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Association of depression and psychotropic medication on cardiac-related outcomes in a nationwide community-dwelling elderly population in Taiwan

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Abstract

The objective of this study was to examine the association of depression, psychotropic medications, and mental illness with cardiovascular disease in a nationwide community-dwelling elderly population in Taiwan. A total of 5664 participants who enrolled in the Healthy Aging Longitudinal Study in Taiwan (HALST) were included in the study. Multiple logistic regression was applied to investigate the association of depression, psychotropic medication use, and mental illness, separately, with cardiovascular disease. The results suggested that cardiovascular disease was significantly associated with various definitions of depression, including: the Center for Epidemiologic Studies-Depression scale (CES-D) $\geq$ 16, self-reported, and physician-diagnosed for depression (adjusted odds ratio [AOR] = 1.51; 95% confidence interval (CI): 1.14–2.00 for CES-D; AOR = 3.29; 95% CI: 1.99–5.42 for self-reported; and AOR = 2.45; 95% CI: 1.51–3.97 for physician-diagnosed). Additionally, significant associations of cardiovascular disease with the use of antipsychotics (AOR = 2.04; 95% CI: 1.25–3.34), benzodiazepines (BZDs) (AOR = 1.84; 95% CI: 1.52–2.21), and Z-drugs (AOR = 1.41; 95% CI: 1.03–1.93), respectively, were also observed, but not the use of antidepressants. In addition, a significant association of cardiovascular disease with mental illness was found in this study (AOR = 2.33; 95% CI: 1.68–3.24). In line with previous reports, these findings provided supportive evidence that depression and/or mental illness were significantly associated with cardiovascular disease in a community-dwelling elderly population in Taiwan. Moreover, significant associations of cardiovascular disease with the use of antipsychotics, BZDs, and Z-drugs, individually, were found. Further investigation would be of importance to clarify the causal relationship of depression and/or psychotropic medications with cardiovascular disease, especially among elderly populations.

Abbreviations: AMI = acute myocardial infarction, AOR = adjusted odds ratio, ATC = Anatomical Therapeutic Chemical, BZD = benzodiazepine, CES-D = Center for Epidemiologic Studies-Depression scale, CI = confidence interval, CVD = cerebrovascular disease, DALYs = Disability-Adjusted Life-Years, HALST = Healthy Aging Longitudinal Study in Taiwan, hs-CRP = high-sensitivity C-reactive protein, MMSE = mini-mental state examination, SD = standard deviation, SSRIs = selective serotonin reuptake inhibitors, T2DM = type 2 diabetic mellitus, TCAs = tricyclic antidepressants, TG = triglyceride.

Keywords: cardiovascular disease, community, depression, older, psychotropic medication

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1. Introduction

It has been estimated that approximately 600,000 people in the United States die due to cardiovascular disease every year.[1] Cardiovascular disease is considered to be the leading cause of death in the United States and most developed countries.[1,2] In 2010, the Disability-Adjusted Life-Years (DALYs) of cardiovascular disease in the United States and most developed countries ranked first in terms of the number of years lost due to ill-health, disability, or early death.[3,4] Cardiovascular disease is a particularly important public health issue in elderly populations as the prevalence of cardiovascular disease increases with age.[5] It has been noted that a higher burden of risk factors is associated with a higher lifetime risk of death from cardiovascular disease with an index age of 55 years.[6]

Several studies have documented the relationship between depression and cardiovascular disease.[7–10] For example, in a population-based cohort study, Huang et al[7] found that participants with depression had a significantly increased risk of developing coronary events than participants without depression. In addition, Meijer et al[11] reported that depression following myocardial infarction was associated with all-cause mortality and cardiovascular events. In a longitudinal prospective cohort study, van Marwijk et al[10] provided supportive evidence that major depressive disorder was associated with an elevated risk of developing a cardiovascular event among older patients. Sun et al[12] also suggested a positive association between depressive symptoms and coronary heart disease mortality in older men in a prospective Chinese population-based study. Moreover, the results from a meta-analysis study concluded that depression is significantly associated with an increased risk of coronary heart disease.[13]

Although numerous studies have reported a positive association between depression and cardiovascular disease, a limited number of studies have concurrently examined the association of depression, psychotropic medications, and mental illness, separately, with the risk of cardiovascular disease, especially among participants at high risk of developing cardiovascular disease, for example, elderly populations or patients with hypertension. In this study, we investigated the association of depression and psychotropic medication and mental illness, individually, with cardiovascular disease in an elderly Asian study population from the Healthy Aging Longitudinal Study in Taiwan (HALST), a cross-sectional community-dwelling cohort of older adults in Taiwan.

