

## ORIGINAL ARTICLE

# Analysis of the trends of polypharmacy and high-dose prescriptions in Japan

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**Abstract**

**Introduction:** After extensive research, this study explored whether high-dose prescriptions and polypharmacy remain more frequent in Japan than elsewhere. If confirmed, we aimed to identify the factors that contributed to this unique trend.

**Methods:** The psychotropic drug prescription patterns for patients with schizophrenia in Japan were reviewed. This was based on a large sample collected from surveys of the Research on Asian Psychotropic Prescription Patterns, an international collaborative research project conducted by Asian psychiatrists to monitor prescriptions of psychotropic drugs for people with mental disorders, in 2001, 2004, 2008, and 2016.

**Results:** The 2016 Research on Asian Psychotropic Prescription Patterns survey revealed that Japan continued to demonstrate the highest rate of polypharmacy and the highest dosages of psychotropic prescription drugs for patients with schizophrenia among the 15 countries and areas that participated in the survey.

**Discussion:** The Research on Asian Psychotropic Prescription Patterns surveys demonstrated that science plays a limited role in the decision-making process for prescriptions of psychotropic medications. Such prescriptions are influenced by a wide range of factors, such as the national mental health policy, prescription-financing systems, the history of psychiatry in each country, and the prevailing culture. Hospital-based national mental health policies and mental health financing systems have been the primary obstacles to reducing polypharmacy in Japan.

**KEYWORDS**

high-dose prescription, Japan, polypharmacy, REAP, schizophrenia

## 1 | INTRODUCTION

In 2001, an international collaborative survey, using a uniform research protocol and a common questionnaire, was conducted by Asian psychiatrists. The survey was designated as REAP, which is an acronym for "Research on Asian Psychotropic Prescription Patterns." REAP examined 2399 prescriptions of inpatients with schizophrenia in six Asian countries and areas: China, Hong Kong, Japan, Korea, Singapore, and

Taiwan. High-dose prescriptions and psychotropic polypharmacy in Japan (Ito et al., 2005) was identified. The average number of psychotropic drugs administered for the treatment of inpatients with schizophrenia in Japan for 627 patients was 5.2 per patient. The average number of antipsychotics administered per patient in Japan was 2.4. The above figures for 2399 patients resulted in an average of 3.4 and 1.6 prescriptions per patient, respectively. The median number of psychotropic and antipsychotic drug prescriptions in Japan was five and

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two per patient, respectively, while it was three and one per patient, respectively, for the total sample. The chlorpromazine equivalence (CL-EQ) of antipsychotic prescriptions was the highest in Japan. The average dose of CL-EQ in Japan was 1003 mg, while the total average dose was 675 mg. The average dose in China is 403 mg. Notably, levomepromazine, known for its strong sedative effects, was prescribed only in Japan (Chong et al., 2004; Ito et al., 2005; Sim et al., 2004). For the first time, these findings provided data regarding high-dose prescriptions and polypharmacy prescribed by Japanese psychiatrists compared to psychiatrists in other Asian countries. The REAP survey, which was followed up in 2004 and 2008, showed a significant decrease in the CL-EQ in Japan. However, the CL-EQ in Japan continued to be the highest among the six countries and areas. This significant decrease from 2001 to 2004 can be attributed to many factors. The revelation of the extremely high dose of CL-EQ to Japanese psychiatrists could be considered as one of these reasons (Shinfuku & Tan, 2008; Tan et al., 2008; Yoshimura et al., 2006).

The third survey was conducted in 2008. In addition to the original six countries and areas, India, Malaysia, and Thailand participated in the third survey. All investigators collected data based on the same unified questionnaire-based research protocol. More than 2000 prescriptions each in 2001, 2004, and 2008 were examined. This resulted in a total number of more than 6000 prescriptions. These data were analyzed and compared (López-Muñoz et al., 2013; Xiang, Kreyenbuhl, Dickerson, Ungvari, Wang, Si, Lee, Chiu, et al., 2012; Xiang, Kreyenbuhl, Dickerson, Ungvari, Wang, Si, Lee, He, et al., 2012). The REAP surveys in 2001, 2004, and 2008 revealed a large international variation in the antipsychotic prescription patterns for individuals with schizophrenia (Ito et al., 2012). The highest doses of psychotropic prescriptions and the highest rates of polypharmacy, per the three surveys, were observed in Japan.

