Chapter

Prevalence and Comorbidity of Anxiety and Depressive Disorders in Studies of PRIME-MD and PHQ (Patient Health Questionnaire) in Japan

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Abstract

We examine two studies on the prevalence and comorbidity of anxiety and depressive disorders in Japanese patients in primary care settings. The PRIME-MD study (Primary Care Evaluation of Mental Disorders) in Japan was conducted in seven primary care sites. The sample group included 601 adult patients (249 males, 352 females, mean age = 58.9 years, SD = 16.5). Of the 12.5% of patients diagnosed with mood disorders, 5.0% (n = 29) were major depressive disorder, and 6.7% (n = 40) were minor depressive disorder. The odds ratio for co-occurrence of major depressive disorder with generalized anxiety disorders and major depressive disorder with anxiety disorders (NOS) was 11.5 (95% CI: 2.17–18.45) and 8.00 (95% CI: 3.19–20.07), respectively. The PHQ (Patient Health Questionnaire) study in Japan was conducted in eleven primary care sites. A total of 1409 adult patients (611 males, 797 females; mean age: 56.2 years, SD: ±20.4) completed the PHQ in full. The prevalence of diagnosis of any mood disorder or any anxiety disorder was 25.0%. Of the 15.8% of patients diagnosed with mood disorders, 5.3% were for major depression and 8.4% for other depressive disorders. The odds ratio for co-occurrence of major depressive disorder with other anxiety disorders was 30.4 (95% CI: 13.19–70.28).

Keywords: anxiety, depression, comorbidity, PRIME-MD, PHQ

1. Introduction

Numerous epidemiological studies in Western countries have shown that anxiety and depressive disorders frequently occur together in [1–4]. Especially, comorbidity of anxiety and depressive disorders has been confirmed in patients presenting in primary care settings [3, 4].

The outcome of co-occurrence of anxiety and depressive disorders is more negative than each single occurrence. According to findings of a large cohort study in the Netherlands, clinically, comorbidity is associated with a greater severity of symptoms, an increased risk of suicide, a more reduced quality of life, and a lower level of functioning [2].

Despite the availability of studies and data examining anxiety and depressive disorders in patients in primary care settings in other countries, such studies are few in Japan. Consequently, recognition of the comorbidity of anxiety and depressive disorders in such patients in Japan remains a major clinical problem. With that issue in mind, here we examine two studies on the comorbidity of anxiety and depressive disorders in Japanese patients in primary care detected by PRIME-MD (Primary Care Evaluation of Mental Disorders) [5, 6] and the PHQ (Patient Health Questionnaire) [7].

2. The PRIME-MD Study in Japan

2.1 Objective

To define the prevalence and comorbidity of anxiety disorders and depressive disorders in primary care patients in Japan.

2.2 Materials and Methods

The PRIME-MD [5] was the first instrument designed for use in primary care as diagnostic criteria based on the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM–III-R) [8], and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM–IV) [9]. It is used in clinical settings and has been widely used in clinical research [10–12].

PRIME-MD is a two-step instrument consisting of a self-administered patient questionnaire and a structured clinical interview administered by the physician. The first step is a brief screening instrument in which the patient is required to complete answers in full. A structured interview is subsequently conducted if the result of the patient's screening suggests the presence of a psychiatric diagnosis, which allows for a DSM-IV diagnosis to be assigned if appropriate.

PRIME-MD was used to determine the presence of DSM-IV in the present study, which was conducted from 1998 to 1999. The sample group included 601 adult patients (249 males, 352 females, mean age = 58.9 years, SD = 16.5), who were selected randomly from seven primary care settings and assessed by twelve primary care physicians. Study protocol was approved by the Ethics Committee at the Niigata City General Hospital and the other participating institutions in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki).

2.3 Results

The percentage of patients with no psychiatric diagnosis was 61.3%, while those with a type of somatoform disorder was 15.5%, a markedly high rate. 12.5% of patients were diagnosed with mood disorders, 8.5% with anxiety disorders, and 2.2% with alcohol use (**Figures 1** and **2**).

