**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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**Supplementary Material**

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| **Table S1. Observed results according to the dementia subtypes** | | | |
| **Dementia Subtype** | **Frequency** | **Proportion** | **Cumulative Frequency** |
| No dementia | 229,502 | 94.74 | 229,502 |
| Alzheimer disease | 9,729 | 4.02 | 239,231 |
| Vascular dementia | 1,306 | 0.54 | 240,537 |
| Other dementias | 1,700 | 0.70 | 242,237 |

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| **Table S2. Lag-time analysis result considering depression as a misdiagnosis or a prodrome of dementia** | | | | |
| **Lag timea** | **aHRb** | **95% CI** | | ***P*-value** |
| 1 year | 1.60 | 1.51 | 1.68 | <.0001 |
| 2 year | 1.29 | 1.21 | 1.36 | <.0001 |
| Abbreviations: *aHR*, adjusted hazard ratio; *CI*, confidence interval.  a If depression occurs between the lag time and dementia onset, it is treated as not having depression.  b All models were adjusted for demographic characteristics (age, sex, residential area, and income level), cerebrovascular disease, 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). | | | | |

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| **Table S3. Sensitivity analysis of the interactions between depression and CVD after matching\*** | | | | | | |
|  | **Risk on Dementia by exposure, HR (95% CI)** | | | | **AP due to Interaction** | |
| **1:1** | **No Depression or CVD** | **Depression** | **CVD** | **Depression and CVD** | **AP (95% CI)** | ***P* -valuea** |
| **Model 1b** | 1 [Reference] | 2.11(1.98-2.26) | 3.95(3.75-4.16) | 5.77(5.32-6.25) | 0.12(0.04-0.2) | 0.002 |
| **Model 2c** | 1 [Reference] | 2.4(2.24-2.56) | 3.46(3.29-3.65) | 5.35(4.93-5.8) | 0.09(0.01-0.17) | 0.026 |
| **Model 3d** | **1 [Reference]** | **2.42(2.26-2.59)** | **3.43(3.25-3.61)** | **5.29(4.88-5.74)** | **0.08(0-0.17)** | **0.041** |
| **Dementia Subtypese** |  |  |  |  |  |  |
| AD | 1 [Reference] | 2.43(2.26-2.62) | 2.9(2.72-3.08) | 4.77(4.34-5.24) | 0.09(0-0.19) | 0.052 |
| VD | 1 [Reference] | 2.1(1.61-2.73) | 9.95(8.41-11.76) | 12.21(9.64-15.47) | 0.10(-0.14-0.33) | 0.426 |
| Non-AD or Non-VDf | 1 [Reference] | 2.56(2.13-3.07) | 3.38(2.92-3.92) | 4.98(3.96-6.25) | 0.01(-0.24-0.25) | 0.952 |
| **Agee** |  |  |  |  |  |  |
| 50 to 64 years | 1 [Reference] | 3.75(3.3-4.27) | 7.45(6.66-8.34) | 11.1(9.53-12.92) | 0.07(-0.08-0.21) | 0.378 |
| Older than 64 years | 1 [Reference] | 2.16(1.99-2.34) | 2.68(2.53-2.85) | 4.08(3.7-4.5) | 0.06(-0.05-0.16) | 0.292 |
| **Sexe** |  |  |  |  |  |  |
| Men | 1 [Reference] | 3.44(3.03-3.92) | 4.89(4.45-5.38) | 7.62(6.56-8.86) | 0.04(-0.12-0.19) | 0.638 |
| Women | 1 [Reference] | 2.13(1.97-2.3) | 2.91(2.73-3.1) | 4.56(4.14-5.03) | 0.12(0.02-0.21) | 0.016 |
| **1:2** | **No Depression or CVD** | **Depression** | **CVD** | **Depression and CVD** | **AP (95% CI)** | ***P* -valuea** |
| **Model 1b** | 1 [Reference] | 1.92(1.81-2.04) | 3.59(3.43-3.75) | 5.22(4.84-5.63) | 0.14(0.06-0.21) | 0.000 |
| **Model 2c** | 1 [Reference] | 2.21(2.08-2.35) | 3.14(3.01-3.29) | 4.85(4.5-5.23) | 0.10(0.03-0.18) | 0.009 |
| **Model 3d** | **1 [Reference]** | **2.23(2.09-2.36)** | **3.11(2.98-3.25)** | **4.77(4.42-5.15)** | **0.09(0.01-0.17)** | **0.024** |
| **Dementia Subtypese** |  |  |  |  |  |  |
| AD | 1 [Reference] | 2.25(2.11-2.41) | 2.66(2.52-2.8) | 4.34(3.97-4.75) | 0.10(0.01-0.19) | 0.034 |
| VD | 1 [Reference] | 1.85(1.45-2.35) | 8.56(7.51-9.75) | 10.44(8.46-12.89) | 0.10(-0.13-0.33) | 0.392 |
| Non-AD or Non-VDf | 1 [Reference] | 2.28(1.94-2.69) | 2.96(2.61-3.35) | 4.36(3.53-5.4) | 0.03(-0.21-0.26) | 0.817 |
| **Agee** |  |  |  |  |  |  |
| 50 to 64 years | 1 [Reference] | 3.26(2.92-3.64) | 6.52(5.95-7.15) | 9.58(8.35-10.99) | 0.06(-0.09-0.2) | 0.427 |
| Older than 64 years | 1 [Reference] | 1.98(1.84-2.14) | 2.48(2.35-2.61) | 3.72(3.39-4.09) | 0.06(-0.03-0.16) | 0.202 |
| **Sexe** |  |  |  |  |  |  |
| Men | 1 [Reference] | 3.03(2.69-3.4) | 4.2(3.89-4.54) | 6.53(5.69-7.51) | 0.05(-0.1-0.2) | 0.542 |
| Women | 1 [Reference] | 2(1.86-2.15) | 2.69(2.55-2.85) | 4.2(3.84-4.6) | 0.12(0.03-0.21) | 0.010 |
| Abbreviations: *AP*, attributable proportion; *CVD*, cerebrovascular disease; *AD*, Alzheimer's disease; *VD*, vascular dementia; *HR*, hazard ratio.  \* A propensity score matching method with replacement was used to match a group with neither depression nor CVD versus a group with at least one of depression or CVD. All covariates described in Table 1 were used for matching.  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.that are not classified elsewhere(G31). | | | | | | |

