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ORIGINAL ARTICLE

Case Control Study

Best early-onset Parkinson dementia predictor using ensemble learning among Parkinson's symptoms, rapid eye movement sleep disorder, and neuropsychological profile

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Author contributions: Byeon H designed the paper, was involved in study data interpretation, preformed the statistical analysis, and assisted with writing the article.

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Abstract

BACKGROUND

Despite the frequent progression from Parkinson's disease (PD) to Parkinson's disease dementia (PDD), the basis to diagnose early-onset Parkinson dementia (EOPD) in the early stage is still insufficient.

AIM

To explore the prediction accuracy of sociodemographic factors, Parkinson's motor symptoms, Parkinson's non-motor symptoms, and rapid eye movement sleep disorder for diagnosing EOPD using PD multicenter registry data.

METHODS

This study analyzed 342 Parkinson patients (66 EOPD patients and 276 PD patients with normal cognition), younger than 65 years. An EOPD prediction model was developed using a random forest algorithm and the accuracy of the developed model was compared with the naive Bayesian model and discriminant analysis.

RESULTS

The overall accuracy of the random forest was 89.5%, and was higher than that of discriminant analysis (78.3%) and that of the naive Bayesian model (85.8%). In the random forest model, the Korean Mini Mental State Examination (K-MMSE) score, Korean Montreal Cognitive Assessment (K-MoCA), sum of boxes in Clinical Dementia Rating (CDR), global score of CDR, motor score of Untitled Parkinson's Disease Rating (UPDRS), and Korean Instrumental Activities of Daily Living (K-IADL) score were confirmed as the major variables with high weight for EOPD prediction. Among them, the K-MMSE score was the most important factor in the final model.

dataset available from the corresponding author at bhwpuma@naver.com.

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CONCLUSION

It was found that Parkinson-related motor symptoms (*e.g.*, motor score of UPDRS) and instrumental daily performance (*e.g.*, K-IADL score) in addition to cognitive screening indicators (*e.g.*, K-MMSE score and K-MoCA score) were predictors with high accuracy in EOPD prediction.

Key Words: Early-onset Parkinson dementia; Ensemble learning method; Neuropsychological test; Risk factor; Discriminant analysis; Naive Bayesian model

Core Tip: It is believed that if the Korean Mini Mental State Examination (K-MMSE) is given priority over other cognitive screening tests in order to distinguish early-onset Parkinson dementia (EOPD) from Parkinson's disease, the accuracy of detecting EOPD will be higher than conducting other screening tests first. However, further epidemiological studies will be needed to fully comprehend the results of better accuracy of the K-MMSE than that of Korean Montreal Cognitive Assessment while detecting EOPD using the developed ensemble-based prediction model.

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INTRODUCTION

Dementia is a typical senile disease and indicates that a person with normal cognition experiences cognitive impairment due to various causes in the aging process. Dementia shows diverse symptoms, such as memory impairment; decreased cognitive functions, including language ability and frontal lobe executive function; and psychological symptoms of dementia (BPDS), depending on the type and progression of the disease[1]. It burdens caregivers psychologically and economically as well as the dementia patients[2]. In particular, care costs are extremely high as there is currently no cure for dementia, and it is necessary to take care of patients for a long time. As of 2019, South Korea spends KRW 14.6 trillion managing dementia, which is 0.8% of the GDP, and it is expected to increase more than seven times (KRW 106.5 trillion)[3]. It was reported that South Korea had 700000 dementia patients out of 7 million elderly people in 2017, which is already over 10% of the total elderly population[3]. It is approximately a 35% increase from 540000 dementia patients in 2012[3]. It tends to increase steadily by more than 7% per year[3]. Therefore, the reduction of dementia prevalence through the prevention, early diagnosis, and early management of dementia is the key to the mental health policy that the South Korean government must resolve as South Korea has an aging society.

Geriatricians evaluate the characteristics of dementia by classifying it into several types to diagnose dementia as soon as possible. Recently, many studies[4,5] examined the characteristics of the disease after categorizing it into early-onset dementia (EOD: Occurring before 65 years old) and late-onset dementia (LOD: Occurring at 65 years old or later) based on the onset of dementia symptoms (age). These studies revealed that EOD and LOD showed differences in imaging tests as the disease progressed. For example, in the case of Alzheimer's disease, EOD caused a greater loss of cerebral synapses or severe infiltration of senile plaques and neurofibrillary tangles than LOD[6-8]. Moreover, even the frontal and parietal lobes, as well as the temporal lobe, atrophied[6-8]. Additionally, since EOD patients are more likely to have a family history of dementia than LOD patients, it is suspected that EOD is affected by genetic predisposition more than LOD[7]. However, these imaging tests are not the ideal way to identify the onset of dementia in the early stages because they can only be used to diagnose dementia accurately by skilled medical personnel after dementia has progressed to some extent. Moreover, previous studies[9] that examined the

characteristics of EOD mostly evaluated Alzheimer's dementia. The demographic and neuropsychological characteristics of early-onset Parkinson dementia (EOPD) are relatively unknown.

In summary, despite the frequent progression from Parkinson's disease (PD) to Parkinson dementia (PDD), the basis to diagnose EOPD in the early stages is still insufficient. Currently, it is impossible to detect EOPD in the early stages just by using the cognitive screening test that is simply and commonly conducted for all types of dementia patients in South Korean public health centers. Although several biomarker candidates have been suggested based on the cerebrospinal fluid (CSF) test (*e.g.*, Aβ1-42 and total tau) for diagnosing dementia in the early stages[10], the CSF test is not versatile because it causes pain in examinees, thus examinees tend to reject the test, and the reliability of it cannot be tested; these are limitations of this test. In other words, because a range of factors (*e.g.*, gender, education level, and depression) affect EOPD[11-13], it would be necessary to develop a prediction model by applying PD motor and non-motor symptoms and sociodemographic indices[11,12] in addition to cognitive characteristics[14]. Byeon[15] argued that previous studies[16,17] were limited to the exploration of individual risk factors because they used regression models for predicting dementia and variables were quite limited because the prediction models mainly included neuropsychological tests. Therefore, there are limitations to developing a highly reliable model to predict EOPD using individual (single) indicators, such as PD symptoms and neuropsychological tests. In order to develop an accurate prediction model, it is necessary to develop a comprehensive model that includes sociodemographic indices, PD motor symptoms, PD non-motor symptoms, rapid eye movement (REM) sleep behavior disorder, and neuropsychological indices.

Recent studies have used machine learning algorithms as a method to predict a high disease risk group[18,19]. Machine learning is a process of analyzing relationships and rules in data to extract valuable information from the data. Random decision forest (RF) has been used widely; it produces many decision trees using an ensemble algorithm to overcome the limitations of overfitting and predicts target variables by combining them[20].

We are not aware of any published RF-based machine learning studies to analyze EOPD prediction capability by considering sociodemographic factors, PD motor symptoms, PD non-motor symptoms, REM sleep disorder, and neuropsychological profiles, together with cognitive function. This study explored the prediction accuracy of sociodemographic factors, PD motor symptoms, PD non-motor symptoms, and REM sleep disorder for diagnosing EOPD using a large-scale PD registry dataset.

MATERIALS AND METHODS

Participants

This study was performed by analyzing the Parkinson's Disease Epidemiology in Korea (PDEPI-Korea) multicenter registry data provided by the National Biobank of Korea (NB-Korea, No. KBN-2019-005). The study was approved by the Research Ethics Review Board of the NB-Korea (No. KBN-2019-005) and the Korea Centers for Disease Control and Prevention (Korea-CDC, No. KBN-2019-1327). The NB-K was founded in 2008 upon the approval of the Ministry of Health and Welfare due to the necessity of managing bio data systematically at the national level. It has been managed by the Korea CDC. The ultimate goal of the NBK is to promote biomedical research and public health. Please see Byeon[20] for details on the data source.

PD was diagnosed by a psychiatrist according to the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank[21]. In this study, PDD was defined as patients who met the diagnostic criteria of probable PDD, suggested by the Movement Disorder Society Task Force[22]. This study excluded patients who had other causative diseases, such as hydrocephalus and vascular Parkinsonism, determined from magnetic resonance imaging. This study analyzed 342 PD patients [66 EOPD patients and 276 PD patients with normal cognition (PD-NC)] who were younger than 65 years. Sample size calculations based on power analysis are shown in Figure 1. As the minimum number of samples calculated based on power analysis was 210 (group 1 = 105, group 2 = 105) with significance level (α) = 0.05, effect size d = 0.5 and power of test (1-β) = 0.95 on the standard of normal distribution, the number of samples (n = 342) in our study was appropriate.

Measurement

The outcome variable was defined as the presence of EOPD (yes or no), a binary

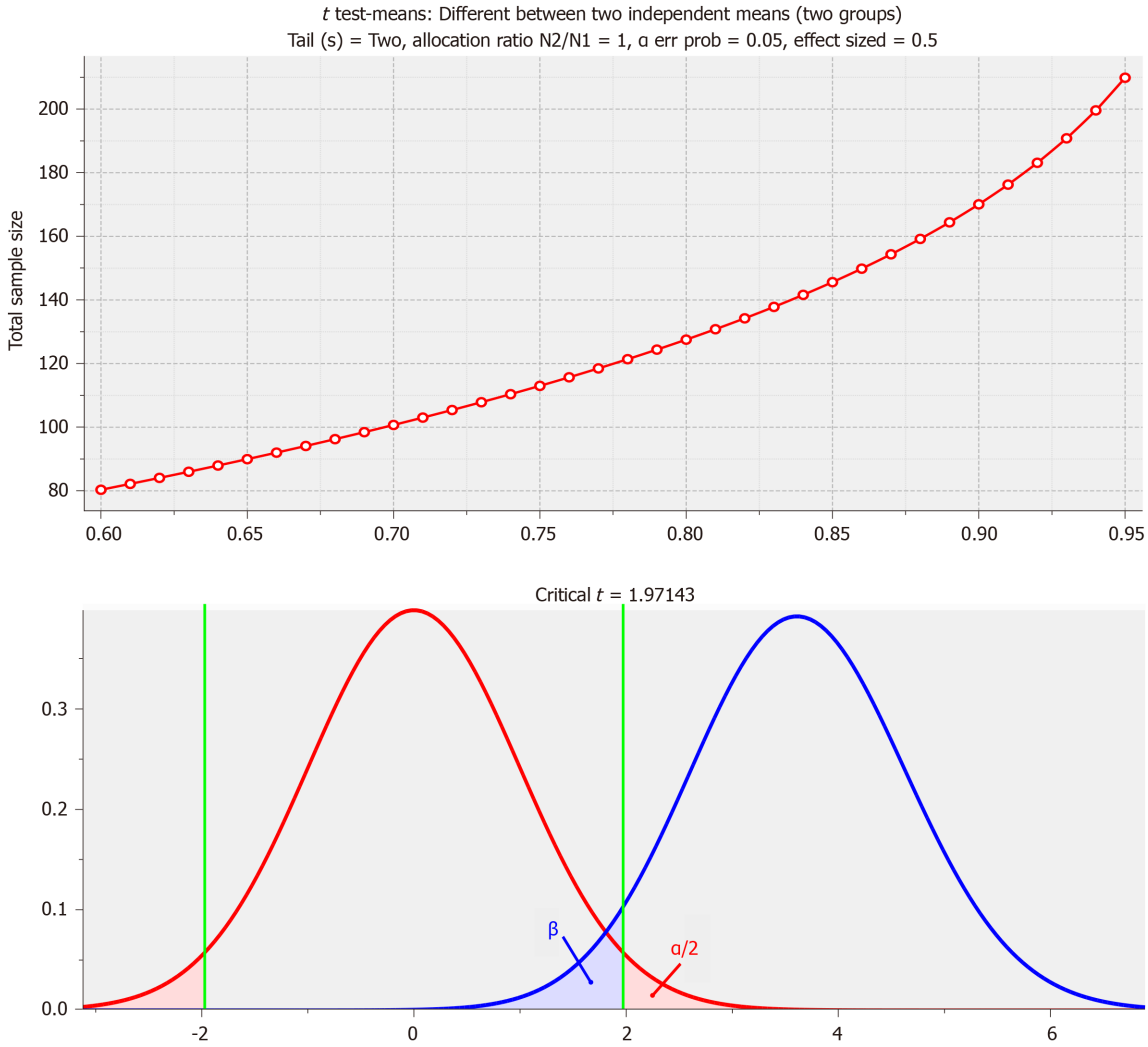

Figure 1 Sample size calculations.

variable, from a diagnosis by a neurologist. The explanatory variables included age; gender; education level (middle school graduate and below, or high school graduate and above); dominant hand (left hand or right hand); family PD history (yes or no); family dementia history (yes or no); pack-years (non-smoking, 1-20, 21-40, 41-60, or ≥ 61 pack-years); coffee-drinking (yes or no); coffee drinking period (no, ≤ 5, 6-9, or ≥ 10 years); mean coffee intake per day (no, ≤ 1, 2-3, or ≥ 4 cups); pesticide exposure recognition (never, currently not exposed but exposed previously, or currently exposed to pesticide); disease history (manganese poisoning, carbon monoxide poisoning, encephalitis, traumatic brain injury, stroke, alcoholism, diabetes, hyperlipidemia, hypertension, and/or atrial fibrillation); PD-related motor signs (tremor, akinesia/bradykinesia, postural instability, and/or late motor complications); neuropsychological characteristics determined by assessments such as the Korean Mini Mental State Examination (K-MMSE)[23], the Korean Montreal Cognitive Assessment (K-MoCA)[24], the sum of boxes in Clinical Dementia Rating (CDR)[25], the global CDR score[26], Korean Instrumental Activities of Daily Living (K-IADL)[27], the total score of Untitled Parkinson's Disease Rating (UPDRS)[28], the motor score of UPDRS[29], Hoehn and Yahr staging (H&Y staging)[30], and the Schwab & England Activities of Daily Living scale (Schwab & England ADL)[31]; and REM sleep behavior disorders. The definitions of the explanatory variables are shown in Table 1.

Development and evaluation of EOPD prediction model

The EOPD prediction model was developed using a RF algorithm and the accuracy of the developed model was compared with the naive Bayesian model and discriminant analysis. All analyses were performed using R version 3.5.2 (Foundation for Statistical Computing, Vienna, Austria).