We compared the results of our PRIME-MD study in Japan with a PRIME-MD study conducted in the USA [5]. The prevalence of any mood disorders in Japan is lower than that in the USA. In particular, the rate of major depression is far

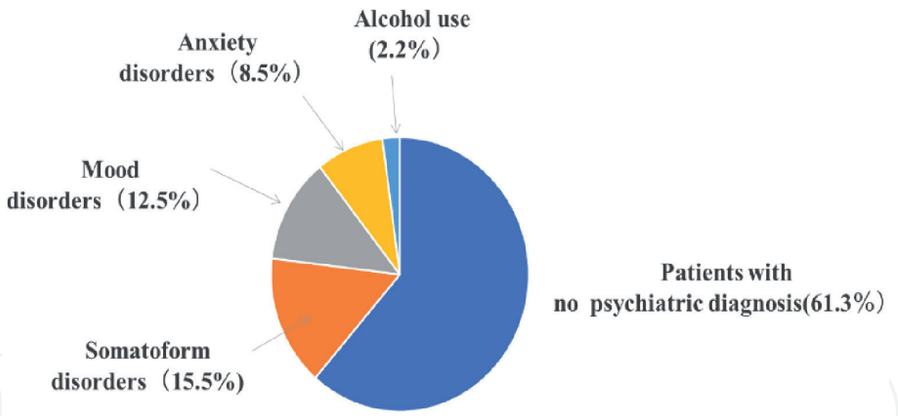

Figure 1.
Prevalence of Mental Disorders Detected by PRIME-MD in Primary Care Patients in Japan (n = 601).

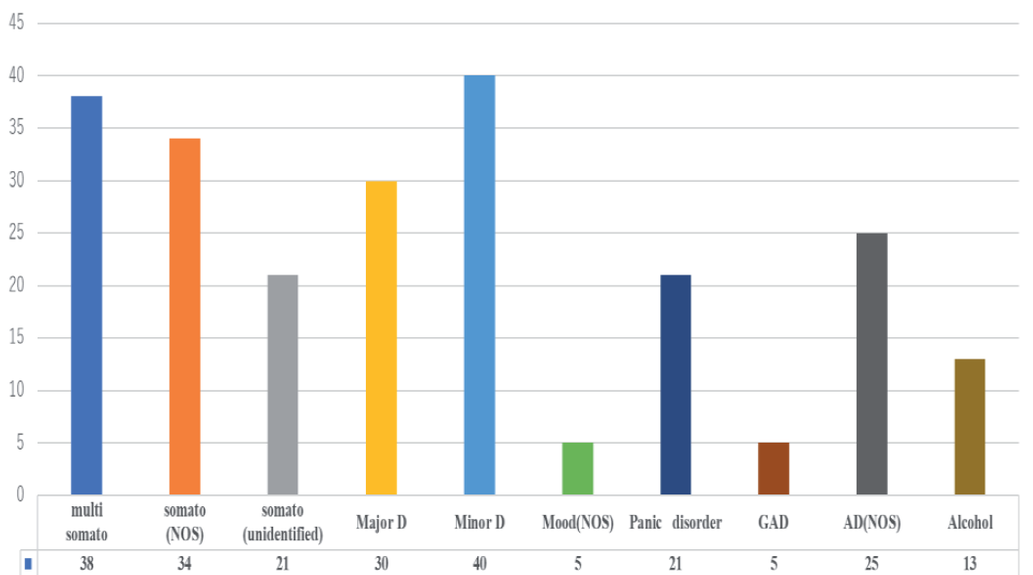

Figure 2.
Breakdown of Mental Disorders Detected by PRIME-MD in Primary Care Patients in Japan (n = 601).

lower in Japan. Minor depression, however, is almost as common in Japan as in the USA. Moreover, the rate of prevalence of any anxiety disorders in Japan is lower than in the USA, while figures for panic disorder are similar in both countries (refer to **Table 1**).

Of the 12.5% of patients diagnosed with mood disorders, 5.0% (n = 29) were major depressive disorder, and 6.7% (n = 40) were minor depressive disorder. 4.2% (n = 21) of patients were diagnosed with panic disorder, only 5 patients with general anxiety disorder (GAD), and 4.2% (n = 25) with anxiety disorders not otherwise specified.

As for diagnosis (n = 93) of somatoform disorders, 6.3% of patients (n = 38) were diagnosed with multisomatoform disorder, 5.7% (n = 34) with somatoform disorders not otherwise specified and 3.5% (n = 21) with identified somatoform disorders (refer to **Figure 3**).

