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Clinically relevant depressive symptoms and peripheral arterial disease in elderly men and women. Results from a large cohort study in Southern China

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Abstract

Objective—Results from previous epidemiological studies on the relationship between depression and peripheral arterial diseases were mixed. Therefore, a study was conducted to investigate this relationship in a large Chinese elderly sample.

Methods—Cross-sectional data from the baseline examination of a large cohort study in Chinese elderly were used in this current study. A stratified convenience sample of 3985 Hong Kong men and women aged 65 to 92 were recruited from the community. Clinically relevant depressive symptoms were assessed by the use of a validated screening instrument for depression: the Chinese version of the Short Form of Geriatric Depression Scale (GDS). Peripheral arterial disease (PAD) was assessed by the ankle-brachial index (ABI), with an index of <0.9 indicating the presence of peripheral arterial disease. Multiple logistic regression was used to compare the presence of PAD in depressed and non-depressed subjects, controlling for confounding variables for the relationship.

Results—In the total subject population, more severe peripheral atherosclerosis was associated with a higher prevalence of depressive disorders. The presence of peripheral atherosclerosis was associated with an adjusted odds ratio (OR) of 1.46 (95% confidence interval = 1.01 to 2.10) of having clinically relevant depressive symptoms.

Conclusion—We showed that depressive symptoms were associated with peripheral atherosclerosis in Asian elderly after adjusting for stroke and cardiovascular diseases. Prospective studies are needed to provide conclusive evidence on the causality on the relationship between peripheral atherosclerosis and depressive symptoms.

Keywords

Ankle brachial index; Chinese; Cross Sectional Study; Elderly; Depression; Peripheral atherosclerosis

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Introduction

Depression is a significant public health problem. It is only second to hypertension as the most common chronic condition encountered in general medical practice [1]. It was postulated by 2020, it will become second only to ischemic heart disease for Disability Adjusted Life Years lost in both men and women [2].

Depression has been shown to be associated with many chronic diseases [3,4]. Among these, the association between depression and vascular diseases has been studied extensively [5–8]. Among all vascular diseases, coronary artery disease and stroke have received the most attention. On the other hand, the association between peripheral arterial disease and depression has received relatively less attention.

Although findings suggested that there was an increased risk of depressive symptoms in patients with known peripheral arterial diseases [9,10], few studies have explored this association in people with sub-clinical peripheral arterial disease. Although a recent large cross-sectional study [11] conducted in community dwelling Caucasian elderly has demonstrated a strong association between severe coronary and aortic calcifications and depression, no association between peripheral arterial diseases and depressive symptoms was found. As a result, it is difficult to know if the depressive symptoms found in those with peripheral arterial diseases are caused by the clinical symptoms associated with the disease; by the disease itself or by a common mechanism for both PAD and depressive symptoms. Moreover, few studies have been conducted in Asian countries. It is important to conduct studies in Asian populations as the high prevalence of depression in this age group in Asia is becoming a serious challenge for health care policymakers [12]. Furthermore, as psycho-social factors are important risk factors for depression and many of these differ among cultures, conducting ethnic specific studies could help us understand the impact of both psychosocial and medical factors on depressive disorders.

Cross-sectional data from a large cohort study, named Mr. and Ms. Os Hong Kong, conducted to study the risk factors for osteoporosis in Asian men and women [13,14] were used in the current study. The objective of this current study was to investigate the relationship between clinically depressive symptoms and sub-clinical peripheral arterial disease in a large sample of community dwelling Chinese elderly.

Methods

Study subjects

Four thousand Chinese men and women who were 65 years and older were recruited for a study on osteoporosis in Asians. Convenience stratified sampling was adopted in order to obtain around 33% of subjects in each of the following age groups: 65–69, 70–74, ≥75 years. Recruitment notices were placed in community centers for the elderly, and subjects were recruited from these centers during visits by the research team. Inclusion criteria were men and women over the age of 65 and who were ambulatory. Subjects were excluded if they had bilateral hip replacements and who were unable to walk independently. Informed consent was obtained from subjects on a one-to-one basis and the study was approved by the local Joint Chinese University of Hong Kong and New Territories East Cluster Clinical Research Ethics Committee. For the present analysis, 13 subjects were excluded because their ankle brachial index were larger than 1.5. Doppler ultrasound examination could not be performed on 2 subjects as the tibial artery could not be located. This resulted in a total of 3985 subjects for this current study.

