厚生労働省主催

「自殺未遂者ケア研修（一般救急版）」

自殺未遂者への対応にお困りになられたことはありませんか？
本研修は、初期対応から継続的な支援まで、臨床現場で役立つ自殺未遂者ケアのポイントを、日本臨床救急医学会が厚生労働省と共に作成したガイドラインに沿って体系的に学んでいただくと共に、モデル症例によるワークショップを通じケアのあり方を実践的に修得していただく内容です。
講師とファシリテータは、自殺未遂者のケアを実践している専門家・専門職が務めます。
奮ってご参加のほどお願い申し上げます。

●**主　催**：厚生労働省
●**共　催**：一般社団法人　日本臨床救急医学会
●**参加費**：無料（定員50名）
●**対象者**：救急医療に従事する医師、看護師、その他コメディカルスタッフなど
●**会場・開催日**：
【東京会場】平成26年1月25日（土）9：50～16：45
東京ファッションタウン（TFT）ビル東館　9階909研修室
〒135-8071　東京都江東区有明3-6-11
【岡山会場】平成26年2月22日（土）9：50～16：45
第一セントラルビル1号館　9階大ホール
〒700-0901　岡山市北区本町6-36
【仙台会場】平成26年3月9日（日）9：50～16：45
フォレスト仙台　2階第7会議室
〒981-0933　仙台市青葉区柏木1-2-45

●**お申込み**
【お申込み締切日　東京会場：1月4日、岡山会場：1月24日、仙台会場：2月10日】

メールでのお申込み　下記アドレスに裏面の申込書記載事項とともに、お申込みください。
メールアドレス：care2013@forumone.co.jp

FAXでのお申込み　裏面の申込書に必要事項をご記入の上、お申込みください。
FAX：03−6454−2482「自殺未遂者ケア研修参加受付係」

●**プログラム**

9:30	開場	
9:50～10:00	事前アンケート	
10:00～10:10	開会挨拶	
10:10～10:30	講義1	「自殺未遂者対策がなぜ必要か」
10:30～10:50	講義2	「自殺未遂者ケア・モデルと地域自殺対策」
10:50～11:05	講義3	「国と地方自治体の自殺対策の取組み」
11:05～11:35	「自殺未遂者ケアガイドラインとワークショップの説明」	
11:35～12:35	昼休み	
12:35～16:05	ワークショップ、成果物発表とディスカッション（途中休憩2回あり）	
16:05～16:25	講義4	「自死遺族への対応と支援」
16:25～16:35	事後アンケート	
16:35～16:45	閉会挨拶	

※ワークショップはモデル症例について救急医療施設における自殺未遂者への対応をグループで討議し部合によりプログラム内容が一部変更になる場合がありますので、予めご了承ください。

●**お問合せ**

自殺未遂者ケア研修参加受付係
自殺未遂者ケア研修事務局　㈱フォーラムワン内
電話：03−6454−2478　FAX：03−6454−2482
対応時間：午前9時～午後6時（土日・祝日を除く平成25年3月

「自殺未遂患者への対応：救急外来（ER）・救急科・救命救急センターのスタッフのための手引き」作成班

有限責任中間法人　日本臨床救急医学会
「自殺企図者のケアに関する検討委員会」
担当理事
有賀　徹（昭和大学）
委員長
三宅　康史（昭和大学）
委　員
大塚耕太郎（岩手医科大学）
岸　泰宏（日本医科大学）
坂本由美子（関東労災病院）
守村　洋（札幌市立大学）
柳澤八恵子（聖路加国際病院）
山田　朋樹（横浜市立大学）
協　力
伊藤　弘人（国立精神・神経センター）
河西　千秋（横浜市立大学）

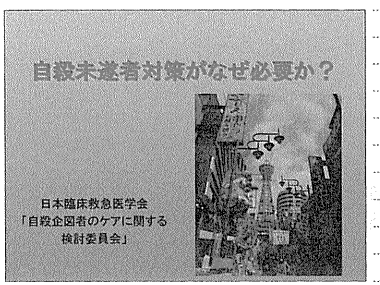
「来院した自殺未遂患者へのケアQ&A ―実践編2011―」執筆

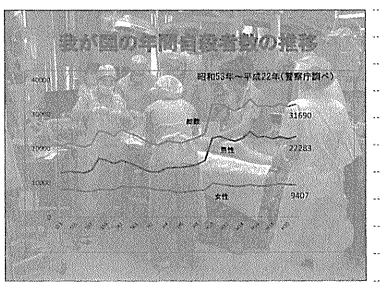
大塚耕太郎（岩手医科大学）
河西　千秋（横浜市立大学）
岸　泰宏（日本医科大学）
坂本由美子（関東労災病院）
三宅　康史（昭和大学）
守村　洋（札幌市立大学）
柳澤八恵子（聖路加国際病院）
山田　朋樹（横浜市立大学）

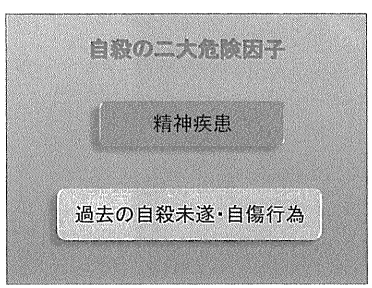
一般社団法人　日本臨床救急医学会
「自殺企図者のケアに関する検討委員会」
担当理事
松田　潔（日本医科大学武蔵小杉病院）
委員長
三宅　康史（昭和大学）
委　員
秋山　恵子（日本赤十字社医療センター）
大塚耕太郎（岩手医科大学）
岸　泰宏（日本医科大学武蔵小杉病院）
坂本由美子（関東労災病院）
橋本　聡（国立病院機構熊本医療センター）
東岡　宏明（関東労災病院）
堀　智志（日本大学附属板橋病院）
守村　洋（札幌市立大学）
柳澤八重子（聖路加国際病院）
山田　朋樹（樹診療所）
オブザーバー
伊藤　弘人（国立精神・神経医療研究センター）
河西　千秋（横浜市立大学）
河嶌　譲（厚生労働省社会・援護局）

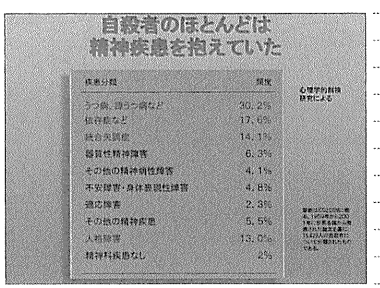
目　次

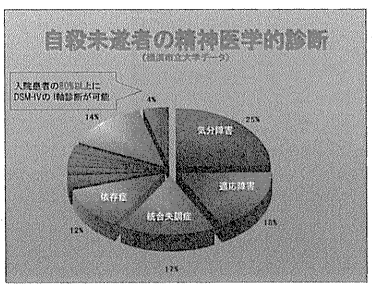
本テキストは、平成25年度厚生労働科学研究費補助金（自殺未遂者および自殺遺族等へのケアに関する研究）の支援を受けて日本臨床救急医学会が作成した。

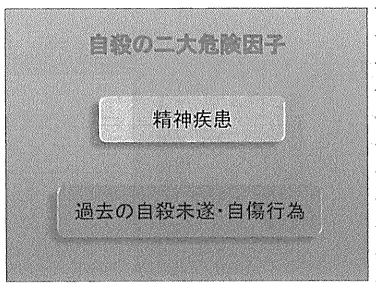


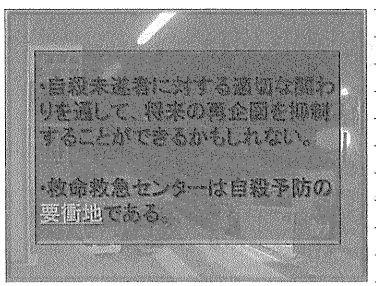


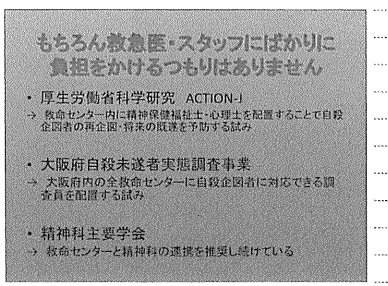


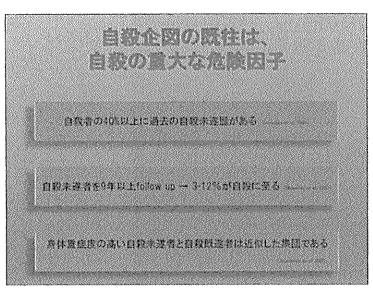


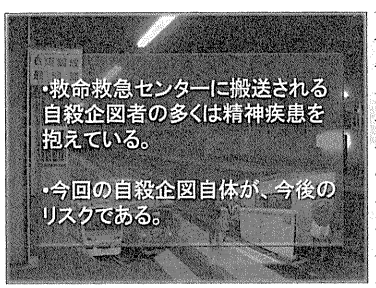

自殺未遂者の精神医学的診断
（横浜市立大学データ）
入院患者の80%以上にDSM-IVの I軸診断が可能
4%
25%
18%
17%
12%
14%
気分障害
適応障害
統合失調症
依存症

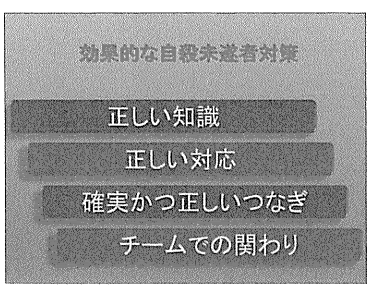

自殺の二大危険因子
精神疾患
過去の自殺未遂・自傷行為

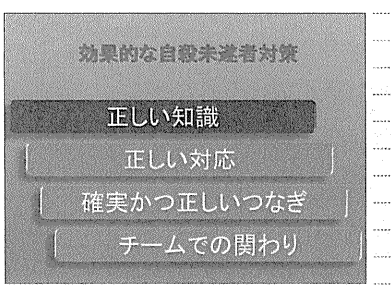

•自殺未遂者に対する適切な関わりを通して、将来の再企図を抑制することができるかもしれない。
•救命救急センターは自殺予防の要衝地である。


もちろん救急医・スタッフにばかりに負担をかけるつもりはありません
• 厚生労働省科学研究 ACTION-J
→ 救命センター内に精神保健福祉士・心理士を配置することで自殺企図者の再企図・将来の自殺を予防する試み
• 大阪府自殺未遂者実態調査事業
→ 大阪府内の全救命センターに自殺企図者に対応できる調査員を配置する試み
• 精神科主要学会
→ 救命センターと精神科の連携を推奨し続けている


自殺企図の既往は、
自殺の重大な危険因子
自殺者の40%以上に過去の自殺未遂歴がある
自殺未遂者を9年以上follow up → 3-12%が自殺に至る
身体重症度の高い自殺未遂者と自殺既遂者は近似した集団である


•救命救急センターに搬送される自殺企図者の多くは精神疾患を抱えている。
•今回の自殺企図自体が、今後のリスクである。


効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり


効果的な自殺未遂者対策
正しい知識
正しい対応
確実かつ正しいつなぎ
チームでの関わり

自殺企図者の心理状態を理解する

Edwin S. Shneidman

- 絶望感、虚無感、自己価値観の低下、焦燥感が強い
  →「精神痛」
- 「死にたい」「生きたい」という両方の気持ちを同時に有している
  →「両価性」
- 「生きたいが、死ぬ事でしかこの苦しみを抜け出す方法がない」という固定観念にとらわれている
  →「精神的視野狭窄」

効果的な自殺未遂者対策

正しい知識

正しい対応

確実かつ正しいつなぎ

チームでの関わり

効果的な自殺未遂者対策

正しい知識

正しい対応

確実かつ正しいつなぎ

チームでの関わり

＜身体治療終了≠退院＞

- 診断が統合失調症やうつ病などで、その精神症状が満発である
- 本人・家族が共に入院治療を望んでいる
- Key Personが不在、あるいは居ても役割を果たすことが困難
- 金銭面、住居が無いなどの問題で、退院後の生活面での見通しが全く立っていない
- 診断に関わらず、不安・焦燥感が大変強く、不眠が連続している
- 希死念慮が変わらず強い
- 精神科の受診先が具体的に決まっていない
- 自殺企図に対する後悔が無く、内省が正しく得られていない

危機介入時の原則（TALKの原則）

T ell: 誠実な態度で話しかける

A sk: 自殺についてはっきり尋ねる

L isten: 相手の訴えに傾聴する

K eep safe: 安全を確保する

適切な対応を妨げるもの

自殺企図者は、普段「死」を否認しようとする傾向のある医療者全般に対して、強い不安、拒否感を喚起する

無意識に行ってしまう、不安感、拒否感の解消法とは？

- 表出
  - 加虐的な言動
    - GODDAMN SYND
- 否認
  - 話題を避ける
- 反動形成
  - 過度な優しさ

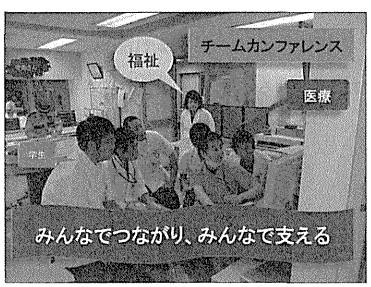
効果的な自殺未遂者対策

正しい知識

正しい対応

確実かつ正しいつなぎ

チームでの関わり



Contents lists available at SciVerse ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

What Should We Do to Improve Patients' Adherence?

Hiroto Ito*

Department of Social Psychiatry, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan

ARTICLE INFO

Article history:
Received: May 7, 2013
Revised: May 8, 2013
Accepted: May 9, 2013

KEY WORDS:
adherence;
compliance;
medication management and use;
shared decision-making

Adherence to treatment regimens is lower than what physicians expect. The impact of poor adherence on treatment outcomes and healthcare costs is significant. As the number of prescribed medications increases with the rising prevalence of chronic diseases and multimorbidity, the risk of nonadherence also increases. This article reviews the research that has explored effective interventions to improve patient adherence to treatment. Recent literature, including meta-analyses and systematic reviews on patients' adherence, were examined in the present study. Barriers to adherence exist at the level of the patient, the healthcare provider, and the healthcare system. Patients' adherence is measured by many methods such as self-report, pill counting, and the medication possession ratio. No single standard intervention exists that improves adherence; however, a combination of interventions seems to be more effective than individual interventions. Physicians and pharmacists should simplify regimens in consideration of a patient's health literacy. Patient education should include behavioral support and reminders through a multidisciplinary approach that involves case management and collaborative care. Shared decision-making ensures the alignment of care with a patient's preferences and value so that they are motivated to participate in medical care. Combined interventions are more effective than individual interventions. Patients' active participation in treatment through shared decision-making is important.

1. Introduction

Patients' nonadherence may be a common underlying cause of treatment failure. The premise is simple. No matter how advanced a drug is, if the patient does not take it properly, the patient and the physician cannot expect to receive the full benefits of the medication. Poor adherence often hinders treatment, especially in patients with chronic diseases such as hypertension or diabetes.[1] The prevalence of chronic diseases is rising with the aging population, and the most common chronic condition in adults is multimorbidity.[2] As the number of prescribed medications increases, the risk of nonadherence also increases. These trends highlight the importance of patient adherence.

Adherence has been the focus of extensive research for decades. This paper reviews the research evidence with regard to effective interventions that improve a patient's adherence.

1.1. What is adherence?

In 2001, the World Health Organization defined the term "adherence" as "the extent to which the patient follows medical instructions".[2] The word "adherence" is preferred to "compliance" because "compliance" suggests that patient is a passive follower of the doctor's orders, whereas the word "adherence" implies that the treatment plan is based on a therapeutic alliance between the patient and the physician.[3] Adherence commonly refers to the patient taking the medication as prescribed; however, the scope of adherence covers all recommended health behaviors such as healthy lifestyle habits and clinic appointments.

1.2. Physicians underestimate the true adherence rate

Poor medication adherence is a serious problem because nearly one-half of patients with chronic diseases do not take their medications as prescribed.[3,4] Adherence to treatment regimens is relatively high in clinical trials because of the strict selection process for enrolled patients; however, only 43–78% of patients with chronic diseases maintain good adherence to medication.[4] The adherence rate is likely to decline over time. By using prescription data on statin therapy in elderly patients, Benner et al.[5] found that 21% of patients stop taking their prescribed medicines within 3 months, and 44% of patients stop taking their medication within 6 months. Medication adherence by patients is better than their adherence to other therapeutic regimens. A meta-analysis shows suboptimal adherence rates to medication (79.4%), screening (72.8%), exercise (72.0%), healthy behaviors (69.7%), clinic appointments (65.9%), and diet (59.3%).[6] To adhere to treatment regimens that cause a lifestyle change is more difficult for patients.

* Hiroto Ito, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553, Japan.
E-mail: H. Ito <ltoffiroto@ncnp.go.jp>

1878-3317/$ – see front matter Copyright © 2013, Taipei Medical University. Published by Elsevier Taiwan LLC. All rights reserved.
http://dx.doi.org/10.1016/j.jecm.2013.05.001

Because patients often pretend to follow the physician's instructions during consultations, adherence to treatment regimens improves for a short time just prior to a clinic visit. This behavioral characteristic is known as the "white-coat effect."[7] A study of patients with epilepsy showed a marked decline in adherence levels in the interval between appointments.[7] The percentage of patients who take medicines as prescribed are 88% for 5 days prior to a clinic visit and 86% for 5 days after the visit; however, this rate declines to 67% 1 month after the visit.[8] Physicians are often disappointed with low treatment adherence; however, treatment adherence around the visit is usually better than during the interval between visits. A previous study reported that more than one-third of patient-reported adherence is not correctly estimated by physicians.[9]

1.3. Low adherence compromises patient outcomes

Nonadherence has negative consequences. Failure to follow prescriptions causes preventable mortality, morbidity, and approximately 10% of hospital admissions,[10,11] and costs billions of dollars each year.[12] Adherence is not limited to medication, therefore the impact of nonadherence is substantial. Patients with diabetes, hypertension, hypercholesterolemia, or congestive heart failure who have high adherence scores have a lower risk of hospitalization than patients with low adherence scores, and patients who have low treatment adherence for diabetes and hypertension have a higher risk of hospitalization.[13] A meta-analysis of 63 studies reveals that low adherence to medication, diet, and exercise is associated with worse overall outcomes (26%) and with intestinal disease (40%), sleep apnea (31%), hypertension (30%), and hypercholesterolemia (25%).[6]

2. Barriers to adherence

There are three levels of barriers to adherence: the patient, the healthcare provider, and the healthcare system.[3,14] These factors are interwined and affect adherence. At the patient level, identified factors include age, socioeconomic status, lifestyle and health beliefs, forgetfulness, and previous treatment failure. In addition, mental health problems such as depression underlie nonadherence. Depressed outpatients are 2.4-fold more likely to forget and 2.2-fold more likely to skip their medications, compared to their nondepressed counterparts.[15] Depressed patients have a 3-fold overall greater risk of nonadherence, compared to nondepressed patients.[16] Patient adherence is also affected by a healthcare provider's practice, including their prescribing of complex treatment regimens, insufficient explanations of drug actions and adverse effects, and lack of communication with patients regarding their lifestyle and economic conditions.[3] A good patient–physician relationship has positive impacts on adherence to treatment.[17]

Adherence is influenced by the healthcare system.[3] Changes in a reimbursement system may affect patient behavior. Patients may not continue costly treatment because of difficulty affording out-of-pocket expenses. If physicians are unaware of such behaviors of their patients, the patients may become less adherent to treatment regimens or may even discontinue treatment. In a systematic review, increased out-of-pocket expenses have been identified as a barrier to adherence at the healthcare system level.[18]

3. Measuring adherence

An accurate measurement of adherence is necessary; however, there is no gold standard. Adherence is measured by various methods. The most appropriate way of measuring adherence depends on the situation since each method has its advantages and disadvantages.