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| **Table S4A. Descriptive characteristics of the study population after 1:1 propensity score matching** | | | | | | | |
|  | **Study Population** | | **No Depression**  **or CVD** | | **Depression**  **or CVD** | | ***P* -value** |
| ***N*** | ***%*** | ***N*** | ***%*** | ***N*** | ***%*** |
| **TOTAL** | 103,956 | 100.0 | 51,978 | 100.0 | 51,978 | 100.0 |  |
| **Age** |  |  |  |  |  |  |  |
| 50 to 64 years | 63,667 | 61.2 | 31,741 | 61.1 | 31,926 | 61.4 | 0.242 |
| Older than 64 years | 40,289 | 38.8 | 20,237 | 38.9 | 20,052 | 38.6 |  |
| **Sex** |  |  |  |  |  |  |  |
| Men | 42,507 | 40.9 | 21,231 | 40.9 | 21,276 | 40.9 | 0.781 |
| Women | 61,449 | 59.1 | 30,747 | 59.2 | 30,702 | 59.1 |  |
| **Residential area a** |  |  |  |  |  |  |  |
| Capital region | 42,503 | 40.9 | 21,308 | 41.0 | 21,195 | 40.8 | 0.480 |
| Non-capital region | 61,453 | 59.1 | 30,670 | 59.0 | 30,783 | 59.2 |  |
| **Income level b** |  |  |  |  |  |  |  |
| Low | 25,706 | 24.7 | 12,829 | 24.7 | 12,877 | 24.8 | 0.900 |
| Middle | 34,519 | 33.2 | 17,291 | 33.3 | 17,228 | 33.1 |  |
| High | 43,731 | 42.1 | 21,858 | 42.1 | 21,873 | 42.1 |  |
| **Comorbidities** |  |  |  |  |  |  |  |
| Myocardial infarction | 1,389 | 1.3 | 673 | 1.3 | 716 | 1.4 | 0.257 |
| Congestive heart failure | 5,836 | 5.6 | 2,895 | 5.6 | 2,941 | 5.7 | 0.544 |
| Peripheral vascular disease | 4,453 | 4.3 | 2,171 | 4.2 | 2,282 | 4.4 | 0.092 |
| Chronic pulmonary disease | 25,868 | 24.9 | 12,951 | 24.9 | 12,917 | 24.9 | 0.813 |
| Connective tissue disorder | 7,186 | 6.9 | 3,585 | 6.9 | 3,601 | 6.9 | 0.855 |
| Peptic ulcer | 29,825 | 28.7 | 14,922 | 28.7 | 14,903 | 28.7 | 0.902 |
| Mild liver disease | 11,936 | 11.5 | 5,941 | 11.4 | 5,995 | 11.5 | 0.606 |
| Uncomplicated diabetes | 18,041 | 17.4 | 8,995 | 17.3 | 9,046 | 17.4 | 0.682 |
| Complicated diabetes c | 7,885 | 7.6 | 3,954 | 7.6 | 3,931 | 7.6 | 0.797 |
| Hemiplegia | 2,450 | 2.4 | 1,225 | 2.4 | 1,225 | 2.4 | 1.000 |
| Moderate or severe renal diseases | 849 | 0.8 | 407 | 0.8 | 442 | 0.9 | 0.241 |
| Non-metastatic solid cancer d | 4,272 | 4.1 | 2,066 | 4.0 | 2,206 | 4.2 | 0.030 |
| Moderate or severe liver diseases | 260 | 0.3 | 128 | 0.3 | 132 | 0.3 | 0.852 |
| Metastatic solid cancer | 745 | 0.7 | 361 | 0.7 | 384 | 0.7 | 0.419 |
