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Original Article

Heart Disease, Other Circulatory Diseases, and Onset of Major Depression among Community Residents in Japan: Results of the World Mental Health Survey Japan 2002-2004

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We examined whether selected circulatory diseases (heart disease, stroke, diabetes and hypertension) were associated with an increased risk of major depression in the Japanese community population. Face-to-face household surveys were carried out in 7 areas, and a total of 2,436 persons participated (overall response rate: 58.4%) from 2002 to 2004. The WHO Composite International Diagnostic Interview 3.0 was used to diagnose major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, and additional interviews assessed the presence of circulatory diseases. Using data from a random subsample of the respondents (n=832), we conducted Cox proportional hazards models to calculate hazard ratios for the onset of major depression with comorbid circulatory diseases as a time-dependent covariate. Heart attack was significantly associated with the onset of major depression (hazard ratio [HR], 7.51 [95% Confidential Interval (CI), 1.36–41.45]) after adjusting for sex, birth cohort, smoking, alcohol intake, and education. Heart disease (HR, 2.12 [95% CI, 0.79–5.70]), diabetes (HR, 2.36 [95% CI, 0.42–13.34]) and hypertension (HR, 0.97 [95% CI, 0.37, 2.50]) were not significantly associated. There were no subjects who developed major depression after stroke. These results suggest that heart attack, and maybe also heart disease and diabetes, affect the onset of major depression.

Key words: heart disease, circulatory diseases, major depression, community residents, world mental health

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The World Health Organization has estimated that by the year 2020 major depression will be second only to cardiovascular disease in contributing to overall health impairment [1]. Major depression is highly prevalent around the world, with societies and economies being disadvantaged both directly and indirectly. In a primary care setting the disorder is often under-recognized and under-treated [2], although major depression could influence the treatment outcome of heart disease, diabetes, high blood pressure, and cancer [3].

Since the late 1960s, high prevalences of major depression in patients with heart disease have been documented. Rudisch and Nemeroff reported that prevalences of depression were 17–27% in patients with coronary artery disease (CAD), unstable angina, acute myocardial infarction (MI), congestive heart failure (CHF), or coronary artery bypass graft surgery [4]. The prevalence of post-MI depression was high, although it varied widely, between 10% and 87% [4–8]. Other research has shown that the prevalence of major depression in patients with ischemic heart disease (IHD) [MI, unstable angina, congestive heart failure (CHF), coronary artery bypass graft] was 2 to 3 times greater than that in the general population [9, 10]. A similar degree of association between heart disease and major depression (odds ratio, 2.5) has also been reported among the elderly in Japan [11]. Recently, the World Health Organization World Mental Health (WHO-WMH) collaborative survey found that the association between current heart disease and the 12-month prevalence of major depression was fairly consistent across 16 countries in Europe, the Americas, the Middle East, Africa, Asia and the South Pacific (pooled odds ratio, 2.1) [12]. However, this study, as well as many other studies [13], was cross-sectional and did not consider the time-order of the 2 disorders. In addition, because this study [12] used only "heart disease" as a comprehensive disease category, there may also be different associations of acute (*e.g.* heart attack) and chronic heart disease with the later onset of major depression that have yet to be documented.

Among circulatory diseases, the epidemiology for developing depression after stroke, or so-called "poststroke depression (PSD)", is well studied. Previous systematic reviews have reported that most studies consistently associated physical disability and stroke severity with major depression [14, 15], and that the prevalence of major depression among stroke patients ranges from 14–33% [15, 16], which is higher than in the general population. Diabetes has also been recognized as a risk factor for depression and major depression [17]. Among diabetic patients, the prevalence of self-reported depression has been reported as 26%, and the prevalence of diagnosed major depression was found to be 9% [18]. However, some studies have reported no association between diabetes and major depression [19, 20]. Thus, previous study findings remain inconsistent. Increased prevalence of major depression has been described in hypertensive patients, with a 3-fold higher frequency of major depression in patients treated for hypertension [21]. However, community-based studies, and in particular the more recent ones, have reported no association between hypertension and major depression [19, 20, 22, 23]. The association between stroke, diabetes, or hypertension with the later onset of major depression has yet to be studied in a community population in Japan despite the fact that the association may vary depending on the genetic disposition, prevalence of the disease, and health care system of each country.

