's Disease. J Alzheimers Dis. 2016;54:445-56.
36. Robinson RG, Jorge RE. Post-Stroke Depression: A Review. Am J Psychiatry. 2016;173:221-31.

37. Sotiropoulos I, Silva JM, Gomes P, Sousa N, Almeida OFX. Stress and the Etiopathogenesis of Alzheimer's Disease and Depression. Adv Exp Med Biol. 2019;1184:241-57.
38. Yasuda S, Baba H, Maeshima H, Shimano T, Inoue M, Ichikawa T, et al. Serum levels and mutual correlations of amyloid beta in patients with depression. Geriatr Gerontol Int. 2020;20:125-9.
39. Devi L, Alldred MJ, Ginsberg SD, Ohno M. Sex- and brain region-specific acceleration of beta-amyloidogenesis following behavioral stress in a mouse model of Alzheimer's disease. Mol Brain. 2010;3:34.
40. Yassi N, Hilal S, Xia Y, Lim YY, Watson R, Kuijf H, et al. Influence of Comorbidity of Cerebrovascular Disease and Amyloid-beta on Alzheimer's Disease. J Alzheimers Dis. 2020;73:897-907.

Figures

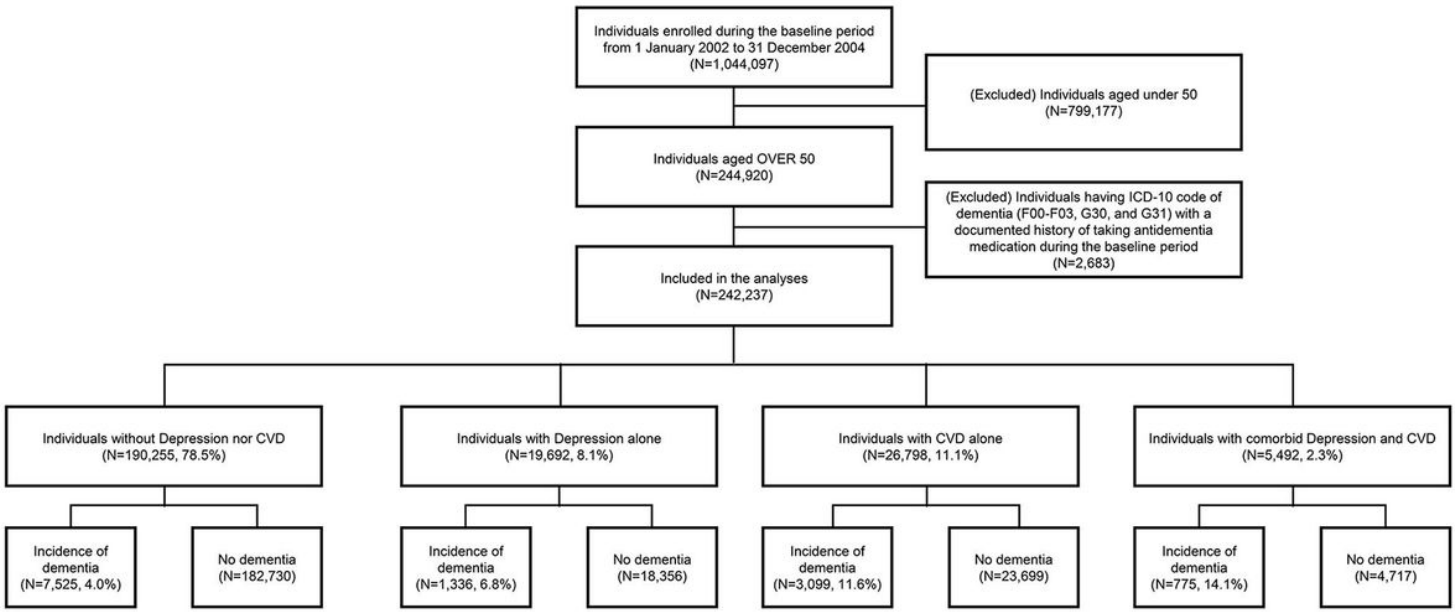

Figure 1

A flow diagram of the study population

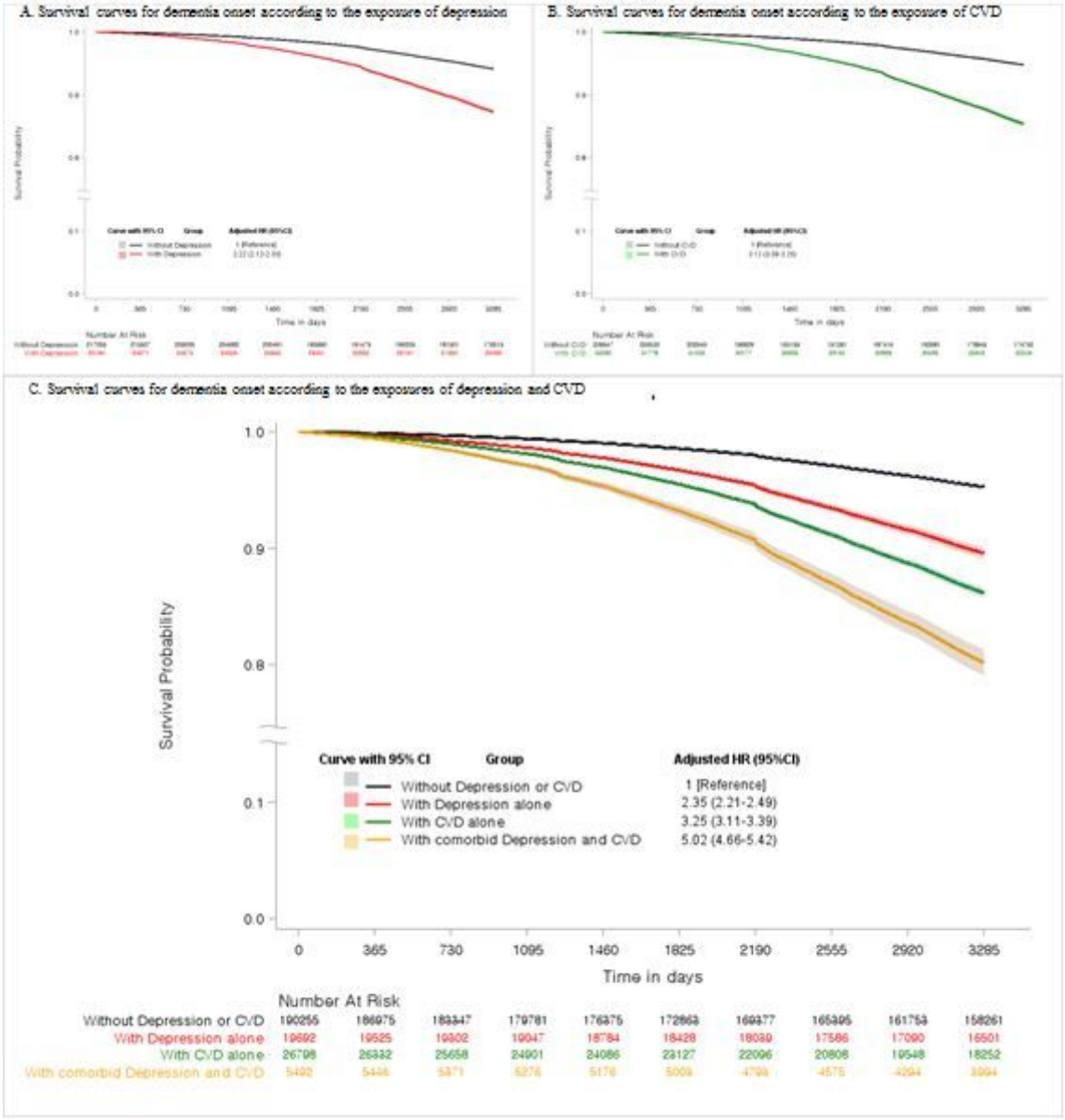

Figure 2

Survival curves for dementia onset according to the exposure diseases

Supplementary Files

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