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| **Table S4B. Descriptive characteristics of the study population after 1:2 propensity score matching** | | | | | | | |
|  | **Study Population** | | **No Depression**  **or CVD** | | **Depression**  **or CVD** | | ***P* -value** |
| ***N*** | ***%*** | ***N*** | ***%*** | ***N*** | ***%*** |
| **TOTAL** | 155,934 | 100.0 | 103,956 | 100.0 | 51,978 | 100.0 |  |
| **Age** |  |  |  |  |  |  |  |
| 50 to 64 years | 95,475 | 61.2 | 63,549 | 61.1 | 31,926 | 61.4 | 0.268 |
| Older than 64 years | 60,459 | 38.8 | 40,407 | 38.9 | 20,052 | 38.6 |  |
| **Sex** |  |  |  |  |  |  |  |
| Men | 63,704 | 40.9 | 42,428 | 40.8 | 21,276 | 40.9 | 0.654 |
| Women | 92,230 | 59.2 | 61,528 | 59.2 | 30,702 | 59.1 |  |
| **Residential area a** |  |  |  |  |  |  |  |
| Capital Region | 63,736 | 40.9 | 42,541 | 40.9 | 21,195 | 40.8 | 0.585 |
| Non-Capital Region | 92,198 | 59.1 | 61,415 | 59.1 | 30,783 | 59.2 |  |
| **Income level b** |  |  |  |  |  |  |  |
| Low | 38,509 | 24.7 | 25,632 | 24.7 | 12,877 | 24.8 | 0.879 |
| Middle | 51,747 | 33.2 | 34,519 | 33.2 | 17,228 | 33.1 |  |
| High | 65,678 | 42.1 | 43,805 | 42.1 | 21,873 | 42.1 |  |
| **Comorbidities** |  |  |  |  |  |  |  |
| Myocardial infarction | 2,073 | 1.3 | 1,357 | 1.3 | 716 | 1.4 | 0.241 |
| Congestive heart failure | 8,823 | 5.7 | 5,882 | 5.7 | 2,941 | 5.7 | 1.000 |
| Peripheral vascular disease | 6,665 | 4.3 | 4,383 | 4.2 | 2,282 | 4.4 | 0.111 |
| Chronic pulmonary disease | 38,826 | 24.9 | 25,909 | 24.9 | 12,917 | 24.9 | 0.761 |
| Connective tissue disorder | 10,748 | 6.9 | 7,147 | 6.9 | 3,601 | 6.9 | 0.703 |
| Peptic ulcer | 44,766 | 28.7 | 29,863 | 28.7 | 14,903 | 28.7 | 0.826 |
| Mild liver disease | 17,914 | 11.5 | 11,919 | 11.5 | 5,995 | 11.5 | 0.692 |
| Uncomplicated diabetes | 26,942 | 17.3 | 17,896 | 17.2 | 9,046 | 17.4 | 0.356 |
| Complicated diabetes c | 11,802 | 7.6 | 7,871 | 7.6 | 3,931 | 7.6 | 0.960 |
| Hemiplegia | 3,675 | 2.4 | 2,450 | 2.4 | 1,225 | 2.4 | 1.000 |
| Moderate or severe renal diseases | 1,243 | 0.8 | 801 | 0.8 | 442 | 0.9 | 0.097 |
| Non-metastatic solid cancer d | 6,434 | 4.1 | 4,228 | 4.1 | 2,206 | 4.2 | 0.099 |
| Moderate or severe liver diseases | 400 | 0.3 | 268 | 0.3 | 132 | 0.3 | 0.916 |
| Metastatic solid cancer | 1,128 | 0.7 | 744 | 0.7 | 384 | 0.7 | 0.612 |
| 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, multiple myeloma | | | | | | | |