This study examines the temporal associations between 1) selected circulatory diseases (heart attack, heart disease, stroke, diabetes, and hypertension), which were assessed by self-reporting, and 2) the later first onset of major depression, based on a retrospective assessment, in a large community-based sample in Japan using a database from the World Mental Health Japan (WMH-J) 2002–2004 survey set [24]. We applied Cox proportional hazard regression to identify the excess lifetime risk of major depression among people with these circulatory diseases compared to those without them.

Materials and Methods

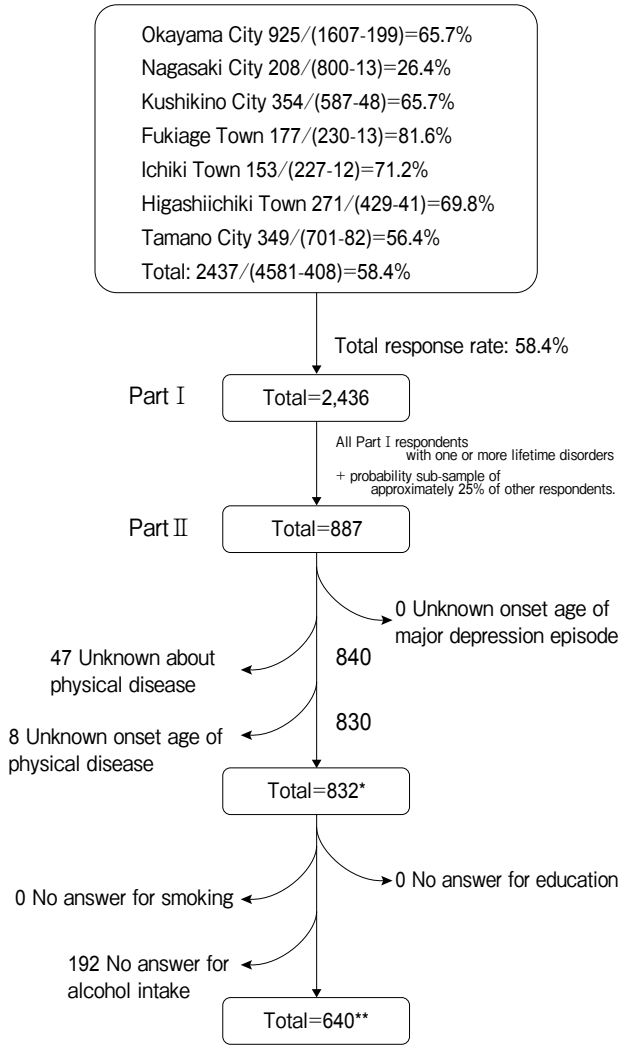
Subjects. The WMH-J is an epidemiologic survey of Japanese-speaking household residents aged 20 years and older. Seven community populations in Japan were selected as study sites for the WMH-J 2002–2004 surveys. These sites included 2 urban areas (Okayama City [population, 660,000] and Nagasaki City [population, 450,000]) and 5 rural municipalities (Kushikino City [population, 25,000],

Fukiage Town [population, 8,500], Ichiki Town [population, 7,000], and Higashiichiki Town [population, 14,000] in Kagoshima Prefecture and Tamano City [population, 70,000] in Okayama Prefecture). These sites were selected based on geographic variation, availability of site investigators, and cooperation of the local government. Mainly due to the last 2 factors, all survey sites were located in western Japan for the 2002–2004 WMH Japan surveys. The average response rate was 58.4%.

At the Okayama site, an invitation letter was sent to each subject, and then an interviewer visited the homes of the subjects to seek permission to participate in the survey. In the 2 Kagoshima prefecture sites, community volunteers first contacted the subjects in their homes to recruit them for the survey. If the subject agreed, the interviewer conducted a face-to-face interview in the home or at the survey center if the participant preferred. At the Nagasaki site, an invitation letter was sent to each subject, and an interviewer conducted face-to-face interviews with those who replied positively. When an invitation letter was mailed twice and no response was received within a month, no further effort was made to contact the individual. Written consent was obtained from each respondent at each site. The Human Subjects Committees of Okayama University (for the Okayama site), the Japan National Center of Neurology and Psychiatry (for the Kagoshima site), and Nagasaki University (for the Nagasaki site) approved the recruitment, consent, and field procedures. A more detailed account of the field procedures is given elsewhere [24].