The odds ratio for co-occurrence of major depressive disorder with generalized anxiety disorders, with anxiety disorders (NOS), and with panic disorders was 11.5 (95% CI: 2.17–18.45) and 8.00 (95% CI: 3.19–20.07), 6.33 (95% CI: 2.17–18.45), respectively (refer to **Table 2**).

Table 3 shows the prevalence of mental disorder in women and men detected by the PRIME-MD study in Japan (n-601). With regards to major depression, a

	PRIME-MD study (n-601) in Japan	PRIME-MD 1000 Study in USA
Patients with psychiatric diagnoses	28.1%	39%
Mood disorders(any)	12.5%	26%
Major depression	5.0%	12%
Minor depression	6.7%	6%
Dysthymia	0.8%	8%
Anxiety disorders(any)	8.5%	18%
Panic disorders	3.5%	4%
GAD	0.8%	7%
Anxiety disorders(any)	4.2%	9%
Somatoform disorders(any)	15.5%	14%
Multisomatoform	6.3%	8%
Somatoform NOS	5.7%	4%
Alcohol abuse	2.2%	5%
Binge eating	0%	3%

Table 1.
The comparison of PRIME-MD study in Japan and USA.

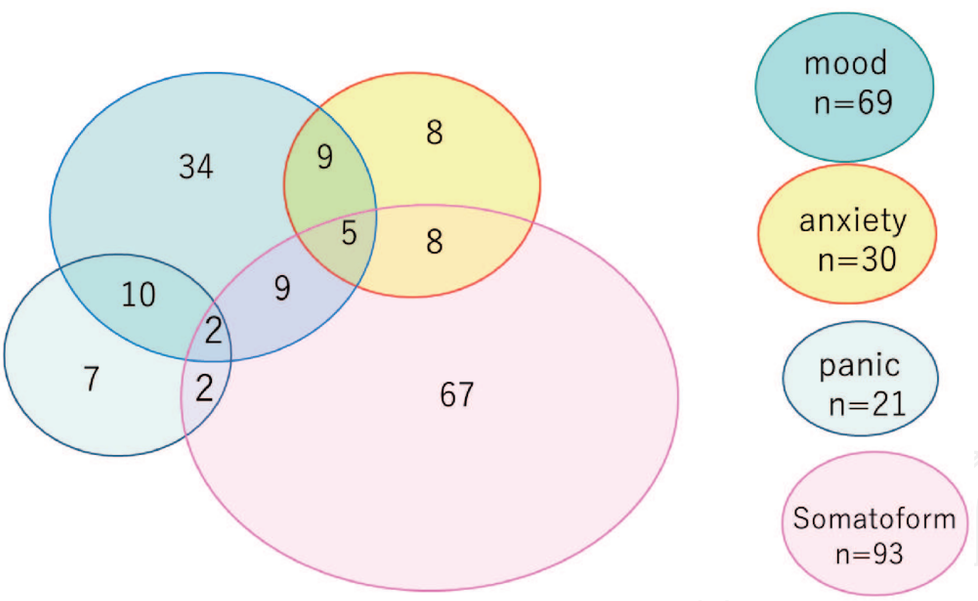

Figure 3.
Comorbidity of mood disorders, panic disorders, anxiety disorders and somatoform disorders detected by PRIME-MD in Japan (n = 601).

Major Depression with Anxiety Disorders	OR	95%CI	99%CI
Generalized Anxiety Disorder	11.5	2.17–18.45	1.55–25.80
Anxiety Disorders (NOS)	8.00	3.19–20.07	2.39–26.79
Panic Disorders	6.33	2.17–18.45	1.55–25.80

OR: odds ratio, CI: Confidence Interval.

Table 2.
Comorbidity of mood Disorders and anxiety Disorders by detected the PRIME-MD study in Japan (n = 601).