2. Materials and methods

2.1. Study population and data collection

A total of 5664 participants were enrolled in the HALST, an ongoing population-based longitudinal study of participants aged 55 years and older that has been enrolling participants since October 2008. This study was approved by the Institutional Review Board of the National Health Research Institutes in Taiwan. Informed consent was obtained from all participants in this study. A detailed description of the HALST study, including participant recruitment and data collection protocols, was published previously.[14] This was a cross-sectional epidemiological study of a sample of older, community-dwelling study participants who were recruited from multiple areas across Taiwan, including 2 areas in the northern region, 2 in the central region, 2 in the southern region, and 1 in the east region. A total of 22,563 participants met our selection criteria. Among those, 6985

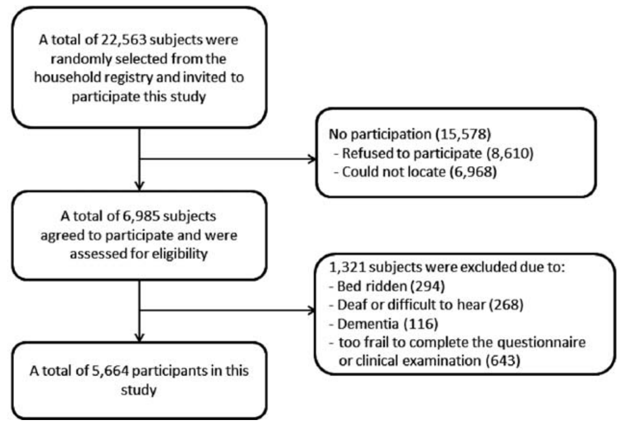

Figure 1. Flow chart of the recruitment process of the study participants.

individuals agreed to participate in the study. We further excluded 1321 potential participants due to the fact that they were too ill to complete the physical performance assessments or because they declined to complete the physical assessments. As a result, a total of 5664 participants were included in the study. The flow diagram for participant recruitment is depicted in Fig. 1. Study participants recruited for this study were those aged 55 years or older. All participants completed interviewer-administered questionnaires to obtain comprehensive information on sociodemographic status, epidemiologic data, health status, and medication utilization. In addition, detailed medication information was collected by the interviewers. In detail, interviewers took pictures of the labels on the drugs that were being taken by all participants. All participants underwent standardized physical performance assessments and laboratory examinations. A venous blood sample from each participant was collected according to standard protocol. Of note, the interviewers and laboratory personnel were all blinded to the physical performance status of the study participants.

2.2. Definition of cardiovascular disease and acute myocardial infarction

For this study, we defined study participants as patients with cardiovascular disease, either self-reported or physician-diagnosed, based on the information collected from the standardized questionnaire interview described above. Specifically, study participants were asked the following question: "Did you have the occurrence of cardiovascular disease before?" The participant could answer "yes," "no," or "unknown." Self-reported cardiovascular disease was defined as "yes" if the participant answered "yes." The participants with a self-reported event of cardiovascular disease were further asked the following: "Was the cardiovascular disease diagnosed by a physician?" Physician-diagnosed cardiovascular disease was further defined as "yes" if the participant answered "yes.". In addition, acute myocardial infarction (AMI) was also defined using a similar algorithm. Of note, we used "physician-diagnosed cardiovascular disease" as the primary outcome and "physician-diagnosed AMI" as the secondary outcome in this study.

2.3. Definition of depression, mental illness, and psychotropic medication use

2.3.1. Definition of depression.

Similarly, we defined depression status based on the information collected during the standardized questionnaire interview described above. Self-reported depression was based on the answer provided by the participants to the following question: "Did you have the occurrence of depression before?" The self-reported depression status was defined as "yes" if the participant answered "yes.". Next, if the participant answered "yes" to the following question: "Was the depression diagnosed by a physician?," then physician-diagnosed depression status was defined as "yes." In addition, depression was also assessed using a Chinese version[15] of the Center for Epidemiologic Studies-Depression scale (CES-D), which consists of 20 questions addressing 6 different depressive symptoms.[16] In addition to self-reported and physician-diagnosed depression, depression was also defined as being present if the participant's CES-D score was ≥16.