3.1. Patient self-report

The simplest way to check adherence is to ask patients: "Do you take your medication as directed? I know it must be difficult to take all your medications regularly." [3] The key to such direct questioning is to allow patients to answer "Yes" or "No" to a closed-ended question.[19,20] Patients may keep diaries to show their healthcare providers. The problem with these approaches is that patients often overestimate their adherence level, although they may be less susceptible to recall bias.[21]

3.2. Questionnaire

Questionnaires have been developed to improve the accuracy of patient reports. The reliability and validity of these questionnaires have been established. The Medication Adherence Questionnaire (MAQ) is the most commonly used adherence scale.[22] The scale was originally developed for hypertension, and was later expanded for use in other diseases. Unlike the MAQ, the Self-efficacy for Appropriate Medication Use Scale (SEAMS)[23] and the Brief Medication Questionnaire (BMQ)[24] assess self-efficacy in evaluating medication adherence. The Hill-Bone Compliance Scale is used in cardiovascular disease.[25] The Medication Adherence Rating Scale (MARS)[26] is often used in mental disorders.[27]

3.3. Pill count

Prescription or pill-based methods estimates a patient's medication adherence by using the dates of prescription refills or pill counts during routine clinic visits.[28] It is easy to monitor a patient's adherence to medication in clinical settings. These methods are often used in clinical trials; however, prescription refill records and pill counts are not sufficiently objective. Patients may simulate adherence by emptying their pill bottles just prior to a clinic visit,[19] and pill counts often overestimate true adherence rates.[20]

The Medication Event Monitoring System (MEMS) and Doser (Meditrack) have been developed to replace pill counts.[19] These systems electronically record the time when the bottle is opened. There is still a concern that a patient may not have taken a pill, even though the bottle was opened. These electronic monitoring systems are expensive, and may not be feasible for clinical practice.[21]

3.4. Medication possession ratio

Administrative data can be effectively used for measuring adherence. The medication possession ratio (MPR)—defined as the number of days for which prescription medication is supplied divided by the days of observation—is useful because it can be easily calculated from a medical chart and does not require continuous measurement.[29] In contrast to the pill count of a patient's pill bottle, the MPR is calculated by using an administrative database, primarily a computerized pharmacy system.[30] The MPR is used as a quality indicator but it requires a closed pharmacy system.[3]

3.5. Serum drug level monitoring

The most accurate way to assess recent adherence prior to a clinic visit is through measuring the serum or urine levels of a medication or its metabolites.[31] The timing of doses, however, is unknown, and some drugs are not easily monitored at clinic visits.[21] This method

would detect only the "white-coat effect" because the serum drug level only shows a patient's adherence within several days prior to the visit.[31] The method is also expensive[4] and is the least acceptable method to patients.[32]

4. Combined interventions

The effect of interventions on improving adherence varies among studies and there is no single standard intervention.[4,18] But it is known that the more comprehensive the approach is, the more adherence is improved.[33] Therefore, a combination approach is key to improving adherence. Each intervention should take into consideration of the balance between adherence benefits and costs.

4.1. Simplified regimen and health literacy

Unless patients do not understand their disease and treatment, physicians cannot expect high patient adherence. The first thing physicians need to do is to simplify treatment plans,[34,35] and to use simple and clear directions with explicit language to instruct patients. It is particularly important that physicians assess the level of health literacy and understanding of their elderly patients.[36,37]

Limited health literacy impedes patient comprehension of medication instructions.[38] Health literacy is defined as "the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions."[39] The adherence rate is higher if the patient takes a medication once a day; however, the adherence rate declines as the number of doses increases.[35] Witticke et al.[39] found that the most prevalent complex characteristics of a medication regimen are: the prescription of one or more drugs with multiple daily doses; the prescription of three or more drugs with different dosing intervals; and tablet splitting. Another study showed that problems with interpreting medication instructions are most commonly caused by the frequency of hourly intervals (e.g., "take 1 pill by mouth every 12 hours with a meal") or by the number of times of day (e.g., "take two tablets by mouth twice daily"), whereas patients are less likely to misinterpret prescription instructions that use time periods (e.g., "take 2 pills in the morning") or specific times (e.g., "take 1 pill at 8 AM").[38] Simple modifications of the medication scheme can reduce one-fifth of the complexity of a regimen.[40]

Physicians may hesitate to give patients negative information such as the adverse effects of medications. Hynese (2008) posed the following question: "Does telling about adverse effects of medication lower adherence?"[4] Several studies have shown that explaining to patients about the adverse effects of their medications does not affect their use of the medications.[4] Lower adherence may be independent of informing of patients regarding side effects.

4.2. Patient education and behavioral support through a multidisciplinary approach

The provision of educational materials alone does not greatly modify patient behavior. Combined educational interventions such as behavioral support with educational materials for several weeks or months are effective for chronic diseases such as hypertension, hyperlipidemia, heart failure, and myocardial infarction.[18] Reminders are important in assisting healthcare providers improve patient adherence. Daily video-telephone or regular telephone reminders[41] and monthly educational letters to patients emphasizing the importance of adherence to treatment[42] are effective in enhancing patient medication adherence.[43,44] In a systematic review, reminders by manual phone calls are more effective than automated reminders, but there is no strong effect if the time between the reminder and the appointment is within a week.[45] Reminders are also the least costly intervention.[46]

In addition to physician efforts to improve patient adherence, other healthcare providers (e.g., nurses, social workers and pharmacists) also have roles to play in a multidisciplinary team approach. Case and medication management are major components of team care.[18] A multidisciplinary team approach has been proven as effective for improving the adherence of patients with diabetes,[47,48] hypertension,[49] heart failure,[50] or depression.[47–49, 51–53] Collaborative care also effectively improves adherence in patients with comorbid depression and chronic illness.[54] Collaborative care is defined as a multifaceted intervention involving the combination of three distinct professionals working collaboratively within the primary care setting: (1) the case manager, (2) the primary care practitioner, and (3) the mental health specialist.[55,56]

The involvement of a clinical pharmacist in multidisciplinary care through assessing patient knowledge and providing instructions about medication use leads to greater medication adherence.[57,58] Pharmacist-provided medication therapy management and a patient's use of medicine consists of patient education and the discussion of problems, but professional input is effective.[46]

4.3. Shared decision-making

An important concept in the practice of healthcare has shifted to shared decision-making, which implies a paradigm of patient adherence.[59] In current practice, the nature of the patient–physician relationship is quite different from the traditional paternalistic model, which is characterized by the physician exercising great control. In place of such an authoritarian approach, a relationship of mutuality is increasingly common in which physicians treat patients as partners and encourage their patients' active involvement in treatment plans. In shared decision-making, the physician offers options with risks and benefits, whereas the patient expresses his or her preferences and values. Thus, the physician and patient both have a better understanding and share responsibility in the decision-making.[60]

Shared decision-making requires patient education and requires physicians to make an effort to improve communication with patients.[60] Poor communication is independently associated with objectively measured inadequate medication refill adherence.[61] Patient adherence to treatment regimens is 2.16-fold greater with physicians that have high communication skills; physician communication training can improve patient adherence by 1.62-fold.[17] Shared decision-making improves medical care—particularly in patients with chronic diseases—and reduces costs; however, its implementation in clinical practice is slow.[62]

5. Conclusion

There is no gold standard with which to measure and improve patient adherence, although various measurements such as pharmacist-provided interventions have been developed. Combined interventions are more effective than individual interventions. Because shared decision-making is emphasized in the practice of healthcare, healthcare providers including clinical pharmacists must focus on the active involvement of their patients. Physicians and patients should both have a better understanding of information and should share responsibility in the decision-making on medication management and medication use. In this way, optimal patient adherence can be achieved.

References

1. Chisholm-Burns MA, Spivey CA. The "cost" of medication nonadherence: consequences we cannot afford to accept. *J Am Pharm Assoc* 2012;**52**:823–6.
2. World Health Organization. *Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.*
3. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**: 487–97.
4. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. *Cochrane Database Syst Rev* 2008;**2**:CD000011.
5. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;**288**:455–61.
6. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. *Med Care* 2004;**42**:200–9.
7. Feinstein A. On white-coat effects and the electronic monitoring of compliance. *Arch Intern Med* 1990;**150**:377–8.
8. Cramer JA, Scheyer RD, Mattson RH. Compliance declines between clinic visits. *Arch Intern Med* 1990;**150**:509–10.
9. Murri R, Ammassari A, Trotta MP, Luca AD, Melzi S, Minardi C, Zaccarelli M, et al. Patient-reported and physician-estimated adherence to HAART: social and clinic center-related factors are associated with discordance. *J Gen Intern Med* 2004;**19**:1104–10.
10. Schiff GD, Fung S, Speroff T, McNutt RA. Decompensated heart failure: symptoms, patterns of onset, and contributing factors. *Am J Med* 2003;**114**:625–30.
11. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to *treatment: three decades of research. A comprehensive review. J Clin Pharm Ther* 2001;**26**:331–42.
12. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *Am J Health Syst Pharm* 2003;**60**:657–65.
13. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Med Care* 2005;**43**: 521–30.
14. Wens J, Vermeire E, Royen PV, Sabbe B, Denekens J. GPs' perspectives of type 2 diabetes patients' adherence to treatment: a qualitative analysis of barriers and solutions. *BMC Fam Pract* 2005;**6**:20.
15. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul study. *Arch Intern Med* 2005;**165**:2508–13.
16. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000;**160**:2101–7.
17. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Med Care* 2009;**47**:826–34.
18. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, et al. Interventions to improve adherence to self-administered *medications for chronic diseases in the United States: a systematic review. Ann Intern Med* 2012;**157**:785–95.
19. Bubalo J, Clark Jr RK, Jiing SS, Johnson NB, Miller KA, Clemens-Shipman CJ, et al. Medication adherence: pharmacist perspective. *J Am Pharm Assoc* 2010;**50**: 394–406.
20. MacLaughlin EJ, Raehl CL, Treadway AK, Sterling TL, Zoller DP, Bond CA. Assessing medication adherence in the elderly: which tools to use in clinical practice? *Drugs Aging* 2005;**22**:231–55.
21. Ruddy K, Mayer E, Partridge A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J Clin* 2009;**59**:56–66.
22. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986;**24**:67–74.
23. Risser J, Jacobson TA, Kripalani S. Development and psychometric evaluation of the Self-Efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. *J Nurs Meas* 2007;**15**:203–19.
24. Svarstad BL, Chewing BA, Sleath BL, Claesson C. The brief medication questionnaire: a tool for screening patient adherence and barriers to adherence. *Patient Educ Couns* 1999;**37**:113–24.
25. Kim MT, Hill MN, Bone LR, Levine DM. Development and testing of the Hill-Bone Compliance to High Blood Pressure Therapy Scale. *Prog Cardiovasc Nurs* 2000;**15**:90–6.
26. Thompson K, Kulkarni J, Sergejew AA. Reliability and validity of a new Medication Adherence Rating Scale (MARS) for the psychoses. *Schizophr Res* 2000;**42**:241–7.
27. Lavsa SM, Holzworth A, Ansani NT. Selection of a validated scale for measuring medication adherence. *J Am Pharm Assoc* 2011;**51**:90–4.
28. McMahon JH, Jordan MR, Kelley K, Bertagnolio S, Hong SY, Christine A, Wanke CA, et al. Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring. *Clin Infect Dis* 2011;**52**:493–506.
29. Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care* 2005;**11**:449–57.
30. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997;**50**:105–16.
31. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 1999;**21**:1074–90.
32. George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *Br J Clin Pharmacol* 2000;**50**:166–71.
33. Roter DL, Hall JA, Merisca R, Ruehle B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Medical Care* 1998;**36**:1138–61.
34. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med* 2008;**31**:213–24.
35. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;**23**:1296–310.
36. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. *Gerontologist* 2009;**49**:447–62.
37. Topinková E, Baeyens JP, Michel JP, Lang PO. Evidence-based strategies for *the optimization of pharmacotherapy in older people. Drugs Aging* 2012;**29**: 477–94.
38. Davis TC, Federman AD, Bass 3rd PF, Jackson RH, Middlebrooks M, Parker RM, Wolf MS. Improving patient understanding of prescription drug label instructions. *J Gen Intern Med* 2009;**24**:57–62.
39. Institute of Medicine of the National Academies. *Health literacy: a prescription to end confusion.* Washington DC: National Academies Press; 2004.
40. Witticke D, Seidling HM, Lohmann K, Send AF, Haefeli WE. Opportunities to reduce medication regimen complexity: a retrospective analysis of patients discharged from a university hospital in Germany. *Drug Saf* 2013;**36**:31–41.
41. Fulmer TT, Feldman PH, Kim TS, Carty B, Beers M, Molina M, Putnam M. An intervention study to enhance medication compliance in community dwelling elderly individuals. *J Gerontol Nurs* 1999;**25**:6–14.
42. Hoffman L, Enders J, Luo J, Segal R, Pippins J, Kimberlin C. Impact of an antidepressant management program on medication adherence. *Am J Manag Care* 2003;**9**:70–80.
43. Schedlbauer A, Schroeder K, Fahey T. How can adherence to lipid-lowering medication be improved? A systematic review of randomized controlled trials. *Fam Pract* 2007;**24**:380–7.
44. Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid *lowering medication. Cochrane Database Syst Rev 2010*;**17**:*CD004371*.
45. Hasvold PE, Wootton R. Use of telephone and SMS reminders to improve attendance at hospital appointments: a systematic review. *J Telemed Telecare* 2011;**17**:358–64.
46. Chapman RH, Ferrufino CP, Kowal SL, Classi P, Roberts CS. The cost and effectiveness of adherence-improving interventions for antihypertensive and lipid-lowering drugs. *Int J Clin Pract* 2010;**64**:169–81.
47. Bogner HR, de Vries HF. Integrating type 2 diabetes mellitus and depression treatment among African Americans: a randomized controlled pilot trial. *Diabetes Educ* 2010;**36**:284–92.
48. Bogner HR, Morales KH, de Vries HF, Cappola AR. Integrated management of type 2 diabetes mellitus and depression treatment to improve medication adherence: a randomized controlled trial. *Ann Fam Med* 2012;**10**:15–22.
49. Bogner HR, de Vries HF. Integration of depression and hypertension treatment: a pilot, randomized controlled trial. *Ann Fam Med* 2008;**6**:295–301.
50. Rich MW, Gray DB, Beckham V, Wittenberg C, Luther P. Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. *Am J Med* 1996;**101**:270–6.
51. Katon W, Rutter C, Ludman EJ, Von Korff M, Lin E, Simon G, Bush T, et al. A randomized trial of relapse prevention of depression in primary care. *Arch Gen Psychiatry 2001*;**58**:*241*–7.
52. Ludman E, Katon W, Bush T, Rutter C, Lin E, Simon G, Von Korff M, et al. Behavioural factors associated with symptom outcomes in a primary care-based depression prevention intervention trial. *Psychol Med* 2003;**33**: 1061–70.
53. Von Korff M, Katon W, Rutter C, Ludman E, Simon G, Lin E, Bush T. Effect on disability outcomes of a depression relapse prevention program. *Psychosom Med* 2003;**65**:938–43.
54. Katon WJ, Lin EH, Von Korff M, Ciechanowski P, Ludman EJ, Young B, Peterson D, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;**363**:2611–20.
55. Katon W, Von Korff M, Lin E, Simon GE. Rethinking practitioner roles in chronic illness: the specialist primary care physician and the practice nurse. *Gen Hosp Psychiatry* 2001;**23**:138–44.
56. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcome. *Arch Intern Med* 2006;**166**:2314–21.
57. Murray MD, Young J, Hoke S, Tu W, Weiner M, Morrow D, Stroupe KT, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Ann Intern Med* 2007;**146**:714–25.
58. *Okeke CO, Quigley HA, Jampel HD, Ying GS, Plyler RJ, Jiang Y, Friedman DS.* Interventions improve poor adherence with once daily glaucoma medications in electronically monitored patients. *Ophthalmology* 2009;**116**:2286–93.
59. Sandman L, Granger BB, Ekman I, Munthe C. Adherence, shared decision-making and patient autonomy. *Med Health Care Philos* 2012;**15**:115–27.
60. Barry MJ, Edgman-Levitan S. Shared decision making: pinnacle of patient-centered care. *N Engl J Med* 2012;**366**:780–1.
61. Ratanawongsa N, Karter AJ, Parker MM, Lyles CR, Heisler M, Moffet HH, Adler N, et al. Communication and medication refill adherence: the Diabetes Study of Northern California. *JAMA Intern Med* 2013;**173**:210–8.
62. Oshima Lee E, Emanuel EJ. Shared decision making to improve care and reduce costs. *N Engl J Med* 2013;**368**:6–8.

Overview

Heart Disease and Depression

Hiroto Ito, Ph.D.[1*], **Yasuyuki Okumura, Ph.D.**[1], **Hiroyuki Yokoyama, M.D., Ph.D.**[2]

Depression is common in patients with physical illness. The National Center of Neurology and Psychiatry has launched a joint project with five other centers in Japan, aiming at improving the quality of mental care in patients with physical illness. In the present overview focusing on heart disease, we review the prevalence of depression in patients with heart disease, the impact of depression on cardiac prognosis, the possible mechanisms of depression in patients with heart disease, drug-drug interactions between cardiac and psychotropic agents and the possible therapeutic approaches to treating these patients. Depression and heart disease often coexist and each can lead to the other. Various biological and behavioral mechanisms have been proposed to explain an association between heart disease and depression, including autonomic nervous system activity, impairment of platelet function, endothelial dysfunction, inflammatory changes, and health-related behaviors. Combination therapy with tricyclic antidepressant and cardiac agents must be approached with caution to avoid drug-drug interactions. Selective serotonin reuptake inhibitors (SSRIs) are the first line treatment for patients with heart disease and moderate to severe depression. Although no single intervention has been established as the standardized treatment, recent studies suggest that collaborative care improves both depressive symptoms and cardiac outcomes, and that patient's participation is a key to successful treatment. Bridging the gap between cardiology and psychiatry is essential, and psychiatrists can play a vital role in taking care of the mental health of patients with heart disease.

Key words: depression, heart disease, antidepressant, collaborative care
(***Taiwanese Journal of Psychiatry*** **[Taipei] 2013; 27: 22-32)**

Introduction

Depression is a subject of growing importance in patients with physical illness. The prevalence of depression varies according to the definition and assessment methods. In general, the prevalence of depression is 13%-20% in patients with cancer [1], 29%-36% with stroke [2], 20% with coronary heart disease [3], and 11% with diabetes mellitus patients [4]. Negative impacts of depression on the outcomes of patients with physical illness are well-known. Depression may raise the mortality risk of patients with cancer 1.25-fold [5] and double the risk in those with myocardial infarction [6], while depression increases the length of stay in hospitalization and clinic visits in patients with stroke [7]. Also, depression may reduce glycemic control [8] and adherence to treatment in patients with diabetes mellitus [9].

To improve the quality of mental health care in patients with physical illness, the National Center of Neurology and Psychiatry (NCNP) has launched a joint project with five other national centers in Japan, including the National Cancer Center (cancer), the National Cerebral and Cardiovascular Center (stroke and heart disease), the National Center for Global Health and Medicine (diabetes mellitus), the National Center for Geriatrics and Gerontology (dementia), and the National Center for Child Health and Development (chronic inflammatory bowel disease). The project is aimed at promoting (A) training of health care providers in medical fields, (B) certification of model institutions and communities to provide high quality of mental health care for patients with physical illness, and (C) clinical research on the effectiveness of collaborative care programs and a support network to facilitates the integration of mental health care into general health care.