The survey results also showed a high rate of adjunctive use of mood stabilizers, benzodiazepines, and anticholinergic drugs in patients with schizophrenia in Japan (Sim et al., 2011; Tor et al., 2011; Xiang et al., 2011a). Low-dose antipsychotic drug use was uncommon in Japan, where many patients were long-term inpatients (Sim et al., 2009). The survey also revealed low recognition of extrapyramidal side effects and a low frequency of reported sexual dysfunction in Asian patients with schizophrenia (Xiang et al., 2011b; Xiang, Dickerson, Kreyenbuhl, Ungvari, Wang, Si, & Chong, 2012d). From 2001 to 2008, there was a major shift from first-generation antipsychotics

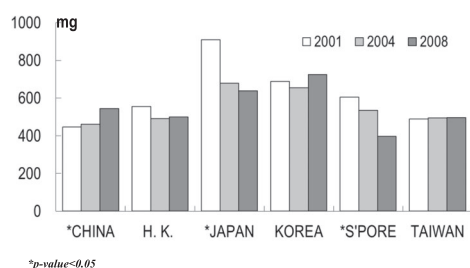
to second-generation antipsychotics (SGA) in all participating countries (Figure 1).

The introduction of SGAs resulted in a novel side effect (Xiang et al., 2015). Patients in Japan were no exception to this situation. The three REAP surveys in 2001, 2004, and 2008 revealed continuous antipsychotic polypharmacy in patients with schizophrenia in several Asian countries (Xiang, Dickerson, Kreyenbuhl, Ungvari, Wang, Si, & Chong, 2012d; Xiang, Wang, Si, Lee, He, Ungvari, & Kua, 2012). In addition, the excessive use of adjunctive mood stabilizers and benzodiazepines was continuously observed among older Asian patients with schizophrenia (Xiang, Dickerson, Kreyenbuhl, Ungvari, Wang, Si, & Chong, 2012e). The survey showed that the availability of a specific drug differed greatly between countries. A significant difference was observed when comparing prescription patterns between China and Japan. China used clozapine as the drug of first choice, and the rate of polypharmacy was low, whereas clozapine has not yet been prescribed in Japan. Certain drugs are marketed in some Asian countries and areas, but not in others (Xiang et al., 2017).

The results of the three REAP surveys (2001, 2004, and 2008) that included patients with schizophrenia in Asia showed that Japan had a significant high-dose antipsychotic prescription trend and a higher frequency of polypharmacy.

## 2 | METHODS

The psychotropic prescription patterns for patients with schizophrenia in Japan were reviewed based on the 2016 REAP survey (Yang et al., 2018), which was a follow-up survey of the previous REAP surveys conducted in 2001, 2004, and 2008. The REAP survey in 2016 was designed as a hospital-based cross-sectional survey to examine the prescription patterns of psychotropic drugs used for inpatients and outpatients in Asia. Data from outpatients were included for the first time in 2016. The research protocol and questionnaire were reviewed and agreed upon by all REAP members. The participants were both inpatients and outpatients with schizophrenia, diagnosed based on either the International Statistical Classification of Diseases and Related Health Problems 10th version (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-4). ICD-10 is used as a basic tool for psychiatric diagnoses. The DSM-4 has also been used in countries where the ICD system is not commonly used in clinical practice. The Anatomical Therapeutic Chemical system, developed by the World Health Organization, was used to classify psychotropic drugs prescribed by REAP members (Dong, Zeng, Zhang, Ungvari, Ng, Chiu, et al., 2019; Dong, Zeng, Zhang, Yang, Chen, Najooan, et al., 2019; Dong, Zeng, Zhang, Yang, Chen, Sim, et al., 2019). Each participating country was asked to provide 100–500 prescriptions of patients with schizophrenia, depending on the size of their psychiatric resources. The REAP studies were approved by the institutional review boards of all participating centers in each country. A total of 15 countries and areas in Asia participated in the 2016 REAP survey. In addition to the countries and areas that participated in the previous surveys, Bangladesh, Indonesia, Myanmar, Sri Lanka, Pakistan, and Vietnam were included in 2016. The