2.3.2. Definition of mental illness. Similar to the process for defining depression, we defined the status of mental illness based on the information collected during the standardized questionnaire interview described above and used similar algorithms as for the definition of depression. Specifically, the psychiatric disorders included in this study were as follows: bipolar disorder, depressive disorder, schizophrenia, panic disorder, obsessive compulsive disorder, and anxiety disorder.

2.3.3. Definition of psychotropic medication use. Five categories of psychotropic drug use (including antipsychotics, antidepressants, benzodiazepines (BZDs), Z-drugs, and mood stabilizers) were determined based on the codes in the Anatomical Therapeutic Chemical (ATC) classification system and were examined in this study. The detailed list included the following: *Antipsychotics* (ATC code: N05A): We classified antipsychotic medications into 2 groups: *first-generation antipsychotics*—chlorprothixene, chlorpromazine, chlorprothixene, clopenthixol, clothiapine, droperidol, flupentixol, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, sulpiride, thioridazine, thiothixene, and trifluoperazine; and *second-generation antipsychotics*—amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine. *Antidepressants*: Antidepressants were classified into the following 3 groups: *SSRIs* (selective serotonin reuptake inhibitors; ATC code: N06AB)—fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram; *TCAs* (tricyclic antidepressants; ATC code: N06AA)—imipramine, amitriptyline, maprotiline, doxepin, clomipramine, and dothiepin; and *other antidepressants* (ATC codes: N06AF, N06AG, and N06AX)—bupropion, venlafaxine, duloxetine, mirtazapine, and moclobemide; *BZDs*: BZDs were grouped into *hypnotics* (ATC code: N05C)—triazolam, midazolam, temazepam, estazolam, flurazepam, flunitrazpam, and lormetazepam; and *anxiolytics* (ATC code: N05B)—alprazolam, bromazepam, brotizolam, chlordiazeproxide, clobazam, clonazepam, clorazepate, cloxazolam, nitrazepam, nordazepam, oxazepam, oxazolam, diazepam, fludiazepam, lorazepam, medazepam, and nimetazepam; *Z-drugs* (ATC code: N05CF): zolpidem, zolpiclone, and zaleplon; and *mood stabilizers*: lithium (ATC code: N05AN) and 3 antiepileptic drugs, including carbamazepine (ATC code: N03AF01), lamotrigine (ATC code: N03AX09), and valproic acid (ATC code: N03AG01).

Of note, the information on psychotropic medication use among the study participants was collected by the interviewer during the personal interview.

2.4. Statistical analysis

We computed the distributions of the demographic and clinical characteristics for the study participants. The results for continuous variables such as age, mini-mental state examination (MMSE), total cholesterol, triglyceride (TG), and serum high-sensitivity C-reactive protein (hs-CRP) are presented as mean and corresponding standard deviation (SD); and the results for categorical variables such as sex (males/females), cardiovascular disease (yes/no), AMI (yes/no), smoking status (yes/no), hypertension (yes/no), type 2 diabetic mellitus (T2DM) (yes/no), bone fracture (yes/no), sleep apnea (yes/no), insomnia (yes/no), and restless leg syndrome (yes/no) are presented as counts and corresponding percentages. As described above, the primary outcome of interest in this study was physician-diagnosed cardiovascular disease, and the secondary outcome of interest was physician-diagnosed AMI.

Next, we performed logistic regression models to examine the association between cardiovascular disease and various definitions of depression, specifically self-reported, physician-diagnosed or CES-D ≥ 16, with and without adjustment of covariates. In addition, we also applied logistic regression models to investigate the association of cardiovascular disease with the effects of psychotropic medication use (including antipsychotics, antidepressants, BZDs, Z-drugs, and mood stabilizers, separately) and mental illness, with and without adjustment of covariates. The list of covariates examined in this study included: age, sex, smoking status, MMSE, hypertension, T2DM, bone fracture, sleep apnea, insomnia, restless leg syndrome, total cholesterol, and hs-CRP (a validated marker of chronic inflammation), respectively. Similar analyses were repeated to examine the association of AMI with depression, psychotropic medication use, and mental illness, separately.