In the present overview, we are focusing on heart disease, and we review the prevalence of depression in patients with heart disease, the impact of depression on cardiac outcomes, the possible mechanisms of depression in patients with heart disease, drug-drug interactions between cardiac and psychotropic agents, and the possible therapeutic approaches to treating these patients.

[1] Department of Social Psychiatry, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan
[2] National Cerebral and Cardiovascular Center, Osaka, Japan
Received: February 20, 2013, accepted: March 6, 2013
*Correspondence author. 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8553, Japan
E-mail: Hiroto Ito <ItoHiroto@ncnp.go.jp>

Prevalence of Depression and its Impact on Cardiac Outcomes

There is a growing body of literature on an association between heart disease and depression. "Heart disease" is a broad term to describe a range of diseases in the heart, including coronary heart disease or coronary artery disease, heart attack, and heart failure. The result of a meta-analysis shows that 20% of patients with coronary heart disease have depression [3]. The results of follow-up community-based study over the past decade show moderate to strong relationships between depression and heart disease such as angina and myocardial infarction [10]. A Swedish twin study in 2009 suggested that heart disease increases the incidence of depression risk 2.8-fold times (95%CI: 1.9-4.2), while depression increases the incidence of cardiovascular disease 2.5-fold times (95%CI: 1.7-3.8) [11]. Patients with heart disease are prone to depression, while depression can lead to heart disease.

Both depression and heart disease are leading causes of disability [12]. The impact of comorbidity of those two diseases has been highlighted in a landmark study demonstrating that the risk of cardiac death in the 6 months after acute myocardial infarction is about 4 times greater in patients with depression compared to those without [13]. The publication of this study in 1993 stimulated further research to determine the impact of depression on cardiac outcomes [10]. Now, depression is known as a predictive factor of poor outcomes after myocardial infarction, including recurrence, cardiac death and all causes of death. Depression increases mortality 2.3-fold times after myocardial infarction [14], 1.8-fold times in congestive heart failure [15], 3.3-fold

times in unstable angina [16], and 2.4-fold times after coronary artery bypass [17]. A Japanese study comparing depression, anxiety, and anger reports that depression in hospitalized cardiovascular patients is a stronger independent risk factor for adverse cardiac events than either anxiety or anger [18]. In addition to the health risks, the comorbid condition is costly, imposing high out-of-pocket burdens on these patients. The out-of-pocket expenditure burden is estimated to double in patients who suffer from both heart disease and psychological distress compared to that in patients with heart disease only [19].

Possible Mechanisms of the Link between Heart Disease and Depression

Many mechanisms have been proposed to explain the link between heart disease and depression from basic science to the epidemiological level. Many studies have suggested that biological, psychosocial, and behavioral factors are related to the association between heart disease and depression [20]. Although the mechanism underlying this relationship remains not fully understood, these efforts help generate possible intervention strategies.

Biological factors

Biological factors representing a possible link between heart disease and depression include (A) neuroendocrine dysregulation, (B) inflammation, and (C) enhanced platelet activation and endothelial dysfunction. In addition to its effects during the acute phase of heart disease, prolonged stress activates the hypothalamic-pituitary-adrenal (HPA) axis and releases cortisol. High levels of cortisol deplete collagen, counteract insulin, decrease bone density and weaken the immune system, often resulting in various health conditions and diseases. On the other hand, a strong association exists between depression and increased cortisol. A previous study revealed that highly stressed women with cardiovascular disease have a 1.6-fold greater risk (95%CI: 1.3-2.2) compared to those without stress [21].

Meta analyses suggest that inflammation may also be a link between heart disease and depression. Depression and C-reactive protein (CRP), interleukin (IL)-1, and IL-6 are positively associated in both clinical and community populations [22]. CRP concentration is related to risks of coronary heart disease, ischemic stroke, and vascular mortality [23].

Platelet activation and endothelial dysfunction are other possible biological mechanisms that connect heart disease with depression. Depression increase susceptibility to blood clotting due to alterations in multiple steps of the clotting cascade, including platelet activation and aggregation [24]. D-dimer, von Willebrand factor and plasminogen activator inhibitor (PAI) levels are related to depression [25]. It is worth noting that treatment with sertraline in depressed patients after acute coronary syndrome is associated with reduced platelet/endothelial activation despite coadministration of antiplatelet regimens such as aspirin [26].

A decrease in nitric oxide (NO) availability would predispose patients to developing atherosclerosis [20]. The levels of both plasma NO metabolite (NOx) and platelet endothelial NO synthase (eNOS) activity are significantly lower in patients with major depression compared with healthy control subjects [27]. These results suggest that patients with depression are at risk for atherosclerosis; however, treatment with a serotonin and norepinephrine reuptake inhibitor (SNRI) (milnacipran) significantly increases the plasma NOx levels [28].

Another interesting topic is brain-derived neurotrophic factor (BDNF). There is a strong evidence that serum BDNF levels are abnormally low in patients with major depressive disorder and that the BDNF levels are elevated with antidepressant treatment [29]. BDNF also plays an important role in atherogenesis and plaque instability [30].

Psychosocial factors

The medical community has accepted that acute myocardial infarction and sudden cardiac death can be triggered by stressors such as heavy physical exertion and severe emotional stress [31], and the meta-analysis shows that depression is as a strong predictor of coronary heart disease [32]. The INTERHERT study, a large global standardized case control study, involving a sample of 24,767 patients in 52 countries, revealed that the presence of psychosocial stressors is associated with increased risk of acute myocardial infarction. The psychosocial stressors are ongoing work-related stress, ongoing home stress, ongoing general stress and financial stress [33]. The effect of psychosocial factors on cardiac function is likely greater than is commonly recognized, resulting in an increasing level of interest in this area.

An increased incidence of acute cardiac events has been reported in communities after stressful events. After the Great Hanshin Earthquake in Japan [34], increased numbers of patients were admitted to emergency departments due to myocardial infarction, and cardiovascular events increased among German supporters during the World Cup match [35]. These consequences clearly show the potential for acute and direct impacts of life events on the human autonomic nervous system.

Since the theory that "Type A" personality, that is, a compound of hostility, competitiveness and impatience, triggers heart attacks, was introduced in the United States in the late 1950s, the personality theory remained highly controversial in the scientific community. Although researchers in recent years have tended to deny any association between heart disease and personality, related constructs to those of the Type A personality are regaining attention. A systematic review in 2009 showed that anger and hostility increased risk of cardiovascular disease [36]. Recently, a new type of personality trait, the Type D, was found to increase the risk of cardiovascular events. The Type D personality was also linked to an increased risk of depression [37]. Biological and behavioral pathways are being studied to explain these adverse effects of the Type D personality on health.

Behavioral factors

Health risk behaviors including smoking, unhealthy diet, and physical inactivity contribute to risk factors of heart disease. These behavioral factors are also prevalent in patients with depression, including smoking [38], and lower levels of physical and social activities [39]. Nonadherence to medication is a risk factor for both adverse outcomes of depression and coronary heart disease [40].

Genetic determinants

Genetic connection is a new avenue of investigation to explain the link between heart disease and depression. An American study of 2,731 male-male twin pairs from the Vietnam Era Twin Registry suggests that 20% of genetic influence is common across heart disease and depression [41]. The Swedish population-based twin registry with 30,374 twins also shows the possibility of genetic factors to explain the relationship between major depression and coronary heart disease [11]. The serotonin transporter gene

(*5-HTTLPR*) polymorphism is related to both emotion and platelet activation and is, therefore, a promising candidate as a genetic determinant of linked heart disease and depression [20]. Carriers of the s allele of *5-HTTLPR* are considered to be more vulnerable to depression in patients with heart disease [42].

Therapeutic Approaches

Medications

Treatment options for depression include antidepressants, cognitive behavioral therapy, and physical activity. The American Heart Association (AHA) recommends SSRI or SNRI as the first-line treatment for moderate to severe depression [43]. There is strong evidence of the safety of the SSRI, sertraline in particular. Sertraline has shown no significant adverse effects in patients with coronary heart disease in the Sertraline Antidepressant Heart Attack Randomized Trial [44]. Citalopram was also recommended as a first-line agent based on a randomized trial; however, in 2012, the US Food and Drug Administration has warned of drug-induced QTc interval prolongation and *torsade de pointes* when using citalopram at doses greater than 40 mg per day (http://www.fda.gov/Drugs/DrugSafety/ucm297391.htm) .

One of the challenges to treating depression in patients with heart disease is that cardiologists must decide whether to use antidepressants as primary treatment. In fact, depression in patients with heart disease is often left untreated, or the best treatment is often not provided. It is also true in reality that there are various barriers to coordinating with the liaison consultation psychiatrist in clinical settings. Even though the cardiologist consults with the psychiatrist, advice from the psychiatrist is often limited to advocating for the temporary discontinuation of psychotropic agents.

New cardiac and psychotropic agents are constantly being introduced into practice. Although the safety of each drug is assessed, every possible combination with other drugs cannot be evaluated. In addition, polypharmacy is common in psychiatric patients as well as in elderly patients, while cardiologists and primary care physicians have more opportunities to prescribe psychotropic medications for comorbid patients. These trends increase the potential risk of drug-drug interaction, but no consensus exists regarding cardiac drug interactions with concurrent psychotrophic prescriptions. Strain et al. conducted a series of studies on the drug combinations among cardiologists, psychiatrists and experts in clinical pharmacology since the 1990s [45-47]. They systematically reviewed commonly prescribed cardiac and psychotropic medications, and rated the level of significance in interaction between cardiac drugs and psychotropic drugs as "major" (potentially life-threatening or capable of causing permanent death), "moderate" (a deterioration in a patient's status, resulting in additional treatment or hospitalization or extension of hospital stay), or "minor" (bothersome or unnoticeable) [45, 47]. In 2002, the review was updated with newly added drugs [47].

Table 1 shows 15 drug combinations that would increase the risk of serious adverse events. Five of the 15 combinations include tricyclic antidepressants. Combination therapy with tricyclic antidepressants may cause fatal ventricular arrhythmia, *torsade de pointes*, due to prolongation of QT interval with ibutilide, and interference with brethylium's effects, and may potentiate the pressure effects of direct acting sympathomimetics (e.g., dobutamine, norepinephrine, epinephrine, and phenylephrine) while decreasing the pressor response to indirect-acting sympathomimetics (e.g., dopamine) [45]. Tricyclic antidepressants have antiarrhythmic effects, and therefore are contraindicated after myocardial infarction [48].

Table 1. Major drug-drug interactions between cardiac and psychotropic agents

Cardiac agents	Psychotropic agents
Adenosine	Carbamazepine
Amiodarone	Trazodone
Atorvastatin	Nefazodone
Bretylium	Tricyclic antidepressants (desipramine, doxepin, imipramine)
Clonidine	Tricyclic antidepressants
Diuretics	Lithium
Furosemide	Fluoxetine
Ibutilide	Phenothiazines/Haloperidol
Ibutilide	Tricyclic antidepressants
Quinidine	Selective serotonin reuptake inhibitors (SSRIs)
Quinidine	Tricyclic antidepressants
Sympathomimetics (dobutamine, dopamine, amphetamines, ephedrine, phenylephrine)	MAO inhibitors
Sympathomimetics (dobutamine, norepinephrine, epinephrine, phenylephrine)	Tricyclic antidepressants
Warfarin	Barbiturates

This table is a summary of the 1999 [45] and 2002 [47] studies by Strain et al.

SSRIs are generally safe, but combining them with furosemid or quinidine requires caution. When furosemid and fluoxetine are co-administered, there is a risk of hyponatremia. Concurrent use of quinidine and an SSRI inhibits metabolic enzyme, and thus the plasma concentration and side effects of both agents should be observed. Drug-drug interactions newly added in 2002 include atorvastatin and nefazone, and warfarin and barbiturates. Because both combinations affect the metabolism of cardiac agents, plasma concentrations of atorvastatin and warfarin should be observed [47]. The data are still limited, and so the risks and benefits of psychotropic agents should be carefully balanced, and potential drug-drug interactions should be closely monitored. Good quality studies are needed to establish standard medication protocols in comorbid patients with depression and heart disease.

Cognitive behavioral therapy

The Harvard research group conducted a large multicenter randomized controlled trial, the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study in 2,481 patients with myocardial infarction receiving treatment for depression with cognitive behavioral therapy and SSRIs. The intervention has not been found to reduce cardiovascular events or mortality, although depression and social isolation are improved [49]. Since that study appeared, no large-scale clinical trial has

been conducted regarding cognitive behavioral therapy in patients with heart disease. A *post hoc* subgroup analysis of ENRICHD during the 29-month follow-up period has revealed a significant reduction in mortality and morbidity in depressed post-myocardial infarction patients receiving SSRIs [50].

Physical activity

The potential benefits of exercise for improving cardiovascular fitness [51] and reducing depressive symptoms [52] have been emphasized in recent studies. Since depression may be a barrier to participating in exercise programs, health care providers should facilitate patient participation in exercise programs tailored to patients' cardiac conditions.

Collaborative care

The results of two studies published in 2010 deserve attention. One described patient-centered management based on guidelines provided by nurses for patients with depression and chronic disease that has shown to improve both depression and chronic disease [53], and the other described collaborative care ("enhanced depression care") for patients with coronary syndrome that has shown to improve depression and cardiac prognosis with a high level of patient satisfaction [54].

Katon et al. conducted a single-blind, randomized, controlled trial in 14 primary care clinics to examine depression management and improvement of glycemic/hypertension/lipid control in 214 participants with poorly controlled diabetes mellitus, coronary heart disease, or both and coexisting depression [53]. The 12-month intervention included self-care support and medication for depression, hyperglycemia, hypertension, and hyperlipidemia. The target goal was determined among the patient, nurse, and the primary care physician. The nurse coordinated care between the primary care physician and a psychiatrist, and played a central role in intervention. The patient visited the clinic 2 or 3 times a week, while the nurse supervised the patient weekly.

Collaborative care is an established program in primary care [55]. It consists of: (A) an enhanced care approach, with treatment delivered by a clinical nurse specialist, psychologist, social worker, and/or psychiatrist; (B) the patient's choice of psychotherapy and/or pharmacotherapy; (C) problem-solving therapy (psychotherapy); (D) a stepped-care approach with reviews of symptom severity and treatment; and (E) a standardized instrument used to track depressive symptoms. Davidson et al. applied this approach to patients with coronary syndrome [54].

In contrast to Berkman et al. who conducted a cross-sectional study in patients with major depression or minor depression [49], Davidson et al. limited the participants in their study to those with persistent depressive symptoms (a Beck Depression Scale score being greater than 10 for more than 3 months). It was a successful strategy to have a specific target population.

In the United Kingdom, the National Institute of Clinical Excellence (NICE) recommends a stepped care model for the treatment of depression [56]. Stepped care provides a framework for the care of patients with chronic illnesses, including hypertension, diabetes mellitus, and depression with the least costly, least intensive, and least restrictive treatment. The care is tailored based on severity, clinical status, and patient preference. The least intensive care includes self-care support, and care can be intensified to cognitive behavioral therapy, medication management, and hospital care (Table 2).

Table 2. Stepped care*

	Targets	Treatments (examples)
Step 1	All known and suspected presentations of depression	Assessment, support, psycho-education, active monitoring
Step 2	Persistent sub-threshold depressive symptoms; mild to moderate depression	Step 1 plus Low-intensity psychosocial interventions, psychological interventions, medication
Step 3	Persistent sub-threshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression	Step 2 plus high-intensity psychological interventions, combined treatments, collaborative care
Step 4	Severe and complex depression; risk to life; severe self-neglect	Step 3 plus , electroconvulsive therapy, crisis service, combined treatments, multi-professional and inpatient care

* National Institute for Health and Clinical Excellence: *Depression in Adults with a Chronic Physical Health Problem: Treatment and Management*. London: British Psychological Society and Gaskell, 2010 [56].

Patient Participation

According to a systematic review, no single intervention has been found to be effective for reducing 30-day rehospitalization in patients with chronic disease; but discharge planning, follow-up telephone call, and patient-centered discharge instructions have shown promising results in combined intervention [57]. Another systematic review found that case management and collaborative care (telephone and in person) can improve medication adherence for more than one condition, particularly in patients with depression [58]. This evidence suggests that patients' views are essential for effective interventions. An interesting systematic review supports that the detection of depression during physical illness must take into account the patients' beliefs and the integration of depression management with management for risk factors for cardiovascular disease [59]. Psychiatric liaison-consultation should be established in the department of cardiology, and training of coordinators who work between cardiologist and psychiatrist is needed for enhanced patient care.

Conclusion

There is a growing interest in the connection between heart disease and depression. Despite the extensive studies of this subject, much remains inconclusive because the association is complex and multifaceted. Depression in patients with heart disease is often overlooked and remains untreated. As health care becomes more specialized and fragmented, these comorbid patients are increasingly at risk to receive suboptimal care. Bridging the gap between cardiology and psychiatry is essential. Psychiatrists can play a vital role in improving mental health of patients with heart disease.