An internal sampling strategy was used in all surveys to reduce the respondent burden by dividing the interview into 2 parts. Part Ⅰ included a core diagnostic assessment of all respondents (n = 2,436) that took an average of about 1h to administer. Part Ⅱ included questions about risk factors, consequences, other correlates, and additional disorders, including a checklist of physical diseases. To reduce the respondent burden and control study costs, Part Ⅱ was administered to only 887 of the 2,436 Part Ⅰ respondents, including all Part Ⅰ respondents with one or more lifetime disorders, plus a probability sub-sample of approximately 25% of the other respondents. The interviews with the respondents not selected for Part Ⅱ were terminated after Part Ⅰ. The data from the Part Ⅱ respondents were used in this study.

We excluded those who did not respond regarding the presence of circulatory diseases, those who had a circulatory disease but did not report the age of onset, and those who did not report the age of onset of major depression (Fig. 1). Crude analyses and analyses that adjusted for sex and age were conducted in the remaining 832 respondents for heart disease and diabetes and 831 respondents for heart attack, stroke, and hypertension. Moreover, analyses that adjusted for sex, age, smoking, and alcohol intake (and education) were conducted in 640 respondents (639 respon-



* 831 for heart attack, stroke, and hypertension due to one missing response.
** 639 for heart attack, stroke, and hypertension due to one missing response.

Fig. 1 Exclusion criteria of respondents.

dents for heart attack, stroke, and hypertension), after further excluding those (n = 192) who did not report alcohol intake.

Measures. Version 3.0 of the World Health Organization Composite International Diagnostic Interview (WMH-CIDI 3.0) [25], a fully structured and lay-administered diagnostic interview designed to be administered by trained interviewers who are not clinicians, was used to collect information on lifetime experience with and age of onset for chronic physical conditions and major depression. The WHO-CIDI 3.0 generates both the International Classification of Diseases, Tenth Revision (ICD-10) (World Health Organization, 1993), and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) diagnoses. DSM-IV criteria were used in the current report.

Circulatory disease. In a series of questions about chronic physical conditions adapted from the U.S. Health Interview Survey (National Center for Health Statistics, 1994), respondents were asked about the presence of selected chronic conditions. Respondents were asked if they had medication/treatment for or were told by a doctor or other health professional that they had any of the following chronic conditions: heart attack, heart disease, stroke, hypertension, or diabetes (or high blood sugar). There were some overlapping responses between heart attack and heart disease, since we presented the respondents with a list of these diseases/conditions without any explanation of their definitions. It is supposed that the respondents understood "heart attack" to mean a painful sudden attack including MI or angina, distinguishing it from non-attack asymptomatic heart diseases such as chronic ischemic heart disease, cardiomyopathy, and arrythmia. Prior research suggests that self-reports of serious diseases like heart disease and diabetes have acceptable validity [26–29]. Kriegsman and colleagues reported strong agreement between the medical records of general practitioners and interview-based self-reported heart disease, with a kappa of 0.64 for ischemic heart disease, which is similar to the agreement found for diabetes (0.74) and asthma (0.58). Earlier studies have reported similar levels of agreement for myocardial infarction and coronary heart disease [27, 30].

Major depression. The WHO-CIDI 3.0 generates diagnoses of major depression according to DSM-IV criteria. Organic exclusion rules and hierarchy rules were used, and the diagnosis was made with hierarchy. Retrospective age of onset (AOO) reports were obtained from the WHO-CIDI 3.0 using a series of questions [25].

Other covariates. Predictor variables included birth cohort (defined by age at interview: 20–34, 35–49, 50–64, and 65+), sex, and education (student versus non-student, with 0–11 [middle school or less], 12 [high school], 13–15 [some college], and 16+ [college or higher] years of education). At the interview, smoking status was coded as "smoker", "ex-smoker", and "non-smoker". Drinking habits were classified into four categories according to the frequency of drinking alcohol in the past 12 months: "More than 3 days a week", "1–2 days a week", "1–3 days a month", and "Less than once a month".