RF is an ensemble classifier that randomly learns multiple decision trees and is a

Table 1 Measurement and definition of variables

Variable	Measurement	Characteristics
Sociodemographic factors	Age	Continuous variable
	Gender	Male or female
	Education	Middle school graduate and below or high school graduate and above
	Mainly used hand	Left hand, right hand, or both hands
	Family dementia history	Yes or No
	Family PD history	Yes or No
Environmental factors	Exposure to pesticide	Never, currently not exposed but exposed previously, or currently exposed to pesticide
Health behaviors	Pack-years	Non-smoking, 1-20, 21-40, 41-60, or ≥ 61 pack-years
	Coffee-drinking	Yes or No
	Mean coffee intake per day (cups/d)	No, ≤ 1, 2-3, or ≥ 4 cups
	Coffee drinking period (yr)	No, ≤ 5, 6-9, or ≥ 10
Disease history	Carbon monoxide poisoning	Yes or No
	Manganese poisoning	Yes or No
	Encephalitis	Yes or No
	Traumatic brain injury	Yes or No
	Stroke	Yes or No
	Alcoholism	Yes or No
	Diabetes	Yes or No
	Hypertension	Yes or No
	Hyperlipidemia	Yes or No
	Atrial fibrillation	Yes or No
Neuropsychological characteristics	Total score of KMMSE	Continuous variable
	Total score of KMoCA	
	Global CDR score	
	Sum of boxes in CDR	
	K-IADL	
	Total score of UPDRS	
	Motor score of UPDRS	
	H&Y staging	
	Schwab & England ADL	
Sleep behavior disorders	REM sleep behavior disorders	Yes or No
Exercise characteristics related to PD (PD related motor signs)	Tremor	Yes or No
	Rigidity	Yes or No
	Bradykinesia	Yes or No
	Postural instability	Yes or No
	LMC	Yes or No

PD: Parkinson's disease; KMMSE: Korean Mini Mental State Examination; KMoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating; H&Y staging: Hoehn and Yahr staging; Schwab & England ADL: Schwab & England Activities of Daily Living scale; REM: Rapid eye movement; LMC: Late motor complications.

machine learning method based on the meta-learning of decision trees. It consists of a training stage composing many decision trees and a test stage that classifies or predicts when an input vector is entered.

The ensemble form of training data can be expressed as Forest F = {f1,… , fn}. The distributions obtained from the decision trees of each forest were averaged by the number (T) of decision trees and were then classified. For combining the predictors of each sample, the average was used when the target variable was a continuous variable, and the majority vote was used when it was a categorical variable (Figure 2).

RF is similar to bagging in that it improves stability by combining decision trees generated from multiple bootstrap samples, based on the majority rule. However, it is conceptually different from bagging because it uses explanatory variables, which are randomly selected in each bootstrap sample. The RF can be theoretically free from overfitting because it contains randomness for both features and learning instances. Moreover, it is not much affected by noise or outliers and it is more accurate than other machine learning methods, such as decision trees. The accuracy of RF increases when the number of trees increases. However, it may suffer from an elbow point, indicating a steep decrease in slope. Moreover, each tree is more likely to have a more complex structure when non-critical explanatory variables are selected. Consequently, this study used the grid search method that can minimize problems such as elbow point by considering mtry number (n_estimator), indicating the number of candidates for explanatory variables among RF hyperparameters in advance. The procedure of developing an RF-based prediction model is presented in Figure 3.

Comparison of model prediction accuracy

This study selected an algorithm with the best model performance as the final model by comparing the overall accuracy of RF, discriminant analysis, and the naive Bayesian model. Moreover, this study showed the variable importance of the final model. A partial dependence plot was presented to visually confirm the marginal effects of an input variable with the highest importance on a response variable. The function of partial dependence is given in the following Equation.

In the above equation, $p_1(x, x_{ic})$ is Pr (Y = 1), calculated from a specific value of an interest variable (x) and a fixed value of the remaining predictor (x_{ic}). This probability is calculated as the ratio classified as Y = 1 category in the corresponding random decision tree. In other words, partial dependence and the log odds of the logic model share the same concept, and it is the mean after calculating the log odds from all observations *i*.

RESULTS

General characteristics of the participants

The general characteristics of 342 participants with PD were analyzed (Table 2). The mean age of the subjects was 57.3 years old (SD = 5.7). The initial age at diagnosis of PD was 56.7 years old (SD = 5.9). Smokers made up 88.6% of the participants, subjects with a family history of PD were 5.1% of the participants, and subjects with a family history of dementia were 7.4% of the participants. It was found that 19.3% of the subjects had EOPD.

Development of the EOPD prediction model using RF

This study changed mtry values, presenting the number of explanatory variables to be used in the decision tree constituting RF, from 3 to 13, and selected values with the smallest error of Out-Of-Bag. The changes in the error of Out-Of-Bag are presented in Table 3. The optimal mtry to be applied in this study was 4, showing the lowest error rate (10.5%). When n tree, the number of tree generations, and mtry were set as 500 and 4, respectively, the final RF model of this study had an overall accuracy of 89.5%.

Selection of the final EOPD prediction model

The overall accuracy of the RF was 89.5%, and it was higher than that of both discriminant analysis (78.3%) and the naive Bayesian model (85.8%). Therefore, the RF was assumed to be the most accurate prediction model among EOPD prediction models, and it was selected as the final prediction model. In Figure 3, the black line indicates the changes in each error rate against 500 bootstrap samples. Figure 4 shows that the changes in error rate became relatively stable when the number of bootstrap samples exceeded 60. Additionally, the multidimensional scaling plot of RF, which

Table 2 General characteristics of the subjects (*n* = 342)

Characteristics	*n* (%)
Age, mean ± SD (yr)	57.3 ± 5.7
K-MMSE, mean ± SD	25.6 ± 4.0
K-MoCA, mean ± SD	21.2 ± 5.1
Global CDR score, mean ± SD	0.4 ± 0.3
Sum of boxes in CDR, mean ± SD	1.5 ± 1.7
K-IADL, mean ± SD	1.0 ± 2.4
Total score of UPDRS, mean ± SD	41.3 ± 21.8
Motor score of UPDRS, mean ± SD	23.1 ± 11.1
H&Y staging, mean ± SD	2.3 ± 0.6
Schwab & England ADL, mean ± SD	77.5 ± 15.0
Gender	
Male	174 (50.9)
Female	168 (49.1)
Education	
Middle school graduate and below	195 (57.0)
High school graduate and above	147 (43.0)
Handness	
Right	318 (93.0)
Left	15 (4.4)
Both hands	9 (2.6)
Family PD history	
No	279 (94.9)
Yes	15 (5.1)
Family dementia history	
No	264 (92.6)
Yes	21 (7.4)
Smoking (pack year)	
1-20	18 (7.9)
21-40	9 (2.6)
41-60	3 (0.9)
61+	303 (88.6)
Coffee consumption	
No	174 (50.9)
Yes	168 (49.1)
Carbon monoxide poisoning	
No	294 (93.3)
Yes	21 (6.7)
Traumatic brain injury	
No	306 (97.1)
Yes	9 (2.9)
Diabetes	

No	276 (82.3)
Yes	60 (17.7)
Hypertension	
No	249 (73.5)
Yes	90 (26.5)
Hyperlipidemia	
No	303 (89.4)
Yes	36 (10.6)
Atrial fibrillation	
No	336 (99.1)
Yes	3 (0.9)
Tremor	
No	120 (36.0)
Yes	213 (64.0)
Rigidity	
No	24 (7.2)
Yes	309 (92.8)
Bradykinesia	
No	21 (6.3)
Yes	312 (93.7)
Postural instability	
No	159 (50.5)
Yes	156 (49.5)
REM sleep behavior disorders	
No	195 (61.3)
Yes	123 (38.7)
Late motor complications	
Only ON-OFF/Wearing OFF	57 (17.9)
Only levodopa-induced dyskinesia	12 (3.8)
Both ON-OFF/Wearing OFF and levodopa-induced dyskinesia are present	48 (15.1)
Both ON-OFF/Wearing OFF and levodopa-induced dyskinesia are absent	201 (63.2)
Depression	
No	147 (67.1)
Yes	72 (32.9)

K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating; H&Y staging: Hoehn and Yahr staging; Schwab & England ADL: Schwab & England Activities of Daily Living; PD: Parkinson's disease; REM: Rapid eye movement.

visualizes the classification results through a two-dimensional diagram, is presented in Figure 5.

Importance of variables in the final EOPD prediction model

The normalized importance of variables in the RF model, the final model, is presented in Figure 6 and Table 4. In this model, K-MMSE score, K-MoCA score, sum of boxes in CDR, global score of CDR, motor score of UPDRS, and K-IADL score were confirmed as the major variables with high weight for EOPD prediction. Among them, K-MMSE score was the most important factor in the final model.

Table 3 Error of Out-Of-Bag

Mtry (*n*)	Error of Out-Of-Bag
3	0.140
4	0.105
5	0.149
6	0.132
7	0.140
8	0.123
9	0.149
10	0.123
11	0.140
12	0.158
13	0.149

The partial dependence plot for K-MMSE, the most important variable in the EOPD prediction model, is presented in Figure 7. When the other factors (variables) were identical, the probability of the absence of EOPD tended to decrease as K-MMSE scores increased (Figure 6). In other words, it was confirmed that K-MMSE had the largest impact on EOPD prediction even after adjusting for other neuropsychological tests, PD symptoms, medical history, REM sleep disorder, depression, and sociodemographic factors.

DISCUSSION

Choosing a test with high feasibility and accuracy is critical to easily detect EOPD from PD in the point-of-care environment. It is required to comprehensively compare prediction accuracy for various predictors of EOPD, such as neuropsychological tests, lifestyle, sociodemographic factors, PD symptoms, depression, and REM sleep disorders. This study analyzed the prediction accuracy of various cognitive screening tests and neuropsychological profiles that could distinguish EOPD from PD using RF. The tests were ranked from greatest to least accurate as follows: K-MMSE score, K-MoCA score, sum of boxes in CDR, global score of CDR, motor score of UPDRS, and K-IADL score. It is noteworthy that the motor score of UPDRS, in addition to cognitive screening tests, was an important test in predicting EOPD. This is probably because participants with EOPD were more likely to show non-typical symptoms, such as movement problems, gait problems, and coordination problems[22], and the motor score of UPDRS could comprehensively measure these PD motor symptoms.

In this study, K-MMSE score was the most important neuropsychological test for detecting EOPD. Moreover, the accuracy of K-MMSE was higher than that of K-MoCA. An essential factor in the diagnosis of EOPD is a decline in cognitive function that began after the onset of PD. This decline in cognitive function gradually progresses in various domains, such as executive function, memory, and visuospatial function. In particular, it has been reported that PDD patients experience impaired executive functions, reflecting the decrease in the ability to solve problems from the early stages of dementia[32] as well as impaired visuospatial function[33]. It is known that the impairment of other types of dementia, such as Alzheimer's disease, was significantly lower than that[34]. K-MMSE and K-MoCA have been widely used as screening tests that simply compare the decline of various cognitive functions by types and comprehensively assess cognitive functions prior to in-depth tests in the point-of-care environment. The results of this study showed that the accuracy of K-MMSE was higher than that of K-MoCA when distinguishing EOPD from PD. Therefore, it is believed that if K-MMSE is given priority over other cognitive screening tests in order to distinguish EOPD from PD, the accuracy of detecting EOPD will be higher than conducting other screening tests first. However, further epidemiological studies will be needed to fully comprehend the results of the better accuracy of K-MMSE than that of K-MoCA while detecting EOPD, using the developed ensemble-based prediction

Table 4 The normalized importance of variables in the random forest model

Variables	Mean decrease Gini
K-MMSE	7.224
K-MoCA	2.992
Sum of boxes in CDR score	2.872
Global CDR score	2.304
Motor UPDRS	2.104
K-IADL	1.720
Total UPDRS	1.587
Schwab & England ADL	1.258
H&Y staging	1.040
Late motor complications	0.775
Consumption of coffee	0.699
Education level	0.527
Pack year	0.505
BDI	0.409
Tremor	0.338
Postural instability	0.338
Rigidity	0.331
Gender	0.255
REM sleep behavior disorders	0.249
Hypertension	0.168
Handness	0.151
Diabetes	0.146
Hyperlipidemia	0.129
Carbon monoxide poisoning	0.124
Family PD history	0.074
Family dementia history	0.066
Bradykinesia	0.034
Manganese poisoning	0.013
Traumatic brain injury	0.002
Atrial fibrillation	< 0.001

K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating; H&Y staging: Hoehn and Yahr staging; Schwab & England ADL: Schwab & England Activities of Daily Living; PD: Parkinson's disease; REM: Rapid eye movement; BDI: Beck Depression Inventory.

model. Machine learning has the disadvantage of being unable to interpret the derived results, although it has better prediction accuracy than the traditional regression model. Therefore, future studies are required to develop explainable artificial intelligence models that have high prediction accuracy and are able to interpret results.

Another finding of this study was that the accuracy of RF was higher than that of both the naive Bayesian model and discriminant analysis. These results agreed with Byeon[35], which showed that the ensemble algorithm was more accurate than a regression analysis or decision trees for predicting cognitive impairment in old age. RF has high prediction performance because it generates various decision trees from a number of bootstrap samples, and the possibility of overfitting is low[35]. In particular,

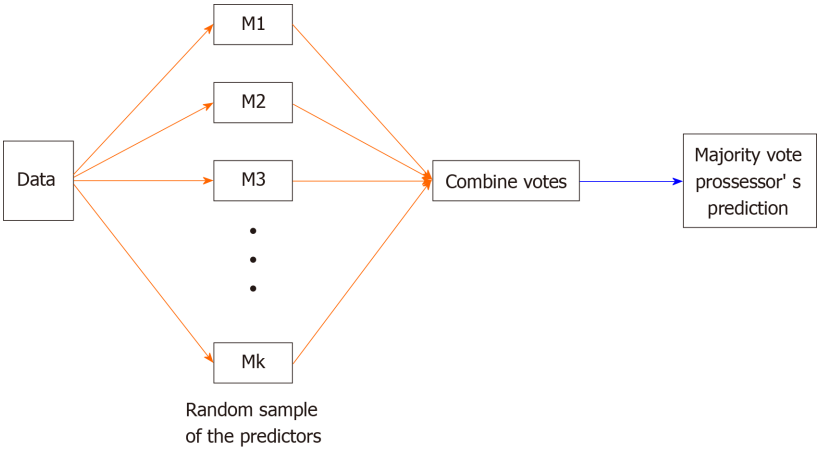

Figure 2 The random forest.