References

1. Mitchell AJ, Chan M, Bhatti H, et al.: Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol* 2011; 12: 160-4.
2. Hackett ML, Yapa C, Parag V, Anderson CS: Frequency of depression after stroke: a systematic review of observational studies. *Stroke* 2005; 36: 1330-40.
3. Thombs BD, Bass EB, Ford DE, et al.: Prevalence of depression in survivors of acute myocardial infarction. *J Gen Intern Med* 2006; 21: 30-8.
4. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ: The prevalence of comorbid depression in adults with diabetes mellitus: a meta-analysis. *Diabetes Care* 2001; 24: 1069-78.
5. Satin JR, Linden W, Phillips MJ: Depression as a predictor of disease progression and mortality in cancer patients: a meta-analysis. *Cancer* 2009; 115: 5349-61.
6. Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P: Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen Hosp Psychiatry* 2011; 33: 203-16.
7. Jia H, Damush TM, Qin H, et al.: The impact of post-stroke depression on healthcare use by veterans with acute stroke. *Stroke* 2006; 37: 2796-801.
8. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE: Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000; 23: 934-42.
9. Gonzalez JS, Peyrot M, McCarl LA, et al.: Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care* 2008; 31: 2398-403.
10. Prince M, Patel V, Saxena S, et al: No health without mental health. *Lancet* 2007; 370: 859-77.
11. Kendler KS, Gardner CO, Fiske A, Gatz M: Major depression and coronary heart disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. *Arch Gen Psychiatry* 2009; 66: 857-63.
12. Murray CJ. Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burdenn of Disease Study. *Lancet* 1997; 349: 1498-504.
13. Frasure-Smith N, Lespérance F, Talajic M: Depression following myocardial infarction: impact on 6-month survival. *JAMA* 1993; 270: 1819-25.
14. Dickens C, McGowan L, Percival C, et al.: New onset depression following myocardial infarction predicts cardiac mortality. *Psychosom Med* 2008; 70: 450-5.
15. Sherwood A, Blumenthal JA, Trivedi R, et al.: Relationship of depression to death or hospitalization in patients with heart failure. *Arch Intern Med* 2007; 167: 367-73.
16. Lespérance F, Frasure-Smith N, Juneau M, Théroux P: Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000; 160: 1354-60.
17. Blumenthal JA, Lett HS, Babyak MA, et al.: Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet* 2003; 362: 604-9.
18. Nakamura S, Kato K, Yoshida A, et al.: Prognostic value of depression, anxiety, and anger in hospitalized cardiovascular disease patients for predicting adverse cardiac outcomes. *Am J Cardiol* (in press).
19. Okumura Y, Ito H: Out-of-pocket expenditure burdens in patients with cardiovascular conditions and psychological distress: a nationwide cross-sectional study. *Gen Hosp Psychiatry* 2013 (in press).
20. Riba M, Wulsin L, Rubenfire M: *Psychiatry and Heart Disease: the Mind, Brain and Heart*. Oxford: Wiley-Blackwell, 2012.
21. Iso H, Date C, Yamamoto A, et al.: Perceived mental stress and mortality from cardiovascular disease among Japanese men and women: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). *Circulation* 2002; 106: 1229-36.
22. Howren MB, Lamkin DM, Suls J: Associations of depression with C-Reactive Protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med* 2009; 71: 171-86.
23. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, et al.: C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010; 375: 132-40.
24. Nemeroff CB, Goldschmidt-Clermont PJ: Heartache and heartbreak: the link between depression and cardiovascular disease. *Nat Rev Cardiol* 2012; 9: 526-39.
25. von Känel R, Mills PJ, Fainman C, Dimsdale JE: Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: a biobehavioral pathway to coronary artery disease? *Psychosom Med* 2001; 63: 531-44.
26. Serebruany VL, Glassman AH, Malinin AI, et al.: Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation* 2003; 108: 939-44.
27. Chrapko WE, Jurasz P, Radomski MW, Lara N, Archer SL, Le Mellédo JM: Decreased platelet nitric oxide synthase activity and plasma nitric oxide metabolites in major depressive disorder. *Biol Psychiatry* 2004; 56: 129-34.
28. Ikenouchi-Sugita A, Yoshimura R, Hori H, Umene-Nakano W, Ueda N, Nakamura J: Effects of antidepressants on plasma metabolites of nitric oxide in major depressive disorder: comparison between milnacipran and paroxetine. *Prog Neuropsychopharmacol Biol Psychiatry* 2009; 33: 1451-3.
29. Sen S, Duman R, Sanacora G.: Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol Psychiatry* 2008; 64: 527-32.
30. Ejiri J, Inoue N, Kobayashi S, et al.: Possible role of brain-derived neurotrophic factor in the pathogenesis of coronary artery disease. *Circulation* 2005; 112: 2114-20.
31. Tofler GH, Muller JE: Triggering of Acute Cardiovascular Disease and Potential Preventive Strategies *Circulation* 2006; 114: 1863-72.
32. Rugulies R: Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am J Prev Med* 2002; 23: 51-61.
33. Rosengren A, Hawken S, Ounpuu S, et al.: Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; 364: 953-62.
34. Ogawa K, Tsuji I, Shiono K, Hisamichi S: Increased acute myocardial infarction mortality following the 1995 Great Hanshin-Awaji earthquake in Japan. *Int J Epidemiol* 2000; 29: 449-55.
35. Wilbert-Lampen U, Leistner D, Greven S et al.: Cardiovascular events during World Cup soccer. *N Engl J Med* 2008; 358: 475-83.
36. Chida Y, Steptoe A: The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. *J Am Coll Cardiol* 2009; 53: 936-46.
37. Denollet J, Schiffer AA, Spek V: A general propensity to psychological distress affects cardiovascular outcomes: evidence from research on the Type D (Distressed) personality profile. *Circ Cardiovasc Qual Outcomes* 2010; 3: 546-57.
38. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH: Smoking and mental illness: a population-based prevalence study. *JAMA* 2000; 284: 2606-10.
39. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P: Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Res* 2010; 178: 230-5.
40. Gehi A, Haas D, Pipkin S, Whooley MA: Depression and medication adherence in outpatients with coronary heart disease: findings from the heart and soul study. *Arch Intern Med* 2005; 165: 2508-13.
41. Scherrer JF, Xian H, Buchoz KK, et al.: A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosom Med* 2003; 65: 548-57.

42. Nakatani D, Sato H, Sakata Y, et al.: Influence of serotonin transporter gene polymorphism on depressive symptoms and new cardiac events after acute myocardial infarction. *Am Heart J* 2005; 150: 652-8.
43. Lichtman JH, Bigger JT, Jr., Blumenthal JA, et al.: Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation* 2008; 118: 1768-75.
44. Glassman AH, O'Connor CM, Califf RM, et al.: Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA.* 2002; 288: 701-9.
45. Strain JJ, Caliendo G, Alexis JD, Lowe RS 3rd, Karim A, Loigman M: Part II: cardiac drug, and psychotropic drug interactions: significance, and recommendations. *Gen Hosp Psychiatry* 1999; 21: 408-29.
46. Strain JJ, Caliendo G, Alexis JD, Karim A, Loigman M, LoweIII RS: Cardiac drug and psychotropic drug interactions: significance and recommendations. *Heart Dis* 2001; 3: 248-62.
47. Strain JJ, Karim A, Caliendo G, Alexis JD, Lowe RS 3rd, Fuster V: Cardiac drug-pyschotropic drug update. *Gen Hosp Psychiatry* 2002; 24: 283-9.
48. O'Brien P, Oyebode F: Psychotropic medication and the heart. *Advances in Psychiatric Treatment* 2003; 9: 414-23.
49. Berkman LF, Blumenthal J, Burg M, et al.: Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003; 289: 3106-16.
50. Taylor CB, Youngblood ME, Catellier D, et al.: Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. *Arch Gen Psychiatry* 2005; 62: 792-8.
51. Clark AM, Haykowsky M, Kryworuchko J, et al.: A meta-analysis of randomized control trials of home-based secondary prevention programs for coronary artery disease. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 261-70.
52. Daley A. Exercise and depression: a review of reviews. *J Clin Psychol Med Settings* 2008; 15: 140-7.
53. Katon WJ, Lin EH, Von Korff M, et al.: Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010; 363: 2611-20.
54. Davidson KW, Rieckmann N, Clemow L, et al.: Enhanced depression care for patients with acute coronary syndrome and persistent depressive symptoms: coronary psychosocial evaluation studies randomized controlled trial. *Arch Intern Med* 2010; 170: 600-8.
55. Unützer J, Katon W, Callahan CM, et al.: Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002; 288: 2836-45.
56. National Institute for Health and Clinical Excellence: *Depression: The Treatment and Management of Depression in Adults*. London: British Psychological Society and Gaskell, 2010.
57. Hansen LO, Young RS, Hinami K, Leung A, Williams MV: Interventions to reduce 30-day rehospitalization: a systematic review. *Ann Intern Med* 2011; 155: 520-8.
58. Viswanathan M, Golin CE, Jones CD, et al.: Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med* 2012; 157: 785-95.
59. Alderson SL, Foy R, Glidewell L, McLintock K, House A: How patients understand depression associated with chronic physical disease: a systematic review. *BMC Fam Pract* 2012; 13: 41.

Contents lists available at SciVerse ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

Out-of-pocket expenditure burdens in patients with cardiovascular conditions and psychological distress: a nationwide cross-sectional study

Yasuyuki Okumura, Ph.D.*, Hiroto Ito, Ph.D.

Department of Social Psychiatry, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo 187-8553, Japan

ARTICLE INFO

Article history:
Received 1 October 2012
Revised 3 December 2012
Accepted 31 December 2012

Keywords:
Burden of disease
Resource allocation
Mental health policy
Equity in health

ABSTRACT

Objectives: This study aimed to estimate the prevalence of psychological distress in individuals with and without cardiovascular risks and events [cardiovascular disease (CVD) conditions] and the incremental effects of psychological distress on the out-of-pocket health care expenditure burdens.
Methods: We used data from the Comprehensive Survey of Living Conditions 2007, a nationally representative cross-sectional survey in Japan. Psychological distress assessed by the K6 scale, the presence of treated CVD conditions and out-of-pocket health care expenditures as a share of household consumption expenditures were self-reported by 20,763 individuals living alone and aged between 20 and 59 years.
Results: Individuals with obesity [adjusted odds ratio (AOR), 4.3], stroke (AOR, 3.2), ischemic heart disease (AOR, 2.3), hyperlipidemia (AOR, 1.8) or diabetes (AOR, 1.7) were more likely than those without to have serious psychological distress (SPD). With the exception of ischemic heart disease, less than half of CVD patients comorbid with SPD received treatment for mental illness. Patients comorbid with SPD and obesity (AOR, 6.1), SPD and ischemic heart disease (AOR, 3.4), and SPD and hypertension (AOR, 2.6) had higher out-of-pocket burdens than patients with only CVD conditions.
Conclusions: Our findings suggest the need for physicians to identify and manage SPD in patients with CVD conditions and for policymakers to find solutions to reduce the high out-of-pocket burdens among these patients.

1. Introduction

Cardiovascular risks and events [cardiovascular disease (CVD) conditions] such as obesity, hyperlipidemia, hypertension, diabetes, ischemic heart disease and stroke have been major public health concerns around the world [1]. Individuals with CVD conditions are about twice as likely to suffer from depression, anxiety and psychological distress as those without the conditions [2–4]. These comorbidities remain significant individual and public health concerns because they lead to poor quality of life [4], nonadherence to cardiac medication [5], excess direct medical costs [6], productivity loss due to absence from work [7] and increased mortality [8].

Available evidence on comorbidities of CVD conditions with psychological distress and their negative consequences has several limitations. First, few studies, most of which were conducted in the United States, have used nationally representative samples to establish unique associations between the presence of psychological distress and particular CVD conditions [3,9–14]. Second, it remains uncertain whether comorbidities of CVD conditions with psychological distress are associated with burdens of out-of-pocket health care expenditures relative to effective income. Identifying high out-of-pocket burdens is important because these burdens may be associated with delaying or foregoing medical care for financial reasons [15], which in turn may lead to severe health conditions. Generally, out-of-pocket burden in Japan is lower than other countries [16] because Japan has a universal health care system that reduces out-of-pocket health care expenditures to less than 30% of medical fees. Even in countries where health care systems provide excellent population health at low cost with equity [17], we hypothesized that there would be an incremental effects of psychological distress on out-of-pocket burdens because psychological distress leads to excess direct medical costs and productivity loss [6,7].

In the present study, we used data from a nationally representative sample of 20- to 59-year-old individuals living alone. We had two specific objectives for the present study. First, we examined whether the prevalence of psychological distress was higher in individuals with CVD conditions than in those without CVD conditions. Second, we examined whether out-of-pocket health care expenditures as a share of household consumption expenditures were higher in individuals with psychological distress than in those without.

* Corresponding author. Tel.: +81 42 346 2046; fax: +81 42 346 2047.
E-mail address: yokumura@ncnp.go.jp (Y. Okumura).

0163-8343/$ – see front matter
http://dx.doi.org/10.1016/j.genhosppsych.2012.12.013

2. Methods

2.1. Data source

We used data from the Comprehensive Survey of Living Conditions (CSLC) 2007, a nationally representative cross-sectional survey of Japanese-speaking household members in Japan, conducted by the Ministry of Health, Labour and Welfare between June and July 2007 [18]. In the present study, we obtained permission to use data by the Ministry of Health, Labour and Welfare. The CSLC assessment has three parts: (a) the Household and Health questionnaires for the entire sample, (b) the Income and Savings questionnaires for the subsample and (c) the Long-term care questionnaire for the subsample. A detailed description of the CSLC has been reported previously [18–20]. Only data from the Household and Health questionnaires were used for the present study and reported below.

The target population of the CSLC comprised a total of ≥120 million individuals in Japan. Of about 940,000 enumeration districts delineated to comprise 50 households per enumeration district in the 2005 Population Census [21], 5440 were selected by a stratified random sampling method. All members were recruited from 287,807 households within the enumeration districts. A total of 624,168 members in 229,821 households answered the questionnaires (response rate, 79.9%).

In the present study, we used a subsample comprising 20,736 participants living alone who were aged between 20 and 59 years and noninstitutionalized and who completed questions on working status, out-of-pocket health care expenditure and household consumption expenditure (Figure). We focused only on individuals living alone to measure individual out-of-pocket health care expenditures that were not shared by financial resources of other family members. In addition, we restricted samples to working-age adults for the following reasons. First, individuals aged ≥60 years are more likely to receive retirement benefits and public pension, which can provide regular effective income irrespective of disability status. Second, Japan's universal health care system pays 70% of medical fees charged to most individuals aged ≤69 years and 90% to most individuals aged ≥70 years. Including those over 59 years would decrease the comparability of out-of-pocket burdens between working-age and elderly adults.

2.2. Measures

2.2.1. Current treated CVD conditions

Current treated medical conditions were assessed with a self-report checklist that included 41 conditions such as diabetes and obesity. Respondents were asked to report whether they were currently being treated for any condition in a noninstitutionalized setting, mark all conditions listed in the checklist and indicate the most worrisome condition. Such checklists have been widely used in prior population-based studies [22,23]. Our report considers only the status of each condition rather than the most worrisome condition. Of the 41 conditions, we selected the following seven highly related cardiovascular risks and events as in previous studies [24,25]: (a) diabetes, (b) obesity, (c) hyperlipidemia, (d) hypertension, (e) stroke, (f) ischemic heart diseases and (g) other CVDs.

2.2.2. Treatment status of mental illness

As mentioned above, current treated medical conditions were assessed with the self-report checklist. We coded whether participants received treatment for mental illness using the item 'depression or other mental illness' in the checklist.

2.2.3. Psychological distress

The CSLC assesses nonspecific psychological distress using the K6 scale [26,27]. The K6 is a self-rated six-item questionnaire that asks respondents how frequently they have experienced symptoms of psychological distress during the past 30 days (e.g., 'During the past

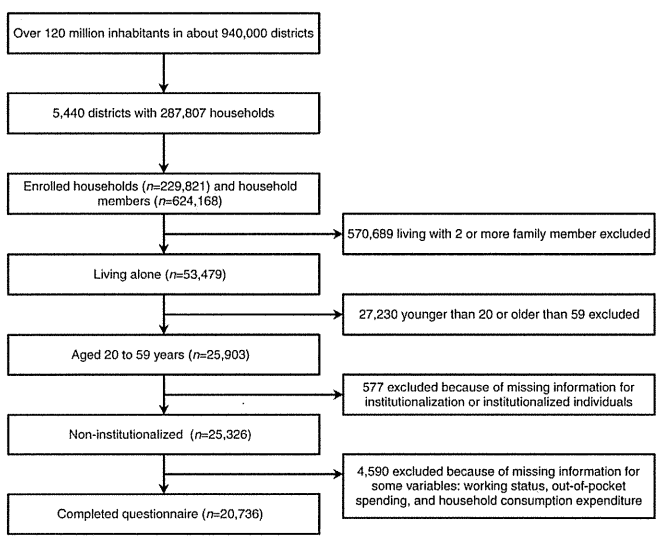


Fig. Flow diagram of included and excluded participants.

30 days, about how often did you feel nervous?'). Respondents rate each question on a five-point scale ranging from 'none of the time' (0) to 'all of the time' (4). The K6 scores range from 0 to 24, with higher scores indicating more severe psychological distress. Based on a previous validation study [27], the K6 scores were classified into four mutually exclusive groups: (a) a probable serious psychological distress (SPD) group defined as a score on the K6 of 14–24, (b) probable mild/moderate psychological distress (MPD) group defined as the K6 of 9–13, (c) probable noncase group defined as the K6 of 0–8 and (d) an unknown group defined as one with any missing values. Although most previous studies have focused only on SPD [3,9–14], we consider it important to examine MPD as well as SPD because of the high rates of hospitalization, work disability, suicide attempts and subsequent SPD [28].

2.2.4. Out-of-pocket expenditure burdens

Respondents were asked about their out-of-pocket health care expenditures in the past month. It included all direct medical costs such as physical examinations, medical treatments and pharmaceuticals. It did not include cash outlays for nursing care, payments for health insurance premiums or direct nonmedical costs such as transportation and parking. Respondents were also asked about their household consumption expenditures in the past month. It included all payments for goods and services, but excluded expenditures that did not translate directly into acquisition of goods and services such as tax, pension and health insurance premiums. Consumption expenditures have been widely used as a proxy for effective income in prior studies [29,30]. We created a variable by dividing out-of-pocket health care expenditures by household consumption expenditures.

2.2.5. Sociodemographic characteristics

The respondents' sociodemographic characteristics included gender, age, marital status, employment status, pension status and urbanicity. Age was divided into four categories (20–29, 30–39, 40–49 and 50–59 years). Marital status was categorized as married, single and widowed/divorced. Urbanicity was divided into major metropolitan area, other urbanized area and rural area.

2.3. Statistical analyses

We used bivariate and multivariate multinomial logit models to examine associations between treated CVD conditions and psychological distress [31]. The outcome variable was the status of psychological distress: (a) probable SPD group, (b) probable MPD group, (c) probable noncase group (the reference group) and (d) the unknown group. The primary explanatory variables were individual CVD conditions. We estimated odds ratios (ORs) and their 95% confidence intervals (CIs) for the SPD and MPD groups compared with the noncase group after simultaneously controlling for potential confounders. The potential confounding variables included in the models were selected based on a priori clinical knowledge and existing literature [2–4] as follows: (a) gender, (b) age, (c) marital status, (d) employment status, (e) pension status and (f) urbanicity. In addition, we estimated the ratios of treated mental illness using data available for both CVD conditions and psychological distress.

We also investigated the association between psychological distress and out-of-pocket expenditure burdens. We used bivariate and multivariate generalized linear models with the log link function and variance proportional to the mean [32,33]. The outcome variable was out-of-pocket expenditures with the natural logarithm of household consumption expenditures included in the model as an offset term. The primary explanatory variable was the status of psychological distress. Estimated coefficients were exponentiated to provide ratios of out-of-pocket burdens for each CVD condition. Because of the known interactions of individual CVD conditions and psychological distress on functional disability [34], all analyses were stratified by individual CVD conditions. The potential confounding variables in the models were selected a priori clinical knowledge and epidemiological evidence [6,7] as follows: (a) gender, (b) age, (c) marital status, (d) employment status, (e) pension status, (f) urbanicity and (g) number of CVD conditions.

Significance levels were set at 5% for all analyses. Data were analyzed using R version 2.15.1 [35].

3. Results

3.1. Participants

Table 1 shows the characteristics for 20,736 participants. The median age was 38 years (interquartile range, 27–57 years). Of the participants, 61.5% were men, 10.3% were married, 85.1% were employed, and 2.7% received disability, survivor or public pensions. Hypertension (4.3%), diabetes (2.1%) and hyperlipidemia (2.1%) were the most prevalent among specific CVD conditions. The average out-of-pocket burden was 2.1% (S.D., 6.2%). Of the participants, 4.7% had out-of-pocket health care expenditures exceeding 10% of household consumption expenditures.

Table 1
Sociodemographic, cardiovascular risks and events, and psychological distress of participants

Characteristic	Total (N=20,736)	
	n	%
Gender		
Men	12,760	61.5
Women	7976	38.5
Age, years		
20–29	6336	30.6
30–39	4632	22.3
40–49	3655	17.6
50–59	6113	29.5
Marital status		
Married	2134	10.3
Single	14,421	69.5
Widowed/divorced	4181	20.2
Employment status		
Employed	17,641	85.1
Unemployed	3095	14.9
Pension status		
Without	20,169	97.3
With	567	2.7
Urbanicity		
Major metropolitan area	5006	24.1
Other urbanized area	13,995	67.5
Rural area	1735	8.4
Number of CVD conditions		
0	19,136	92.3
1	1187	5.7
≥2	413	2.0
Type of CVD conditions		
Diabetes	441	2.1
Obesity	59	0.3
Hyperlipidemia	427	2.1
Hypertension	893	4.3
Stroke	97	0.5
Ischemic heart disease	110	0.5
Other cardiovascular diseases	123	0.6
Psychological distress (scores on the K6)[a]		
SPD (≥14)	1126	5.4
MPD (9–13)	2425	11.7
Noncase (0–8)	15,838	76.4
Unknown	1347	6.5
OOP burdens		
0%	13,932	67.2
0.1%–1.9%	2245	10.8
2%–4.9%	2235	10.8
5%–9.9%	1345	6.5
≥10%	979	4.7

OOP burdens, out-of-pocket health care expenditures as a share of household consumption expenditures.
[a] SPD group was defined as K6 scores of ≥14, MPD group as 9–13, noncase group as 0–8 and unknown group as any missing values.