	Women n = 352	Men n = 249	OR	*P*
Any Prime diagnosis	29.0%	27.3%	1.07	ns
Mood disorders (any)	11.9%	10.8%	1.07	ns
Major depression	6.5%	2.8%	2.41	0.0449
Minor depression	6.0%	7.6%	0.77	ns
Anxiety disorders (any)	8.5%	6.0%	1.44	ns
Panic disorder	1.4%	6.4%	2.32	ns
GAD	1.1%	0.4%	2.85	ns
Anxiety disorders (nos)	3.9%	4.4%	0.90	ns
Somatoform disorders (any)	16.4%	14.1%	1.21	ns
Multisomatoform	6.5%	6.0%	1.11	ns
Somatoform (nos)	6.5%	4.4%	1.52	ns
Alcohol use	0.3%	4.8%	0.56	0.0058

GAD = generalized anxiety disorder, nos = not otherwise specified, OR = odds ratio.

Table 3.
Prevalence of Mental Disorder in Women and Men Detected by the PRIME-MD Study in Japan (n = 601).

significantly higher odds ratio was observed in women than in men (p = 0.0449). Alternatively, the odds ratio for alcohol use in men far exceeds that for women (p = 0.0058) (**Table 3**).

3. The PHQ (Patient Health Questionnaire) Study in Japan

3.1 Objective

We defined the prevalence and comorbidity of anxiety disorders and mood disorders in primary care patients in Japan using the PHQ.

3.2 Background

The clinical usefulness of the PRIME-MD is limited due to its time-consuming procedures. The PHQ, which was developed from the original PRIME-MD, is a self-administered version used for making criteria-based diagnoses of mental disorders that are common in primary care. The diagnostic validity of the PHQ has been established in two studies involving 3000 patients in eight primary care clinics [7] and 3000 patients in seven obstetrics-gynecology clinics in the USA [6]. We examined the validation study of the Japanese version of PHQ in primary care settings [13].

The PHQ can be entirely self-administered by the patient. The clinician scans the completed questionnaire, verifies positive responses, and applies diagnostic algorithms that are abbreviated at the bottom of each page. The questionnaire assesses eight diagnoses, divided into threshold disorders (disorders that correspond to the following specific DSM-IV diagnoses: major depressive disorder, panic disorder, and bulimia nervosa), and subthreshold disorders (disorders whose criteria encompass fewer symptoms than are required for any specific DSM-IV diagnoses: other depressive disorder, other anxiety disorder, probable alcohol abuse/dependence, probable somatoform disorder, and binge eating disorder).

Major depression is diagnosed if five or more of the nine depressive symptom criteria have been present at least "more than half the days" over the last two weeks, and one of the symptoms is depressed mood or anhedonia. Other depression is diagnosed if two, three, or four depressive symptoms have been present at least "more than half the days" over the last two weeks, and one of the symptoms is depressed mood or ahendonia. One of the nine symptom criteria ("thoughts that you would be better off dead or hurting yourself in some way") counts if present at all, regardless of the duration. Panic disorder is diagnosed if the patient has had three of the anxiety attack symptoms in the last four weeks and also has experienced such anxiety attacks before, and during the last four weeks the patient had an anxiety attack in which at least four panic attack symptoms were present. Other anxiety disorder is diagnosed if the patient has been bothered by anxiety feelings, and if also at least three anxiety symptoms have been present "more than half the days" over the last four weeks [6, 7, 14]. A module for probable somatoform disorder is diagnosed on the PHQ as a severe form of DSM-IV undifferentiated somatization with a lower threshold [15].

3.3 Materials and Methods

The PHQ study in Japan was conducted from 2004 to 2005 at eleven primary care sites in Niigata, in addition to one site in Fukui, Nagano, and Tokyo. Patients coming in for a routine medical appointment with their physician or psychiatrist were approached for entry into the study. The purpose of the study was briefly explained to them and written informed consent was obtained. A total of 1409 adult patients (611 males, 797 females; mean age: 56.2 years, SD: ±20.4) completed the PHQ in full.

Here, results of the PHQ were analyzed to determine the presence of mood disorders and anxiety disorders. Moreover, the score obtained for the question related to difficulty in daily life was used to evaluate a patient's impairment in social and occupational functioning. The protocol for the study was approved by the Ethics Committee at the Faculty of Dentistry, Niigata University and the other participating institutions in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki).