**FIGURE 1** Mean doses of antipsychotics (in CPZ equivalent means\*) 2001–2004–2008

**TABLE 1** REAP-AP 1, 2, 3, and 4: Participating countries and areas

	Prescription																
	2001		2004		2008		2016		Four surveys all		Psychiatrists		Centers				
	Inpatient	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient	2001-2016	2001	2004	2008	2016	2001	2004	2008	2016
China	611	14	504	14	409	14	146	14	1684	3	36	3	24	3	4	3	2
Hong Kong	108	0	100	0	100	0	31	0	339	1	1	10	11	1	1	1	1
Japan	627	100	583	100	514	100	229	100	1953	55	77	68	46	10	10	8	8
Korea	442	125	412	125	284	125	131	125	1269	51	32	31	17	12	4	4	3
Singapore	300	43	91	43	100	43	171	43	662	4	10	2	11	1	1	1	2
Taiwan	311	179	446	179	499	179	403	179	1659	30	48	58	17	4	5	7	5
India		329	181	329	181	329	479	329	660			5	31			5	5
Malaysia		202	100	202	100	202	305	202	405			2	21			1	10
Thailand		182	39	140	182	182	322	182	361			1	51			4	4
Bangladesh		51	48	51	99	51	99	51	99				4				1
Myanmar		74	90	74	164	74	164	74	164				25				5
Pakistan		156	142	156	298	156	298	156	298				49				3
Sri Lanka		47	50	47	97	47	97	47	97				18				3
Vietnam		0	274	0	274	0	274	0	274				95				10
Indonesia		292	289	292	581	292	581	292	581				66				9
Total	2399	1794	2136	1794	2226	1794	3744	1794	10 505	144	204	180	486	31	25	34	71

Note: REAP-AP 1, 2001; REAP-AP 2, 2004; REAP-AP 3, 2008; and REAP-AP 4, 2016.

number of prescriptions collected by each participating country or area is attached. Indonesia, India, Taiwan, Malaysia, and Japan collected information on the Brief Psychiatric Rating Scale, Drug Induced Extra-Pyramidal Symptoms Scale comorbidity, and laboratory data, in addition to the standard requirements.

Table 1 shows the number of prescriptions, number of psychiatrists, and the centers that contributed to the surveys in 2001, 2004, 2008, and 2016.

In total, 10 505 prescriptions for patients with schizophrenia were collected and analyzed. Notably, in the fourth survey of REAP in 2016, 71 major psychiatric research institutes and more than 400 psychiatrists from 15 countries and areas in Asia contributed to the collection of 3744 prescriptions for patients with schizophrenia.

### 3 | RESULTS

A total of 15 countries and areas in Asia joined the REAP survey in 2016, and 3744 prescriptions of persons with schizophrenia were collected and analyzed.

The REAP survey in 2016 revealed that Japan continued to have the highest rate of polypharmacy and the highest dosages of psychotropic drugs among the 15 countries and areas that participated in the survey (Yang et al., 2018).

Japan continued this trend in the 2016 REAP survey and showed a high rate of polypharmacy. More than 50% of patients with schizophrenia received more than two antipsychotics. However, our REAP data from 2001 to 2016 showed a continuous decrease in the trend for polypharmacy of antipsychotics in Japan (Dong, Zeng, Zhang, Yang, Chen, Sim, et al., 2019; Yang et al., 2018).

The average prescribed daily doses/defined daily dose (PDD/DDD) of antipsychotic use for all 3744 cases was 1.5, with Japan showing the

highest PDD/DDD rate (2.29) (Lin et al., 2018). The average psychotropic drug loading for all cases was 2.02. Japan had the highest level at 4.13. The dose of psychotropic drugs in Japan was the highest in the 2016 survey among the 15 countries and areas (Figure 2).

In addition to antipsychotic polypharmacy, frequent use of other psychotropic drugs was observed in Japan. Of the 3744 patients with schizophrenia, mood stabilizers were prescribed to 523 patients (14.0%). The combined use of mood stabilizers was high in Japan (30.1%). The rate of combined use with antidepressants was 12.0% for all patients. In Japan, only six cases out of 229 cases (2.6%) were prescribed antidepressants. This indicated that Japanese psychiatrists more frequently prescribed mood stabilizers than antidepressants as combination drugs to patients with schizophrenia (Dong, Zeng, Zhang, Yang, Chen, Najoan, et al., 2019).