Table 2
Multinomial logistic analyses examining the comorbidities of treated cardiovascular risks and events with psychological distress

CVD conditions	n	Prevalence, %		Crude OR[a,b] (95% CI)		AOR[a,b,c] (95% CI)	
		SPD	MPD	SPD	MPD	SPD	MPD
Diabetes							
With	441	6.6	12.5	1.33 (0.91–1.96)	1.17 (0.88–1.56)	1.66 (1.11–2.46)*	1.38 (1.02–1.85)*
Without	20,295	5.4	11.7	1	1	1	1
Obesity							
With	59	16.9	11.9	3.93 (1.95–7.95)*	1.27 (0.56–2.86)	4.31 (2.10–8.82)*	1.41 (0.63–3.19)
Without	20,677	5.4	11.7	1	1	1	1
Hyperlipidemia							
With	427	7.0	12.9	1.42 (0.97–2.07)	1.20 (0.90–1.61)	1.82 (1.23–2.69)*	1.43 (1.06–1.92)*
Without	20,309	5.4	11.7	1	1	1	1
Hypertension							
With	893	4.5	11.1	0.91 (0.66–1.26)	1.06 (0.85–1.31)	1.22 (0.87–1.70)	1.29 (1.03–1.61)*
Without	19,843	5.5	11.7	1	1	1	1
Stroke							
With	97	11.3	15.5	2.94 (1.53–5.64)*	1.85 (1.04–3.29)*	3.16 (1.62–6.13)*	2.04 (1.14–3.64)*
Without	20,639	5.4	11.7	1	1	1	1
Ischemic heart disease							
With	110	8.2	12.7	1.93 (0.96–3.87)	1.39 (0.78–2.47)	2.29 (1.12–4.66)*	1.60 (0.90–2.88)
Without	20,626	5.4	11.7	1	1	1	1
Other cardiovascular							
With	123	5.7	17.1	1.41 (0.65–3.07)	1.97 (1.21–3.21)*	1.57 (0.72–3.45)	2.18 (1.33–3.57)*
Without	20,613	5.4	11.7	1	1	1	1

[a] The reference groups for primary independent variables were defined as individuals without each CVD condition.
[b] The reference groups for dependent variables were defined as a score on the K6 of 0–8.
[c] ORs after simultaneously controlling for potential confounders that were gender, age, marital status, employment status, pension status and urbanicity.
* P<.05.

3.2. Prevalence of psychological distress

The prevalence ratios for SPD and MPD were estimated to be 5.4% and 11.7% in all participants. Among specific CVD conditions, individuals with obesity [adjusted odds ratio (AOR), 4.3; 95% CI, 2.1–8.8], stroke (AOR, 3.2; 95% CI, 1.6–6.1), ischemic heart disease (AOR, 2.3; 95% CI 1.1–4.7), hyperlipidemia (AOR, 1.8; 95% CI, 1.2–2.7) or diabetes (AOR, 1.7; 95% CI, 1.1–2.5) were more likely to have SPD compared with those without each CVD condition (Table 2). With the exception of ischemic heart disease, less than half of CVD patients comorbid with SPD received treatment for mental illness (Table 3).

3.3. Psychological distress and out-of-pocket expenditure burdens

Table 4 shows out-of-pocket health care expenditures as a share of household consumption expenditures by individual CVD conditions. For example, average out-of-pocket burdens for SPD, MPD and noncase groups were estimated to be 11.3%, 4.8% and 6.4% among individuals with diabetes and 3.6%, 2.5% and 1.7% among individuals without diabetes, respectively. Among specific CVD conditions, patients comorbid with SPD and obesity (AOR, 6.1; 95% CI, 2.1–16.6), SPD and ischemic heart disease (AOR, 3.4; 95% CI, 1.3–8.5), and SPD and hypertension (AOR, 2.6; 95% CI, 1.6–4.0) had higher out-of-pocket expenditure burdens than patients with only CVD conditions. In comparison, no significant differences in burdens were observed between CVD patients comorbid with MPD and patients with only CVD conditions. Among individuals without each CVD conditions, SPD and MPD groups had higher out-of-pocket burdens than noncase group.

Table 3
Ratios of treated mental illness in patients comorbid with CVD conditions and psychological distress

CVD conditions	Ratios of treated mental illness, % (95% CI)	
	SPD	MPD
Diabetes	31.0 (15.3–50.8)	12.7 (5.3–24.5)
Obesity	40.0 (12.2–73.8)	14.3 (0.4–57.9)
Hyperlipidemia	50.0 (31.3–68.7)	20.0 (10.4–33.0)
Hypertension	30.0 (16.6–46.5)	10.1 (5.0–17.8)
Stroke	0.0 (0.0–38.5)	0.0 (0.0–30.2)
Ischemic heart disease	55.6 (21.2–86.3)	14.3 (1.8–42.8)
Other cardiovascular	42.9 (9.9–81.6)	14.3 (3.0–36.3)

4. Discussion

This cross-sectional study of a nationally representative sample of Japanese noninstitutionalized 20- to 59-year-old individuals living alone had two major findings. First, the prevalence ratios for SPD were over 1.6 times higher in individuals with obesity, stroke, ischemic heart disease, hyperlipidemia or diabetes than in those without each CVD condition after controlling for potential confounders. Second, average out-of-pocket burdens were over 2.5 times higher in patients comorbid with SPD and obesity, SPD and ischemic heart disease, and SPD and hypertension than in those with only CVD conditions.

Consistent with previous findings, we found associations between the presence of psychological distress and obesity [12], stroke [11,12], ischemic heart disease [11–13], hyperlipidemia [12] and diabetes [12,13]. In addition, we found that less than half of CVD patients comorbid with SPD received treatment for mental illness, with the exception of ischemic heart disease. These results confirm the need for identifying and managing psychological distress in patients with CVD conditions [36,37].

Comorbidities of obesity, ischemic heart disease or hypertension with SPD lead to excess out-of-pocket health care expenditure burdens. Several potential explanations account for the high out-of-pocket burdens among CVD patients comorbid with SPD. First,

Table 4
Generalized linear regression models stratified by CVD conditions examining associations of comorbid psychological distress and out-of-pocket burdens

CVD conditions and psychological distress	OOP burdens, *M*	Crude burden ratio[a] (95% CI)	Adjusted burden ratio[a,b] (95% CI)
With diabetes			
SPD	11.3	1.74 (0.86–3.15)	1.76 (0.98–2.95)
MPD	4.8	1.11 (0.66–1.78)	1.20 (0.79–1.78)
Noncase	6.4	1	1
Without diabetes			
SPD	3.6	1.97 (1.66–2.33)*	2.08 (1.77–2.43)*
MPD	2.5	1.41 (1.23–1.62)*	1.42 (1.25–1.62)*
Noncase	1.7	1	1
With obesity			
SPD	14.1	5.70 (2.09–14.67)*	6.07 (2.14–16.63)*
MPD	4.1	0.45 (0.06–1.78)	2.09 (0.35–8.44)
Noncase	5.0	1	1
Without obesity			
SPD	3.7	1.91 (1.61–2.25)*	2.02 (1.72–2.35)*
MPD	2.6	1.42 (1.24–1.62)*	1.42 (1.25–1.61)*
Noncase	1.8	1	1
With hyperlipidemia			
SPD	10.5	2.82 (1.39–5.16)*	1.53 (0.84–2.67)
MPD	7.1	1.24 (0.62–2.26)	1.28 (0.74–2.11)
Noncase	6.4	1	1
Without hyperlipidemia			
SPD	3.6	1.91 (1.60–2.25)*	2.03 (1.73–2.37)*
MPD	2.5	1.42 (1.24–1.63)*	1.41 (1.24–1.60)*
Noncase	1.7	1	1
With hypertension			
SPD	10.3	3.44 (2.02–5.51)*	2.56 (1.58–4.00)*
MPD	6.0	1.24 (0.74–1.97)	1.09 (0.70–1.63)
Noncase	5.6	1	1
Without hypertension			
SPD	3.5	1.91 (1.60–2.27)*	1.93 (1.63–2.26)*
MPD	2.4	1.46 (1.27–1.68)*	1.39 (1.21–1.58)*
Noncase	1.7	1	1
With stroke			
SPD	17.2	2.54 (0.76–6.92)	2.95 (0.86–9.04)
MPD	5.1	0.57 (0.11–1.86)	0.57 (0.12–1.87)
Noncase	7.4	1	1
Without stroke			
SPD	3.6	1.92 (1.62–2.26)*	2.03 (1.73–2.37)*
MPD	2.5	1.42 (1.24–1.62)*	1.41 (1.25–1.60)*
Noncase	1.8	1	1
With ischemic heart disease			
SPD	11.1	0.96 (0.20–2.86)	3.43 (1.29–8.53)*
MPD	6.6	0.48 (0.08–1.57)	1.38 (0.51–3.19)
Noncase	9.5	1	1
Without ischemic heart disease			
SPD	3.7	1.98 (1.67–2.31)*	2.07 (1.77–2.41)*
MPD	2.5	1.44 (1.26–1.64)*	1.44 (1.26–1.63)*
Noncase	1.8	1	1
With other cardiovascular			
SPD	13.3	2.19 (0.65–5.69)	2.11 (0.75–5.30)
MPD	4.7	0.73 (0.24–1.79)	0.89 (0.37–1.91)
Noncase	7.7	1	1
Without other cardiovascular			
SPD	3.7	1.95 (1.64–2.29)*	2.05 (1.75–2.39)*
MPD	2.5	1.42 (1.23–1.62)*	1.42 (1.25–1.60)*
Noncase	1.8	1	1

OOP Burdens, out-of-pocket health care expenditures as a share of household consumption expenditures.

[a] The reference groups were defined as a score on the K6 of 0–8.

[b] Burden ratios after simultaneously controlling for potential confounders that were gender, age, marital status, employment status, pension status, urbanicity, and number of cardiovascular risks and events.

* $P<.05$.

comorbid SPD may increase the severity of CVD conditions (or vice versa), which would in turn increase direct medical costs. For example, patients with heart failure and depression had 29% greater direct medical costs than those with only heart failure because of increased utilization of inpatient and outpatient treatments [6]. Second, the presence of SPD may lead to loss of income due to absence from work. A large cross-sectional study revealed that patients with chronic illness and depression were more likely to be absent from work than those with only chronic illness in the Canadian general population [7]. Our results suggest that CVD patients comorbid with SPD face a dual economic burden, namely, excess direct medical costs and income loss. To measure individual out-of-pocket burdens, we focused on the general population who lived alone, and thus, they could not share financial resources of other family members to overcome their out-of-pocket burdens. Policymakers need to find solutions to reduce the high out-of-pocket burdens for CVD patients comorbid with SPD. Such solutions may be preferable and effective for patients comorbid with SPD rather than MPD, out-of-pocket burdens of which are similar to the burdens of patients with only CVD conditions.

Our results may be conservative estimates of out-of-pocket burdens among Organization for Economic Co-operation and Development (OECD) countries. In general, the average out-of-pocket burden in Japan (2.2%) is 70% lower than the OECD average (3.1%) [16] because Japan's universal health care system has led to excellent public health at low costs with equity [17]. Therefore, CVD patients comorbid with SPD would face more out-of-pocket burdens in other countries.

Our study had several limitations. First, there was a possibility for false-positive and false-negative results because the status of psychological distress was based on self-rated data using the K6 scale. A previous validation study [27] showed that the positive predictive value for the K6 scores of 14–24 is 85% in a population with a 5% prevalence of any *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, mood or anxiety disorder at present (e.g., patients with CVD conditions). Based on a validation study [27] and the hypothetical prevalence of 5%, 15% of defined CVD patients comorbid with SPD would not meet current diagnoses for any mood or anxiety disorder. Second, CVD condition status was also based on a self-report checklist that noted whether they were currently being treated for any condition for CVD conditions in a noninstitutionalized setting. Therefore, current findings may not be generalized to either untreated or institutionalized individuals with CVD conditions. Third, the generalizability of the present study was also limited to 20- to 59-year-old individuals living alone. In addition, we cannot rule out the possibility of selection bias caused by including only individuals living alone because living status might be associated with both psychological distress and CVD conditions. Finally, the present study had limitations inherent to cross-sectional studies that cannot establish causality of associations.

In conclusion, our findings indicate that individuals with CVD conditions may have SPD and that this comorbidity was associated with high out-of-pocket burdens in a representative sample of Japanese individuals living alone. The present study suggests that physicians should identify and manage SPD in patients with CVD conditions and that policymakers should find solutions to reduce the high out-of-pocket burdens among these patients.

Acknowledgments

Funding for analyzing and writing this article was supported by Comprehensive Research on Disability Health and Welfare (Ministry of Health, Labour, and Welfare, H21-KOKORO-IPPAN-007).

References

[1] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3(11):e442.
[2] Scott KM, Bruffaerts R, Tsang A, Ormel J, Alonso J, et al. Depression–anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. J Affect Disord 2007;103(1–3):113–20.

[3] Ferketich AK, Binkley PF. Psychological distress and cardiovascular disease: results from the 2002 National Health Interview Survey. Eur Heart J 2005;26(18):1923–9.
[4] Sareen J, Jacobi F, Cox BJ, Belik SL, Clara I, et al. Disability and poor quality of life associated with comorbid anxiety disorders and physical conditions. Arch Intern Med 2006;166(19):2109–16.
[5] Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. Arch Intern Med 2005;165(21):2508–13.
[6] Sullivan M, Simon G, Spertus J, Russo J. Depression-related costs in heart failure care. Arch Intern Med 2002;162(16):1860–6.
[7] Stein MB, Cox BJ, Afifi TO, Belik SL, Sareen J. Does co-morbid depressive illness magnify the impact of chronic physical illness? A population-based perspective. Psychol Med 2006;36(5):587–96.
[8] Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med 2004;66(6):802–13.
[9] Chittleborough CR, Winefield H, Gill TK, Koster C, Taylor AW. Age differences in associations between psychological distress and chronic conditions. Int J Public Health 2011;56(1):71–80.
[10] Li C, Ford ES, Zhao G, Strine TW, Dhingra S, et al. Association between diagnosed diabetes and serious psychological distress among U.S. adults: the Behavioral Risk Factor Surveillance System, 2007. Int J Public Health 2009;54(Suppl 1):43–51.
[11] Fan AZ, Strine TW, Jiles R, Berry JT, Mokdad AH. Psychological distress, use of rehabilitation services, and disability status among noninstitutionalized US adults aged 35 years and older, who have cardiovascular conditions, 2007. Int J Public Health 2009;54(Suppl 1):100–5.
[12] Zhao G, Ford ES, Li C, Strine TW, Dhingra S, et al. Serious psychological distress and its associations with body mass index: findings from the 2007 Behavioral Risk Factor Surveillance System. Int J Public Health 2009;54(Suppl 1):30–6.
[13] Shih M, Simon PA. Health-related quality of life among adults with serious psychological distress and chronic medical conditions. Qual Life Res 2008;17(4):521–8.
[14] Centers for Disease Control, Prevention. Serious psychological distress among persons with diabetes — New York City 2003. MMWR Morb Mortal Wkly Rep 2004;53(46):1089–92.
[15] Banthin JS, Bernard DM. Changes in financial burdens for health care: national estimates for the population younger than 65 years, 1996 to 2003. JAMA 2006;296(22):2712–9.
[16] Organization for Economic Co-operation and Development. Government at a glance 2011. Paris, France: OECD publications; 2011.
[17] Shibuya K, Hashimoto H, Ikegami N, Nishi A, Tanimoto T, et al. Future of Japan's system of good health at low cost with equity: beyond universal coverage. Lancet 2011;378(9798):1265–73.
[18] Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Comprehensive survey of living conditions. Tokyo: Health and Welfare Statistics Association; 2009.
[19] Inoue A, Kawakami N, Tsuchiya M, Sakurai K, Hashimoto H. Association of occupation, employment contract, and company size with mental health in a national representative sample of employees in Japan. J Occup Health 2010;52(4):227–40.
[20] Shibuya K, Hashimoto H, Yano E. Individual income, income distribution, and self rated health in Japan: cross sectional analysis of nationally representative sample. BMJ 2002;324(7328):16–9.
[21] Bureau Statistics. Population census of Japan. Tokyo: Japan Statistical Association; 2005. 2007.
[22] Merikangas KR, Ames M, Cui L, Stang PE, Ustun TB, et al. The impact of comorbidity of mental and physical conditions on role disability in the US adult household population. Arch Gen Psychiatry 2007;64(10):1180–8.
[23] Suliman S, Stein DJ, Myer L, Williams DR, Seedat S. Disability and treatment of psychiatric and physical disorders in South Africa. J Nerv Ment Dis;198(1):8–15.
[24] Schwarz EB, Ray RM, Stuebe AM, Allison MA, Ness RB, et al. Duration of lactation and risk factors for maternal cardiovascular disease. Obstet Gynecol 2009;113(5):974–82.
[25] Sullivan PW, Ghushchyan V, Wyatt HR, Hill JO. The medical cost of cardiometabolic risk factor clusters in the United States. Obesity (Silver Spring) 2007;15(12):3150–8.
[26] Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 2002;32(6):959–76.
[27] Furukawa TA, Kawakami N, Saitoh M, Ono Y, Nakane Y, et al. The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. Int J Methods Psychiatr Res 2008;17(3):152–8.
[28] Kessler RC, Merikangas KR, Berglund P, Eaton WW, Koretz DS, et al. Mild disorders should not be eliminated from the DSM-V. Arch Gen Psychiatry 2003;60(11):1117–22.
[29] Xu K, Evans DB, Kawabata K, Zeramdini R, Klavus J, et al. Household catastrophic health expenditure: a multicountry analysis. Lancet 2003;362(9378):111–7.
[30] Xu K, Klavus J, Kawabata K, Evans DB, Hanvoravongchai P, et al. Household health system contributions and capacity to pay: definitional, empirical and technical challenges. Health systems performance assessment: debates, methods and empiricism. Geneva: World Health Organization; 2003.
[31] Long JS. Regression models for categorical and limited dependent variables. Thousand Oaks, CA: Sage; 1997.
[32] Dobson AJ, Barnett G. An introduction to generalized linear models. Chapman and Hall; 2008.
[33] Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. Health Serv Outcomes Res Methodol 2000;1(2):185–202.
[34] Schmitz N, Wang J, Malla A, Lesage A. Joint effect of depression and chronic conditions on disability: results from a population-based study. Psychosom Med 2007;69(4):332–8.
[35] R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2012.
[36] Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 2009;374(9690):609–19.
[37] Lichtman JH, Bigger Jr JT, Blumenthal JA, Frasure-Smith N, Kaufmann PG, et al. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation 2008;118(17):1768–75.