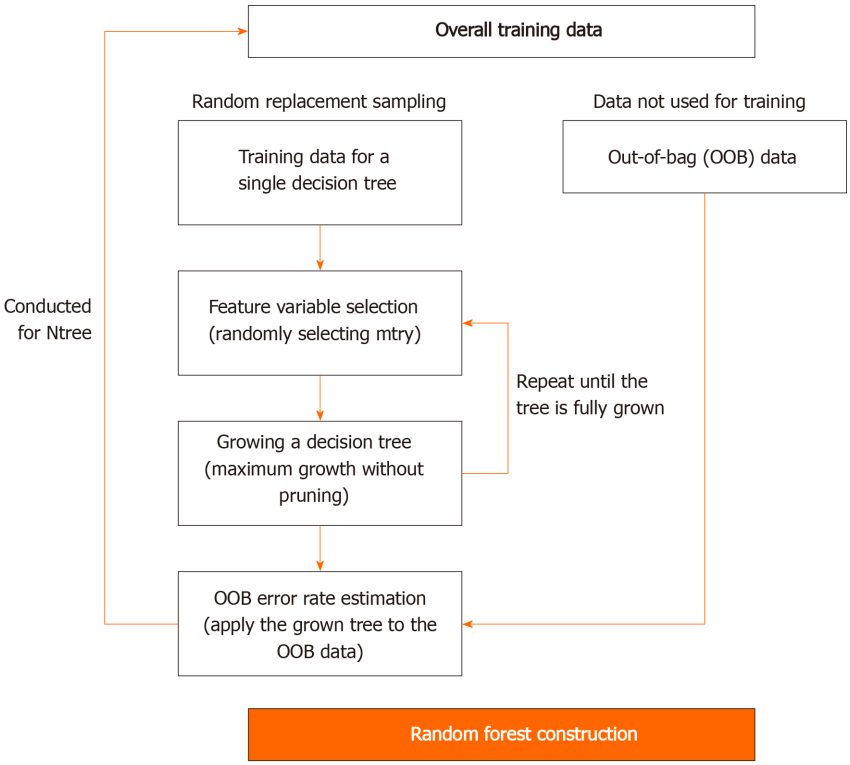

Figure 3 The development process of a random decision forest-based prediction model.

Equation: $f(x) = \frac{1}{n}\sum_{i=1}^{n} log\left(\frac{p_1(x, x_{ic})}{p_0(x, x_{ic})}\right)$

RF showed good predictive performance even when classifying binary variables using imbalanced disease data[15,18]. Therefore, it is believed that, compared to traditional statistical techniques such as discriminant analysis, using RF will increase accuracy while exploring major variables, allowing us to predict EOPD.

The importance of this study was that it identified the prediction accuracy of sociodemographic factors, PD motor symptoms, PD non-motor symptoms, REM sleep disorder, and neuropsychological profiles for distinguishing EOPD from PD, using national examination data conducted by the National Biobank of Korea. The limitations of the study are as follows: (1) The data source of this study was the registry data of multiple institutions and subjects were not randomly sampled; (2) The prediction model did not include candidate markers, genetic information, or biomarkers; (3) Genes such as *PRKN* and *LRRK2* are known to be risk factors for PD

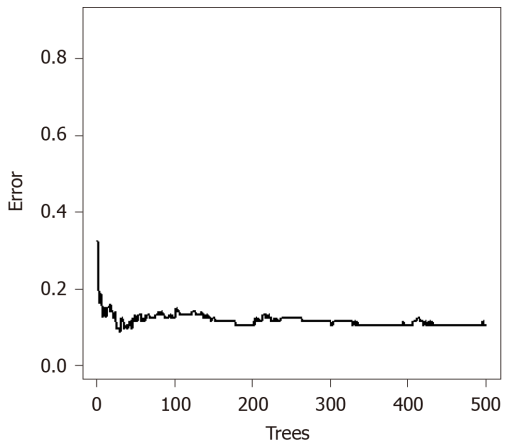

Figure 4 Error rate of the random forest model (500 trees).

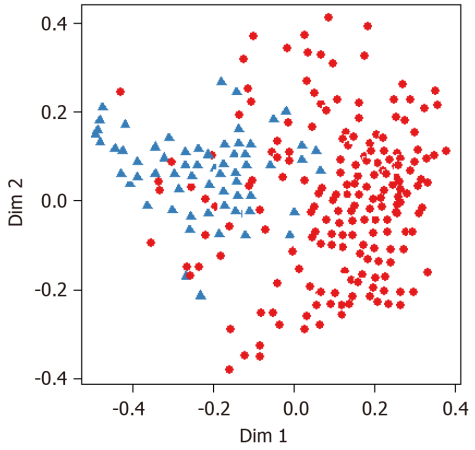

Figure 5 Multidimensional scaling plot of random forest (blue = early-onset Parkinson dementia and red = Parkinson's disease)

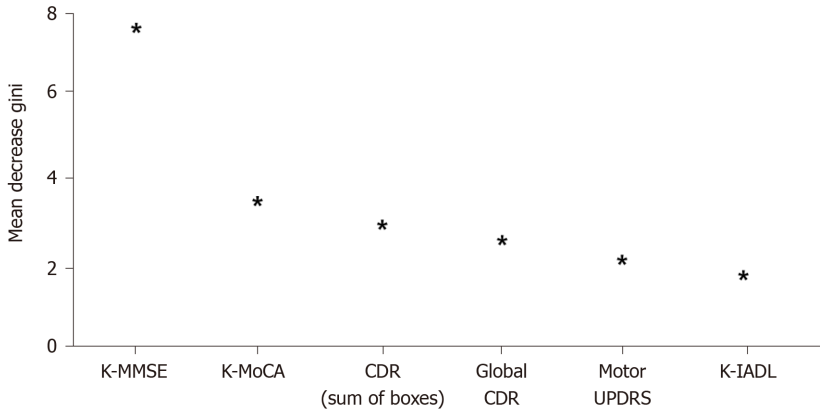

Figure 6 Importance of variables in the random forest-based early-onset Parkinson dementia prediction model (only the top six are presented). K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; K-IADL: Korean Instrumental Activities of Daily Living; UPDRS: Score of Untitled Parkinson's Disease Rating.

and highly related to cognitive functions; and (4) Even though administration of PD medicine could affect the results of cognitive tests, it was not considered as an input variable of the prediction model. Therefore, it is expected that it will be possible to derive more clinically meaningful results when a prediction model is developed by including genetic information or biomarkers in addition to neuropsychological tests. Furthermore, since PD medicine influences the expression of behavioral symptoms

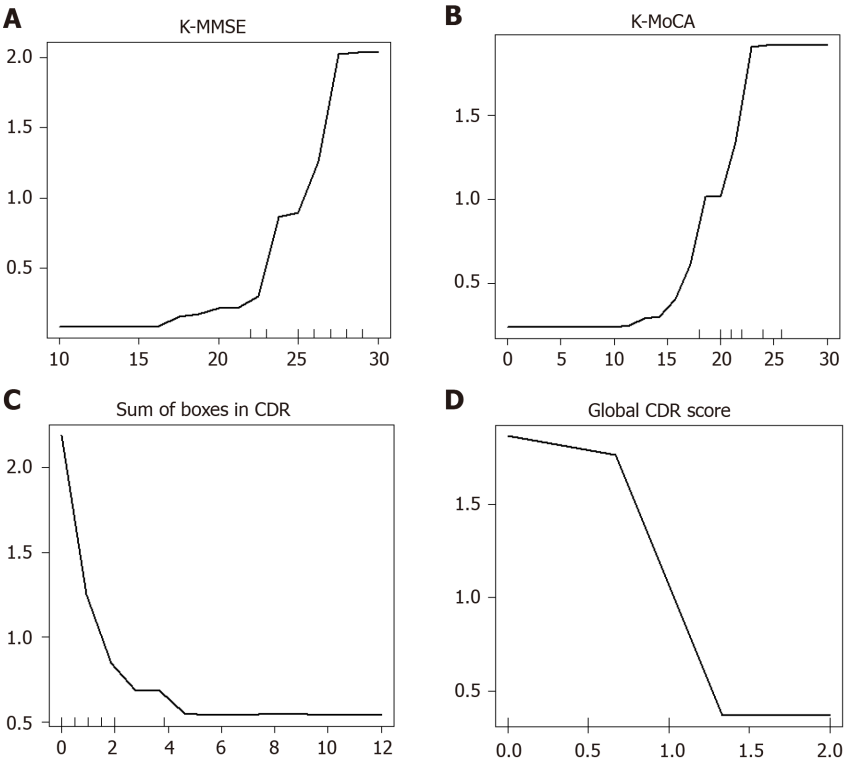

Figure 7 Partial dependence plot. K-MMSE: Korean Mini Mental State Examination; K-MoCA: Korean Montreal Cognitive Assessment; CDR: Clinical Dementia Rating.

and cognitive symptoms, it is necessary to investigate the application of it when developing an EOPD prediction model in the future.

CONCLUSION

It was found that Parkinson-related motor symptoms (*e.g.*, motor score of UPDRS) and instrumental daily performance (*e.g.*, K-IADL score), in addition to cognitive screening indicators (*e.g.*, K-MMSE score and K-MoCA score), were highly accurate predictors in EOPD prediction. Moreover, the accuracy of RF was higher than that of both the naive Bayesian model and discriminant analysis. This study showed the need for a customized screening test that can detect EOPD early using biomarkers or genetic big data.

ARTICLE HIGHLIGHTS

Research background

Despite the frequent progression from Parkinson's disease (PD) to Parkinson dementia, the basis to diagnose early-onset Parkinson dementia (EOPD) in the early stage is still insufficient.

Research motivation

It is limited to develop a highly-reliable model to predict EOPD using individual indicators such as PD symptoms and neuropsychological tests. In order to develop an accurate prediction model, it is necessary to develop a comprehensive model that includes sociodemographic indices, Parkinson's motor symptoms, Parkinson's non-motor symptoms, rapid eye movement (REM) sleep behavior disorder, and neuropsychological indices.

Research objectives

The objectives of our study were to explore the prediction accuracy of sociodemographic factors, Parkinson's motor symptoms, Parkinson's non-motor

symptoms, and REM sleep disorder for diagnosing EOPD using PD multicenter registry data.

Research methods

This study was performed by analyzing the Parkinson's Disease Epidemiology multicenter registry data provided by the National Biobank of Korea. This study analyzed 342 Parkinson patients (66 EOPD patients and 276 PD patients with normal cognition, younger than 65 years). The EOPD prediction model was developed using a random forest algorithm and the accuracy of the developed model was compared with the naive Bayesian model and discriminant analysis.

Research results

When the factors of EOPD were compared using "normalized importance of variables", the Korean Mini Mental State Examination score was the most important factor of EOPD. Also, the accuracy of random decision forest was higher than that of naive Bayesian model and that of discriminant analysis.

Research conclusions

It is believed that using random forest will increase accuracy while exploring major variables allowing us to predict EOPD, compared to traditional statistical techniques such as discriminant analysis.

Research perspectives

It is necessary to develop a customized screening test that can early detect EOPD using biomarkers or genetic big data.

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ORIGINAL ARTICLE

Observational Study

Testing the hypothesis of subtypes of nonadherence in schizophrenia and schizoaffective disorder: A prospective study

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Author contributions: Acosta FJ designed the study and wrote the protocol, wrote the first draft of the manuscript, and coordinated the project; Vega D managed the literature searches and was in charge of the recruitment and assessments of all patients; Saavedra P was in charge of data management and undertook the statistical analysis; and all authors contributed to and have approved the final manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

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Abstract

BACKGROUND

Nonadherence is a major problem in the treatment of psychotic disorders. It has been hypothesized that nonadherent patients with schizophrenia are not a homogeneous population and subtypes of nonadherence might exist, but this hypothesis has not been specifically tested.

AIM

To test the hypothesis of subtypes of nonadherence in schizophrenia and schizoaffective disorder.

METHODS

This prospective study included 110 consecutively admitted patients diagnosed with schizophrenia or schizoaffective disorder. Assessments were performed at baseline and at 6 mo follow-up after discharge. Sociodemographic, clinical, psychopathological and treatment-related variables were evaluated. Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic

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treatment was defined as the concurrence of objective and subjective adherence. Sixty-four patients (58%) fulfilled nonadherence criteria at the end of the follow-up period and were categorized according to their subtype of nonadherence.

RESULTS

In nonadherent patients (n = 64), 32 (50%) fulfilled criteria of intentional nonadherence, and 32 (50%) of unintentional nonadherence (UNA). Unintentional nonadherent patients, as compared to intentional nonadherent patients, are characterized by older age, lower educational level, worse cognitive and negative symptoms, greater severity, worse knowledge of their treatment regimen, greater prevalence of supervision of the treatment, lower number of prior hospitalizations and greater use of nonpsychiatric treatment, anticholinergics and hypnotics. Low educational level (OR = 26.1; 95%CI: 2.819-241), worse treatment knowledge at six months (OR per unit = 0.904; 95%CI: 0.853-0.957) and nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139) were independently associated to UNA.

CONCLUSION

Differentiated subtypes of nonadherence according to intentionality seem to exist in patients with schizophrenia and schizoaffective disorder. Our findings suggest the need for differentiated approach, both in future research and in clinical practice.

Key Words: Adherence; Hospitalization; Psychosis; Hypothesis; Unintentional nonadherence; Intentional nonadherence

Core Tip: Nonadherence is a major problem in the treatment of psychotic disorders. The scarcity of consistently identified variables associated with nonadherence could be due, at least in part, to real heterogeneity among nonadherent patients. Although in recent years the existence of two main subtypes according to intentionality has been hypothesized, no previous studies have specifically tested this hypothesis. This research aimed to fill this gap. We found differentiated profiles in nonadherent patients according to intentionality. Our results support the nonadherence subtypes hypothesis in psychotic disorders.

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INTRODUCTION

Despite important advances in the management of schizophrenia in recent decades, nonadherence is still a frequent phenomenon, around 40% to 50%[1-3]. Unfortunately, there are still few predictive factors of note and the current state of the evidence may be somewhat disheartening for the practicing clinician[4]. To date, the most consistent risk factors for nonadherence include previous nonadherence, poor insight, negative attitude towards treatment and substance abuse[1,4-7].

The heterogeneity of findings related to several risk factors for nonadherence[4] has been regarded as a consequence of the methodologic limitations of most available studies, especially the absence of a valid assessment method[4,8]. Moreover, only recently has there been expert consensus providing a conceptual and operative definition of adherence[3,8,9]. Finally, although prospective studies provide robust findings regarding cause-effect relationships, most studies are cross-sectional[1,4].

Nevertheless, the scarcity of consistently identified correlates[4] could also be due to real heterogeneity among nonadherent patients. Thus, in recent years the existence of two main subtypes has been hypothesized: Intentional and unintentional[9-14].