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| **Table S5. ICD-10 Code definitions of dementia, depression, CVD, and 14 other diseases from Charlson's comorbidity index** | | | | | | |
| **Condition** | **ICD-10 Code** | | | | | |
| **Exposure Diseases** |  |  |  |  |  |  |
| Depression | F32, F33 | | | | | |
| CVD | I60, I61, I62, I63, I64, I65, I66, I67, I68, I69 | | | | | |
| **Outcome disease** |  |  |  |  |  |  |
| Dementia | F00, F01, F02, F03, G30, G31 | | | | | |
| AD | F00, G30 |  |  |  |  |  |
| VD | F01 |  |  |  |  |  |
| Non-AD or non-VDa | F02, F03, G31 |  |  |  |  |  |
| **Covariates** |  |  |  |  |  |  |
| Comorbidities |  |  |  |  |  |  |
| Myocardial infarction | I21, I22, I252 | | | | | |
| Congestive heart failure | I110, I130, I132, I255, I42, I43, I50 | | | | | |
| Peripheral vascular disease | I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959 | | | | | |
| Chronic pulmonary disease | I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703 | | | | | |
| Connective tissue disorder | M05, M06, M32, M33, M34, M315, M351, M353, M360 | | | | | |
| Peptic ulcer | K25, K26, K27, K28 | | | | | |
| Mild liver disease | B18, K73, K74, K700, K701, K702, K703, K709, K713, K714, K715, K717, K760, K762, K763, K764, K768, K769, Z944 | | | | | |
| Uncomplicated diabetes | E100, E101, E106, E108, E109, E110, E111, E116, E118, E119, E120, E121, E126, E128, E129, E130, E131, E136, E138, E139, E140, E141, E146, E148, E149 | | | | | |
| Complicated diabetes b | E102, E103, E104, E105, E107, E112, E113, E114, E115, E117, E122, E123, E124, E125, E127, E132, E133, E134, E135, E137, E142, E143, E144, E145, E147 | | | | | |
| Hemiplegia | G81, G82, G041, G114, G801, G802, G830, G831, G832, G833, G834, G839 | | | | | |
| Moderate or severe renal diseases | I120, I131, N032, N033, N034, N035, N036, N037, N052, N053, N054, N055, N056, N057, N18, N19, N250, Z490, Z491, Z492, Z940, Z992 | | | | | |
| Non-metastatic solid cancer c | C0, C1, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C6, C70, C71, C72, C73, C74, C75, C76, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C95, C96, C97 | | | | | |
| Moderate or severe liver diseases | I850, I859, I864, I982, K704, K711, K721, K729, K765, K766, K767 | | | | | |
| Metastatic solid cancer | C77, C78, C79, C80 | | | | | |