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

Validity of the Patient Health Questionnaire (PHQ)-9 and PHQ-2 in general internal medicine primary care at a Japanese rural hospital: a cross-sectional study☆,☆☆,★

Masatoshi Inagaki, M.D., Ph.D. [a,b,*], Tsuyuka Ohtsuki, Ph.D. [b], Naohiro Yonemoto, Ph.D. [c], Yoshitaka Kawashima, Ph.D. [d], Akiyoshi Saitoh, Ph.D. [d], Yuetsu Oikawa, M.D. [e], Mie Kurosawa, M.D., Ph.D. [f], Kumiko Muramatsu, M.D., Ph.D. [g], Toshi A. Furukawa, M.D., Ph.D. [h,i], Mitsuhiko Yamada, M.D., Ph.D. [d]

[a] Department of Neuropsychiatry, Okayama University Hospital, Okayama, Japan
[b] Center for Suicide Prevention, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan
[c] Translational Medical Center, National Center of Neurology and Psychiatry, Tokyo, Japan
[d] Department of Neuropsychopharmacology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan
[e] Oshu City Magokoro Hospital, Iwate, Japan
[f] Iwate Mental Health Center, Iwate, Japan
[g] Clinical Psychology Course, Graduate School of Niigata Seiryo University, Niigata, Japan
[h] Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan
[i] Department of Clinical Epidemiology, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto, Japan

ARTICLE INFO

Article history:
Received 17 May 2013
Revised 22 July 2013
Accepted 6 August 2013

Keywords:
Depression
Primary care
Internal medicine
Screening
Patient Health Questionnaire

ABSTRACT

Objective: Two depression screening tools, Patient Health Questionnaire (PHQ)-9 and PHQ-2, have not had their validity examined in general internal medicine settings in Japan. We examined the validity of these screening tools.

Methods: A total of 598 outpatients of an internal medicine clinic in a rural general hospital were enrolled consecutively and stratified by PHQ-9 score. Seventy-five patients randomly selected and 29 patients whose results from the PHQ-9 were considered to be positive for depressive disorder were then interviewed with a semistructured interview, the Mini International Neuropsychiatric Interview. We calculated diagnostic accuracy of the PHQ-9 and PHQ-2 to detect major depression and that of the suicidality item of the PHQ-9 to detect suicidality using sampling weights with multiple imputations.

Results: Sensitivity and specificity for depression were 0.86 and 0.85, respectively, for the PHQ-9 with cutoff points of 4/5, and 0.77 and 0.95, respectively, for the PHQ-2 with cutoff points of 2/3. Sensitivity and specificity of the suicidality item of the PHQ-9 were 0.70 and 0.97, respectively.

Conclusion: In internal medicine clinics in Japanese rural hospitals, the PHQ-2 with an optimal cutoff point for each setting plus the suicidality item of the PHQ-9 can be recommended to detect depression without missing suicidality.

1. Background

Depression is prevalent [1–4], and its influence on quality of life is profound. In middle-income and high-income countries including Japan, depression was the leading cause of disability in 2004 [5]. Prevalence of depression is reported to be high in health care settings [6–8]. The World Health Organization performed a primary care mental health survey across 14 countries and found that 14% of primary care patients suffered from major depression [7]. However, a meta-analysis showed that many depressed patients were overlooked and that many nondepressed patients were misdiagnosed as having depression [9]. Thus, development of a valid screening tool is required in health care settings.

The Patient Health Questionnaire (PHQ)-9 is one of the commonly used validated screening tools for depression in various settings including primary care and general practice [10–14]. The PHQ-9 has two different assessment methods. One uses a categorical (yes/no) algorithm to screen for depression. In the categorical algorithm, the depression screening is positive if five or more of the nine depressive symptom criteria are endorsed and one of the symptoms is anhedonia or depressed mood. The other is a dimensional (continuous scale) assessment. In the dimensional assessment, the sum of the PHQ-9 scores is calculated, and an a priori cutoff score is applied. Using the categorical algorithm, the sensitivity and specificity shown in a meta-analysis were 0.77 [95% confidence interval (CI): 0.71–0.84] and 0.94 (95% CI: 0.90–0.97), respectively [14]. In comparison, the sensitivity and specificity of the dimensional assessment using cutoff scores for the PHQ-9 in primary care settings that were calculated in another meta-analysis were 0.86 (95% CI: 0.66–0.97) and 0.88 (95% CI: 0.80–0.93), respectively [12]. A third meta-analysis showed the sensitivity and specificity of the dimensional assessment using the cutoff score 9/10 as 0.81 (95% CI: 0.72–0.88) and 0.92 (95% CI: 0.83–0.97), respectively [10]. However, these studies showed major variability in the optimal cutoff point [10,12]. A cutoff point of around 10 was recommended in a previous publication [15] and shown to be the optimal cutoff point in a previous study using meta-analysis [12]. However, the optimal cutoff point score has been reported as lower in elderly populations [16,17], a population in Korea [16] and a community sample in rural Pakistan [18]. In addition, the sensitivity using this cutoff point was relatively low (sensitivity: 0.50–0.69) [19–21] in some settings including a hospital setting [22,23] and a family practice clinic (sensitivity: 0.53) [24].

In Japan, especially in rural areas, most patients consult a general internist who plays a role similar to that of a primary care physician or a general practitioner. We reported the prevalence of depression in an internal medicine outpatient clinic in a rural general hospital as 7.4% [25]. In that study, we showed that a critical symptom, suicidality, was present in 12.7% [25]. In a previous study, however, we also reported that physicians overlooked many symptoms of depression and did not pay attention to diagnosing depression [26]. Thus, a screening tool to support depression identification has to be developed and used widely. However, there is no screening tool for which the validity has been confirmed in such primary care settings in Japan.

Therefore, in the present study, we examined the validity of the Japanese versions of the PHQ-9 and PHQ-2 in an internal medicine outpatient clinic in a rural general hospital, which has a role in the primary care of the residents in the area. In addition, we examined the validity of the suicidality item of the PHQ-9 to detect suicide ideation as ascertained by a semistructured interview because the PHQ-2 does not include the question of suicidality and may cause the clinician to miss this critical symptom.

2. Methods

2.1. Participants

The sampling process and procedures of the study have been reported previously [25] and are described briefly below. This study was conducted on 9 consecutive consultation days between July 12 and 23, 2010, at an internal medicine outpatient clinic in a general hospital having no mental health specialties. This hospital is located in a small city (population of 124,756 in 2010) in the Tohoku region of Japan. The hospital serves as a regional public hospital and is funded by the National Health Insurance Society in Oshu. The city is located in a typical rural area about 500 km north of Tokyo with low population influx. There are high proportions of elderly people and people engaged in primary industry [27].

We used the following inclusion criteria to define a target population to be assessed for depression: (1) patients aged 20 or older who visited the outpatient clinic to consult a physician for their own primary care and (2) patients who have no communication difficulties, such as hearing loss or language problems, and who have no severe cognitive impairment, such as dementia or disturbance of consciousness. Thus, we did not include visitors who came in for admission preparation or those who consulted for their family members. We did not include patients who lived outside the catchment area of the hospital. Severe cognitive impairment was judged based on a semistructured interview using the first two questions of the Mini-Mental State Examination concerning time and place orientation [28,29]. This was administered by research staff consisting of two psychiatrists (M.I. and M.Y.), a research assistant (T.O.) having experience in surveys using the Mini-Mental State Examination and PHQ-9 in internal medical clinics, and nurses. The staff sometimes conducted an additional interview about patients' lifestyle factors and dementia history if accompanying persons were present. For ethical reasons and for the feasibility of the survey, we also excluded patients who were too physically ill to be interviewed.

This study was approved by the ethics committee of the National Center of Neurology and Psychiatry in Japan. The researchers provided all participants with detailed information using a written document and administered a battery of self-report questionnaires (PHQ-9) [15,30] after the patients provided oral informed consent. After this first-stage screening to stratify the participants, we conducted the structured psychiatric interviews [Mini International Neuropsychiatric Interview (MINI)] [31,32] with patients who provided further written informed consent.

2.2. Measurements

2.2.1. PHQ-9

The PHQ-9 is a widely used screening tool in health care settings [15,30]. The PHQ-9 is a self-report questionnaire consisting of nine questions asking about depression symptoms such as anhedonia, depressed mood and suicidality. The PHQ-9 was translated into Japanese (the Japanese version of PHQ-9) through back translation and validated in a previous study [30]. We asked patients to choose from the following options how often they had been bothered by each of the nine symptoms over the last 2 weeks: "Not at all," "Several days," "More than half the days" and "Nearly every day."

A categorical algorithm has been proposed in the literature [15,30] to assess the PHQ-9 results. In the categorical algorithm, the depression screening is positive if five or more of the nine depressive symptom criteria are endorsed as having been present at least "more than half the days" and one of the symptoms was anhedonia or depressed mood. One of the nine items, "thoughts that you would be better off dead or of hurting yourself in some way," is counted if present at all. In addition to the categorical algorithm of the PHQ-9, we adopted a two-item categorical algorithm with the first two items of the PHQ-9 (anhedonia and depressed mood). In the two-item categorical algorithm, depression screening is positive if one or more of the two depressive symptom criteria are endorsed as having been present.

Alternatively, we calculated the sum of the PHQ-9 scores as a dimensional assessment of the PHQ-9. Each item of the PHQ-9 is scored from 0 to 3, with a total possible score of 27 for the nine items. Also, we calculated the sum of the PHQ-2. A total possible score of the PHQ-2 was 6.

2.2.2. MINI

We diagnosed major depressive episode using the Major Depression Episode module of the MINI [31,32]. The interview was originally developed as a semistructured diagnostic interview compatible with the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, (DSM-III-R) and *International Classification of Diseases, 10th Revision*, criteria [33,34]. The MINI was translated in a previous study [31] through the standard procedure of back translation for the cross-cultural adaptation of an original English psychometric instrument [35]. The Japanese version of the MINI was validated using the

☆ Authors' contributions: All authors have read and approved the final version of the manuscript. M.I. was the principal investigator and developed the original idea for the study. M.I., T.O., N.Y., Y.O., T.A.F. and M.Y. designed the study. M.I., T.O., N.Y. and T.A.F. analyzed data, and all authors discussed and prepared the manuscript.

☆☆ Funding: This work was supported by a grant for Research on Psychiatric and Neurological Disease and Mental Health from the Ministry of Health, Labour and Welfare. We thank Ms. Kyoko Sakurai, Ms. Hiromi Muramatsu and Ms. Mayumi Matsutani for their kind support.

★ The authors declare that they have no competing interests.

* Corresponding author. Department of Neuropsychiatry, Okayama University Hospital, 2-5-1, Sikada-cho, Kita-ku, Okayama, 700-8558, Japan. Tel.: +81 86 235 7242; fax: +81 86 235 7246.

E-mail addresses: masatoshiinagaki@okayama-u.ac.jp (M. Inagaki), ohtsuki@ncnp.go.jp (T. Ohtsuki), yonemoto@ncnp.go.jp (N. Yonemoto), kawashima@ncnp.go.jp (Y. Kawashima), asaitoh@ncnp.go.jp (A. Saitoh), yuetsu-o@city.oshu.iwate.jp (Y. Oikawa), miek@pref.iwate.jp (M. Kurosawa), muramatu@n-seiryo.ac.jp (K. Muramatsu), furukawa@kuhp.kyoto-u.ac.jp (T.A. Furukawa), mitsu@ncnp.go.jp (M. Yamada).

0163-8343/$ – see front matter
http://dx.doi.org/10.1016/j.genhosppsych.2013.08.001

Table 1
Characteristics of participants

Characteristics		n = 511
Age	Mean (S.D.) years old	73.5 (12.3)
	Median (range) years old	75 (21–102)
Sex (male): *n*, %	*n* = 208	40.7%
Clinical diagnosis of primary illness: *n*, %		
Hypertension	*n* = 300	58.7%
Diabetes	*n* = 82	16.0%
Hyperlipidemia	*n* = 81	15.9%
Brain infarction	*n* = 43	8.4%
Arrhythmia	*n* = 35	6.8%
Number of visits in the past 6 months: median (range)		4 (0–74)
Patients diagnosed as having major depressive episode by MINI: *n*, %		
	n = 37	7.4%
Patients assessed as having current suicidality by MINI: *n*, %		
	n = 65	12.7%

Additional detailed information has been reported previously [25].

Structured Clinical Interview for DSM-III-R in the previous study [31]. Additionally, we assessed risk of suicide using the Suicide module of the MINI.

2.3. Procedure

We adopted a random sampling stratified by the PHQ-9 results [36]. We used the following two criteria to stratify patients to receive the next step of the MINI interview session as "probable depression": more than two items were present, of which one item was either of the first two items in the PHQ-9 (item 1: anhedonia or item 2: depressed mood), or the score of the dimensional assessment of the PHQ-9 was more than 10. Trained psychiatrists (M.I. or M.Y.), who were blind to the results of the PHQ-9, conducted semistructured MINI interviews of patients who met either of the two criteria and of patients who were randomly selected from among those who did not meet either of the two criteria [36,37]. The MINI interviews were performed after the PHQ-9 screening in a different room on the same day. The interval between the MINI interview and the PHQ-9 was approximately 120 min, depending on the availability of the room and the interviewers and on the timing of participants' routine clinical consultation with internal medical physicians.

We defined the target population to estimate the validity of the PHQ-9 and the PHQ-2 by the inclusion criteria described in the participant section.

2.4. Statistical analysis

We calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), odds ratio, likelihood ratio of a positive test and likelihood ratio of a negative test of the categorical algorithm of the PHQ-9 and the PHQ-2 using sampling weights [36,37] with multiple imputations for the missing data [38]. The weight was based on the inverse of the sampling probability for age, sex, clinical diagnosis of primary illness and PHQ-9 dimensional score. In this way, we estimated the point values and the 95% confidence intervals (CIs) of the screening indices statistically in the targeted population of 511 outpatients.

In addition to the categorical algorithms, we calculated the same values for the dimensional assessment of the PHQ-9 using various cutoff points. For the dimensional scores of the PHQ-9 and the PHQ-2, we illustrated the receiver operating characteristic (ROC) curves, calculating the area under the curves (AUC). Cutoff points based on the Youden index [39] were determined.

We calculated stratum-specific likelihood ratios (SSLRs) [40] of the PHQ-9 dimensional score. The cutoff thresholds recommended in the literature for the PHQ-9 were 4/5 for mild depression and 9/10 for moderate to severe depression [15,30]. Thus, we calculated SSLRs for the PHQ-9 for the scores 0–4, 5–9 and 10 and over.

We estimated the validity of item #9 of the PHQ-9 to detect current suicidality as measured by the MINI suicidal module. Then, as a supplemental analysis, to confirm whether the PHQ-2 would miss suicidality or not, we showed the sensitivity, specificity and other indices of the PHQ-2 to screen for suicidality as measured by item #9 of the PHQ-9.

We performed all statistical analyses using the statistical software packages SPSS 17.0 (IBM, Tokyo, Japan) and Statistical Analysis System (SAS) 9.2 (SAS Institute, Tokyo, Japan).

3. Results

3.1. Sampling process

The results of the sampling process have been reported in our previous study [25]. During the study period, 598 patients visited the clinic. We randomly selected 107 of the outpatients. From the selected 107 patients, we excluded 21 based on our inclusion criteria: 1 was less than 20 years old, 7 consulted family members, 1 resided outside the area, and 12 were severely cognitively impaired. Among the 86 patients, 5 patients were physically too ill, and 1 refused to participate in the study. Then, we administered the PHQ-9 to 80 patients who agreed to participate in the survey.

Among the remaining 491 patients who were not selected randomly, we excluded 66 based on our inclusion criteria: 16 were less than 20 years old, 15 consulted for family members, 1 visited to prepare for admission, 2 resided outside the area, and 32 were severely cognitively impaired. Among the 425 patients, 12 were physically too ill, 4 were missed, and 5 refused to participate in the study. Then, we administered the PHQ-9 to 404 patients and acquired PHQ-9 data for 396 of the 404 patients, with eight sets of PHQ-9 data being incomplete. As a result, 36 patients out of the 396 were screened as positive for probable depression.

Among the total 116 participants (80 and 36 participants), 104 received a structured interview using the MINI. Twelve patients were not interviewed (seven were missed, one was physically ill, and four refused the interview).

The target population to estimate prevalence was 511 patients (86 and 425 patients).

Table 2
Screening performance of the dimensional assessments of the PHQ-9 and PHQ-2

	Se	Sp	PPV	NPV	OR	LR+	LR−
PHQ-9 cutoff point							
3/4	0.86	0.80	0.26	0.99	25.37	4.31	0.17
4/5	0.86	0.85	0.32	0.99	36.9	5.88	0.16
5/6	0.67	0.90	0.35	0.97	18.08	6.69	0.37
6/7	0.67	0.93	0.42	0.97	25.76	9.25	0.36
7/8	0.67	0.95	0.53	0.97	39.96	13.99	0.35
8/9	0.55	0.96	0.53	0.96	29.88	14.08	0.47
9/10	0.55	0.98	0.65	0.96	50.0	23.2	0.46
10/11	0.45	0.99	0.72	0.96	59.36	32.84	0.55
11/12	0.45	0.99	0.82	0.96	105.87	58.21	0.55
12/13	0.37	1.00	0.86	0.95	124.68	78.33	0.63
PHQ-2 cutoff point							
1/2	0.77	0.89	0.36	0.98	26.77	6.97	0.26
2/3	0.77	0.95	0.54	0.98	60.61	14.81	0.24
3/4	0.61	0.98	0.66	0.97	62.30	24.75	0.40
4/5	0.31	1.00	0.90	0.95	162.32	112.72	0.69

Se, sensitivity; Sp, specificity; OR, odds ratio; LR+, likelihood ratio of positive test; LR−, likelihood ratio of negative test.

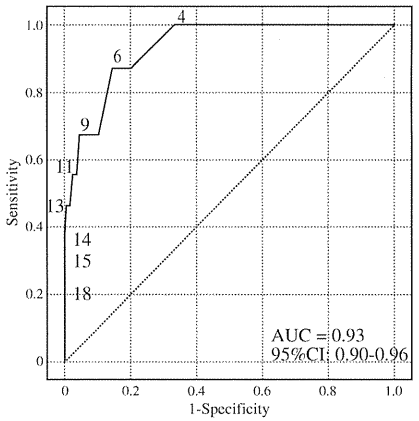


Fig. 1. ROC curve and AUC of the PHQ-9.

3.2. Participants' characteristics

The characteristics of the 511 subjects who were the target population to estimate the validity of the PHQ-9 and the PHQ-2 were reported in a previous study [25]. Table 1 summarizes the characteristics of the participants.

3.3. Dimensional assessment of the PHQ-9 and PHQ-2

Table 2 shows the results of the sensitivity, specificity, PPV, NPV, odds ratio, likelihood ratio of a positive test and likelihood ratio of a negative test using each of the cutoff points of the PHQ-9 and the PHQ-2. It was shown that the cutoff point of the PHQ-9 determined by the Youden index was 4/5 and the cutoff point of the PHQ-2 determined by the Youden index was 2/3 (Table 2).

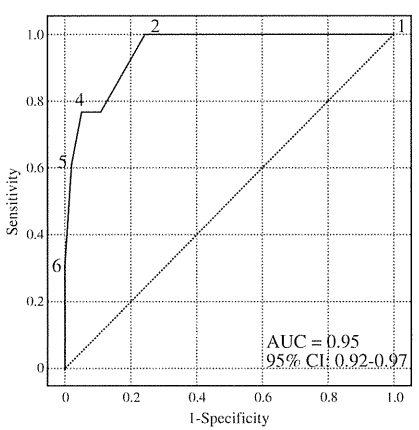


Fig. 2. ROC curve and AUC of the PHQ-2.

ROC curves of the PHQ-9 and the PHQ-2 are displayed in Figs. 1 and 2. The AUC of the PHQ-9 was 0.93 (95% CI: 0.90–0.96), and that of the PHQ-2 was 0.95 (95% CI: 0.92–0.97).

The SSLRs with their 95% CIs of the PHQ-9 weighted back to the target population are shown in Table 3.

3.4. Categorical algorithm of the PHQ-9 and PHQ-2

Using the categorical algorithm of the PHQ-9 and PHQ-2, the sensitivity, specificity, PPV, NPV, odds ratio, likelihood ratio of a positive test and likelihood ratio of a negative test are shown in Table 4.