Statistical significance was declared using a P-value <0.05. All of the analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

3. Results

A total of 5664 participants were included in this study. Table 1 presents the demographic and clinical characteristics of the study participants. For demographic characteristics, the mean and corresponding SD for age were 69.61 ± 8.26 years; 52.8% of participants were females and 87.2% of participants were nonsmokers. For clinical characteristics, the prevalence of cardiovascular disease, hypertension, T2DM, bone fracture, sleep apnea, insomnia, and restless leg syndrome in the study participants was 22.5%, 45.3%, 18.8%, 9.5%, 0.9%, 8.8%, and 0.2%, individually (Table 1). Of note, the mean and corresponding SD for MMSE were 26.12 ± 3.79 in this study. To avoid the potential confounding effect due to antidepressant use, 195 participants taking antidepressants were removed for the analysis when we examined the association between cardiovascular disease and various definitions of depression.

Table 2 presents the association between cardiovascular disease and various definitions of depression, including: CES-D ≥ 16, self-reported, and physician-diagnosed for depression, respectively. The results suggest that cardiovascular disease is significantly associated with depression (adjusted odds ratio [AOR] = 3.29; 95% confidence interval (CI): 1.99–5.42 for self-report; AOR = 1.51; 95% CI: 1.14–2.00 for CES-D; and AOR = 2.45; 95% CI: 1.51–3.97 for physician-diagnosed), age (AOR = 1.04; 95% CI: 1.03–1.05 for CES-D, self-report, and physician-diagnosed, individually), MMSE (AOR = 1.03; 95% CI: 1.01–1.06 for self-report; AOR = 1.03; 95% CI (CI): 1.01–1.06 for CES-D; and AOR = 1.03; 95% CI: 1.01–1.05 for physician-diagnosed), hypertension (AOR = 1.97; 95% CI:

Table 1

Demographic and clinical characteristics among HALST participants (N = 5664).

Characteristic	N or mean	% or SD
Demographic		
Age, y (mean ± SD)	69.61	8.26
Sex		
Females	2988	52.75
Males	2676	47.25
Smoking (yes)	723	12.76
Clinical		
Cardiovascular disease (yes)	1273	22.48
AMI (yes)	87	1.54
CES-D (mean ± SD)	4.03	6.02
MMSE (mean ± SD)	26.12	3.79
Depressive status (yes)*	318	5.61
Antidepressant use (yes)	195	3.44
Antipsychotic use (yes)	88	1.55
Z-drug use (yes)	248	4.38
Benzodiazepine use (yes)	853	15.06
Hypertensive disorder (yes)	2564	45.27
T2DM (yes)	1062	18.75
Bone fracture (yes)	539	9.52
Sleep apnea (yes)	51	0.92
Insomnia (yes)	495	8.84
Restless leg syndrome (yes)	10	0.18
hs-CRP, mg/dL	0.24	0.62
Total cholesterol, mg/dL	194.67	36.87
TG, mg/dL	124.11	87.64
HDL, mg/dL	52.52	13.65
LDL, mg/dL	118.05	33.08

AMI = acute myocardial infarction, CES-D = Center for Epidemiologic Studies-Depression scale, HALST = Healthy Aging Longitudinal Study in Taiwan, HDL = high-density lipoprotein, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, MMSE = mini-mental state examination, SD = standard deviation, T2DM = type 2 diabetes mellitus, TG = triglyceride.

* Depressive status is defined based on CES-D ≥ 16.

1.71–2.27 for self-report; AOR = 1.95; 95% CI: 1.69–2.24 for CES-D; and AOR = 1.94; 95% CI: 1.69–2.23 for physician-diagnosed), sleep apnea (AOR = 2.01; 95% CI: 1.06–3.79 for self-report; AOR = 2.25; 95% CI: 1.24–4.09 for CES-D; and AOR = 2.24; 95% CI: 1.24–4.08 for physician-diagnosed), and insomnia (AOR = 1.65; 95% CI: 1.30–2.09 for self-report; AOR = 1.81; 95% CI: 1.45–2.25 for CES-D; and AOR = 1.74; 95% CI: 1.40–2.17 for physician-diagnosed), respectively, no matter which algorithm we used to define depression (Table 2). In addition, we also examined the association between AMI and various definitions of depression, but no association was found, although this was mainly due to the small sample size of AMI (Supplementary Table 1, http://links.lww.com/MD/B154).