Statistical analyses. All analyses were performed using survey procedures in either SAS version 9.1.3 (SAS Institute Inc, Cary, NC, USA) or SAS-callable SUDAAN version 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA) to account for the complex survey design of the WMHJ. The associations between circulatory diseases and major depressive disorder (MDD) were examined as follows. First, we examined the cross-sectional association of lifetime comorbidities between circulatory diseases and MDD using logistic regression analysis adjusted for sex, age-cohort, smoking, drinking and education [31]. Next, temporal priorities between circulatory diseases and MDD were calculated using retrospective AOO. Third, to clarify the temporal effect of prior circulatory disorders on the succeeding onset of major depression, we used Cox proportional hazards models to calculate the hazard ratios (HRs) for the onset of major depression with co-morbid circulatory diseases as the time-dependent covariate adjusted for sex, age-cohort, smoking, drinking and education. In this proportional hazard analysis, in order to obtain a conservative estimate it was assumed that the circulatory diseases came after major depression if the 2 disorders had the same age of onset. Statistical significance was evaluated using 2-sided, design-based $p < 0.05$-level tests.

Results

Characteristics of respondents. The respondents included 354 (39.9%) men and 533 (60.1%) women, with an average age of 52.3 years. As for education level, 26.9% had graduated middle school, 35.9 % high school, and 37.2% university or another institute of higher education. As for smoking status, current smokers comprised 24.8% of respondents, ex-smokers 20.7%, and never-smokers 54.5%; as for drinking, 42.4% drank alcohol "more than 3 days a week", 12.4% "1–2 days a week", 14.9% "1–3 days a month", 30.2% "less than once a month", and 0.2% "I don't know". The lifetime prevalences for heart attack, heart disease, stroke, diabetes, and hypertension were 3.2%, 6.6%, 1.5%, 6.9%, and 18.8%, respectively. Diabetes was more prevalent among men than women ($p < 0.05$). All circulatory diseases were more prevalent among respondents aged 50 years old or over.

Lifetime prevalence of major depression among those with circulatory disease. The cross-sectional association between the lifetime prevalences of any circulatory disease and of major depression was not significant, while heart disease, heart attack, and diabetes were associated with a slightly higher risk of major depression; hypertension was associated with a slightly lower risk (Table 1). The results were unchanged after adjusting for sex, age, education, smoking, and alcohol intake.

Temporal ordering of age of onset of circulatory disease and major depression. Among respondents, 60–67% had heart disease, heart attack or hypertension before the onset of major depression (Table 2). Major depression was more likely to occur before stroke and diabetes.

Effects of temporally primary circulatory disease on first onset of major depression. In the Cox proportional hazard analyses used to examine the effect of primary circulatory disease on the suc-

Table 1 Lifetime prevalences of major depression among WMHJ respondents with lifetime circulatory disease

Disorders ‡	Circulatory disease +			Circulatory disease −		
	Major depression		total	Major depression		total
	+	−		+	−	
Heart attack	6	20	26	143	662	805
Heart disease	10	45	55	140	637	777
Stroke	2	8	10	147	674	821
Hypertension	21	136	157	129	545	674
Diabetes or high blood sugar	7	19	26	143	663	806

Crude		Sex and age adjusted		Sex, age, smoking, and alcohol intake adjusted		Sex, age, smoking, alcohol intake, and education adjusted	
OR	(95% CI) †	OR	(95% CI) †	OR	(95% CI) †	OR	(95% CI) †
1.51	(0.46–4.99)	1.90	(0.53–6.82)	2.28	(0.51–10.07)	1.67	(0.23–12.05)
1.11	(0.48–2.55)	1.62	(0.69–3.83)	1.71	(0.62– 4.76)	2.39	(0.83– 6.86)
1.03	(0.20–5.34)	1.51	(0.30–7.51)	2.10	(0.27–16.25)	2.99	(0.35–25.31)
0.52	(0.29–0.92)	0.67	(0.36–1.25)	0.76	(0.37– 1.56)	0.77	(0.36– 1.65)
1.57	(0.59–4.21)	1.80	(0.64–5.05)	2.00	(0.59– 6.81)	2.15	(0.62– 7.49)

*Significant at the 0.05 level.