3.4 Results

The prevalence of diagnosis of any mood disorder or any anxiety disorder was 25.0%. Of the 15.8% of patients diagnosed with mood disorders, 6.4% were for major depressive disorder and 9.4% for other depressive disorders. Anxiety disorders

	Total Sample, NO (%)	**PHQ study in the United States (n = 3000)**
Any mood disorders	223(15.8%)	476(16%)
Major Depressive Disorders (MDD)	90 (6.4%)	292(10.0%)
Other Depressive Disorders (ODD)	133(9.4%)	184(6.0%)
Any anxiety disorders	186(13.2%)	317(11%)
Panic Disorders (PD)	133 (9.4%)	165(6%)
Other anxiety disorders(OAD)	53 (3.8%)	221(7%)
Any mood disorders or any anxiety disorders	351 (25.0%)	

Table 4.
Prevalence of Mood Disorders and Anxiety Disorders Detected by PRIME-MD PHQ in Japan (n = 1409).

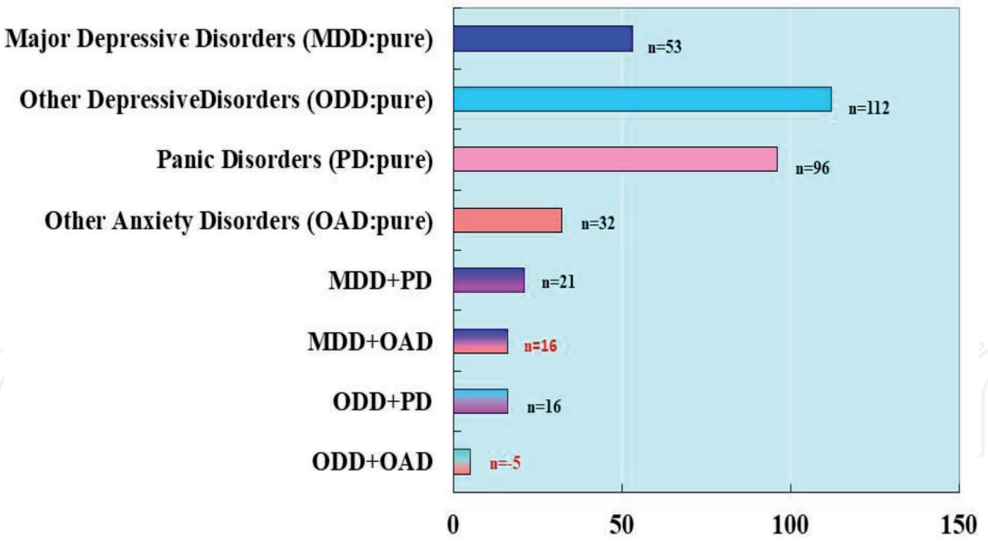

Figure 4.
Comorbidity of mood disorders and anxiety disorders by detected by PHQ study in Japan (n = 1409).

Major Depressive Disorders with Anxiety Disorders	OR	95%CI
Major Depressive Disorders with Other Anxiety Disorders	30.4	13.19–70.28
Major Depressive Disorders with Panic Disorders	5.45	3.03–9.73

OR: odds ratio CI: Confidence Interval.

Table 5.
Odds Ratios of Major Depressive Disorders with Other Anxiety Disorders or Panic Disorders Detected by PHQ in JAPAN (n = 1409).

were diagnosed in 13.2% of patients, comprising 9.4% with panic disorder and 3.8% with other anxiety disorders with other anxiety disorders (refer to **Table 4**).

Figure 4 shows the comorbidity of mood disorders and anxiety disorders. Co-occurrence of major depressive disorders with other anxiety disorders not specified was observed in sixteen patients, while overlapping of other depressive disorders with other anxiety disorders presented in five patients.

The odds ratio for co-occurrence of major depressive disorder with panic disorders and major depressive disorder with other anxiety disorders was 5.45 (95% CI: 3.03–9.73) and 30.4 (95% CI: 13.19–70.28), respectively, (refer to **Table 5**).

4. Discussion

4.1 The prevalence of anxiety, depression, and other mental disorders in Japan

The World Mental Health Japan Survey First (WMHJ1) was conducted from 2002 to 2006. A total of 4134 randomly selected residents aged 20 years or over (participation rate 55.1%) took part in the WMHJ1 from eleven areas throughout Japan. This was followed by the World Mental Health Japan Survey Second (WMHJ2), which was conducted from 2013 to 2015. The WHO Composite International Diagnostic Interview (CIDI) version 3.0 was used in WMHJ1, and a Japanese version of a computer-assisted personal interview derived from the WHO Composite International Diagnostic Interview (CIDI) version 3.0 was applied in WMHJ2 [16, 17].