Next, we investigated the association between the use of psychotropic medications (including: antipsychotics, antidepressants, BZDs, Z-drugs, and mood stabilizers, separately) and cardiovascular disease. The results in Table 3 show significant associations of cardiovascular disease with the use of antipsychotics (AOR = 2.04; 95% CI: 1.25–3.34), BZDs (AOR = 1.84; 95% CI: 1.52–2.21), and Z-drugs (AOR = 1.41; 95% CI: 1.03–1.93), respectively, but no significant association was found for the use of antidepressants or mood stabilizers. Similarly, there was no association between AMI and the use of psychotropic medications except for antipsychotic use (Supplementary Table 2, http://links.lww.com/MD/B154).

Furthermore, we evaluated the association between cardiovascular disease and mental illness. The results in Table 4 indicate that cardiovascular disease is significantly associated with mental illness (AOR = 2.38; 95% CI: 1.73–3.27 for self-report, and AOR = 2.33; 95% CI: 1.68–3.24 for physician-diagnosed). As noted earlier, we found no association between AMI and mental illness, although this was likely due to the small sample size of AMI (Supplementary Table 3, http://links.lww.com/MD/B154).

4. Discussion

In this study sample of a community-dwelling elderly population in Taiwan we found that cardiovascular disease was significantly associated with depression and mental illness. The results were showed that cardiovascular disease was significantly associated with use of the most examined psychotropic medications, except for antidepressants. To the best of our knowledge, this is one of only a few studies to investigate the association of depression, psychotropic medication use, and mental illness, respectively,

Table 2

Association between depression and cardiovascular disease.

	Model 1*		Model 2*		Model 3*	
	AOR†	95% CI	AOR	95% CI	AOR	95% CI
Depression	**3.29**‡	(1.99–5.42)	**1.51**	(1.14–2.00)	**2.45**	(1.51–3.97)
Age	**1.04**	(1.03–1.05)	**1.04**	(1.03–1.05)	**1.04**	(1.03–1.05)
Sex	1.09	(0.93–1.27)	1.06	(0.91–1.24)	1.07	(0.92–1.25)
Smoking	0.93	(0.74–1.17)	0.89	(0.71–1.11)	0.90	(0.72–1.13)
MMSE	**1.03**	(1.01–1.06)	**1.03**	(1.01–1.06)	**1.03**	(1.01–1.05)
Hypertension	**1.97**	(1.71–2.27)	**1.95**	(1.69–2.24)	**1.94**	(1.69–2.23)
T2DM	1.06	(0.89–1.26)	1.04	(0.88–1.24)	1.06	(0.89–1.25)
Bone fracture	1.07	(0.85–1.35)	1.01	(0.81–1.27)	1.04	(0.83–1.30)
Sleep apnea	**2.01**	(1.06–3.79)	**2.25**	(1.24–4.09)	**2.24**	(1.24–4.08)
Insomnia	**1.65**	(1.30–2.09)	**1.81**	(1.45–2.25)	**1.74**	(1.40–2.17)
Restless leg syndrome	2.76	(0.61–12.55)	1.29	(0.31–5.48)	1.42	(0.33–6.19)
Total cholesterol	0.99	(0.99–1.00)	0.99	(0.99–1.00)	0.99	(0.99–1.00)
Hs-CRP	1.09	(0.97–1.22)	1.07	(0.96–1.19)	1.07	(0.96–1.19)

AOR = adjusted odds ratio, CI = confidence interval, hs-CRP = high-sensitivity C-reactive protein, MMSE = mini-mental state examination, T2DM = type 2 diabetic mellitus.

* Depression status is defined based on self-report in Model 1; depression status is defined based on CES-D ≥ 16 in Model 2; depression status is defined based on physician-diagnosed in Model 3.