Intentional nonadherence (INA) has been defined as a conscious patient decision to stop taking medication or to take less medication than prescribed, whereas unintentional nonadherence (UNA) occurs when practical problems or impairments related to having an illness interfere with taking medication[7], thus involving patient-related, environment and treatment-related factors[15], such as forgetfulness[11], suboptimal awareness of their treatment[16], inadequate health literacy[17], mistakes[18] or barriers to access mental health care[19]. However, there are no clear limits between both subtypes, and overlaps and comorbidities exist[12,15,20,21]. Despite its importance, few specific studies on patients with psychoses have been performed[12,13,21]. Identification of subtypes as well as specific reasons for nonadherence would guide towards different types of interventions[13,18,22].

In this context, we performed this prospective study in hospitalized patients diagnosed with schizophrenia or schizoaffective disorder. Hospitalizations are an important event in the course of illness. For its part, nonadherence has been found to be the main reason for admission in 58.6% of patients[23], it is frequent in the months after discharge[24-26] and discharge can be a good time to introduce strategies aimed at improving adherence[27].

Therefore, this study had the following objectives: (1) To evaluate the prevalence of nonadherence at six-months post discharge; and (2) To evaluate the possible subtypes of nonadherence according to intentionality and to determine whether identified subtypes have a differential profile. We hypothesized that two different subtypes according to intentionality would be identified, and these would have a different profile.

MATERIALS AND METHODS

Patients

This naturalistic, observational and 6-mo follow-up prospective study included 110 patients diagnosed with schizophrenia or schizoaffective disorder according to ICD-10 criteria; patients were consecutively admitted to the Acute Patients' Unit of the Insular University Hospital of Gran Canaria, The Canary Islands, Spain, over an 18-mo period since recruitment commenced (February 2017), and whose follow-up was due to take place at the Community Mental Health Unit (CMHU) of Vecindario, which covers a population of 195410 people. As additional inclusion criteria, patients had to be aged over 18 years, understand the information concerning the study and agree to participate. Exclusion criteria were suffering intellectual disability or dementia. Out of 115 eligible patients, 5 (4.35%) refused to participate. This study was carried out in compliance with the latest version of the Declaration of Helsinki and approved by the Ethics Committee of Insular University Hospital of Gran Canaria. All patients were informed about the characteristics of the study and gave their written consent.

Procedure

Baseline evaluation was performed during any of the 7 d prior to discharge. Follow-up assessment was performed 6 mo from discharge. All patients were evaluated by the same psychiatrist. Baseline evaluation included sociodemographic, clinical, psychopathologic and treatment-related variables, which are shown in Tables 1 and 2. Psychopathology was evaluated by the Clinical Global Impression-Schizophrenia Scale (CGI-SCH), severity subscale, validated in Spanish[28], at baseline and follow-up. Insight was evaluated by the first three items of the Amador Insight Scale, which assess general disorder awareness[29], validated in Spanish[30]. Cognitive performance was assessed by means of the SCIP-S scale (Screen for Cognitive Impairment in Psychiatry), validated in Spanish[31].

Treatment-related variables included several objective and subjective measures. Regarding the latter, attitude towards medication was evaluated by the Drug Attitude Inventory (DAI)[32], Spanish validated version[33]. Beliefs about treatment were assessed through the Beliefs about Medicines Questionnaire (BMQ)[34] in its Spanish validated version[35]. Perceptions about shared decisions were evaluated by the 9-item Shared Decision Making Questionnaire (SDM-Q-9) in its Spanish validated version[36].

Knowledge was evaluated by means of an ad hoc questionnaire (Supplementary Material). Treatment knowledge was restricted to that of the main antipsychotic, as considered by the psychiatrist. To avoid potential bias due to the "Hawthorne effect"[37] patients were not informed that their knowledge of treatment, diagnosis and follow-up was to be assessed at 1 h, 2 wk and 6 mo from the time of instruction.

Table 1 Sociodemographic, clinical, and treatment-related characteristics of the sample at admission and differences between unintentional and intentional nonadherent patients

	Total non-adherence (*n* = 64)	Unintentional (*n* = 32)	Intentional (*n* = 32)	*P* value
Age (yr)	40.6 ± 9.6	44.4 ± 10.1	36.8 ± 7.4	0.001
Sex (male)	39 (60.9)	23 (71.9)	16 (50.0)	0.073
Marital status				0.522
Married or stable relationship	12 (18.8)	5 (15.6)	7 (21.9)	
Single, separated, divorced, or widowed	52 (81.2)	27 (84.4)	25 (78.1)	
Educational level				< 0.001
Primary or lower	34 (53.1)	25 (78.1)	9 (28.1)	
Secondary or higher	30 (46.9)	7 (21.9)	23 (71.9)	
Socio-economic level				0.376
Low	49 (76.6)	26 (81.2)	23 (71.9)	
Medium-High	15 (23.4)	6 (18.8)	9 (28.1)	
Employment situation				0.162
Active	5 (7.8)	1 (3.1)	4 (12.5)	
No active	59 (92.2)	31 (96.9)	28 (87.5)	
Cohabitation				0.794
Living with family	41 (64.1)	20 (62.5)	21 (65.6)	
Living alone	23 (35.9)	12 (37.5)	11 (34.4)	
Length of admission (d)	23 (14-32)	25 (14-35)	21 (14-26)	0.179
Length of the disorder (yr)	11 (5-19)	11 (5-20)	10 (6-17)	0.577
Number of previous psychiatric admissions	2.0 (1.0-5.0)	1.0 (1.0-4.0)	3.0 (1.0-5.2)	0.036
Time since last hospitalization (yr)	2.0 (1.1-5.0)	2.0 (1.0-7.3)	2.0 (1.3-3.0)	0.435
ICD diagnosis				0.079
Schizophrenia	35 (54.7)	21 (65.6)	14 (43.8)	
Schizoaffective disorder	29 (45.3)	11 (34.4)	18 (56.2)	
Current substance use or abuse	36 (56.2)	18 (56.2)	18 (56.2)	1
History of substance use or abuse	44 (68.8)	22 (68.8)	22 (68.8)	1
Daily doses (oral antipsychotic)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.243
Psychotropic pills per day	6 (4-8)	6 (4-8)	5 (3-9)	0.479
Attitude towards treatment				0.664
Negative	41 (64.1)	19 (59.4)	22 (68.8)	
Neutral	15 (23.4)	9 (28.1)	6 (18.8)	
Positive	8 (12.5)	4 (12.5)	4 (12.5)	

Data are means ± SD, frequencies (%) and medians (IQR).

Adherence

Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic treatment was defined as the concurrence of objective and subjective adherence.

Objective adherence was defined as taking more than 80% of prescribed medication, as recommended by expert consensus[3]. Medication possession ratio (MPR) was used to assess adherence to oral antipsychotics, and clinical records to assess adherence to

Table 2 Psychopathological, treatment-related, and other characteristics of nonadherent patients during hospitalization and at 6 mo post discharge, and differences between unintentional and intentional nonadherence

	Hospitalization				6 mo			
	Total Nonadherence (*n* = 64)	Unintentional (*n* = 32)	Intentional (*n* = 32)	*P* value	Total nonadherence (*n* = 64)	Unintentional (*n* = 32)	Intentional (*n* = 32)	*P* value
Amador insight scale, general disorder awareness	11 (9-15)	11 (9-15)	11 (9-15)	0.634	9 (9-11)	9 (6-11)	9 (9-13)	0.467
Mental disorder	5 (3-5)	5 (3-5)	5 (3-5)	0.750	3.0 (3.0-5.0)	3.0 (2.0-4.5)	3.0 (3.0-5.0)	0.177
Effects of the medication	3.0 (3.0-5.0)	3.0 (3.0-5.0)	3.0 (3.0-5.0)	0.638	3.0 (2.0-3.0)	3.0 (2.2-3.0)	3.0 (2.5-4.0)	0.907
Social consequences	3.0 (3.0-5.0)	3.0 (3.0-5.0)	4.0 (3.0- 5.0)	0.441	3.0 (2.0-5.0)	3.0 (2.2-4.8)	3.0 (2.5-5.0)	0.861
CGI-SCH severity. Total score	11 (10-13)	11 (10-13)	10 (9-12)	0.086	10 (9-12)	12 (10-13)	9 (8-10)	0.003
Psychotic symptoms	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0- 3.0)	0.645	2.0 (2.0- 3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.118
Negative symptoms	2.0 (1.0-2.2)	2.0 (1.0-2.2)	2.0 (1.0-2.2)	0.186	2.0 (1.0-2.0)	2.0 (2.0-3.0)	2.0 (1.0-2.0)	< 0.001
Depressive symptoms	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.413	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.346
Cognitive symptoms	2.0 (1.0-2.0)	2.0 (2.0-2.0)	1.0 (1.0-2.0)	< 0.001	2.0 (1.0-2.0)	2.0 (2.0-2.8)	1.0 (1.0-2.0)	< 0.001
Global severity	3.0 (3.0-3.0)	3.0 (3.0- 3.0)	3.0 (2.8-3.0)	0.679	3.0 (2.0-3.0)	3.0 (2.0-3.0)	2.0 (2.0-3.0)	0.210
SCIP. Total score	49 (40-55)	42 (32-52)	52 (46-59)	0.002	48 (41-59)	42 (33-49)	56 (48-62)	< 0.001
Verbal learning-immediate	13 (10-15)	12 (9-15)	13 (11-15)	0.073	15 (11-17)	13 (10-16)	15 (12-18)	0.032
Working memory	16 (13-20)	14 (11-18)	18 (16-21)	0.004	17 (14-20)	14 (12-17)	19 (17-20)	0.001
Verbal fluency	10 (8-13)	10 (7-11)	12 (9-14)	0.022	11 (8-12)	10 (7-11)	11 (8-13)	0.045
Verbal learning-delayed	4.0 (2.0-5.0)	3.0 (2.0-4.0)	4.0 (3.0-5.0)	0.003	4.0 (3.0-5.0)	3.0 (1.2-4.0)	5.0 (4.0-6.0)	< 0.001
Processing speed	4.0 (3.0-6.0)	3.0 (2.0-5.0)	5.0 (3.0-7.0)	0.004	4.0 (3.0-5.0)	3.0 (2.0-4.0)	5.0 (4.0-6.0)	< 0.001
Type of antipsychotic treatment				0.114				0.114
Oral	22 (34.4)	8 (25.0)	14 (43.8)		22 (34.4)	8 (25.0)	14 (43.8)	
Injectable or injectable + oral	42 (65.6)	24 (75)	18 (56.2)		42 (65.6)	24 (75)	18 (56.2)	
Supervision of the treatment	40 (65.6)	21 (67.7)	19 (63.3)	0.717	51 (79.7)	29 (90.6)	22 (68.8)	0.03
SDM-Q-9. total score	17 (9-23)	10 (8-19)	20 (11-30)	0.010	18 (11-21)	17 (10-21)	18 (14-22)	0.235
BMQ, beliefs about medicines, general	22 (18-27)	22 (20-27)	22 (17-25)	0.509	22 (18-26)	22 (18-26)	22 (16-25)	0.623
BMQ, beliefs about medicines, specific	6 (5-7)	6 (6-7)	6 (5-7)	0.142	31 (26-34)	31 (27-35)	30 (26-34)	0.479
DAI	3.0 (-3.0-7.0)	3.0 (-1.0-5.0)	1.0 (-3.0-7.0)	0.914	1.0 (-3.0-3.0)	1.0 (-3.0-6.5)	1.0 (-3.0-3.0)	0.374
Morisky-Green test	2.0 (2.0-3.0)	2.0 (1.8-2.2)	2.0 (2.0-3.0)	0.302	2.0 (2.0-3.0)	2.0 (2.0-3.0)	2.5 (2.0-3.0)	0.084

BARS	100 (100-100)	100 (100-100)	100 (100-100)	0.329	55 (30-74)	60 (20-78)	50 (40-70)	0.586
Knowledge of the treatment at 1 h[1]	75 (58-92)	67 (58-75)	83 (75-92)	< .001				
Knowledge of the treatment at 20 d[1]	79 (62-92)	65 (42-77)	83 (81-92)	< .001				
Knowledge of the treatment at 6 mo[1]					80 (60-90)	60 (40-70)	90 (80-100)	< 0.001

Data are means ± SD, frequencies (%) and medians (IQR).

[1]There were 3 lost cases regarding knowledge of the treatment (n = 61; unintentional, n = 30; intentional, n = 31). Knowledge of the treatment: Knowledge of the treatment, diagnosis, and follow-up from the time of instruction. The values represent means of percentages. BMQ: Beliefs about medicines questionnaire; CGI-SCH: Clinical Global Impression–Schizophrenia; IQR: Inter-quartile range; SCIP: Screen for Cognitive Impairment in Psychiatry; SDM-Q-9: Shared Decision Making Questionnaire; SD: Standard deviation; DAI: Drug attitude inventory; BARS: Brief adherence rating scale.

long-acting injectables (LAI). The MPR is a ratio of total days' supply to number of days of study participation per participant[38], and were calculated by each patient by dividing the number of outpatient days' supply of medication the patient received during the study period by the number of days' supply they needed to receive if they were taking their outpatient medication continuously, as previously done[39]. When there were two or more oral antipsychotics, the mean of the respective MPR was obtained. Regarding LAI, correct administration was considered as a dose administered within three days of the scheduled dose, as performed previously[10].

Subjective adherence was defined as a score of 3 or 4 in the Morisky-Green test, as performed previously[40,41] and a score higher than 80% on the BARS scale at six months. The BARS is a 4-item scale specifically developed to measure adherence to antipsychotics in schizophrenia[42].

Adherence to outpatient follow-up was defined as the concurrence of attendance at scheduled visits greater than 80% (after excluding justified absences) and the absence of dropout, defined as nonattendance at scheduled visits for at least six months.

Therefore, nonadherence was defined as the occurrence of nonadherence to antipsychotic treatment, nonadherence to outpatient follow-up, or both. For its part, nonadherence to antipsychotic treatment was defined as the occurrence of objective nonadherence, subjective nonadherence or both.