† OR columns report odds ratios between lifetime circulatory disease and mood disorders.

‡ Number of total respondents were 832 for heart disease and diabetes or high blood sugar; 831 for heart attack, stroke, and hypertension (due to one missing response).

Table 2 Temporal ordering of age of onset of circulatory disease and major depression among WMHJ respondents with a history of both disorders

	Major depression	
	n	%
Heart attack		
Heart attack temporally primary	3	60.0
Major depression temporally primary	2	40.0
Same-year onset of both disorders	0	0.0
Heart disease		
Heart disease temporally primary	6	66.7
Major depression temporally primary	3	33.3
Same-year onset of both disorders	0	0.0
Stroke		
Stroke temporally primary	0	0.0
Major depression temporally primary	2	100.0
Same-year onset of both disorders	0	0.0
Hypertension		
Hypertension temporally primary	12	60.0
Major depression temporally primary	7	35.0
Same-year onset of both disorders	1	5.0
Diabetes or high blood sugar		
Diabetes temporally primary	2	28.6
Major depression temporally primary	4	57.1
Same-year onset of both disorders	1	14.3

ceeding onset of major depression while considering the temporal relationship (Table 3), heart attack was significantly and positively associated with major depression, with an HR of 6.41 (95% CI: 1.71–24.03). The association was still significant [HR, 7.51 (95% CI, 1.36–41.45) after adjusting for sex, age, education, smoking, and alcohol intake. Heart disease and diabetes were associated with a slightly higher risk of major depression, while the association was not significant. We could not calculate the HR for the association of major depression with stroke because no cases of major depression occurred after the onset of stroke in this study. Hypertension was not associated with major depression.

Discussion

In our analysis considering the temporal order of the 2 diseases, heart attack was strongly associated with the risk of the later onset of major depression in a community population in Japan. The presence of heart disease was also associated with about a two-fold higher risk of major depression, although the associa-

Table 3 Effects of temporally primary circulatory disease in predicting the first onset of a major depression episode

Circulatory disease	Major depression episode				
	% †	Crude		Sex and age adjusted	
		Hazard ratio	95% CI	Hazard ratio	95% CI
Heart attack	2.60	6.41*	(1.71–24.03)	4.22*	(1.04–17.09)
Heart disease	4.37	1.92	(0.73– 5.02)	1.9	(0.78–4.58)
Stroke	–	0.0	NC ‡	0.0	NC
Hypertension	6.71	1.17	(0.54– 2.53)	0.95	(0.44–2.05)
Diabetes or high blood sugar	1.69	2.07	(0.39–11.09)	1.49	(0.27–8.13)

Major depression episode			
Sex, age, smoking, and slcohol intake adjusted		Sex, age, smoking, alcohol intake, and education adjusted	
Hazard ratio	95% CI	Hazard ratio	95% CI
8.08*	(1.87–34.90)	7.51*	(1.36–41.45)
1.65	(0.56– 4.85)	2.12	(0.79– 5.70)
0.0	NC	0.0	NC
1.02	(0.41– 2.50)	0.97	(0.37– 2.50)
2.03	(0.36–11.37)	2.36	(0.42–13.34)

*Significant at the 0.05 level.
† Percentage columns report the prevalences of current circulatory disease in the year of onset of the mood disorder.
‡ Not computable.

tion was not significant. This result is consistent with previous findings of a positive association between heart disease and major depression [4–8]. While heart attack was associated with a statistically significantly increased risk of depression, heart disease was associated with a moderate increase in the risk of major depression (two-fold) in our study; these results are similar to the relative risks reported in previous studies of Western countries [4], Japan [11], and global populations [12]. Although the mechanisms underlying the link between depression and cardiovascular events in patients with CAD remain unclear [32], they are partially explained by the psychological and pathophysiological effects of heart disease on mood [4]. In addition, heart attacks (cardiac infarction, angina, and fatal arrhythmia), unlike asymptomatic chronic heart disease, are usually accompanied by extreme pain and fatality risk (and possibly fear of death), both of which could have psychologically traumatic impacts. These differences in the severity of the experienced symptoms and the perceived fatality risk may be one reason why heart attack was more strongly associated with a risk of major depression than heart disease. However, because we classified these circulatory diseases based on self-reporting by the respondents, the distinction between heart attack and heart disease was not fully clear in this study. This distinction and its effect on the association with major depression needs to be further investigated.