† Adjusted covariates are: age, sex, smoking, MMSE, hypertension, T2DM, bone fracture, sleep apnea, insomnia, restless leg syndrome, total cholesterol, and hs-CRP.

‡ Significant result (*P* < 0.05) is in bold.

Table 3

Association between psychotropic use and cardiovascular disease.

	Unadjusted		Adjusted*	
	OR	95% CI	OR	95% CI
Antipsychotics use	**2.55**†	(1.66–3.91)	**2.04**	(1.25–3.34)
Antidepressants use	**1.64**	(1.21–2.23)	1.29	(0.91–1.81)
Benzodiazepine use	**2.34**	(2.00–2.74)	**1.84**	(1.52–2.21)
Z-drug use	**1.89**	(1.45–2.48)	**1.41**	(1.03–1.93)
Mood stabilizers use	0.69	(0.24–2.02)	0.57	(0.19–1.75)

CI = confidence interval, OR = odds ratio.
* Adjusted covariates are: age, sex, smoking, mini-mental state examination, hypertension, type 2 diabetic mellitus, bone fracture, sleep apnea, insomnia, restless leg syndrome, total cholesterol, and high-sensitivity C-reactive protein.
† Significant result ($P < 0.05$) is in bold.

with cardiovascular disease in a single study of an elderly Asian population.

Consistent with previous studies, we observed that cardiovascular disease was significantly associated with depression in an elderly study population.[7,9,17,18] For example, Penninx et al[9] found that depression was associated with an increased risk for cardiac mortality at baseline in older participants drawn from a community-based longitudinal study in Netherlands. In addition, Huang et al[7] also documented that depression was associated with an increased risk for coronary heart disease, based on a population-based study in Taiwan. In the Nord-Trøndelag Health Study, Gustad et al[17] reported that symptoms of depression were associated with increased risk for heart failure. However, the answer to the question of whether depression is a causal risk factor for cardiovascular disease remains inconclusive.[19] Although previous studies have been conducted to postulate the causal relationship between depression and cardiac disease,[20–24] further investigation is warranted.

Table 4

Association between mental illness* and cardiovascular disease.

	Model 1†		Model 2†	
	AOR‡	95% CI	AOR	95% CI
Mental illness	**2.38**§	(1.73–3.27)	**2.33**	(1.68–3.24)
Age	**1.04**	(1.03–1.05)	**1.04**	(1.03–1.05)
Sex	1.07	(0.92–1.25)	1.07	(0.92–1.25)
Smoking	0.89	(0.71–1.12)	0.90	(0.71–1.12)
MMSE	**1.03**	(1.01–1.05)	**1.03**	(1.01–1.05)
Hypertension	**1.95**	(1.69–2.24)	**1.95**	(1.69–2.24)
T2DM	1.06	(0.89–1.25)	1.05	(0.89–1.25)
Bone fracture	1.04	(0.83–1.31)	1.04	(0.83–1.31)
Sleep apnea	**2.14**	(1.17–3.91)	**2.14**	(1.17–3.90)
Insomnia	**1.63**	(1.30–2.04)	**1.64**	(1.31–2.06)
Restless leg syndrome	1.37	(0.32–5.90)	1.37	(0.32–5.89)
Total cholesterol	0.99	(0.99–1.00)	1.00	(0.99–1.01)
Hs-CRP	1.07	(0.96–1.20)	1.07	(0.96–1.20)

AOR = adjusted odds ratio, CI = confidence interval, hs-CRP = high-sensitivity C-reactive protein, MMSE = mini-mental state examination, T2DM = type 2 diabetic mellitus.
* The mental illness included in this study was listed as follows: bipolar disorder, depressive disorder, schizophrenia, panic disorder, obsessive compulsive disorder, and anxiety disorder.
† Mental illness is defined based on self-report in Model 1; mental illness is defined based on physician-diagnosed in Model 2.
‡ Adjusted covariates are: age, sex, smoking, MMSE, hypertension, T2DM, bone fracture, sleep apnea, insomnia, restless leg syndrome, total cholesterol, and hs-CRP.
§ Significant result ($P < 0.05$) is in bold.