Subtypes of nonadherence

Subtypes were assigned at 6 mo follow-up, after clinical assessment, information from the CMHU therapeutic team, details of medical record, and interview of family members when needed. Based on extensive literature reviews[14,43], we established a set of reasons for nonadherence. Patients were assigned to UNA if the main reason was any of items 2, 4, 7 or 8, and to INA for the remaining reasons. When there were two or more reasons for nonadherence, these were also recorded for descriptive purposes. The reasons included: (1) The patient does not believe in the need for treatment; (2) Forgetfulness; (3) To minimize or to avoid possible adverse effects; (4) Misunderstanding; (5) To minimize or to avoid possible risk of addiction; (6) To make the regimen more acceptable in order to fit with their daily schedule; (7) Regimen complexity; (8) Financial reasons and/or accessibility problems; (9) To see what happens without treatment; (10) Replacing medicines with non-pharmacological treatments; (11) Poor therapeutic alliance; and (12) To avoid stigma associated to antipsychotics.

Statistical analysis

Categoric and continuous variables were expressed respectively as frequencies and percentages and as mean and standard deviation (SD) when data followed a normal distribution, or as median and interquartile range (IQR = 25th-75th percentile) when distribution departed from normality. Percentages were compared, as appropriate, using Chi-square (χ^2) test or exact Fisher tests; means and medians were compared by the student t-test and Wilcoxon test for independent data, respectively. In order to identify factors that maintain independent association with each outcome (nonadherence; unintentional subgroup), a multivariate logistic regression analysis was performed. Variables that revealed statistically significant association with the corresponding outcome in univariate analysis were entered into the multivariate analysis. Variables based on the best subset regression and Akaike information

criterion were then selected. Models were summarized as coefficients (SE), *P* values (likelihood ratio test) and odds-ratio, which were estimated by means of 95% confidence intervals. Statistical significance was set at $P < 0.05$. Data were analyzed using the R package, version 3.3.1.[44]. The statistical review of the study was performed by a biomedical statistician.

RESULTS

Nonadherence and characteristics of the sample

We recruited 110 patients, of whom 64 (58%) fulfilled nonadherence criteria; 56.4% nonadherence to antipsychotic treatment, and 20.9% nonadherence to outpatient follow-up. Since this study is focused on evaluation of possible subtypes of nonadherence, the total sample was comprised of nonadherent patients ($n = 64$). The percentage of men (60.9%) was higher than that of women, and mean age was 37.4 years. The most common diagnosis was schizophrenia (54.7%), the length of the psychiatric disorder showed a median of 11 years, the length of admission was 23 d, and prevalence of current substance use or abuse was high (56.2%). Sociodemographic, clinical, psychopathologic and treatment-related variables are shown in Tables 1 and 2.

Subtypes and subgroups of nonadherence

In nonadherent patients ($n = 64$), 32 (50%) fulfilled criteria of INA, and 32 (50%) of UNA. The prevalence of the main reasons identified in INA patients was: The patient does not believe in the need for treatment (75%), to minimize or to avoid possible adverse effects (18.8%), to make the regimen more acceptable in order to fit with their daily schedule (3.1%), to see what happens without treatment (3.1%). The prevalence of the main reasons identified in UNA patients was: Forgetfulness (65.6%), financial reasons and/or accessibility problems (15.6%), misunderstanding (12.5%), regimen complexity (6.3%). Mixed reasons (*i.e.*, concurrence of two or more reasons, belonging to both INA and UNA) were found in 42.2% of the patients.

Variables associated with nonadherence subgroups

UNA patients, as compared to INA patients, showed older age (44.4 *vs* 36.8 respectively, $P < 0.001$), higher prevalence of low educational level (78.1% *vs* 28.1%, $P < 0.001$), lower number of prior hospitalizations (1.0 *vs* 3.0, $P = 0.036$), greater severity at six months (12 *vs* 9, $P = 0.003$), worse negative symptoms at 6 mo (2 *vs* 2, $P < 0.001$), worse cognitive symptoms at admission and at 6 mo, as assessed both by the CGI (2 *vs* 1 respectively, $P < 0.001$) and the SCIP (42 *vs* 56, $P < 0.001$), worse knowledge of the treatment regimen at 1 h (67 *vs* 83, $P < 0.001$), at 20 d (65 *vs* 83, $P < 0.001$), and at 6 mo (60 *vs* 90, $P < 0.001$), greater prevalence of supervision of the treatment (90.6% *vs* 68.8%, $P = 0.03$), greater use of anticholinergics at admission (35.5% *vs* 12.5%, $P = 0.032$) and at six-month follow-up (35.5% *vs* 12.5%, $P = 0.032$), hypnotics at admission (90% *vs* 71.9%, $P = 0.055$), and nonpsychiatric treatment at admission (60% *vs* 25%, $P = 0.005$) and at 6 mo (60% *vs* 25%, $P = 0.005$).

Tables 1 and 2 summarize the sociodemographic, clinical, psychopathologic and treatment-related differences between unintentional and intentional nonadherent patients. The multivariate logistic regression model for nonadherence according to subgroups is shown in Table 3. Factors that revealed an independent association with UNA were nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139), low educational level (OR = 26.1; 95%CI: 2.819-241), and treatment knowledge at six months (average) (OR per unit = 0.904; 95%CI: 0.853-0.957).

DISCUSSION

Nonadherence in the post discharge period was high. Up to 58% of patients did not fulfil adherence criteria at six-month follow-up. This high rate is consistent with that found in other prospective studies using electronic monitoring devices. Thus, nonadherence rates were 48% at 3 mo[45] and 62.7% at six months from discharge[26]. In addition to the alarming high rate of nonadherence, identification of distinguishable profiles of nonadherent patients according to their intentionality was the main finding of this study. Our findings are consistent with the hypothesis regarding the existence of nonadherence subtypes according to intentionality[9-14] and, therefore, support this hypothesis.

Table 3 Variables associated with nonadherence according to intentionality after multivariate logistic regression (reference: Unintentional nonadherence)

	P value[1]	AIC[2]	Odds ratio (95%CI)
Low educational level	< 0.001	52.1	26.1 (2.819; 241)
Non-psychiatric treatment at 6 mo	0.003	47.7	15.8 (1.790; 139)
Treatment knowledge at 6 mo, mean	< 0.001	64.9	0.904 (0.853; 0.957)

[1]Likelihood ratio test.
[2]If the variable is removed. AIC for the full model = 41.1; AIC is a measure of lack of fit. The removal of any variable leads to a model with more lack of fit.
AIC: Akaike information criterion.

Worse negative symptoms and cognitive deficits were associated with UNA patients. Persistent negative symptoms[3,46] and cognitive symptoms[7,47] can affect the ability to manage medications. Cognitive deficits may hinder understanding the treatment regimen, its awareness as well as the organizational capacity needed for adherence, particularly with complex regimens[7,48]. In this regard, nonpsychiatric treatment at six months was strongly and independently associated with UNA patients in this study. However, the relationship between cognition and nonadherence is still inconclusive[4]. This heterogeneity of findings may have been influenced by methodologic difficulties and by the fact that the impact of cognitive deficits likely depends on other conditions and circumstances, such as whether or not there is good family support involved in planning and monitoring medication intake[7]. Nevertheless, an additional factor may be the hypothesized heterogeneity of nonadherent patients. According to this hypothesis, cognitive deficits could be relevant only or especially for UNA. To the best of our knowledge, this is the first study that specifically assesses the association between cognitive features and different nonadherence subtypes.

For its part, knowledge of treatment, diagnosis and follow-up was lower in UNA at the three time points assessed. In addition, worse knowledge of the treatment regimen at six months was independently associated with this subtype. This area remains little studied. Most studies have found suboptimal knowledge of the treatment[16,49,50]. Moreover, physicians have been found to overestimate understanding the treatment by their patients[51]. Some authors have found an association between knowledge of the purpose for taking medication and adherence, but not with other aspects[49], while others have not found such an association[50]. This disparity of findings may have been influenced by methodologic issues, such as the absence of a uniform description of what adequate knowledge of treatment is and absence of operational definitions; or again, by a real heterogeneity within nonadherent patients, as we hypothesize. To the best of our knowledge, this is the first study that specifically assesses the association between knowledge of the treatment and different nonadherence subtypes.

Lower educational level and older age were found to be associated with UNA patients. In addition, educational level was independently associated with this subtype. Most studies have not found an association between educational level and adherence[1,3,4]. Nevertheless, when considering the possible subtypes of nonadherence, it seems plausible that a lower educational level may contribute to inadequate understanding of treatment regimen, and this in turn may lead to UNA. In this context, in a study on community-dwelling seniors admitted to acute medicine services, inadequate and marginal health literacy patients were likely to have UNA, whereas those with adequate health literacy were more likely to have INA[17]. Future studies that assess the possible association between educational level and UNA in schizophrenia would shed light on this issue. With regard to age, this variable has also yielded contradictory results. Whereas some studies have found younger age associated with adherence problems[3,52], others have failed to find such an association[1,10].

Finally, neither insight nor any of its three basic components were associated with different subtypes of nonadherence. This finding contrasts with the notion that poor insight is an important reason for INA[7], or specifically a risk factor likely to affect willingness to take medication[3,53]. It is likely that this absence of differences has been influenced by the fact that the global sample of nonadherent patients showed poor insight. This finding was to be expected, since our sample consisted of admitted patients evaluated both during hospitalization and at follow-up. Another factor may

be that we found mixed reasons in 42.2% of the patients, which is consistent with the notion that overlapping between both subgroups seems to exist[11,12,20,21]. In any case, although poor insight is an unquestionable risk factor for nonadherence[1,3,5,10,54], the role of insight in intentional *vs* unintentional adherence has not been sufficiently studied.

This study has certain limitations and strengths. The assessment method of adherence was not the reference standard, *i.e.*, electronic monitoring[55-57]. However, this method is an indirect measure of treatment adherence and also has drawbacks[7,58], and we have combined objective and subjective methods from multiple sources to assess adherence, as recommended[3,4,7,59]. Moreover, we worked in accordance with the operational criteria for nonadherence recommended in the expert consensus[3]. Furthermore, one of the scales used to assess adherence has revealed similar estimates of adherence to those produced by electronic monitoring[42]. Unfortunately, intentional and unintentional dimensions of patient medication taking are poorly categorized within adherence literature[60]. Thus, there is neither consensus regarding the differentiation of these subtypes nor standardized instruments to assess them. Finally, the modest sample size and the nature of the sample may affect both the statistical power and the generalizability of our findings. The main strengths of this study are its prospective design - which confers strength in the establishment of cause-effect relationships - and a wide evaluation of variables including subjective aspects, treatment-related variables and knowledge of the treatment, usually neglected in the literature.

CONCLUSION

In conclusion, we have found differentiated profiles among nonadherent patients according to intentionality. UNA patients, as compared to INA patients, are characterized by lower educational level, worse knowledge of their treatment regimen, worse cognitive and negative symptoms, older age, greater use of nonpsychiatric treatment, and fewer prior hospitalizations, as most prominent features. These findings support the hypothesis that there are nonadherence subtypes in patients with psychotic disorders, and suggest the need for a differentiated approach, both in future research and clinical practice.

ARTICLE HIGHLIGHTS

Research background

Despite important advances in the management of schizophrenia in recent decades, nonadherence remains a common phenomenon, with prevalence rates of approximately 40%-50%. The heterogeneity of findings regarding several risk factors for nonadherence could also be due to real heterogeneity among nonadherent patients.

Research motivation

The existence of two main subtypes according to intentionality has been hypothesized: Intentional and unintentional. Identification of subtypes as well as specific reasons for nonadherence would provide guidance in terms of different types of interventions.

Research objectives

To evaluate possible subtypes of nonadherence according to intentionality and to determine whether identified subtypes show a differential profile.

Research methods

This naturalistic, observational, and 6-mo follow-up prospective study included 110 admitted patients diagnosed with schizophrenia or schizoaffective disorder. Baseline evaluation included sociodemographic, clinical, psychopathologic and treatment-related variables. Adherence was defined as the concurrence of adherence to antipsychotic treatment and outpatient follow-up during the six-month period. Adherence to antipsychotic treatment was defined as the concurrence of objective and subjective adherence. Subtypes were assigned at 6 mo follow-up based on a set of reasons for nonadherence.

Research results

Sixty-four patients (58%; n = 64) fulfilled nonadherence criteria at the end of the follow-up period and were categorized according to subtype of nonadherence: 32 (50%) fulfilled criteria of intentional nonadherence, and 32 (50%) unintentional nonadherence (UNA). Several variables were independently associated with UNA: Low educational level (OR = 26.1; 95%CI: 2.819-241), worse treatment knowledge at six months (OR per unit = 0.904; 95%CI: 0.853-0.957) and nonpsychiatric treatment at six months (OR = 15.8; 95%CI: 1.790-139).

Research conclusions

This study specifically tests the subtypes hypothesis in psychotic disorders. We found two subtypes of nonadherence according to intentionality, as well as differentiated profiles. Our results support the nonadherence subtypes hypothesis in psychotic disorders.

Research perspectives

We propose some directions for future research: (1) Replication studies to confirm the existence of differentiated subtypes of nonadherence in psychotic disorders; and (2) If confirmed, adoption of a differentiated approach, both in future research and clinical practice.

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META-ANALYSIS

Effects of smartphone-based interventions and monitoring on bipolar disorder: A systematic review and meta-analysis

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Abstract

BACKGROUND

Recently, there has been a range of studies about smartphone-based interventions and monitoring for reducing symptoms of bipolar disorder (BD). However, their efficacy for BD remains unclear.

AIM

To compare the effect of smartphone-based interventions and monitoring with control methods in treating patients with BD.

METHODS

A systematic literature search was performed on PubMed, Embase, Clinical trials, psycINFO, Web of Science, and Cochrane Library. Randomized clinical trials (RCTs) or single-group trials in which smartphone-based interventions and monitoring were compared with control methods or baseline in patients with symptoms of BD were included. Data were synthesized using a random-effects or a fixed-effects model to analyze the effects of psychological interventions and monitoring delivered *via* smartphone on psychiatric symptoms in patients with BD. The primary outcome measures were set for mania and depression symptoms. Subgroups were created to explore which aspects of smartphone interventions are relevant to the greater or lesser efficacy of treating symptoms.