Assessment of Peripheral Atherosclerosis

Pulse and ankle/arm index was calculated and was used as the assessment of peripheral atherosclerosis. Resting pulse rate was measured twice with subjects in sitting position for 30 seconds, after at least 5 minutes of rest in a quiet room. The average pulse rate was obtained. Duplicate measures of supine blood pressure in right arm and both ankles were performed using a standard mercury sphygmomanometer and an 8-MHz Doppler probe. The study coordinator placed an appropriately sized cuff over the right brachial artery and around each ankle, proximal to the malleolus. The blood pressure cuff was rapidly inflated to 30 mmHg above the audible systolic pressure and deflated over each artery slowly. Using a hand-held Doppler (Pocket Doppler Model 841-A, Parks Medical Electronics, Inc. ALOHA, OR, USA) with an 8-MHz probe, the pressure in each artery was recorded as the first audible systolic pressure. For each subject, systolic pressure was measured in the right brachial artery first, then in the right lower extremity and left lower extremity. Two measurements were performed at each site. The ABI was calculated for each leg by dividing the posterior tibial systolic pressure in each lower extremity by the upper extremity pressure. The lower ankle-arm index of the two was used to determine the extent of ischemic disease. It was used as a measure of peripheral arterial disease (PAD) in lower extremities. The current standard for diagnosing peripheral arterial disease was followed in this study which was defined as an ABI of less than 0.90. Absence of PAD was defined as an ABI equals 0.90 or higher [15]. It was shown that an ABI of less than 0.90 was 95% sensitive and 99% specific for diagnosing angiographically defined PAD [16]. Individuals with an ABI greater than 1.50 were excluded from this study as it indicated poorly compressible leg arteries [17,18].

Assessment of Depressive Symptoms

Clinically relevant depressive symptoms were assessed by the use of a validated screening instrument for depression, the Chinese version of the Short Form of the Geriatric Depression Scale (GDS). A score of 8 or more was used as a cutoff to indicate clinically relevant depressive symptoms [19,20]. The use of the short form was found to be a useful measure and screening tool for geriatric depression due to the elderly's tendency to fatigue with long questionnaire [20]. The GDS short form was found to be a highly reliable (reliability coefficient of 0.90) and valid screening device for assessing geriatric depression in Hong Kong [19]. In the study conducted by Lee et al. [19], the 8 symptom cut-point yielded 96% sensitivity and 87.5% specificity for a DSM based clinician diagnosis of depression.

Other Measurements

Subjects were interviewed using a standardized, structured questionnaire which covered the following aspects. The interviews were conducted between August 2001 and February 2004.

1. General Characteristics—Information on age, address, education levels (primary or below vs. secondary or above) were obtained.

2. Overall health and medication—Subjects were questioned about any medical conditions leading to hospital admission and/or operations. Furthermore, they were asked the presence of medical conditions that have been diagnosed by registered physicians. There were 17 medical conditions in the questionnaire, which included (1) Diabetes, (2) High thyroid, (3) Low thyroid, (4) Osteoporosis, (5) Stroke, (6) Parkinson's disease, (7) Hypertension, (8) Heart attack, coronary or myocardial infarction, (9) Angina, (10) Congestive heart Failure, (11) COPD, (12) Glaucoma, (13) Cataracts, (14) Gastrectomy, (15) Arthritis, (16) Kidney stone, and (17) Cancer. Subjects were asked to bring in all medications for identification.

3. Cigarette smoking and alcohol consumption—Cigarette smoking and alcohol consumption were based on self-report using validated methods [21]. Information on the duration and dosage of past and current use of cigarettes, cigars and pipes were obtained. Cigarette smoking was quantified and recorded as pack years. For alcohol consumption, subjects were asked to report their daily frequency of intake of alcohol and other beverages in portion sizes specified on the semi-quantitative food frequency questionnaire. They were also asked to report on how many days of the week they consumed alcohol. Drinking status was defined as never, former or current drinker. Current drinkers were defined as those who drank at least 12 drinks of beer, wine (including Chinese wine), or liquor over the previous 12 months. For estimation of total alcohol intake in grams per day, servings of specified types of alcoholic beverages were multiplied by the number of grams per serving. A standard drink was one that contained 10gms of alcohol.