3.5. PHQ-9 item #9 (suicidality)

The estimated sensitivity, specificity, PPV, NPV, odds ratio, likelihood ratio of a positive test and likelihood ratio of a negative test of the PHQ-9 item #9 (suicidality) for detecting suicidality as measured by the MINI are shown in Table 5. The cutoff score of 0/1 of item #9 of the PHQ-9 showed good sensitivity (0.70) and specificity (0.97) (Table 5).

Among the 476 patients who completed the PHQ-9, 54 patients (11.3%) endorsed item #9 of the PHQ-9 (suicidality). Among the 54 patients, the PHQ-2 categorical assessment for depression screened 21 patients as probably depressed. However, the PHQ-2 did not pick up the remaining 33 patients with probable suicidality (61.1% of the 54 patients with probable suicidality as judged by item #9 of the PHQ-9), suggesting that many suicidal patients would be missed without performing item #9 of the PHQ-9.

4. Discussion

In the present study, the validity of the Japanese version of PHQ-9 and PHQ-2 was examined. Compared with the results of the categorical assessment of the PHQ-9, the PHQ-2 and the dimensional algorithm using a cutoff point of 4/5 on the PHQ-9 had preferable sensitivity and specificity in screening for major depressive disorders.

Using the cutoff point of 9/10 recommended in previous publications [15,30], the sensitivity of the dimensional assessment of the PHQ-9 was low. The cutoff point 4/5, which was a cutoff point determined by the Youden index for the subjects of the present study, was more adequate. However, even using the cutoff point of 4/5, 14% of depressed patients were overlooked and 15% of nondepressed patients were overdiagnosed as having depression. Comparing the PHQ-2 and the dimensional algorithm of the PHQ-9 with a cutoff point of 4/5, the PHQ-9 with cutoff point 4/5 had a preferable sensitivity but a lower specificity. Given the small differences in sensitivities and specificities between the PHQ-2 and the PHQ-9 with a 4/5 cutoff point and given the simplicity of the evaluation, the PHQ-2 may be preferred in screening for depression in this setting.

However, applying the cutoff point 4/5 would lead to overdiagnoses, as more than 13% of patients would be erroneously judged to have depression in a setting where the prevalence of depression was 7.4% [25]. In addition, the PPV was only 0.32, which may not be sufficient for routine clinical use. Meanwhile, the PPV of the cutoff point 7/8 exceeded 0.5. Although the cutoff point 7/8 would miss 2.4%

Table 3
SSLRs of the PHQ-9 dimensional assessment

Stratum	0–4	5–9	10 and over
SSLR	0.16 (95% CI: 0.07–0.33)	2.54 (95% CI: 1.54–4.20)	23.05 (95%CI: 12.51–42.47)

Posterior probability is greater than the prior probability if the SSLR is >1.0. The former is smaller than the latter if the SSLR is <0.1. An SSLR >10 makes the target disorder highly probable, whereas one smaller than 0.1 usually rules it out. SSLRs between 10 and 5 or between 0.1 and 0.2 are often very informative, while those between 0.5 and 2 would be of little assistance in the diagnosis [40].

Table 4
Screening performance of the categorical algorithms of the PHQ-9 and PHQ-2

	Se	Sp	PPV	NPV	OR	LR+	LR−
PHQ-9	0.42	1.00	0.93	0.96	308.5	178.7	0.58
PHQ-2	0.77	0.91	0.40	0.98	32.5	8.37	0.26

of patients, the percentage of patients who would be erroneously overdiagnosed as having depression would now be only 4.6%. Given the risk of overdiagnosis, the cutoff point 7/8 of the PHQ-9 may be more useful than the cutoff point 4/5. In a different context, the cutoff point 10/11, the specificity and the PPV for which were 0.99 and 0.76, respectively, may be more useful so as not to overdiagnose depression in routine clinical practices.

For patients in an internal medicine outpatient clinic in a rural general hospital in Japan, the categorical algorithm of the PHQ-9 had lower sensitivity, whereas the higher specificity seems to be excessive given the cost of overlooking a significant proportion of depressed patients. Meanwhile, the PHQ-2 had adequate sensitivity and specificity. In such an internal medicine outpatient clinic, the PPV of 0.40 and the NPV of 0.98 of the PHQ-2 may be acceptable. In a setting where the prevalence of depression was 7.4% [25], the PHQ-9 overlooked about 58% of patients with major depressive disorders, while the PHQ-2 overlooked about 23% of those. However, the PHQ-2 overdiagnosed 8.3% of patients without major depressive disorders as having depression. Thus, follow-up clinical diagnosis or follow-up monitoring is needed to exclude these pseudopositive patients as not having a depression diagnosis.

Previous studies showing sensitivity and specificity of the PHQ-9 among Korean people and/or the elderly showed a lower score as the cutoff point, such as 4/5 and 6/7 [16,17]. Thus, the elderly, especially in Asian populations, may hesitate to express their depressive symptoms in a self-reported questionnaire. The World Health Organization and the World Psychiatric Association have stated that depression in old age is stigmatized in several ways [41], and the stigmatization against depression in elderly people may cause them to underreport their depressive symptoms as discussed in a previous study [17]. Other studies discussed different reasons, such as that the elderly generally focus on somatic rather than cognitive and emotional symptoms and thus the PHQ-9 may not fully recognize the core features of depression [16].

The sensitivity of the PHQ-9 categorical algorithm as shown in the present study was lower than that in previous meta-analyses including primary care and general practice settings [10,12,14]. Lower sensitivities of the PHQ-9 categorical algorithm were shown in a study among inpatients in a hospital department of internal medicine in Geneva, Switzerland [22]; among chronically ill elderly patients in general practices in Limburg, a province in the Netherlands [17]; and among patients with medical disorders in Spain [23]. These previous studies showing lower sensitivities of the PHQ-9 categorical algorithm were all targeting patients with physical illness. Considering that the PHQ-9 included vegetative symptoms, such as appetite loss and fatigue, patients with chronic illness may have attributed their depressive symptoms to their physical conditions and not to their depressive disorder, as discussed in the previous study [22]. Although we have no data and have no clear-cut explanation for it, patients with physical illness may be apt to recognize their vegetative depressive symptoms as symptoms of their physical illness and may respond to the vegetative symptom items as "none" even though they are present.

Table 5
Performance of item #9 of the PHQ-9 in screening for suicidality

	Se	Sp	PPV	NPV	OR	LR+	LR−
Score of item #9 of PHQ-9							
0/1	0.70	0.97	0.76	0.96	70.60	21.99	0.31
1/2	0.17	1.00	1.00	0.89	–	–	0.83
2/3	0.13	1.00	1.00	0.89	–	–	0.87

"–": Because these are cells with zero, it is impossible to estimate the value.

Item #9 of the PHQ-9, which asks about current suicidality, had applicable validity, given the sensitivity and specificity of 0.70 and 0.97, respectively, in screening for suicidality. The values were not so different from those reported in a previous study among depressed primary care patients (sensitivity: 0.84; specificity: 0.69), which were calculated using the suicide item in the mood module of the Structured Clinical Interview for DSM-IV Axis I Disorders [42]. Meanwhile, the PHQ-2 missed more than 60% of patients who endorsed item #9 of the PHQ-9. Administration of only the two questions included in the PHQ-2 may not be sufficient to identify such patients. This study suggests that the routine use of the PHQ-9 or PHQ-2 plus item #9 of the PHQ-9 would be recommended to identify individuals at risk for suicide who would not otherwise have been identified.

In the present study, we calculated the SSLRs [40] of the PHQ-9. Our previous study showed the estimated prevalence of major depressive episodes was 7.4% in a general internal medicine polyclinic in rural Japan [25]. The physician working at the clinic has information that those with a score ≥10 have a 65% chance of having depression based on the SSLR=23.1, while those whose scores are 0–4 (SSLR= 0.16) have only a 1% chance of having depression. This information is more useful than adopting the single recommended threshold.

The study has several limitations. First, we selected only a single hospital located in a rural area for convenience. The findings of the present study can be generalized to outpatients in general internal medicine in Japanese rural hospitals, where patients are generally elderly and have chronic physical illness. However, this population may not be representative of other populations in Japan, such as those in urban hospitals and those in specific outpatient clinics. A survey of multiple, randomly selected sites from across Japan should be performed to generalize the findings. Second, the number of subjects was relatively small. Third, the present study used the MINI. Although the MINI is a validated interview tool to diagnose psychiatric disorders, a semistructured interview for DSM-IV may have been more appropriate. In a validation study of the Japanese version of the MINI using the structured clinical interview for DSM-III-R [31], the sensitivity and specificity to detect major depression were 1.0 and 0.87, respectively, suggesting the MINI may overlook a segment of those patients with major depression. This may have caused the apparent low sensitivity of the PHQ-9 and is one of limitations of the present study.

In conclusion, the PHQ-2 may be preferred in screening for patients with major depression in internal medicine outpatient clinics of rural general hospitals in Japan from the viewpoint of validity and ease of use. However, performing only the PHQ-2 may miss many suicidal patients. Given that item #9 of the PHQ-9 can detect suicidality, performing the PHQ-2 plus item #9 of the PHQ-9 is recommended.

References

[1] Copeland JR, Beekman AT, Dewey ME, et al. Depression in Europe. Geographical distribution among older people. Br J Psychiatry 1999;174:312–21.
[2] Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005;62:1097–106.
[3] Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617–27.
[4] McDougall FA, Kvaal K, Matthews FE, et al. Prevalence of depression in older people in England and Wales: the MRC CFA Study. Psychol Med 2007;37:1787–95.
[5] World Health Organization. The global burden of disease 2004 update. Geneva, 2008.
[6] Herrman H, Patrick DL, Diehr P, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO study. Functional status, health service use and treatment of people with depressive symptoms. Psychol Med 2002;32:889–902.

[7] Ustun TB, Von Korff M. Primary mental health serviceis. In: Ustun TB, Sartorius N, editors. Mental illness in general health care: an international study. Chichester, UK: Wiley & Sons; 1995. p. 347–60.
[8] Wittchen HU, Pittrow D. Prevalence, recognition and management of depression in primary care in Germany: the Depression 2000 study. Hum Psychopharmacol 2002;17(Suppl 1):S1–S11.
[9] Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 2009;374:609–19.
[10] Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J Gen Intern Med 2007;22:1596–602.
[11] Kroenke K, Spitzer RL, Williams JB, Lowe B. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. Gen Hosp Psychiatry 2010;32:345–59.
[12] Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. Cmaj 2012;184: E191–6.
[13] Meader N, Mitchell AJ, Chew-Graham C, et al. Case identification of depression in patients with chronic physical health problems: a diagnostic accuracy meta-analysis of 113 studies. Br J Gen Pract 2011;61:e808–20.
[14] Wittkampf KA, Naeije L, Schene AH, Huyser J, van Weert HC. Diagnostic accuracy of the mood module of the Patient Health Questionnaire: a systematic review. Gen Hosp Psychiatry 2007;29:388–95.
[15] Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient Health Questionnaire. JAMA 1999;282:1737–44.
[16] Han C, Jo SA, Kwak JH, et al. Validation of the Patient Health Questionnaire-9 Korean version in the elderly population: the Ansan Geriatric study. Compr Psychiatry 2008;49:218–23.
[17] Lamers F, Jonkers CC, Bosma H, et al. Summed score of the Patient Health Questionnaire-9 was a reliable and valid method for depression screening in chronically ill elderly patients. J Clin Epidemiol 2008;61:679–87.
[18] Husain N, Gater R, Tomenson B, Creed F. Comparison of the Personal Health Questionnaire and the Self Reporting Questionnaire in rural Pakistan. J Pak Med Assoc 2006;56:366–70.
[19] McManus D, Pipkin SS, Whooley MA. Screening for depression in patients with coronary heart disease (data from the Heart and Soul Study). Am J Cardiol 2005;96:1076–81.
[20] Persoons P, Luyckx K, Desloovere C, Vandenberghe J, Fischler B. Anxiety and mood disorders in otorhinolaryngology outpatients presenting with dizziness: validation of the self-administered PRIME-MD Patient Health Questionnaire and epidemiology. Gen Hosp Psychiatry 2003;25:316–23.
[21] Picardi A, Adler DA, Abeni D, et al. Screening for depressive disorders in patients with skin diseases: a comparison of three screeners. Acta Derm Venereol 2005;85: 414–9.
[22] Carballeira Y, Dumont P, Borgacci S, et al. Criterion validity of the French version of Patient Health Questionnaire (PHQ) in a hospital department of internal medicine. Psychol Psychother 2007;80:69–77.
[23] Orive M, Padierna JA, Quintana JM, et al. Detecting depression in medically ill patients: comparative accuracy of four screening questionnaires and physicians' diagnoses in Spanish population. J Psychosom Res 2010;69:399–406.
[24] Lotrakul M, Sumrithe S, Saipanish R. Reliability and validity of the Thai version of the PHQ-9. BMC Psychiatry 2008;8:46.
[25] Inagaki M, Ohtsuki T, Yonemoto N, et al. Prevalence of depression among outpatients visiting a general internal medicine polyclinic in rural Japan. Gen Hosp Psychiatry 2013;35:286–90.
[26] Ohtsuki T, Inagaki M, Oikawa Y, et al. Multiple barriers against successful care provision for depressed patients in general internal medicine in a Japanese rural hospital: a cross-sectional study. BMC Psychiatry 2010;10:30.
[27] Ministry of Internal Affairs and Communications. 2005 Population census. The Population census: Ministry of Internal Affairs and Communications; 2005.
[28] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12: 189–98.
[29] Mori E, Mitani Y, Yamadori A. Usefulness of a Japanese version of the Mini-Mental State in neurological patients. Shinkeishinrigaku 1985;1:82–90.
[30] Muramatsu K, Miyaoka H, Kamijima K, et al. The patient health questionnaire, Japanese version: validity according to the mini-international neuropsychiatric interview-plus. Psychol Rep 2007;101:952–60.
[31] Otsubo T, Tanaka K, Koda R, et al. Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. Psychiatry Clin Neurosci 2005;59: 517–26.
[32] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22–33 [quiz 4-57].
[33] Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D. DSM-IH-R psychotic disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. Eur Psychiatry 1998;13:26–34.
[34] World Health Organization. The Composite International Diagnostic Interview (CIDI). Geneva: World Health Organization; 1990.
[35] Brislin RW. Back-translation for cross-cultural research. J Cross-Cult Psychol 1986;1:185–216.
[36] Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia, PA: Lippincott, Williams & Wilkins; 2008.
[37] Dunn G, Pickles A, Tansella M, Vazquez-Barquero JL. Two-phase epidemiological surveys in psychiatric research. Br J Psychiatry 1999;174:95–100.
[38] Rubin DB. Multiple imputation for nonresponse in survey. New York: J. Wiley & Sons; 1987.
[39] Youden WJ. Index for rating diagnostic tests. Cancer 1950;3:32–5.
[40] Furukawa TA, Strauss S, Bucher HC, Guyatt G. Diagnostic tests. In: Guyatt G, Drummond R, Meade MO, Cook DJ, editors. Users' guides to the medical literature: a manual for evidence-based practice. 2nd ed. New York: The McGraw-Hill Companies, Inc.; 2008.
[41] Graham N, Lindesay J, Katona C, et al. Reducing stigma and discrimination against older people with mental disorders: a technical consensus statement. Int J Geriatr Psychiatry 2003;18:670–8.
[42] Uebelacker LA, German NM, Gaudiano BA, Miller IW. Patient health questionnaire depression scale as a suicide screening instrument in depressed primary care patients: a cross-sectional study. Prim Care Companion CNS Disord 2011;13(1). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3121214/.

Contents lists available at SciVerse ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

Prevalence of depression among outpatients visiting a general internal medicine polyclinic in rural Japan☆,☆☆

Masatoshi Inagaki, M.D., Ph.D. [a,b,*], Tsuyuka Ohtsuki, Ph.D. [a], Naohiro Yonemoto, Ph.D. [c], Yuetsu Oikawa, M.D. [d], Mie Kurosawa, M.D., Ph.D. [e], Kumiko Muramatsu, M.D., Ph.D. [f], Toshi A. Furukawa, M.D., Ph.D. [g], Mitsuhiko Yamada, M.D., Ph.D. [b]

[a] Center for Suicide Prevention, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira City, Tokyo, Japan
[b] Department of Psychopharmacology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira City, Tokyo, Japan
[c] Translational Medical Center, National Center of Neurology and Psychiatry, Kodaira City, Tokyo, Japan
[d] Oshu City Magokoro Hospital, Oshu City, Iwate, Japan
[e] Iwate Mental Health Center, Morioka City, Iwate, Japan
[f] Clinical Psychology Course, Graduate School of Niigata Seiryo University, Niigata City, Niigata, Japan
[g] Department of Health Promotion and Human Behavior, Kyoto University, Kyoto City, Kyoto, Japan

ARTICLE INFO

Article history:
Received 24 September 2012
Revised 27 November 2012
Accepted 27 November 2012

Keywords:
Internal medicine
Primary care
Depression
Suicide
Prevalence

ABSTRACT

Objective: In Europe and the US, primary care has been anticipated in identifying untreated depression. Findings show a high prevalence of depression in such settings. However, the prevalence of depression in an internal medicine clinic in a rural area of Japan, which has a role in primary care, is unclear.
Method: The prevalence of depression and comorbid psychiatric disorders among outpatients of an internal medicine clinic in a rural general hospital was measured by a structured interview using the Mini International Neuropsychiatric Interview. Outpatients were recruited consecutively and stratified by Patient Health Questionnaire-9 (PHQ-9) scores. Among 598 outpatients, we interviewed 75 randomly selected patients and 29 whose results of the PHQ-9 were positive. We estimated prevalence of depressive episode using age, sex, physical findings by internal medical doctors and PHQ-9 scores as covariates.
Results: The estimated prevalence of major and minor depressive episodes were 7.4% [95% confidence interval (CI): 3.4%–11.4%] and 6.8% (95% CI: 2.6%–10.9%), respectively. Among major depressed patients, 71.4% had current suicidal ideation.
Conclusion: Given the high rate of depression and suicidality, identification of depression and collaboration between internal medical doctors in a rural area of Japan and mental health professionals are needed.

1. Background

Depression is a prevalent, disabling disorder that has a profound influence on quality of life. It is estimated to become the leading cause of disability worldwide in 2030 and was already the leading cause of morbidity in middle- and high-income countries, including Japan, in 2004 [1].

Previous studies have invariably reported a high prevalence of depression in the general population [2–5] and in health care settings [6–8]. For example, the World Health Organization (WHO) performed a primary care mental health survey of 14 countries and found that 14% of primary care patients suffered from major depression [6]. Given the high prevalence of depression, primary care settings play an important role in identifying and treating depressed patients [9–11]. In Japan, there are few doctors specialized to primary care because its medical system has no clear definition of primary care and the specific providers responsible. Most patients, especially those in rural areas, consult an internal medical doctor for their primary care.

A previous study of patients in a general medicine clinic showed a 4.7% lifetime prevalence of major depressive episodes [12]. Another survey, also performed about 20 years ago, showed a 3.0% prevalence of major depressive episodes [13]. However, there are few recent studies showing depression prevalence in primary care settings.