RESULTS

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We identified ten articles, including seven RCTs (985 participants) and three single-group trials (169 participants). Analysis of the between-group study showed that smartphone-based interventions were effective in reducing manic [g = -0.19, 95% confidence interval (CI): -0.33 to -0.04, $P = 0.01$] and depressive (g = -0.28, 95%CI: -0.55 to -0.01, $P < 0.05$) symptoms. In within-group analysis, smartphone-based interventions significantly reduced manic (g = 0.17, 95%CI: 0.04 to 0.30, $P < 0.01$) and depressive (g = 0.48, 95%CI: 0.18 to 0.78) symptoms compared to the baseline. Nevertheless, smartphone-based monitoring systems significantly reduced manic (g = 0.27, 95%CI: 0.02 to 0.51, $P < 0.05$) but not depressive symptoms. Subgroup analysis indicated that the interventions with psychoeducation had positive effects on depressive (g = -0.62, 95%CI: -0.81 to -0.43, P < 0.01) and manic (g = -0.24, 95%CI: -0.43 to -0.06, $P = 0.01$) symptoms compared to the controlled conditions, while the interventions without psychoeducation did not ($P > 0.05$). The contacts between therapists and patients that contributed to the implementation of psychological therapy reduced depression symptoms (g = -0.47, 95%CI: -0.75 to -0.18, $P = 0.01$).

CONCLUSION

Smartphone-based interventions and monitoring have a significant positive impact on depressive and manic symptoms of BD patients in between-group and within-group analysis.

Key Words: Smartphone; Bipolar disorder; Monitoring; Interventions; Meta-analysis; Systematic review

Core Tip: To date no study has used meta-analysis to pool the existing evidence to examine the efficacy of smartphone-based interventions and monitoring for bipolar disorder. This is the first systematic review and meta-analysis investigating the effects of interventions and monitoring delivered *via* smartphone on bipolar disorder.

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INTRODUCTION

Bipolar disorder (BD) is a serious mood disorder that is characterized by depressive, manic, and mixed episodes[1]. It is estimated that the lifetime prevalence of BD is 1.0% for bipolar disorder I and 1.1% for bipolar disorder II[2]. Patients who do not receive adequate and appropriate treatment are then at risk for experiencing plentiful social and occupational impairments, even suicidal behavior[3].

Fortunately, many available treatments aim to cure manic or depressive episodes and stabilize mood[4]. However, there is a range of obstacles towards professional BD treatment. The transportation of mental health services and high-quality medications make treatment unaffordable[5]. Additionally, medication and psychotherapy are not acceptable to some patients who are ashamed of receiving treatment for mood disorder, so the therapeutic effectiveness is limited[6,7]. Therefore, innovative methods of treatment are urgently needed.

Digital technology may represent a feasible and novel solution. The majority of adults own smartphones. In recent years, the number of smartphone users has continually increased[8]. Additionally, using smartphones as a tool for psychological treatment is well-accepted for most people because it is cost-effective[9]. Use of smartphone also breaks the limitation of distance between patients and therapists, therefore it is a viable method to apply smartphones to treat someone who has difficulty in accessing health care[10]. Meanwhile, privacy and individuation are

guaranteed in the use of smartphones so that treatment acceptance and compliance are enhanced[11]. Therefore, people can accept smartphone-based interventions at any time they want.

This promising therapeutic potential of smartphones has aroused the interest of different organizations such as governments, advocacy groups, technology companies, and research groups internationally[12,13]. Recently, there has been a range of articles[14-23] about smartphone mental health interventions used for reducing symptoms of BD. Although the idea of smartphone use in health care is becoming more popular, it is difficult to separate actual efficacy from overstated aspirational claims. With thousands of mental disorder treatments readily available, it is urgent to find strong evidence to prove it useful, making sure that people have an understanding of smartphone-based interventions for BD.

Recent meta-analyses have suggested that smartphone interventions can have a positive impact on physical diseases, such as diabetes[24]. Also, the efficacy of smartphone interventions for a series of mood disorders is explained with recent meta-analyses, such as depression, anxiety, and post-traumatic stress disorder[25-27]. To date, no study has used meta-analysis to pool the existing evidence to examine the efficacy of smartphone interventions for BD. Moreover, there are three reviews related to the smartphone monitoring systems collecting data to predict severity of symptoms[28-30]. However, the clinical effect of the smartphone-based monitoring system on symptoms of BD patients has yet to be established. More recently, several single-group trials are relevant to the effectiveness of the smartphone-based intervention for BD. However, no systematic review and meta-analysis has examined the efficacy of the smartphone-based intervention and monitoring for symptoms in single-group trials. Nevertheless, there is evidence that the estimates from high-quality single-group trials can overcome the paucity of prospective randomized evidence. The estimated results may be similar to those of randomized controlled trials (RCTs). Pooling of high-quality single-group trials may be as accurate as pooling of RCTs[31-34].

We conducted the present meta-analysis to provide the first overall estimated effects of smartphone-based interventions and monitoring for reducing symptoms in BD patients. We conducted between-group analyses using the data extracted from the RCTs. We also performed within-group analyses of RCTs and single-group trials. Subgroups were created to explore which aspects of smartphone interventions are relevant to the greater or lesser efficacy of treating symptoms.

MATERIALS AND METHODS

This review and meta-analysis followed the PRISMA statement for the transparency and comprehension of the methodology and results reporting[35]. The PROSPERO ID of this meta-analysis is CRD42018092539.

Literature search

We searched PubMed, Embase, Clinical trials, psycINFO, Web of Science, and Cochrane Library from 1993 to August 1, 2019. In the case of any other eligible studies, we looked up reference lists of related reviews and articles. Besides, key researchers in this field were asked whether they knew about unpublished trials.

Study selection

The included studies fulfilled the following criteria: (1) All articles in English language; (2) Patients with a diagnosis of BD. Nevertheless, participants with BD and other types of mood disorders that had no influence on the cure of BD at the same time were also included; (3) Intervention: Website, smartphone-based apps, instruction of therapists *via* smartphone to facilitate psychotherapy; (4) RCTs and single-group studies; and (5) Outcomes: Reported either mania or depression symptom severity scores before and after intervention. The exclusion criteria were: (1) The intervention was not clearly defined; (2) Specific outcomes were not reported; (3) Unavailability of full text; and (4) Studies investigating the feasibility and satisfaction of smartphone-based intervention.

Two authors (Jia-Yuan Liu and Kang-Kang Xu) selected the articles according to the inclusion criteria after retrieval and screening of the relevant citations in full text. To identify the applicable articles, they read the abstracts and titles. A third reviewer resolved any disagreement that emerged in the process of searching and selection. The procedure of specific inclusion and extraction is shown in Figure 1.

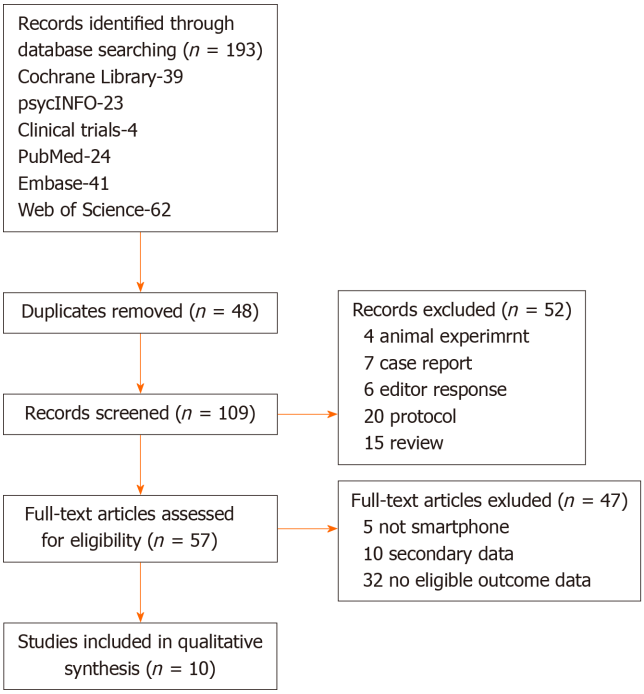

Figure 1 Study selection.

Data extraction

An extraction form was used for each article to collect the following data: (1) Participant information: Sample size, mean age, inclusion criteria, and diagnosis; (2) Study design: Trial quality, whether controlled or not; (3) Smartphone intervention: Study duration, details of intervention, and frequency of intervention; and (4) Effects on mania and depression: Changes in total depressive and manic symptoms scored before and after interventions using any clinically validated rating scale.

Risk of bias

The Cochrane risk of bias assessment tool was used for assessment of the RCT methodological quality. Bias risk in each domain of selection, performance, detection, attrition, and reporting ranking as high, low, or unknown was assessed independently by two reviewers. And inconsistencies were resolved through discussion. For publication bias, it was inappropriate to make a funnel plot to determine it because the number of included trials was no more than 10[36]. We did not have enough studies to make a meaningful funnel plot that was proposed by Egger *et al*[37].

Statistical analysis

Statistical analyses were performed with Review Manager version 5.3 (free software downloaded from http://www.cochrane.org). Between-group analysis was conducted for RCTs. The differences in changes in manic and depressive symptoms between smartphone-based intervention and control groups were pooled for calculation of the overall effect size using Hedges' g[38] with 95% confidence intervals (CIs). We conducted heterogeneity tests among these studies. In case of $I^2 > 50\%$ and $P \leq 0.05$, which indicated the presence of high heterogeneity, we chose a random-effects model; otherwise, we used a fixed-effects model. We next implemented within-group effect size of smartphone-based interventions and monitoring on manic and depressive symptoms. We computed Hedges' g statistic as the estimate of within-group effect size for changes from pre- to post-treatment with RCTs and the single-group trials. Lastly, we conducted subgroup analyses to investigate the different effects of components of smartphone-based interventions.

RESULTS

Study selection

A total of 193 articles were retrieved. Eighty-four duplicate articles were excluded. After reading the abstract and title of the remaining 109, we removed 52 case reports, editor responses, reviews, and studies that included animal experiments. Full versions were retrieved for 57 papers, of which ten met eligibility criteria, including seven RCTs and three single-group trials.

Characteristics of included studies

Table 1 displays the full details of the included studies. Available data were extracted from seven RCTs with two arms[15-19,21] or three arms[22] and three trials with single arms[14,20,23]. All but five articles had graphically reported data, which were extracted with graphical digitizer (Get Data Graph Digitizer) from the reported figures[14,18,19-21]. Two of the ten eligible studies included patients with BD and patients with other mood disorders[15,21]. Eight studies included only participants with BD diagnosed according to DSM or ICD-10[14,16-20,22,23]. The mean age of the sample ranged from 16 to 59 years (median, 38 years). Three studies were related to monitoring systems[14,18,19]. Three articles highlighted the heterogeneity in the analysis of the depressive symptoms[14,18,19]. The smartphone interventions and monitoring lasted from 4 wk to 12 mo. Manic and depressive symptoms were measured as an outcome in ten articles.

Risk of bias assessment

The results from the Cochrane Risk of Bias assessment are displayed in Figure 2. The most frequent risk factor for bias was inadequate blinding of participants and personnel with only five of seven studies using the blinding method for which the participants would not be aware of their treatment or control status, as well as the hypothesized outcomes of the trial.

Between-group effect sizes of smartphone interventions on manic and depressive symptoms

The pooled effect size of smartphone-based interventions on manic symptom changes in comparison to control conditions is shown in Figure 3A. Meta-analysis indicated a positive effect size of smartphone-based interventions for reducing manic symptoms compared to control groups (k = 6, n = 785, g = -0.19, 95%CI: -0.33 to -0.04, P = 0.01, I^2 = 0). There was no heterogeneity across the studies, therefore, we chose a fixed-effects model. Smartphone-based interventions were significantly more efficacious than control conditions in improving depressive symptoms (k = 8, n = 985, g = -0.28, 95%CI: -0.55 to -0.01, P < 0.05, I^2 = 75%) (Figure 3B). We found high heterogeneity among the studies. Therefore, sensitivity analyses were conducted to explore the reasons for this high heterogeneity. After excluding one article[18], the heterogeneity was lower, while the pooled effect size was still significant (k = 6, n = 863, g = -0.38, 95%CI: -0.61 to -0.14, P < 0.01, I^2 = 63%).

Within-group effect sizes of smartphone-based interventions on manic and depressive symptoms

In within-group analysis, comparing changes from baseline to post-treatment scores, smartphone-based interventions resulted in significant improvements in manic symptoms (k = 8, n = 914, g = 0.17, 95%CI: 0.04 to 0.30, P < 0.01, I^2 = 0) (Figure 4A). Heterogeneity did not exist, and the fixed-effects model was chosen. In within-group analysis, smartphone-based interventions significantly reduced depressive symptoms (k = 11, n = 1154, g = 0.48, 95%CI: 0.18 to 0.78, I^2 = 81%) after the interventions (Figure 4B). High heterogeneity across article data was found. Therefore, sensitivity analyses were conducted to examine the reasons for the high heterogeneity. After removing two articles[14,21], the heterogeneity was lowered, whereas the effect size was still significant (k = 9, n = 932, g = 0.25, 95%CI: 0.10 to 0.39, I^2 = 15%).

Within-group effect sizes of smartphone-based monitoring on manic and depressive symptoms

In order to investigate whether monitoring *via* smartphone had positive effects on manic and depressive symptoms, we performed within-group analyses. Smartphone-based monitoring appeared effective for manic symptoms (k = 3, n = 257, g = 0.27, 95%CI: 0.02 to 0.51, P < 0.05, I^2 = 0) compared with changes from baseline to post-treatment scores (Figure 5). The pooled effect size from smartphone-based monitoring

Table 1 Characteristics of included studies

Ref.	Sample type	*n*	Age (yr)	Female	Study design	Design	Measure	Smartphone intervention details
Depp *et al*[17]	Outpatient diagnosed with BD	41, 41	47.5	58.50%	RCT	10 wk of PRISM (self-management and monitoring app) *vs* paper and pencil monitoring	YMRS, MADRS	Mood monitoring and self-management APP
Faurholt-Jepsen *et al*[18]	BD patients previously treated for affective disorder	85, 44	43.1	88.40%	RCT	9 mo of MONARCA II (monitoring app) *vs* controlled conditions	YMRS, HDRS	Self-monitoring APP
Ben-Zeev, *et al*[15]	People with mental illness	75, 74	49	41%	RCT	3 mo of FOCUS (self-management app) *vs* clinical treat	PSYRATS, BDI-II	App and phone call from specialist to facilitate APP use
Faurholt-Jepsen *et al*[19]	Outpatients diagnosed with BD	33, 34	29.3	67.10%	RCT	6 mo of MONARCA (self-monitoring app) *vs* Controlled conditions	YMRS, HAMD-17	Self-monitoring APP
Gliddon *et al*[22]	Participants with bipolar disorder	96, 95, 87	39.5	82%	RCT	9 mo of Mood Swings 2.0 *vs* control conditions	YMRS, MADRS	Mood Swing is a web site
Celano, *et al*[16]	BD patients with an acute depressive episode	14, 11	45	68%	RCT	4 wk of telephone-based positive psychology *vs* the control group	None, QIDS-SR	Phone call from specialist to instruct the self-management
Kilbourne, *et al*[21]	People with unipolar and bipolar disorder	115, 123	41.3	66%	RCT	12 mo of CCM (psychosocial intervention) *vs* usual care from provider	None, PHQ-9	Phone call from care manager to facilitate the psychosocial intervention
Depp *et al*[23]	Outpatients with bipolar disorder	10	41	/	Single-group trials	2 wk of PRISM (monitoring and self-management app)	YMRS, MADRS	Mood monitoring and self-management APP
Beiwinkel, *et al*[14]	Outpatients with bipolar disorder	14	47.2	38%	Single-group trials	12 mo of a smartphone-based monitoring system	YMRS, HAMD	Monitoring APP
Miklowitz *et al*[20]	Patients with bipolar disorder	19	37.2	68.40%	Single-group trials	4 mo of FIMM (psychoeducation and monitoring)	YMRS, QIDS-SR	Monitoring and self-management APP

BD: Bipolar disorder; RCT: Randomized clinical trial; ASRM: Altman self-rating mania; APP: Application; BDI: Beck depression inventory; BHS: Beck hopelessness scale; HAMD-17: 17-item hamilton depression rating scale; HRSD: Hamilton rating scale for depression; MADRS: Montgomery–Asberg depression rating scale; PHQ-9: Nine-item patient health questionnaire; PSYRATS: Psychotic symptom rating scales; QIDS-SR: Quick inventory of depressive symptoms–self report; YMRS: Young mania rating scale.