4. Physical Activity—Physical activity was measured by the validated Physical Activity Scale for the Elderly Questionnaire (PASE) [22]. It measured the level of physical activity in individuals aged 65 years and older. The instrument is a self report/interview-based measure designed to capture and assess occupational, household, and leisure activities typically performed by older adults. For example, under the category of leisure activities, separate items query the amount of time individuals spend each week (a) walking, (b) in light sport and recreational activities, (c) in moderate sport and recreational activities, (d) in strenuous sport and recreational activities, and (e) exercising to increase muscular strength and endurance. Time spent participating in each activity area was multiplied by a weighted value that reflected the amount of energy expended by an older person engaged in that activity. These weighted values were then summed to yield a composite PASE score. This was adapted in Hong Kong Chinese by adding activity items which were popular in the local culture [22,23].

5. Assessment of Dementia—The Chinese Mini-Mental Status Examination (CMMSE) [24] was used as a cognitive evaluation of dementia. CMMSE is a validated Chinese version of Folstein's Mini-Mental Status Examination [25]. Score by the CMMSE is ranged from 0 to 30; a lower CMMSE score reflects more dementia-related cognitive impairment. An individual with MMSE score of 23 or less is identified as demented [26].

6. Anthropometry—Body weight was measured, with subjects wearing a light gown, by the Physician Balance Beam Scale (Healthometer, Illinois, USA). Height was measured by the Holtain Harpenden stadiometer (Holtain Ltd, Crosswell, UK).

Statistical Methods

The relationship between the presence versus absence of PAD and patient characteristics were assessed using logistic regression for categorical variables and analysis of covariance for continuous variables adjusted for age and sex. Multiple logistic regression models were used to examine the relationships between the presence versus absence of PAD and depressive symptoms using a GDS cut-off point of 8 [19]. Model variables were chosen for their known or potential confounding effects on the relationship between PAD and depressive symptoms, based on findings from literature or initial bivariate analyses with significant results ($p < 0.05$). These variables included age, sex, education level, cigarette smoking in pack years, alcohol use, body mass index, history of diabetes mellitus, myocardial infarction and stroke.

In addition to the analyses described, GDS score was treated as a continuous variable in an analysis to explore the dose-response relationship between peripheral atherosclerosis and depressive symptoms.

Results

The characteristics of the subjects who scored below a score of 8 on GDS for depression (control) and those above (depressed) were presented in Table 1. Persons with depression were more likely to be older (73.5 years of age vs. 72.4 years of age), less educated (18.7% vs 29.4% for secondary education) and more likely to be identified as demented (36.6% vs 24.1% of subjects with MMSE<24). Furthermore, they are more likely to have had cardiovascular diseases (13.3% vs. 9.5%) and strokes (6.8% vs. 4.2%). They were also more likely smoke more (12.6 pack years vs. 10.9 pack years) than the persons in the control group.

There were 272 subjects whose ABI were lower than 0.9; in other words, there were 272 subjects with PAD. Of these 272 PAD cases, 179 were women, constitutes approximately 66% of all PAD cases.

The prevalence of clinically relevant depressive symptoms in this sample was 9.3%. The relationship between depression and peripheral arterial disease was shown in Table 2. It showed that after adjustment for potential confounding variables for the relationship between peripheral arterial disease and depressive symptoms, peripheral arterial disease was associated with an adjusted odds ratio (OD) of 1.46 (95% Confidence Interval: 1.01 to 2.10, $p=0.045$) of having clinically relevant depressive symptoms.

As previous study has demonstrated gender differences in the association between depressive symptoms and cardiovascular diseases [13,27], statistical analyses were therefore performed separately in men and women (Table 3). In men, peripheral arterial disease was independently associated with an increased OR of 1.94 (95% CI: 1.07, 3.52) for having clinically relevant depressive symptoms (GDS > 8) when stroke and MI were controlled in the multiple logistic regression analysis.

On the other hand, in women, although peripheral arterial disease was associated with increased odds of being depressed, the relationship did not reach statistical significance (OR=1.21; 95% CI: 0.76, 1.93).

When the analysis was performed using the GDS score as a continuous variable, a dose-response relationship between atherosclerosis and depression was observed. Persons with more severe atherosclerosis had higher scores on the GDS: 0.1 point increase of depressive score was associated with one standard deviation decrease of ABI index.