Both were community-based mental health epidemiological studies. However, the number of epidemiological studies focusing on primary care in Japan is very few. Thus, we studied the prevalence of anxiety, depression, and other mental disorders in primary care patients in Japan using the PRIME-MD and the PHQ. Utilizing PRIME-MD, 12.5% and 8.5% of patients were diagnosed with mood disorders and anxiety disorders, respectively. With detection via the PHQ, 13.7% patients were diagnosed with mood disorders and 11.1% patients with anxiety disorders.

The PRIME-MD study in Japan was conducted from 1998 to 1999, however, the PHQ study in Japan was undertaken from 2004 to 2005. Despite being conducted in different decades and with different assessment instruments, the prevalence rate of mood disorders and anxiety disorders was similar in primary care patients. Likewise, the prevalence of CMD (common mental disorders), such as mood, anxiety, and substance-related disorders in Japan was relatively stable from the WMHJ1 in 2002 to the WMHJ2 in 2015. Similar trends are observed between the PRIME-MD of 1998 and the PHQ study in 2005. These findings suggest that the prevalence rate of mood disorders and anxiety disorders has remained relatively stable in primary care patients and the general population.

For an international comparison, we compared the prevalence rate in the PRIME-MD and the PHQ study between Japan and US. The prevalence rate of major depression is far lower in Japan. Minor depression, however, is almost as common in Japan as in the USA. Moreover, the rate of prevalence of other anxiety disorders in Japan is lower than in the USA, while figures for panic disorder are similar in both countries.

We compared the prevalence rate in the PRIME-MD and the PHQ study between Japan and Spain [4], and Japan and France [18]. Similarly, the rate of prevalence of any mood disorders and any anxiety disorders in Japan is lower than in Spain or France.

In 1995, the WHO concluded the largest international multicentric survey on Psychological Problems in General Health Care (PPGHC) [19]. The PPGHC investigated the psychological problems commonly seen in primary care settings. This research was comprised from the collaboration of fifteen centers in fourteen countries. The rate of current depression in Japan's Nagasaki research center was lower than in any other of the participating research centers.

Interestingly, according to results of studies in Japan detected by PRIME-MD, PHQ, WHMJ1, WHMJ2 and PPHGC, the rate of prevalence of major depressive disorders has been and continues to be lower in Japan than in other countries.

First, it remains possible that the diagnoses of the ICD and DSM do not accurately assess the intrinsic characteristics of depression that are unique to Japanese people. Kessler pointed out that there is no guarantee that the same good validity of the CIDI will be found in other parts of the world [20]. The DSM, in particular, only assesses symptoms at a cross-sectional level and does not capture cultural differences in the essential psychopathology of major depression.

Secondly, there are differences between Japanese and other nationalities, particularly Americans, in the way they perceive stressful events and in the emotional expression of depression. Recently, Vanderkruik and Whisman examined the associations between pleasant or reinforcing activities and depressive symptoms across cultures. Their results indicated that frequency, enjoyment, and obtained pleasure from pleasant events were significantly and negatively associated with depressive symptoms for both American and Japanese adults, and these associations were significantly greater in magnitude for American adults relative to Japanese adults [21]. Their findings suggest that there is a cross-sectional association between

pleasant events and depressive symptoms in both the USA and Japan, and that this association is stronger in the USA.

In other words, Americans have more emotional ups and downs than Japanese in terms of how they perceive both pleasant and stressful events. Possibly, their results would support the findings of the present study, in which the rate of prevalence of major depressive disorders is lower in Japan than in other countries.

Third, epidemiological differences in depression and anxiety between Japan and other western countries may be related to genetic factors such as serotonin-related factors. Tsuchimine et al. reported that there was no association between a polymorphism in the serotonin receptor 2B (HTR2B) gene and personality traits in healthy Japanese subjects [22]. On the other hand, the prevalence of panic disorder in PRIME-MD and PHQ Study in Japan is similar with those in the USA. Recently, Ohi et al. investigated and suggested that transethnic polygenetic features are shared between Japanese panic disorder patients and European patients with psychiatric disorders by conducting polygenic risk score (PRS) analyses [23].