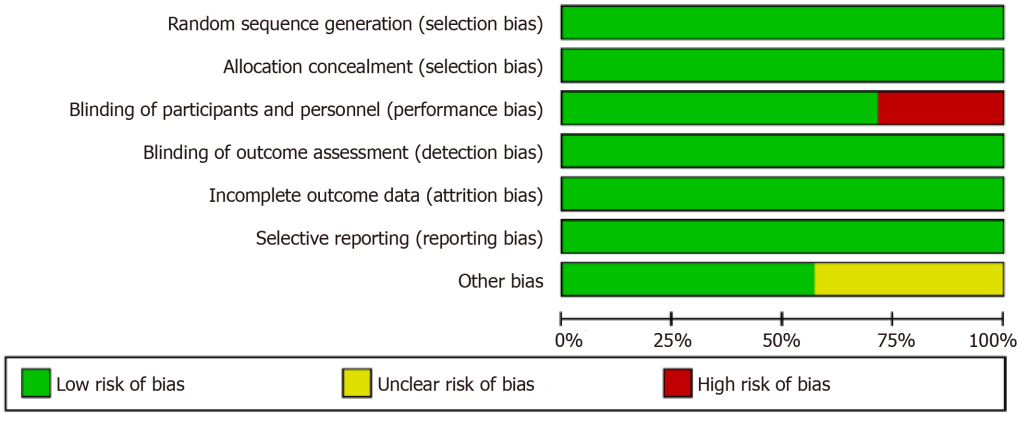

Figure 2 Quality assessments of randomized clinical trials.

on depressive symptoms was near to significant (k = 3, n = 257, g = 1.26, 95%CI: -0.14 to 2.67, P = 0.08, I^2 = 94%).

Subgroup analysis

In order to explore which details of smartphone interventions make them effective for

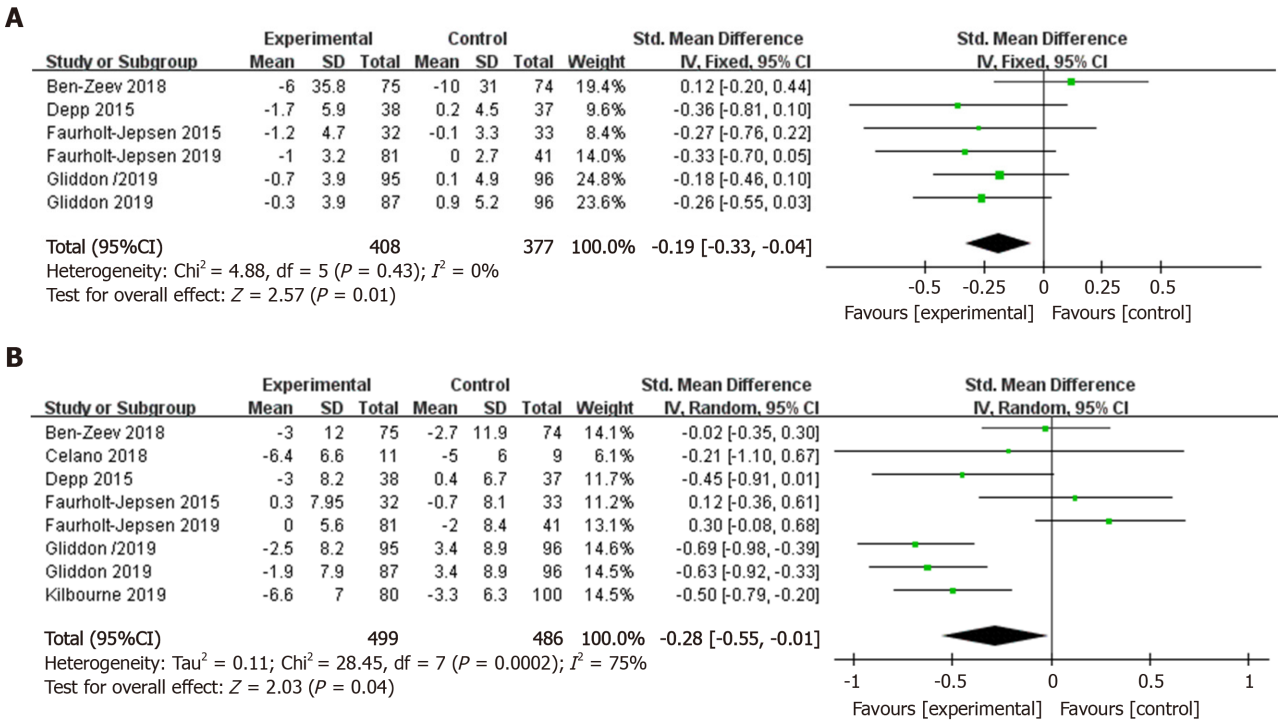

Figure 3 Between-group effect size of smartphone-based interventions on bipolar disorder. A: Meta-analysis of effects of smartphone-based interventions on manic symptoms; B: Meta-analysis of effects of smartphone-based interventions on depressive symptoms.

manic and depressive symptoms, we conducted further subgroup analyses. Smartphone interventions that involved psychoeducation had positive effects on manic symptoms (k = 3, *n* = 449, g = -0.24, 95%CI: -0.43 to -0.06, *P* = 0.01, I^2 = 0) compared to control groups, while those without psychoeducation did not (k = 3, *n* = 336, g = -0.13, 95%CI: -0.43 to 0.17, *P* = 0.39, I^2 = 45%) (Figure 6A). There was no significant subgroup difference (c^2 = 0.36, df = 1, *P* = 0.55) in the effect size obtained for smartphone interventions that involved psychoeducation compared to those without. Our meta-analysis revealed a positive effect size of smartphone mental health interventions for reducing depressive symptoms (k = 3, *n* = 449, g = 0.62, 95%CI: -0.81 to -0.43, *P* < 0.01, I^2 = 0) compared to control groups, while those without psychoeducation were not significantly more efficacious than control conditions in improving depressive symptoms (k = 5, *n* = 536, g = -0.06, 95%CI: -0.39 to 0.26, *P* = 0.71, I^2 =67%) (Figure 6B). There was a significant subgroup difference (c^2 = 8.52, df = 1, *P* = 0.004) in the overall effect size gained for smartphone interventions that involved psychoeducation compared to that did not.

Interventions that involved instruction *via* smartphone had a significantly great effect size on depression outcomes compared to control conditions (k = 2, *n* = 200, g = -0.47, 95%CI: -0.75 to -0.18, *P* = 0.01, I^2 = 0), whereas those without instruction through smartphone did not reduce manic and depressive symptoms compared to control groups (k = 6, *n* = 785, g = -0.24, 95%CI: -0.58 to 0.10, *P* = 0.17, I^2 = 82%) (Figure 7). There was no significant subgroup difference (c^2 = 1, df = 1, *P* = 0.32) in the pooled effect size obtained for interventions that involved instruction *via* smartphone compared to those that did not.

DISCUSSION

As far as we know, this is the first meta-analysis to examine the effects of smartphone-based interventions and monitoring on BD. Ten studies with a total sample of 1028 participants who received smartphone-based treatment or monitoring were used for meta-analysis. The studies were comprehensive in this field. The number of included articles for this meta-analysis was similar to that of a previous meta-analysis that found positive effects from smartphone apps across nine studies with 1837 participants with anxiety[25]. The literature base for BD appears larger than that for other affective disorders, such as post-traumatic stress disorder, according to a recent meta-analysis in this field that included only five relevant articles[27]. Furthermore, six

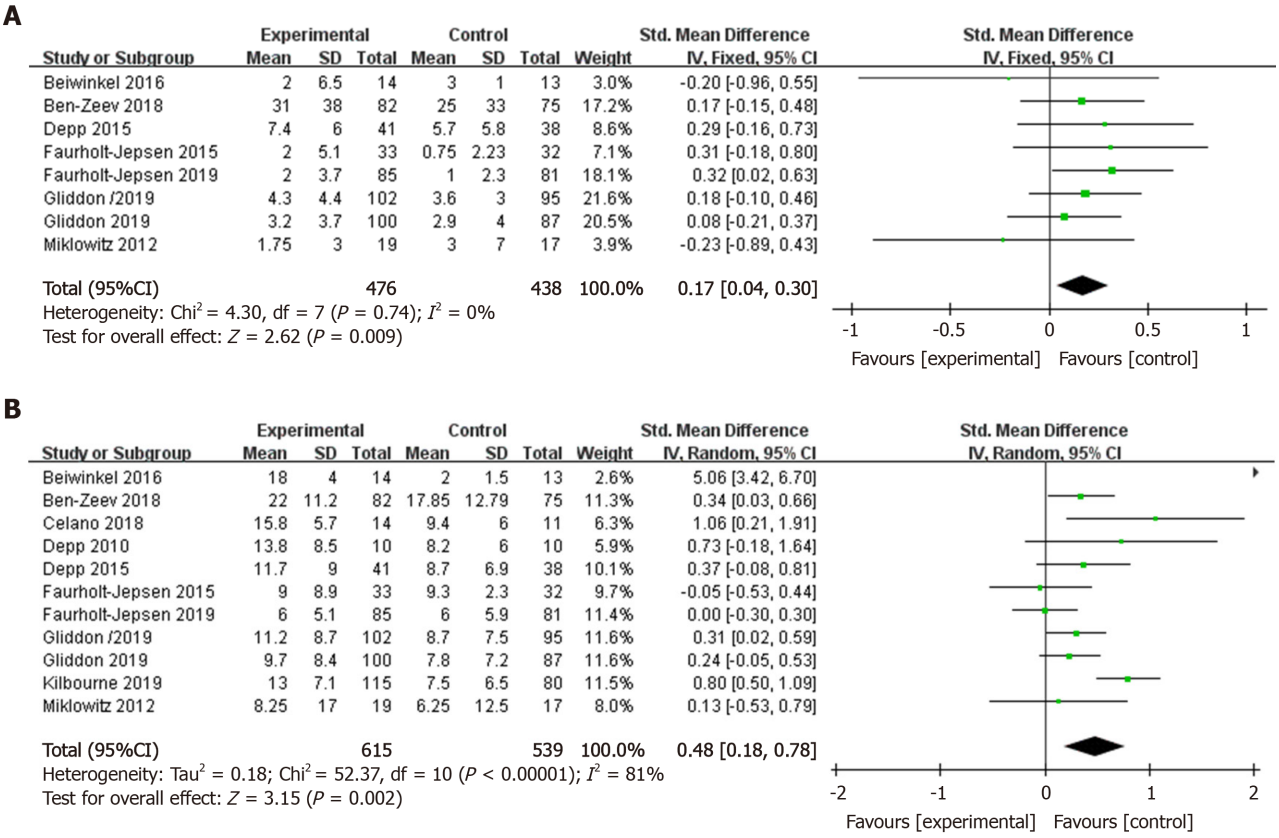

Figure 4 Within-group effect size of smartphone-based interventions on bipolar disorder. A: Meta-analysis of effects of smartphone-based interventions on manic symptoms; B: Meta-analysis of effects of smartphone-based interventions on depressive symptoms.

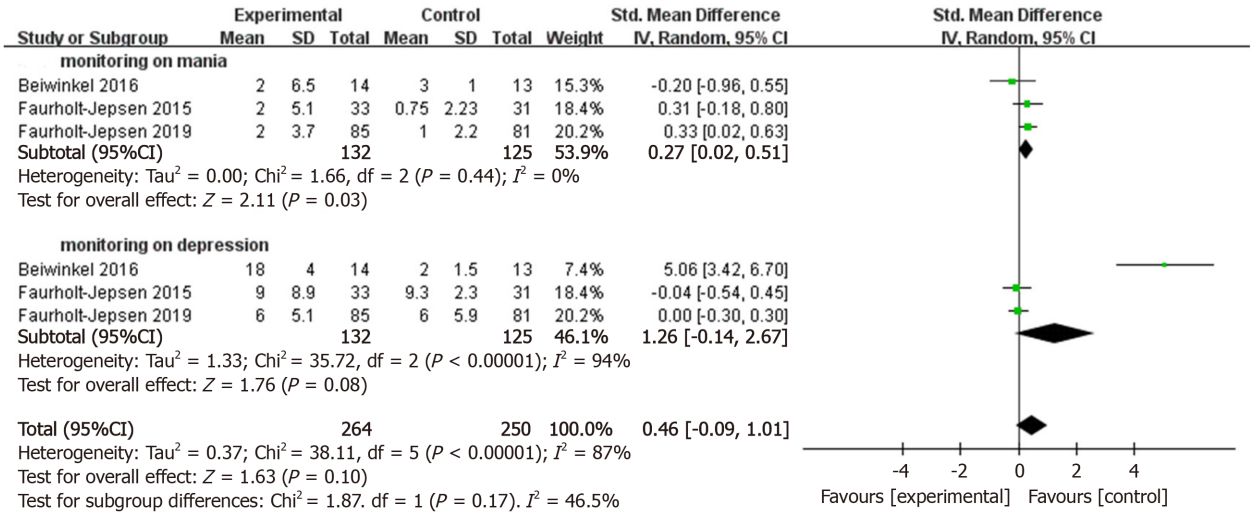

Figure 5 Within-group effect size of smartphone-based monitoring on manic and depressive symptoms.

of our ten articles were published within the past 5 years[14-16,18,21,22], which means that our analysis reflected the effectiveness of the most updated smartphone-based intervention tools.