The number of combined prescriptions with anxiolytics was 1044 (27.9%) for all cases. In Japan, 73 patients (total 229) with schizophrenia received anxiolytics, with a rate of 31.9%, which was slightly higher than the average value. Of all cases (total 3744), hypnotics were prescribed to 9.3% of patients with schizophrenia. In Japan, 140 out of 229 patients (61.1%) received hypnotics. This rate is the highest among all the countries and areas that participated in the survey (Dong, Zeng, Zhang, Ungvari, Ng, Chiu, et al., 2019).

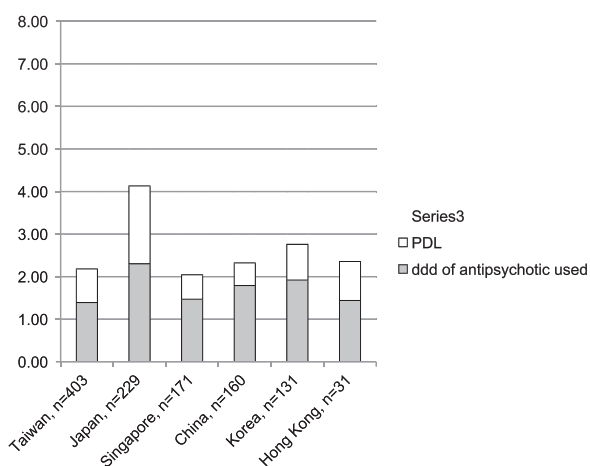
### 4 | DISCUSSION

#### 4.1 | Prescription surveys in Europe and the United States

In Europe and the United States, issues related to prescription behavior have often been highlighted. Gallego et al. conducted a systematic review of psychotropic prescription patterns in Europe, North America, Asia, and Oceania based on 147 research papers published between 1970 and 2009. The review showed a high prevalence of polypharmacy in Asia (Gallego et al., 2012). During the 40 years of this review period, North America was characterized by a lower rate of polypharmacy of antipsychotic drugs, a higher rate of combined prescription with mood stabilizers and antiepileptic drugs, and a lower rate of combined use with anticholinergics compared with those of other regions. European countries revealed a higher rate of antipsychotic polypharmacy, frequent use of anxiolytics and antidepressants, and fewer combined use of anticholinergic drugs. The average polypharmacy rate of antipsychotic drugs was approximately 20% for all regions throughout the survey duration. The polypharmacy rate in each region was 15% in North America, 32% in Asia, 23% in Europe, and 16% in Oceania. In the past 20 years, polypharmacy has decreased in Asia.

#### 4.2 | Polypharmacy in Asia

The REAP surveys demonstrated that the prescription of psychotropic drugs was influenced by several factors: the mental health service system, the mental health financing systems, and the training of



	Taiwan, n=403	Japan, n=229	Singapore, n=171	China, n=160	Korea, n=131	Hong Kong, n=31
PDL, mean	2.18	4.13	2.04	2.32	2.76	2.36
SD	1.45	3.13	1.33	1.72	2.03	1.55

Dark Column, DDD antipsychotic drug  
White column, PDL all psychotropic drugs

**FIGURE 2** Comparison of psychotropic drug load between countries 2016

psychiatrists. These factors contribute to the actual prescription decision-making process (Dong, Zeng, Zhang, Ungvari, Ng, Chiu, et al., 2019; Dong, Zeng, Zhang, Yang, Chen, Najoan, et al., 2019; Dong, Zeng, Zhang, Yang, Chen, Sim, et al., 2019; Yang et al., 2018). There is a huge difference in the number of mental health resources among the countries that participated in the REAP surveys. Japan has more than 300 000 psychiatric beds in more than 1600 hospitals. Most of these hospitals are privately owned, and more than half of the patients stay at these hospitals for more than 1 year. Therefore, data from Japan include prescriptions for patients with chronic-stage schizophrenia. Another sampling bias is related to the financing system governing the use of psychotropic drugs. The financing of drugs was significantly different among the 15 countries. The national insurance system in Japan allows psychiatrists to prescribe psychotropic drugs at their discretion without limitations. On the other hand, in countries with limited financial resources, governments control drug expenditures at public hospitals. Psychiatrists are directed to prescribe the minimum amount of psychotropic drugs with the most reasonable prices for cost containment purposes. Additionally, psychiatrists in countries with limited mental health resources are prohibited from prescribing expensive newly introduced psychotropic drugs. When analyzing the REAP data, it is necessary to consider the possible bias resulting from the various mental health financing systems in each Asian country.