Recently, we reported the prevalence of depression in a rural general hospital, where many of the patients were elderly [mean age (S.D.)= 72.9 (12.5) years]. Approximately 53%, 12% and 10% of the patients suffered from hypertension, hyperlipidemia and diabetes, respectively, which suggested that this rural general hospital played a role in the primary care of chronic physical illnesses of elderly patients [14]. Using the Patient Health Questionnaire-9 (PHQ-9), 8.7% [95% confidence interval (CI), 5.5%–11.8%] presented with probable major depression and, 16.7% (12.5%–20.8%), with a probable mood disorder. However, these prevalence estimates were based only on self-reports, and we did not perform any structured interviews to diagnose depression. There were also no data regarding comorbid psychiatric disorders that are commonly observed in primary care settings [15,16]. Therefore, the present study used structured psychiatric interviews to elucidate the prevalence of depression and other psychiatric disorders among patients of a general internal medicine outpatient clinic in a rural area of Japan.

2. Methods

2.1. Participants

This study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry in Japan. The researchers provided all participants with detailed information using a written document and administered a battery of self-report questionnaires after the patients provided oral informed consent. After this first-stage screening, we conducted structured psychiatric interviews with patients who provided further written informed consent.

This study was conducted on nine consecutive consultation days between July 12 and 23, 2010, at a general internal medicine outpatient clinic in a general hospital having no mental health specialties. This hospital is located in a small city (population of 124,756 in 2010) in the Tohoku region of Japan. The hospital serves as a regional public hospital and is funded by the National Health Insurance Society of Oshu City. Oshu City is a typical rural area about 500 km north of Tokyo with low population influx. There are high proportions of elderly people and people engaged in primary industry [17].

We used the following inclusion criteria to define a target population that can be assessed for depression in routine clinical practice: (a) patients aged 20 years or older who visited the outpatient clinic to consult a physician for their own primary care and (b) patients who have no communication difficulties, such as hearing loss or language problems, and who have no severe cognitive impairment, such as dementia or disturbance of consciousness. Thus, we did not include visitors who came in for admission preparation or those who consulted for their family members. We also did not include patients who lived outside the catchment area of the hospital. Severe cognitive impairment was judged based on a semistructured interview, using the first two questions of the Mini-Mental State Examination concerning time and place orientation [18,19] by research staff consisted of psychiatrists (MI and MY), a research assistant (TO) having experience in survey using the Mini-Mental State Examination and PHQ-9 in internal medical clinics and nurses. All were trained for the procedure of the present study. The staff sometimes conducted an additional interview regarding patient lifestyle factors and dementia history if accompanying persons were present. Due to ethical considerations and feasibility of the survey, we also excluded patients who were too physically ill to be interviewed.

2.2. Measurements

2.2.1. PHQ-9

We used the PHQ-9 [20,21] to stratify participants. We asked patients to choose from the following options how often they had been bothered by each of nine symptoms over the last 2 weeks: "not at all," "several days," "more than half the days" and "nearly every day." Two scoring methods, a categorical algorithm and a dimensional assessment, have been proposed in the literature. In the categorical algorithm, depression screening is positive if five or more of the nine depressive symptom criteria were present at least more than half the days and one of the symptoms is depressed mood or anhedonia. One of the nine items, "thoughts that you would be better off dead or of hurting yourself in some way," was counted if present at all. In addition to the categorical algorithm, we judged depression severity using a dimensional scale, with a cutoff score of 10 reported as optimal for screening probable depression. Each item is scored from 0 to 3, with a total possible score of 27 for the nine items.

We used a categorical algorithm to screen probable depression positive. In the categorical algorithm, depression is positive if one of two items (depressed mood or anhedonia) was present. Based on the results of the PHQ-9, patients were screened as probable depression positive using either the categorical algorithm (one of the two items) or the dimensional assessment (score of more than 10).

2.2.2. Mini International Neuropsychiatric Interview (MINI)

We used the MINI [22,23] to diagnose depression and other psychiatric disorders. The interview was originally developed as a structured diagnostic interview compatible with *DSM-III-R* and *ICD-10* criteria [25,26]. The MINI focuses on current diagnoses and only explores lifetime diagnoses clinically if relevant to the present status. For most diagnostic sections, one or two screening questions are used to rule out the diagnosis when answered in the negative. The MINI includes 19 disorders chosen as most common from epidemiological data [27,28]. In the present study, we used the modules related to depression, anxiety, eating disorders and alcohol/substance dependence/abuse, which are often observed in primary care settings [16]. We evaluated current suicidality using the suicidality module (C) of the MINI, although the validity has not been completely established [22–24]. The module consists of six items that identify any suicide-related episodes or phenomena, including suicidal ideation within the last month (five items) and history of suicide attempts (one item) in the life. If any items in the suicidal ideation within the last month (five items) were relevant, we judged that current suicidality was present. In addition, we calculated the score (e.g., lifetime histories of attempting suicide=4, presence of having suicidal ideation within a month=6, planning or attempting suicide within a month=10) and showed the number of patients with a high risk (MINI suicide risk >= 10) as sever suicidality [22–24]. In addition to the current suicidality evaluated by the MINI, we investigated score of the Item 9 in the PHQ-9 (thoughts that you would be better off dead or of hurting yourself in some way: *not at all*: 0; *several days*: 1; *more than half the days*: 2; and *nearly every day*: 3, over the past 2 weeks). We confirmed that scores of the Item 9 among patients with current suicidality by the MINI (median: 1; range: 0–3) were significantly higher than those among patients without (median: 0; range: 0–1) ($U=273.5$, $P<.01$ by the Mann–Whitney U test). We also used the MINI to assess minor depressive episodes, defined as having two to four items, with one of the items being depressed mood or anhedonia in the major depressive episode module (A) of the MINI.

2.3. Procedure

We defined the target population by the inclusion criteria described in the participant section and adopted a random sampling stratified by the PHQ-9 results. Trained psychiatrists (MI or MY), who were blind to the results of the PHQ-9, conducted structured MINI interviews of patients who were screened as probable depression positive as well as randomly selected patients.

☆ Authors' contributions: All authors have read and approved the final version of the manuscript. MI is the principal investigator and developed the original idea for the study. MI, TO, NY, YO and MY designed the study. MI, TO and NY analyzed data, and all authors discussed and prepared the manuscript. TAF was a supervisor.
☆☆ Competing interests: The authors declare that they have no competing interests.
* Corresponding author. Center for Suicide Prevention, National Institute of Mental Health, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashimachi, Kodaira, Tokyo 187–8553, Japan. Tel.: +81 42 341 2711; fax: +81 42 346 1994.
E-mail addresses: minagaki@ncnp.go.jp (M. Inagaki), ohtsuki@ncnp.go.jp (T. Ohtsuki), yonemoto@ncnp.go.jp (N. Yonemoto), yuetsu-o@city.oshu.iwate.jp (Y. Oikawa), miek@pref.iwate.jp (M. Kurosawa), muramatu@n-seiryo.ac.jp (K. Muramatsu), furukawa@kuhp.kyoto-u.ac.jp (T.A. Furukawa), mitsu@ncnp.go.jp (M. Yamada).

0163-8343/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.genhosppsych.2012.11.013

2.3.1. Statistical analyses

We calculated the prevalence estimates of any depressive episode (major depressive episode and minor depressive episode), other psychiatric disorders and their 95% CIs using sampling weights. The weight was based on the inverse of the sampling probability for age, sex, clinical diagnosis of primary illness and PHQ-9 score. We performed multiple imputations for the missing data. We performed all statistical analyses using the statistical software packages SPSS 17.0 (IBM, Tokyo) and Statistical Analysis System (SAS) 9.2 (SAS Institute Japan, Tokyo).

3. Results

During the study period, 598 patients visited the clinic. We randomly selected 107 of the outpatients. From the selected 107 patients, we excluded 21 based on our inclusion criteria: 1 was less than 20 years old, 7 consulted for family members, 1 resided outside the area and 12 were severely cognitively impaired. Among the 86 patients, 5 patients were physically too ill, and 1 refused to participate in the study. Then we administered the PHQ-9 to 80 patients who agreed to participate in the survey.

Among the remaining 491 patients who were not selected randomly, we excluded 66 based on our inclusion criteria: 16 were less than 20 years old, 15 consulted for family members, 1 visited to prepare for admission, 2 resided outside the area and 32 were severely cognitively impaired. Among the 425 patients, 12 were physically too ill, 4 were missed and 5 refused to participate in the study. Then, we administered the PHQ-9 to 404 patients and acquired PHQ-9 data for 396 of the 404 patients, and 8 of PHQ-9 data were incomplete. As a result, 36 patients out of the 396 were screened as probable depression positive.

Among the total 116 participants (80 and 36 participants), 104 received a structured interview using the MINI. Twelve patients were not interviewed (seven were missed, one was physically ill and four refused the interview).

The target population to estimate prevalence was 511 patients (86 and 425 patients).

Table 1 shows characteristics of the target population (n=511). The median age of the population was 75 years, with more than 81.8% of participants being 65 years old or older. As shown in Table 1, chronic physical illnesses, such as hypertension, diabetes and hyperlipidemia, were frequent. The median number of visits in the past 6 months was four, which means many patients consulted the clinic approximately once every 6 weeks.

Of the 104 patients who we interviewed using the MINI, we diagnosed 21 as having experienced a major depressive episode and 15 with a minor depressive episode. One had a hypomanic episode, two had posttraumatic stress disorder (PTSD) and five had alcohol dependence. Twenty-seven patients had suicidal thoughts. No one had a high risk of suicide among 99 patients who completed the suicidality module of the MINI (five had incomplete data). Table 2 shows weighted prevalences of depression and other psychiatric disorders. The estimated prevalence of having a major depressive episode was 7.4% (95% CI: 3.4% to 11.4%). That of any depressive episode, including both major and minor depressive episode, was 14.1% (95% CI: 8.2% to 20.0%), which means that one in every seven patients was estimated to have depression. Prevalence of current suicidality was 12.7% or one in every eight patients. Alcohol dependence was also frequent (5.4%).

Table 3 shows the prevalence of comorbid psychiatric disorders and current suicidality among patients that experienced a depressive episode. Prevalence of suicidality was high in patients with a major depressive episode as well as those with any depressive episode. Among the patients with major depressive episode (n=21), median (range) of the scores of Item 9 of the PHQ-9 was 1 (0–3). Among those diagnosed as having any depressive episode (n=36), median (range) of the scores was 0 (0–3). And among those who had no depressive episode, median (range) of the scores was 0 (0–1). Proportions of patients who scored the Item 9 of the PHQ-9 as 3 (nearly every day over the past 2 weeks) were 38.1%, 22.2% and 0% among patients with major depressive episode (n=21), those with any depressive episode (n=36) and those without any depressive episode (n=68), respectively.

Table 1
Characteristics of the study participants

Median age (range) in years	75 (21–102)
Sex: female (%)	59.3
Clinical diagnosis of primary illness (%)	
Hypertension	58.7
Diabetes	16.0
Hyperlipidemia	15.9
Brain infarction	8.4
Arrhythmia	6.8
Number of visits in the past 6 months	
Median (range)	4 (0–74)

Table 2
Prevalence of depression and other psychiatric disorders

	Estimated prevalence (%)	(95% CI)
Any depressive episode	14.1	8.2–20.0
Major depressive episode (current, 2 weeks)	7.4	3.4–11.4
Minor depressive episode (current, 2 weeks)	6.8	2.6–10.9
Hypomanic episode (current)	0.8	0.0–2.4
PTSD (current, past month)	1.4	0.0–3.4
Alcohol dependence (past 12 months)	5.4	0.3–10.5
Current suicidality	12.7	6.6–18.9

Table 3
Rate of comorbid psychiatric disorders in patients with depression

	Number	%
Major depressive episode (n=21)		
Current suicidality	15	71.4
PTSD	1	4.8
Alcohol dependence	0	0
Any depressive episode (n=36)		
Current suicidality	18	50.0
PTSD	2	5.6
Alcohol dependence	1	2.8

4. Discussion

The present study investigated the prevalence of depression and other psychiatric disorders in a general internal medicine outpatient clinic of a Japanese rural general hospital using structured interview conducted by trained psychiatrists followed by screening of PHQ-9. Patients were elderly and had chronic physical illnesses. The prevalence of major depressive disorder was 7.4% and, that of depression including both major and minor depressive disorders, was 14.1%. The prevalence of alcohol dependence was high, and suicidality was prevalent among patients with major or minor depressive disorders.

A previous survey conducted by the WHO nearly 20 years ago reported the prevalence of depression as 3.0% in internal medicine outpatient clinics in Japan [13]. The prevalence of PTSD in the previous survey (0.2%) was also lower than that of the present study (1.4%). The prevalence of alcohol dependence in the previous survey was 6.2%, which was comparable to that of the present study (5.4%). In contrast, the prevalence of generalized anxiety disorder was 5.0% in the previous survey, while no patients had generalized anxiety disorders in the present study.

These discrepancies may be explained by differences in participants and methods between the previous survey and the present study. The previous survey was conducted in a hospital located in a medium-sized city, whereas we examined prevalence of psychiatric disorders in a rural hospital. The previous survey excluded patients older than 65 years old, while the majority of participants in the present study were older than 65 years old. In addition, we need to consider that the previous survey was performed nearly 20 years ago.

A previous study performed in the US showed that the prevalence of major depression in rural primary care (8.3%) was lower than that in urban primary care settings (14.8%) [29]. The internal medicine clinic in the present study was located in a rural area, and the prevalence of major depression (7.4%) was similar to that previously reported [29]. However, the prevalence of depression in an urban clinic in Japan may be different.

Our previous study using the PHQ-9 to identify probable depression in the same clinic showed that prevalence of probable major depressive disorders (8.7%, 95% CI: 5.5%–11.8%) [14] was similar to that of the present study, suggesting that the results are reproducible.

The present study showed a high prevalence of current suicidality. In addition to the high prevalence, there was a higher rate of current suicidality among patients with major depressive episodes. Thus, current suicidality should be considered in addition to depression in patients evaluated at internal medicine clinics of rural general hospitals. In particular, referral of depressed patients with suicidal thought more than several days in the past 2 weeks to mental health professionals is required.

Previous studies in other countries showed that the prevalence of major depression in primary care settings for people aged 65 or older is 19.5% [30], which is higher than the prevalence found in the present study. The prevalence of depression in the general Japanese population is 2.9% [31], which is lower than that in other countries [32]. The lower prevalence in the general population may reflect the lower prevalence of depression in general internal medicine outpatient clinics.

The prevalence of depression in the internal medical outpatient clinic shown in the present study was higher than that previously reported for the general population in Japan [31]. This is similar to findings from other countries where the prevalence of depression in primary care settings is higher than in the community [30,33]. These results suggest that depressed patients more frequently consult internists. Thus, it is important that physicians appropriately identify, treat and/or refer untreated depressed patients that consult the clinic to mental health specialists.

The study has two major limitations. First, we selected only a single hospital for convenience. A survey of multiple, randomly selected sites from across Japan should be performed to generalize the findings. Second, the number of participants in the study was too small to effectively investigate comorbidities.

The present study showed a high prevalence of depression in an internal medicine outpatient clinic of a rural general hospital that plays a role in primary care for residents of its catchment area. We also showed a high prevalence of suicidality and its higher comorbidity rate with depression. Given the high rate of depression and suicidality, identification of depression and collaboration between internal medical doctors and mental health professionals, such as psychiatrists, are needed.

Acknowledgments and funding

This work was supported by a grant for Research on Psychiatric and Neurological Diseases and Mental Health from the Ministry of Health, Labour and Welfare. We thank Ms. Kyoko Sakurai, Ms. Hiromi Muramatsu and Ms. Mayumi Matsutani for their kind support.

References

[1] World Health Organization. The global burden of disease 2004 update; 2008. Geneva.
[2] Copeland JR, Beekman AT, Dewey ME, et al. Depression in Europe. Geographical distribution among older people. Br J Psychiatry 1999;174:312-21.
[3] McDougall FA, Kvaal K, Matthews FE, et al. Prevalence of depression in older people in England and Wales: the MRC CFA Study. Psychol Med 2007;37: 1787-95.
[4] Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005;62:1097-106.
[5] Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-27.
[6] Ustun TB, Von Korff M. Primary mental health serviceis. In: Ustun TB, Sartorius N, editors. Mental illness in general health care: an international study. Chichester, UK: Wiley & Sons; 1995. p. 347-60.
[7] Herrman H, Patrick DL, Diehr P, et al. Longitudinal investigation of depression outcomes in primary care in six countries: the LIDO study. Functional status, health service use and treatment of people with depressive symptoms. Psychol Med 2002;32:889-902.
[8] Wittchen HU, Pittrow D. Prevalence, recognition and management of depression in primary care in Germany: the Depression 2000 study. Hum Psychopharmacol 2002;17(Suppl 1):S1–S11.
[9] Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. Arch Intern Med 2006;166:2314-21.
[10] Hegerl U, Wittenburg L, Arensman E, et al. Optimizing suicide prevention programs and their implementation in Europe (OSPI Europe): an evidence-based multi-level approach. BMC Public Health 2009;9:428.
[11] Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 2002;288:2836-45.
[12] Sato T, Takeichi M. Lifetime prevalence of specific psychiatric disorders in a general medicine clinic. Gen Hosp Psychiatry 1993;15:224-33.
[13] Nakane Y, Michitsuji S. Results from the Nagasaki Center. In: Ustun TB, Sartorius N, editors. Mental Illness in General Health Care: An International Study. Chichester, UK: John Wiley & Sons; 1995. p. 193-209.
[14] Ohtsuki T, Inagaki M, Oikawa Y, et al. Multiple barriers against successful care provision for depressed patients in general internal medicine in a Japanese rural hospital: a cross-sectional study. BMC Psychiatry 2010;10:30.
[15] Schurman RA, Kramer PD, Mitchell JB. The hidden mental health network. Treatment of mental illness by nonpsychiatrist physicians. Arch Gen Psychiatry 1985;42:89-94.
[16] Spitzer RL, Williams JB, Kroenke K, et al. Utility of a new procedure for diagnosing mental disorders in primary care. The PRIME-MD 1000 study. JAMA 1994;272: 1749-56.
[17] Ministry of Internal Affairs and Communications. 2005 Population Census. The Population Census: Ministry of Internal Affairs and Communications; 2005.
[18] Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12: 189-98.
[19] Mori E, Mitani Y, Yamadori A. Usefulness of a Japanese version of the mini-mental state in neurological patients. Shinkei shinrigaku 1985;1:82-90.
[20] Muramatsu K, Miyaoka H, Kamijima K, et al. The patient health questionnaire, Japanese version: validity according to the mini-international neuropsychiatric interview-plus. Psychol Rep 2007;101:952-60.
[21] Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary care evaluation of mental disorders. Patient Health Questionnaire. JAMA 1999;282:1737-44.
[22] Otsubo T, Tanaka K, Koda R, et al. Reliability and validity of Japanese version of the mini-international neuropsychiatric interview. Psychiatry Clin Neurosci 2005;59: 517-26.
[23] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22-33 [quiz 4–57].
[24] Roaldset JO, Linaker OM, Bjørkly S. Predictive validity of the MINI suicidal scale for self-harm in acute psychiatry: a prospective study of the first year after discharge. Arch Suicide Res 2012;16:287-302.
[25] Amorim P, Lecrubier Y, Weiller E, Hergueta T, Sheehan D. DSM-IH-R psychotic disorders: procedural validity of the Mini International Neuropsychiatric Interview (MINI). Concordance and causes for discordance with the CIDI. Eur Psychiatry 1998;13:26-34.
[26] World Health Organization. The composite International Diagnostic Interview (CIDI). Geneva: World Health Organization; 1990.
[27] Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19.
[28] Regier DA, Myers JK, Kramer M, et al. The NIMH Epidemiologic Catchment Area program. Historical context, major objectives, and study population characteristics. Arch Gen Psychiatry 1984;41:934-41.
[29] Friedman B, Conwell Y, Delavan RL. Correlates of late-life major depression: a comparison of urban and rural primary care patients. Am J Geriatr Psychiatry 2007;15:28-41.