Our analysis found that smartphone interventions had a positive effect on BD between and within groups. Meta-analysis indicated a positive effect of smartphone-based interventions for reducing manic (g = -0.19) and depressive (g = -0.28) symptoms compared to control groups. In within-group analyses, the effects of smartphone-based interventions appeared effective for manic (g = 0.17) and depressive (g = 0.48) symptoms. Similar positive effects were observed in the meta-analysis of smartphone interventions for other mood disorders, such as anxiety,

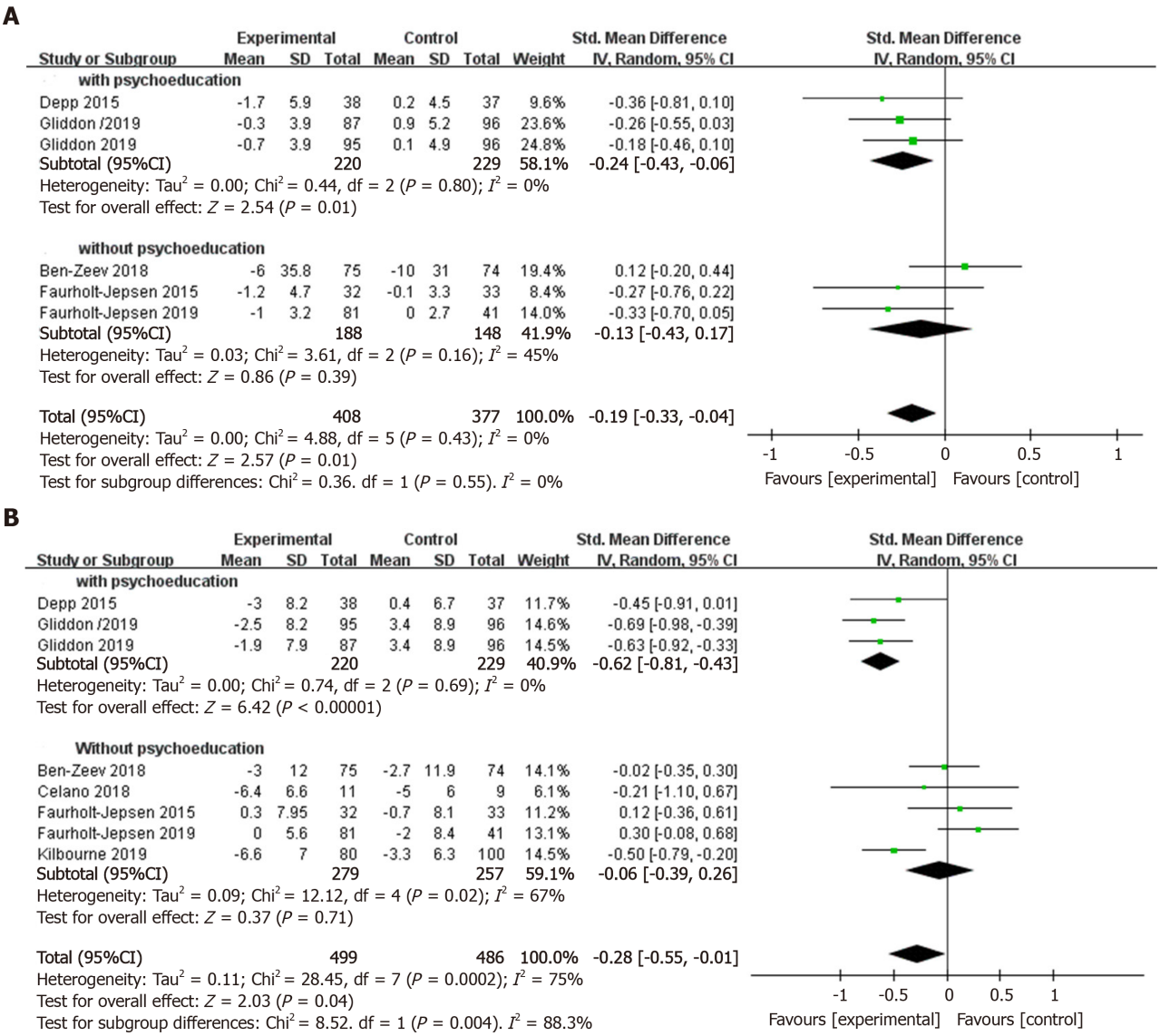

Figure 6 Subgroup analysis of interventions with psychoeducation on bipolar disorder. A: Meta-analysis of effects of smartphone-based interventions on manic symptoms; B: Meta-analysis of effects of smartphone-based interventions on depressive symptoms.

depression, post-traumatic stress disorder, and obsessive compulsive disorder[25-27,37]. These findings indicate that delivering psychological treatments *via* smartphone devices is an efficacious and promising method to treat BD. The potential mechanism by which smartphone interventions reduce symptoms of BD might be explained by using these devices to support and enhance the delivery of existing face-to-face therapy[25]. The use of smartphone-based interventions may provide creative and innovative interventions, filling the gap between feasibility and the demand for treatment[39]. Additionally, interventions *via* smartphone devices may remedy some limitations of existing traditional therapy in the future, with the advantages of convenience and lower treatment cost.

Our analysis showed that BD participants with mania who used the smartphone monitoring systems experienced benefits (g = 0.27). Meanwhile, a recent review of the smartphone application for mood disorders had similar finding that smartphone application with mood monitoring features reduces depressive symptoms[26]. Additionally, a previous study proposed that using a digital device in itself may produce some psychological benefits[40]. The smartphone-based monitoring system was used to collect data on phone usage, social communication, social activity, and mobility, which were irrelevant to psychotherapy. To some extent, using the smartphone-based monitoring system was equivalent to only using the device itself. Therefore, our results that monitoring systems have positive effect on manic symptoms may contribute to the hypothesis that smartphones may offer some psychological benefits. There were three reviews related to the smartphone monitoring

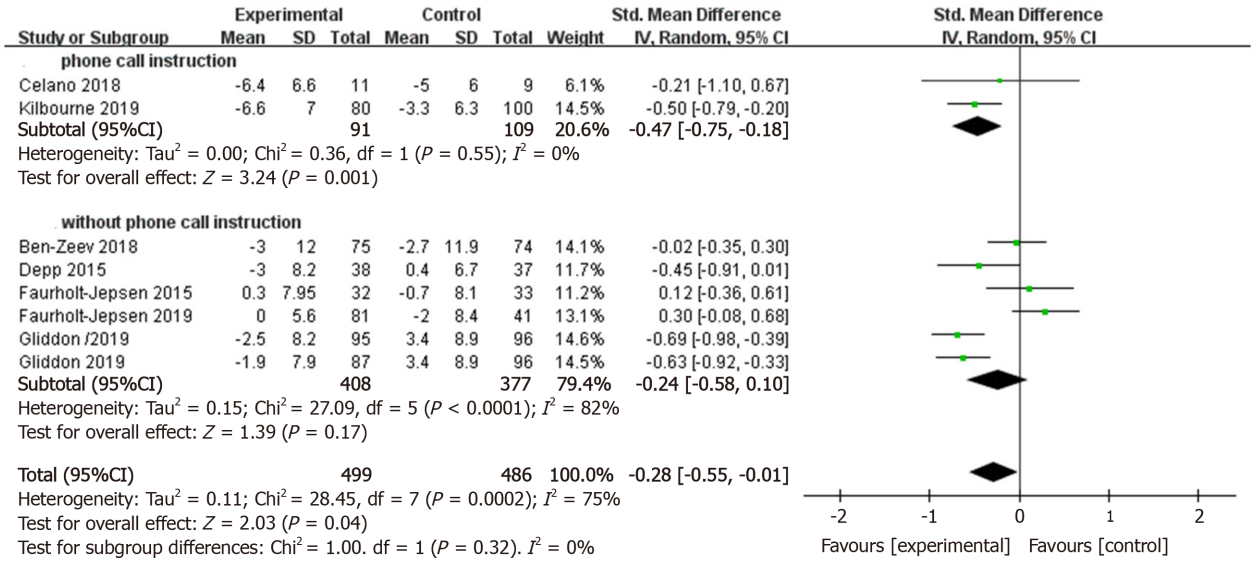

Figure 7 Subgroup analysis of interventions with instruction on depressive symptoms.

system collecting data to predict severity of symptoms[28-30]. Therefore, we conclude that the monitoring system may contribute to treatment of BD and predictions of clinically assessed depressive and manic symptoms. In the future, using smartphone-based monitoring and treatment simultaneously may form a complete treatment system that is convenient and efficient.

With regards to intervention features, in our subgroup analysis, smartphone interventions that involved psychoeducation had great effects on manic (g = -0.24) and depressive (g = -0.62) symptoms of BD compared to control conditions. A similar finding was reported in a recent meta-analysis about psychoeducation for the management of BD patients[41]. The effects of smartphone interventions that involved instruction from the therapist (g = -0.47) appeared significant, while the effect size of those without instruction was not significant. A previous study found that therapist guidance bolstered the effectiveness of smartphone interventions[42]. Instruction from therapists may be conducive to improvement of patient engagement and completion rate of therapy. Although smartphone-based interventions reduced symptoms, there are numerous factors that may affect outcomes of smartphone interventions. Therefore, to design these interventions to be effective in the future, more analyses are needed.

In general, smartphone-based interventions and monitoring reduced symptoms in BD patients. BD is always associated with poor quality of life in addition to personal suffering from depression[43]. Although there are many treatments for BD, there is a limitation in the availability of therapy. The use of smartphones is accessible and affordable[44], which ensures the implementation of mental health interventions and monitoring for BD. It enhances and facilitates the delivery of existing therapy programs and makes them more acceptable. However, there are some complex issues generated by the use of smartphones and the technology itself, including low resource settings somewhere, privacy policy, clinical utility, commercialization, and evolving technology[45-48]. Therefore, in order to achieve satisfactory therapeutic effects in the use of smartphone interventions for BD patients, the influential factors in the whole treatment process should be studied and resolved in the future. Additionally, communication between the users and designers of smartphone-based interventions is not adequate. In the future, the treatment methods will need to be optimized according to the users' feedback and the researchers' thoughts.

Our study had a few limitations. First, two studies in this meta-analysis were considered to have a high risk of bias because of inadequate blinding of participants and personnel[15,18]. Second, the absolute number of available applications is unknown and the applications are frequently updated. It is impossible to examine total smartphone interventions. Third, there were only three eligible articles regarding smartphone-based monitoring patterns[14,18,19], which was not sufficient to provide definitive results. Future research that directly tests the monitoring effectiveness against BD would add value to our results. Lastly, to explore potential factors relevant to smartphone interventions, details about demographics, severity of BD, and

engagement need to be collected. Nevertheless, with limited data that can be extracted, we could not conduct subgroup analysis on these variables that might impact statistical results. In the future, a more standard data reporting format needs to be implemented with research data, thus improving the validity and reliability of meta-analysis.

CONCLUSION

In summary, smartphone-based interventions are effective in reducing manic and depressive symptoms. Nevertheless, the smartphone-based monitoring systems only worked for participants with manic but not depressive symptoms. Our results contribute to the literature on smartphone-based interventions and monitoring for manic and depressive symptoms in BD patients, although much work remains to be done. This meta-analysis shows that smartphone-based intervention and monitoring have the potential to enhance the methods of treatment with its characteristics of low expenditure and highly-convenience in addition to available medications and psychological interventions.

ARTICLE HIGHLIGHTS

Research background

Recently, a range of studies about smartphone-based interventions and monitoring for reducing symptoms of bipolar disorder (BD) have been published. However, their efficacy for BD remains unclear.

Research motivation

The present study aimed to assess randomized controlled trials and single-group trials of smartphone-based interventions and monitoring for reducing the symptoms of BD.

Research objectives

The main objective was to update and evaluate innovative treatment suggestions for BD.

Research methods

We performed a systematic literature search on PubMed, Embase, Clinical trials, psycINFO, Web of Science, and Cochrane Library. Randomized clinical trials or single-group trials in which smartphone-based interventions and monitoring were compared with control methods or baseline in patients with symptoms of BD were included. We synthesized data using a random-effects or a fixed-effects model by Review Manager version 5.3 to analyze the effects of psychological interventions and monitoring delivered *via* smartphone on psychiatric symptoms in patients with BD. The primary outcome measures were set for mania and depression symptoms. The subgroups were created to explore which aspects of smartphone interventions are relevant to the greater or lesser efficacy of treating symptoms.

Research results

We identified ten articles, including seven randomized clinical trials (985 participants) and three single-group trials (169 participants). Analysis of the between-group study showed that smartphone-based interventions had positive effects in reducing manic (g = -0.19, 95%CI: -0.33 to -0.04, $P = 0.01$) and depressive (g = -0.28, 95%CI: -0.55 to -0.01, $P < 0.05$) symptoms. In within-group analysis, smartphone-based interventions significantly reduced manic (g = 0.17, 95%CI: 0.04 to 0.30, $P < 0.01$) and depressive (g = 0.48, 95%CI: 0.18 to 0.78) symptoms compared to the baseline. Nevertheless, smartphone-based monitoring systems significantly reduced manic (g = 0.27, 95%CI: 0.02 to 0.51, $P < 0.05$) but not depressive symptoms. Subgroup analysis indicated that the interventions with psychoeducation were effective for depressive (g = -0.62, 95%CI: -0.81 to -0.43, P < 0.01) and manic (g = -0.24, 95%CI: -0.43 to -0.06, $P = 0.01$) symptoms compared to the controlled conditions, while the interventions without psychoeducation did not ($P > 0.05$). The contacts between therapists and patients that contributed to the implementation of psychological therapy reduced depression symptoms (g = -0.47, 95%CI: -0.75 to -0.18, $P = 0.01$).

Research conclusions

Smartphone-based interventions and monitoring have a significant positive impact on depressive and manic symptoms of BD patients in between-group and within-group analysis.

Research perspectives

The current meta-analysis suggests that smartphone-based interventions provide evidence of any reduction in manic and depressive symptoms. Nevertheless, smartphone-based monitoring systems are only effective for participants with manic but not depressive symptoms. The findings have implied that these digital tools can be used as the clinically future treatments for symptoms of BD. However, future trials need to keep pace with the development of these apps and a better understanding of the numerous factors that influence outcomes of smartphone interventions for BD are also required.

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