While we found a cross-sectional, moderate association between lifetime prevalences of stroke and major depression, we could not estimate the hazard risk of a succeeding major depression in association with stroke because there were no cases of major depression after stroke. This is attributable to the small number of stroke cases in our study, and is also due to the exclusion rule of organic causes of major depression in the DSM-IV, which we applied in our study. Another possible explanation is that people who have experienced a stroke may be more likely to have impaired cognitive functions and thus did not participate in the study. There is plenty of evidence linking MRI-defined vascular brain pathology with depression [33, 34]. Since we assessed the experience of stroke by self-reporting, the present finding does not exclude the possible association between asymptomatic cerebrovascular disease and MDD.

In a previous meta-analysis, diabetes was reported to double the risk of major depression [18]. We also found a non-significant, but twice as high, risk of major depression among those who had diabetes or high blood sugar, which is consistent with previous research. Major depression may occur secondary to the hardships of developing complications of diabetes, the restriction of daily activities due to the treatment of diabetes, or diabetes-related impairments in neurohormonal or neurotransmitter function [35, 36]. Although the association was not significant, our study supports the previous findings.

We found no increased risk of major depression associated with hypertension. This finding is consistent with previous findings that hypertension did not increase the risk of depression [19, 20, 22, 23]. While research has shown a positive association between hypertension and major depression among psychiatric outpatients [21], this association is not easily comparable with research findings from community samples because individuals with both hypertension and major depression may be more likely to visit or be referred to a psychiatric clinic than are those who have only major depression. Hypertension usually causes less severe impairment in daily life than heart disease or diabetes [37]. In addition, the early stages of hypertension are associated with less of a degree of atherosclerosis compared to heart disease and diabetes. Thus, while in the past, widely used medications for hypertension, such as Reserpine, were well-known to cause depression [38], such medications are no longer the primary choice for the treatment of hypertension. Thus, hypertension itself may not be strongly associated with the risk of succeeding major depression.

Implications of the findings. Our study suggests that non-psychiatrist physicians need to consider the possible occurrence of major depression among patients who have suffered a heart attack, and maybe also among those with heart disease or diabetes. Major depression itself greatly affects the quality of life of such patients. In addition, patients with comorbid major depression are reported to have lower rates of treatment adherence and higher rates of adverse health behaviors such as sedentary lifestyle and smoking [39–41]. Recent studies suggest that such patients have significantly higher use of medical services and significantly higher medical costs than those without depressive conditions [42–45]. Thus, when

physicians first see a patient who has had a heart attack and follow such a patient for the long term, they should screen for major depression and monitor any depressive symptoms in order to identify major depression, which would allow them to manage such patients more appropriately.

Limitations. The limitations of this research include the problem of correctly ascertaining the medical history of the selected circulatory diseases based only on self-reports, even though prior research has shown that this method has acceptable validity. Nonetheless, the effects of physical disease on major depression as obtained by self-reporting, as in this study, are likely to be underestimated because of the erosion of cognitive function or a paucity of effort to remember one's history of disease in participants with major depression. Moreover, the severity of the circulatory diseases was not assessed in this study. People with a history of major depression might have been less likely to participate in the study, and in particular, those with a history of stroke causing serious impairment might not have been recruited, resulting in the further underestimation of the association. Further, because the survey excluded those who were institutionalized, and the sampling was done in several rural and urban areas, but not in metropolitan areas, the results did not reflect the features of metropolitan areas. Finally, although age, sex, drinking and smoking habits, and education were adjusted for as confounders, we assessed smoking and drinking habits at the time of the interview, and did not examine the lifetime history of these health-related habits. The number of cigarettes smoked and the duration of smoking, or the amount of drinking, were not considered when making the adjustment. These possible confounding variables should be considered in future research.

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