Discussion

This study provides further information on the relationship between peripheral arterial disease and depression in a large non-Caucasian sample. It shows that subclinical peripheral arterial disease may be independently associated with clinically relevant depressive symptoms even after adjustment for cardiovascular diseases including stroke and heart diseases. Previous studies on the association between peripheral arterial disease and depressive symptoms have yielded conflicting results. In a sample of 167 men and women clinic patients, using similar assessment instruments, Arseven et al [9] was unable to find an association between depressive symptoms and ABI. In another study consisting of a larger population with 4019 men and women aged 60 years or older, Tiemier et al [11] investigated the association between depression and atherosclerosis. They studied atherosclerosis at various body locations (the common carotid intima-media thickness, plaques in the carotid arteries, the ABI and aortic atherosclerosis) and screened these individuals for depressive symptoms using a screening instrument supplemented with psychiatric diagnostic interviews.

Extra-coronary atherosclerosis (a combined measurement) was found to be associated with increased odds of having depressive disorders, although the relationship between ABI and depressive disorders alone was not significant. The lack of positive relationship in the study by Arseven et al [9] could be due to the small sample size. On the other hand, the lack of association between ABI and depressive disorders in the study by Tiemier et al [10] could be due to differences in the severity of peripheral atherosclerosis when compared to those in our study. This is supported by the fact that when extra-coronary atherosclerosis was used to study the association between depressive symptoms and peripheral atherosclerosis, the results are similar to those found in our study. There is ample evidence to support a consistent and independent association between depression and overt cardiovascular diseases [27], however, whether depressive symptoms observed are a result of the clinical symptoms such as pain or discomfort from the disease or from atherosclerosis itself is less clear. Lyness et al [28] hypothesized that cerebrovascular risk factors contributed to the pathogenesis of depression in later life and showed that the severity of initial cumulative cerebrovascular risk factors were significantly associated with depressive symptoms and diagnoses at one year. Stewart et al [29] showed that stroke was independently associated with depression even with adjustment for disablement resulting from stroke, showing that depression observed in stroke patients may not be caused purely by disability from stroke. These studies, together with our findings, suggest that the relationship between atherosclerosis and depressive symptoms is a complex one and that both depressive symptoms and atherosclerosis could be caused by a common mechanism [30,31].

The strength of our present study lies in its large sample size and the use of standardized instrument for measurement of peripheral arterial disease and clinically relevant depressive symptoms. GDS [19,20] has been shown to be a valid instrument in Chinese elderly with a high sensitivity and specificity for diagnosing depression. This makes possible misclassification for those who were depressed less likely.

On the other hand, there were several limitations in our study. Our study was limited by its cross-sectional design, where the temporal relationship between depression and peripheral arterial disease could not be shown. Moreover, as the study population consisted of a convenient volunteer sample, selection bias could be present. Although the prevalence of depressive symptoms in our study was comparable to the prevalence of depression in the community reported in the US [32], bias could still occur if depressed subjects with physical health problems including coronary disease and stroke are more likely to participate in our study than depressed persons without such physical problems.

In conclusion, our findings suggest that there is a significant relationship between sub-clinical peripheral arterial diseases and clinically relevant depressive symptoms, although the causality of the relationship awaits further research.

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Glossary

ABI	Ankle Brachial Index
GDS	Geriatric Depression Scale
MI	Myocardial Infarction
OR	Odds Ratio
PASE	Physical Activity Scale for the Elderly
PAD	Peripheral Arterial Disease

Fig. 1.
Age distribution of Male

Fig. 2.
Age distribution of Female

Fig. 3.
Age distribution of Control

Fig. 4.
Age distribution of Depressed

Table 1

Characteristics of the study subjects (n=3985)