### 4.3 | Polypharmacy and high-dose prescriptions in Japan

The survey findings illustrate that high-dose prescriptions and polypharmacy continue to be observed more frequently in Japan than elsewhere. These findings are the result of extensive research collected over the past few decades. There are many reasons why psychiatrists in Japan continue to prescribe polypharmacy and high doses of psychotropics. Possible contributing factors are the mental health service system, various stigmas, the national insurance system, physician's culture, patient's attitude, and lack of training in psychopharmacology.

#### 4.3.1 | The mental health service system

Japan is known for its unique mental health service system. There are more than 1600 psychiatric hospitals, and more than 90% of patients are hospitalized in privately owned hospitals (Shinfuku, 1998; Shinfuku, 2017). In addition, inpatients with schizophrenia remain hospitalized for extended periods of time. Approximately 100 000 patients stay for more than 1 year (Shinfuku, 2017). Extended-stay patients tend to receive polypharmacy and high doses of psychotropics. The examples collected by Japanese psychiatrists are representative of a cohort of Japanese inpatients. The rate of polypharmacy decreased slightly from 2001 to 2004 and from 2004 to 2008 (Chong et al., 2004; Shinfuku & Tan, 2008; Xiang, Kreyenbuhl, Dickerson, Ungvari, Wang, Si, Lee, Chiu, et al., 2012; Xiang, Kreyenbuhl, Dickerson, Ungvari, Wang, Si, Lee, He, et al., 2012).

#### 4.3.2 | Stigma

There is a concealed strong stigma toward individuals with schizophrenia in Japanese society. The stigma toward patients with mental disorders is deeply rooted in Japanese history. It has been and remains a source of shame for a family to have a member with schizophrenia. Therefore, once hospitalized, family members are reluctant to have a sick family member return home (Shinfuku, 1998). They prefer to hide the patient far from the eyes of the community for as long as possible. In Japanese history, individuals with schizophrenia are considered to be dangerous and exhibit bizarre behavior. It is difficult for individuals with schizophrenia to find work post-discharge. Rehabilitation facilities are poorly developed in the Japanese mental health service system. Given these circumstances, the major objective of pharmacotherapy is the sedation of patients with abnormal behavior, such as aggression. After each episode of abnormal behavior, various types and dosages of medications are added. In the long run, patients with schizophrenia receive polypharmacy and high doses of psychotropic drugs (Shinfuku, 2017).

#### 4.3.3 | National insurance system

The Japanese national insurance system has also contributed to polypharmacy and the high dosages of prescriptions. In 1961, the national medical insurance system began to cover and subsidize all medical costs. Generally, medical insurance covers the hospitalization fee for patients with schizophrenia who are hospitalized for extended periods. In the case of private psychiatric hospitals, it is desirable for patients to stay longer. Most of the hospital fees are covered by the national insurance system and other public funding. Families and patients are often exempt from paying for hospitalization costs. The greater the number of patients and the longer their stay, the greater is the financial stability of a private psychiatric hospital. This system encourages polypharmacy and high-dose prescriptions. Medical fees, including the cost of prescription drugs, are covered by the national insurance system. It is notable that the owner of the hospital may receive a larger reimbursement if the physician prescribes several drugs at higher doses.

#### 4.3.4 | Physician's culture

In Japan, the culture surrounding physicians is an important contributing factor to the high dose of prescription medications and polypharmacy. The right of medical doctors to prescribe drugs is protected by law. Few mechanisms exist to control the number of prescriptions.