In addition to depression, our findings indicated that cardiovascular disease was significantly associated with mental illness. In fact, several studies have suggested that psychiatry disorders are related to cardiovascular disease.[25–28] For instance, Harter et al[28] showed that anxiety disorder increased by 4.6-fold the risk of cardiac disorders. Vogelzangs et al[27] reported a 2.7-fold increase risk of coronary heart disease in participants with depressive and anxiety disorders. Furthermore, Chalmers et al[26] indicated that reductions in heart rate variability might be one of the possible mechanisms linking anxiety disorders to cardiovascular disease. It also has been previously reported that elevated risk for cerebrovascular disease (CVD) and CVD-related deaths have been observed in patients with schizophrenia.[25] It is likely that schizophrenia and CVD might have shared not only common risk factors such as elevated prevalence of metabolic syndrome, unhealthy life pattern, and tobacco smoking, but also some underlying pathophysiological mechanisms such as overlapping gene associations, hypothalamic–pituitary–adrenal axis alterations, and inflammatory mechanisms.[29–31]

In this study, we found that insomnia and sleep apnea increased the risk of cardiovascular disease. In a meta-analysis study, insomnia was significantly associated with increased risk of cardiovascular outcomes and mortality after adjusting for established cardiovascular risk factors.[32] Additionally, previous studies have also provided evidence that prevalent obstructive sleep apnea has been associated with increased carotid intima-media thickness and plaque, indicating increased risk of cardiovascular disease.[33,34] As such, it would be of interest to further investigate the relationship of insomnia and/or sleep apnea with cardiovascular disease.

Of note, this study focused on a community-dwelling elderly population. The prevalence of self-reported and physician-diagnosed depression in the study population was 1.5% and 0.92%, respectively; in addition, we found that 5.6% of the study participants had a CES-D $\geq$ 16. However, the observed prevalence of depression was lower than what has been reported among other community-dwelling elderly populations, specifically, 9.6% in the United States, 4.1% in Sweden, and 12.9% in Japan.[35–38] Since individuals who could not complete the physical performance assessments or who declined the physical assessments were excluded from the study, it was likely that the study population was relative healthy, which may have led to the lower observed prevalence of depression than what has been reported in other studies. As such, we also assessed the relationship between psychotropic medication use and cardiovascular disease; we found that the use of antipsychotics, Z-drugs, and BZDs, respectively, was positively associated with cardiovascular disease. Numerous studies have demonstrated an association between antipsychotic use and increased risk of cardiovascular disease.[14,39,40] However, in addition to antipsychotics, we also found a positive association between the use of BZDs and/or Z-drugs and cardiovascular disease, though we acknowledge that this was possibly due to confounding by indication since BZDs and Z-drugs have been commonly administered to treat participants with sleep disorders such as insomnia and sleep apnea.

There are several limitations of the present study. First, because this was a cross-sectional study our findings could not be used to determine a causal relationship between depression and/or psychotropic medication use and cardiovascular disease in this study population. Second, the information that was gathered on the presence of cardiovascular disease such as severity and duration, and for depression and mental illness were collected based on participant report. The accuracy of this collected information might be a main concern since the study participants were aged 55 years or older. Thus, we included MMSE, a measurement of cognitive status, in the models to help ensure the accuracy of the observed results, and to control for the confounding effect of cognitive function. In addition, after taking into account the use of cardiac medications, we repeated the analyses and found comparable results to those presented in Table 2 (Supplementary Table 4, http://links.lww.com/MD/B154). Third, although we included potentially important confounding factors and adjusted for those factors in the analyses, it is likely that the observed association might be still be partially explained by residual confounding due to unmeasured factors such as exercise, daily activity, and diet. Fourth, cardiovascular disease is considered to be a heterogeneous disease. In this study, we attempted to investigate the association of depression, psychotropic medication use, and mental illness with AMI. However, due to the constraints of a small sample size, we did not observe any statistically significant results when examining these associations. As such, further investigation of the subphenotypes of cardiovascular disease would be merited when the sample size allows.

In summary, our results suggested that depression and/or mental illness was significantly associated with cardiovascular disease in an elderly population in Taiwan. Moreover, the results indicated significant associations of cardiovascular disease with the use of antipsychotics, BZDs, and Z-drugs, individually. Further investigation is needed to clarify the causal relationships between depression, psychotropic medication use, and mental illness, respectively, with cardiovascular disease, especially among participants at high risk.

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