Genetic research about cultural differences between Japan and other countries and their potential relationship with depression and anxiety is underway, but at this point, many questions remain unanswered. Although some studies have been conducted on this subject, much greater investigation is required. Consequently, we did not address the issue in detail here.

In addition, with regards to major depression, a significantly higher rate was observed in women than in men detected by PRIME-MD in Japan, as with PRIME-MD in USA and Spain [4, 24, 25], and in the WHMJ1 and WHMJ2.

4.2 Comorbidity between depression and anxiety detected using PRIME-MD and the PHQ in Japan

Co-occurrence of major depressive disorder with generalized anxiety disorders and major depressive disorder with anxiety disorders (NOS) were detected using PRIME-MD (n-601) in Japan. The co-occurrence of major depressive disorder with generalized anxiety disorders had a far higher odds-ratio than major depressive disorder with anxiety disorders (NOS), along with panic disorders.

In addition, the findings of co-occurrence of major depressive disorder with other anxiety disorders and major depressive disorder with panic disorders were observed in the PHQ (n = 1409) study in Japan. Results showed a higher odds-ratio in the co-occurrence of major depressive disorder with other anxiety disorders than in major depressive disorder with panic disorders.

The results of the PRIME-MD and PHQ studies in Japan suggest that major depressive disorder is more likely to be comorbid with generalized anxiety disorder and other anxiety disorders than with panic disorder in Japanese primary care settings.

The comorbidity between depressive and anxiety disorders was not analyzed in detail in the WMHJ1 or WMHJ2. The Netherlands Study of Depression and Anxiety (NESDA) reported that 67% of subjects had a current and 75% had a lifetime comorbid anxiety disorder diagnosis and similarly, of those with a primary anxiety disorder diagnosis, 63% had a current and 81% a lifetime depressive disorder diagnosis [2]. In separate studies, Hirschfeld and Wittchen et al. reported that comorbidity rates in community samples are slightly lower the rates reported in NESDA [3, 25].

Using data from a previous WHO study of mental disorders in general medical and primary care settings in fourteen countries [19], Goldberg et al. [26]

revealed a high correlation between anxious and depressive symptoms. Moreover, their analysis showed that anxious depression is much more common in primary care settings than "comorbid generalized anxiety and depression," where the individual meets the diagnostic requirements of both a depressive episode and generalized anxiety disorder and a duration requirement of 6 months for anxiety symptoms.

The findings of NESDA, Goldberg et al., and other studies in Western countries are in line with the results achieved in the PRIME-MD and PHQ studies in Japan. Goldberg and Silverstone and von Studnitz proposed that the revised primary care classification for ICD-11 Mental and Behavioral Disorders (ICD-11 PHC) should consider anxious depression to be an important form of depressive episode in general medical practice [27, 28].

Whiteford et al. pointed out that in spite of the prevalence and importance of the comorbidity of depression and anxiety in primary care and its substantial contribution to disability [29], rates of identification and treatment remain very low, with less than half of all depressive episodes correctly identified even in high-resource primary care.

From a clinical viewpoint, Weitz and Kleiboer [30] and Cuijpers et al. [31] learned via meta-analysis that comorbid symptoms decreased during treatment of the more clinically significant disorder. This holds true for treating depression with psychotherapy regarding anxiety symptoms [30] and treating anxiety disorders with cognitive behavioral therapy regarding depressive symptoms [31].

Kalinin proposed a new concept, the comorbidity of anxiety and affective disorders as neuropsychiatric and evolutionary problems. He suggested a potential mechanism for comorbidity development based on neuropsychiatric and evolutionary data [32]. Stein et al. mentioned that the research of anxiety disorder will require the integration of nosological, epidemiological, and psychobiological viewpoints utilizing methods such as genomic data, physiological markers, and experiential sampling from a wider community and clinical survey. [33] Future research from their perspective is also needed.

There are very few studies on the comorbidity of depression and anxiety in Japan, therefore, data from these PRIME-MD and PHQ studies contribute to consideration of clinical treatment for depression and anxiety in primary care settings in Japan.

5. Conclusion

We detected the prevalence of anxiety, depression, and other mental disorders in primary care patients in Japan using the PRIME-MD and the PHQ. There were findings of comorbidity of depression and anxiety as seen in other countries.

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Conflict of interest

The authors declare no conflict of interest.

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