Abbreviations: *AP*, attributable proportion; *CVD*, cerebrovascular disease; *AD*, Alzheimer's disease; *VD*, vascular dementia; *ICD-10*, International Classification of Diseases 10th revision.

a Includes dementia in other diseases classified elsewhere (F02), unspecified dementia (F03), and other degenerative diseases of nervous system that have not been classified elsewhere (G31).

b Diabetes complicated with retinopathy, neuropathy, renal disease

c Non-metastatic solid cancer including leukemia, lymphoma, multiple myeloma

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| **Table S6. Medications prescribed according to the respective dementia and depression ICD-10 codes** | | | | |  |  |
| **Condition** | **Name** | **Drug Code** | | | | |
| **Outcome disease** | |  |  |  |  |  |
| **Dementia** | donepezil | 148601ATB 148601ATD 148602ATB 148602ATD 148603ATB | | | | |
|  | rivastigmine | 224501ACH 224502ALQ 224503ACH 224504ACH 224505ACH 224506CPC 224507CPC 224508CPC | | | | |
|  | galantamine | 385201ATB 385202ATB 385203ACR 385203ATR 385204ACR 385204ATR 385205ACR 385205ATR | | | | |
|  | memantine | 190001ALQ 190001ATB 190001BIJ 190002ASY | | |  |  |
| **Exposure Disease** | |  |  |  |  |  |
| **Depression** | escitalopram | 474801ATB 474801ATB 474802ATB 474803ATB 474804ATB 521101ATD 521102ATD | | | | |
|  | fluoxetine | 161501ACH 161501ATB 161502ACH 161502ATB 161502ATD 161502ATR 161504ACR | | | | |
|  | fluvoxamine | 162501ATB 162502ATB | | | | |
|  | paroxetine | 209301ATB 209302ATB 209304ATR 209305ATR 209306ATR 209304ATE 09305ATE | | | | |
|  | citalopram | 428301ATB | | | | |
|  | sertraline | 227001ATB 227002ATB | | | | |
|  | Amitriptyline | 107501ATB 107502ATB 107504ATB | | | | |
|  | amoxapine | 108001ATB 108002ATB | | | | |
|  | bupropion | 428101ATB 428102ATR 428103ATR | | | | |
|  | clomipramine | 136301ACH 136302ACH | | | | |
|  | desvenlafaxine | 626401ATR 626402ATR | | | | |
|  | duloxetine | 495501ACE 495501ACH 495501ATE 495501ATB 495502ACE 495502ACH 495502ATB | | | | |
|  | imipramine | 173701ATB | | | | |
|  | milnacipran | 355801ACH 355802ACH 355803ACH | | | | |
|  | mirtazapine | 196201ATB 196201ATD 196202ATB 196202ATD 196204ATB 196204ATD | | | | |
|  | moclobemide | 196701ATB | | | | |
|  | nortriptyline | 203401ATB 203402ATB | | | | |
|  | rasagiline | 625201ATB | | | | |
|  | selegiline | 226401ATB | | | | |
|  | tandospirone | 484401ATB 484402ATB | | | | |
|  | trazodone | 242901ACH 242901ATB 242902ATB 242903ATR | | | | |
|  | venlafaxine | 247502ACR 247502ATR 247504ACR 247504ATR | | | | |
|  | vortioxetine | 628501ATB 628502ATB 628503ATB 628504ATB | | | | |