Furthermore, a weak verification system exists, and it does not prevent polypharmacy and high-dose prescriptions. The majority of extended-stay patients receive several drugs for various complaints such as psychotic symptoms, depressive moods, insomnia, and irritability. They are prescribed by different doctors. It is easy to increase the number of drugs prescribed. However, it is cumbersome to reduce

the number of previously prescribed drugs. Moreover, it is considered inappropriate for young doctors to discontinue a drug prescribed by senior doctors. When a young doctor wants to change a prescription, the only way is to add a new drug. This Japanese culture of respect for seniority may result in long-term polypharmacy and high-dose prescriptions.

#### 4.3.5 | Patient's attitude

Japanese patients tend to receive numerous drugs. In traditional herbal medicine, multiple drugs increase the medication's potency and efficacy. Certain Japanese people believe that drugs are good and that multiple drugs are better. This encourages physicians to prescribe high doses of drugs and use polypharmacy. Some experts mention traditional medicine as the origin of polypharmacy. One Chinese herbal medicine typically contains 5–10 ingredients. The philosophy behind polypharmacy is that a higher number of drugs are more effective.

#### 4.3.6 | Lack of training in psychopharmacology

The REAP survey results demonstrate poor recognition of the side effects of drugs prescribed by Asian psychiatrists, and Japanese psychiatrists were no exception. The dangers of high-dose prescriptions and polypharmacy are not sufficiently understood by Japanese psychiatrists. One REAP study showed a rather low recognition of drug side effects by Asian psychiatrists (Xiang et al., 2011a, 2011b; Xiang et al., 2015). This may be true for Japanese psychiatrists as well.

Side effects are not sufficiently considered when a doctor prescribes a new drug. When a doctor adds a psychotropic drug, the existing drug should be reduced. However, this is seldom practiced, and results in polypharmacy and high-dose prescriptions. Excessive intake of psychotropic drugs damages both the patient's mind and body.

#### 4.3.7 | Market factors

Additional factors in the actual decision-making process for prescribing psychotropic drugs may exist, including the marketing and advertising of drugs. Psychiatrists are urged to prescribe newly approved antipsychotics/psychotropics. It is notable that a number of new drugs entered Asian markets in 2001 (López-Muñoz et al., 2013; Xiang, Kreyenbuhl, Dickerson, Ungvari, Wang, Si, Lee, Chiu, et al., 2012; Xiang, Kreyenbuhl, Dickerson, Ungvari, Wang, Si, Lee, He, et al., 2012).

### 4.4 | Efforts to improve prescriptions in Japan

Prescription guidelines and scientific data play a limited role in decisions regarding actual prescriptions. In the past 20 years, Japanese psychiatrists have introduced prescription guidelines developed in

Europe and the United States to reduce polypharmacy. At present, most Japanese psychiatrists are well aware of the harmful effects of polypharmacy and high-dose prescriptions. Nevertheless, most patients with schizophrenia continue to receive polypharmacy and high-dose prescriptions. There are some limitations to reducing polypharmacy and high-dose prescriptions, including the efficacy of the prescription guidelines and the ethical behavior of the psychiatrist. Past efforts to reduce polypharmacy on a scientific basis can be summarized as having had a limited impact on clinical practice.

The Ministry of Health, Welfare, and Labor introduced changes in the payment system to prevent polypharmacy. However, these do not address high-dose prescriptions (Hirano & Ii, 2019).

### 4.5 | What we have learned and what should we focus on?

The REAP surveys have demonstrated that science plays a limited role in the decision-making process for psychotropic prescriptions. These decisions are influenced by a wide range of factors, such as the national mental health policy, financing systems for prescription drugs, and the history of psychiatry in each country as well as the prevailing culture. Hospital-based national mental health policy and mental health financing systems have been the primary obstacles to reducing polypharmacy in Japan. The development of mental health services in communities separate from hospitals is a prerequisite. High-dose prescriptions and polypharmacy will continue as long as large numbers of extended-stay patients with schizophrenia remain in custodial psychiatric hospitals. The situation in Japan clearly demonstrates the abuse of polypharmacy. However, there has been a change in the focus of pharmacotherapy from sedation to rehabilitation. Further training and education of psychiatrists on the side effects of psychotropic medications is essential.

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#### CONFLICT OF INTEREST

The author declares no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in the publication list at the REAP homepage website (<http://www.reap.asia>).



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