Characteristic	Controls (N=3616)	Depressed (N=369)	Sex age adj. Odds ratio (95% CI)
Age, mean (range), year	72.4(65–98)	73.5(65–90)	1.04 (1.02, 1.06) [‡]
Sex			
Male	50.3%	45.0%	1
Female	49.7%	55.0%	1.23 (0.99, 1.53)
Education			
Primary or below	70.6%	81.3%	1
Secondary or above	29.4%	18.7%	0.59 (0.45, 0.78) [‡]
Demented (MMSE<24)	24.1%	36.6%	1.67 (1.30, 2.14) [‡]
History of stroke	4.2%	6.8%	1.69 (1.09, 2.63) [*]
History of MI	9.5%	13.3%	1.44 (1.04, 1.98) [*]
Smoking: pack-years ^a	10.9(22.9)	12.6(25.1)	1.01 (1.0003, 1.01) [*]
Current use of alcohol	13.4%	10.0%	0.83 (0.57, 1.20)
Antidepressant medication	0.6%	2.4%	3.66 (1.69, 7.96) [†]
Antihypertensive medication	43.7%	47.2%	1.13 (0.91, 1.40)
Body mass index	23.7(3.3)	23.6(3.5)	0.99 (0.96, 1.03)
Diabetes mellitus	14.1%	17.9%	1.30 (0.98, 1.73)
Peripheral arterial disease ^b	6.4%	11.1%	1.57 (1.10, 2.26) [*]
PASE	92.0(43.1)	85.4(41.5)	1.00 (0.99, 1.0002)
Cancer	4.2%	6.2%	1.50 (0.95, 2.35)

^a Calculated as: (number of cigarettes per day/20) × years.^b Defined as an ankle-brachial blood pressure index below 0.9.[‡] P<0.001,[†] P<0.01,^{*} P<0.05 vs control group by logistic regression, adjusted for age and sex.

Table 2

Relationship between Peripheral Atherosclerosis (measured by ABI) and Depression Expressed as adjusted Odds Ratio (n=3985)

Variable	Percentage (%) / Mean(SD)		Odds ratio (95% CI)	p-value
	Controls (N=3616)	Depressed (N=369)		
Peripheral arterial disease (ankle-brachial index <0.9)	6.4%	11.1%	1.46 (1.01, 2.10)	0.0450
Age	72.2(5.0)	75.9(6.3)	1.02 (0.999, 1.04)	
Sex				
Male	50.3%	45.0%	1	
Female	49.7%	55.0%	1.06 (0.81, 1.38)	
Education				
Primary or below	70.6%	81.3%	1	
Secondary or above	29.4%	18.7%	0.65 (0.48, 0.86)	
Demented (MMSE<24)	24.1%	36.6%	1.51 (1.17, 1.94)	
Smoking: pack-years	10.9(22.9)	12.6(25.1)	1.00 (0.999, 1.01)	
History of stroke	4.2%	6.8%	1.68 (1.07, 2.62)	
History of MI	9.5%	13.3%	1.42 (1.02, 1.96)	
Antidepressant medication	0.6%	2.4%	4.52 (2.02, 10.11)	

Table 3
Relationships between Peripheral Atherosclerosis and Depression Expressed as adjusted Odds Ratio in Men (n=1986) and Women (n=1999)

Variable	Male			Female		
	Percentage (%)/Mean(SD)			Percentage (%)/Mean(SD)		
	Controls (N=1820)	Depressed (N=166)	Odds ratio (95% CI)	Controls (N=1796)	Depressed (N=203)	Odds ratio (95% CI)
Peripheral arterial disease (ankle-brachial index <0.9)	4.3%	9.0%	1.94 (1.07, 3.52)	8.5%	12.8%	1.21 (0.76, 1.93)
Age	72.3(5.0)	73.0(5.4)	1.01 (0.97, 1.04)	72.4(5.3)	73.8(5.7)	1.03 (1.003, 1.06)
Education						
Primary or below	59.3%	71.1%	1	82.0%	89.7%	1
Secondary or above	40.7%	28.9%	0.63 (0.44, 0.91)	18.0%	10.3%	0.66 (0.41, 1.08)
Demented (MMSE<24)	10.6%	17.5%	1.48 (0.94, 2.33)	37.8%	52.2%	1.54 (1.13, 2.10)
Smoking: pack-years	20.5(28.6)	25.3(32.0)	1.00 (0.998, 1.01)	1.3(6.4)	2.1(8.6)	1.01 (0.99, 1.03)
History of stroke	5.3%	7.8%	1.51 (0.82, 2.78)	3.0%	5.9%	1.93 (0.998, 3.73)
History of MI	9.8%	13.3%	1.43 (0.89, 2.31)	9.2%	13.3%	1.41 (0.90, 2.20)
Antidepressant medication	0.4%	1.8%	5.30 (1.32, 21.31)	0.8%	3.0%	4.34 (1.61, 11.74)