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ORIGINAL RESEARCH

The Attitudes Toward Polypharmacy and Willingness to Deprescribe Among Patients with Multimorbidity in Rural Areas of Shandong Province in China: A Cross-Sectional Study

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Purpose: Multimorbidity and polypharmacy have emerged as significant global issues, heightening the risks of potentially inappropriate medications (PIMs). This necessitates medication optimization through deprescribing. Understanding patients' decision-making preferences regarding medication cessation is crucial for mitigating medication-related risks. This study aims to capture the attitude of patients with multimorbidity towards deprescribing in rural China and to ascertain whether individual characteristics were linked to these attitudes.

Patient and Methods: A cross-sectional study employing the validated Patients' Attitudes Towards Deprescribing (PATD) questionnaire was performed in rural regions of Eastern China. The PATD Questionnaire was utilized to investigate patients' attitudes towards the concurrent use of multiple medications, with response elicited on a 5-point Likert scale. Utilizing multistage random sampling, a total of 560 participants with multimorbidity were randomly selected from two counties in Shandong Province. Descriptive statistics were reported on participant characteristics. Binary logistic regression analysis was conducted to identify the factors that influenced participants' willingness to discontinue or reduce their medication.

Results: The median age of patients was 69.5 years (SD=8.2 years), and 314 were female. Nearly one in four patients experienced polypharmacy, while 42.2% had two chronic diseases. More than half of the participants (55.2%) reported that they would be willing to stop one or more medications if their physicians agreed, and 52.9% of participants agreed to reduce the medications taken. Participants with two chronic conditions (OR=3.038, 95% CI=1.342–6.881), taking less than 10 tablets (OR=2.994, 95% CI=1.113–8.054), having their own source of healthcare expenditure (OR=0.639, 95% CI=0.432–0.945), and hospitalization in the prior year (OR=0.636, 95% CI=0.429–0.944) were significantly associated with patients' attitudes toward deprescribing.

Conclusion: Over half of patients with multimorbidity expressed a willingness to have one or more of their medicines deprescribed. Physicians can be trained in the integrated care of chronic diseases and encouraged to engage in discussions about deprescribing with patients having multimorbidity and polypharmacy during their routine practice.

Keywords: deprescribing, patient perspective, polypharmacy, potentially inappropriate medication

Introduction

Multimorbidity has been acknowledged as a major challenge within healthcare system, especially as the aging process accelerates. Recent studies reported the prevalence of multimorbidity ranged from 3.5% to 100% globally,^{1,2} increasing with age. It is predicted that the elderly populations will account for one-third of the total population in China by 2035.³ According to data from the China Health and Retirement Longitudinal Study (CHARLS), the prevalence of self-reported multimorbidity among 19559 participants aged 45 years and older was 56.73%.⁴

Multimorbidity is significantly associated with polypharmacy, defined as patient taking five or more medicines at the same time. As chronic conditions proliferate, the likelihood of taking multiple medications also increases, along with the risks of potentially inappropriate medications.⁵ For some patients, polypharmacy is inevitable.⁶ However, polypharmacy is often excessive for older individuals with multiple chronic conditions, leading to adverse drug events, increased hospitalizations, higher mortality rates, and great healthcare costs.⁷ When the potential risks of medications outweigh the potential benefits, potentially inappropriate medications (PIMs) may arise. Relevant studies have demonstrated that deprescribing is an essential intervention capable of reducing harm and enhancing patients' health.⁸

As a Patients Safety Strategy, deprescribing refers to the process of discontinuing or reducing inappropriate medication therapy with the aim of reducing the risks of inappropriate medication and improving patients' quality of life.⁹ Although the concept of deprescribing is clear, there are several barriers to the implementation of deprescribing. Physicians have often complained that patient resistance or refusal to discontinue medications presents a significant barrier to deprescribing.¹⁰ In addition, patient-centered medication discontinuation strategies have been proposed to optimize health outcomes.¹¹ Understanding patients' attitudes towards medication can facilitate shared decision-making between physicians and patients.¹²

The Patients' Attitudes Towards Deprescribing (PATD) questionnaire have been used to quantify patients' perceptions regarding their medications and their willingness to discontinue them.¹³ Previous studies using the PATD have primarily concentrated on hospitalized patients and those in urban communities.^{14–16} However, the attitudes of patients living in rural areas toward medicine withdrawal remain largely unknown. One study indicates that the prevalence of multimorbidity in rural areas is higher (58.4%) compared to that of community-dwelling residents in urban areas (50.4%).¹⁷

The level of education and health literacy among the elderly in rural areas of China are relatively low. When confronted with medical decisions, they tend to place significant trust in their physicians and emphasize adherence to prescribed medications. Moreover, medical services in rural areas are often inefficient, resulting in the potential underdiagnosis of chronic diseases.¹⁸ Due to the absence of regular follow-up checks, many patients with multiple long-term conditions are more likely to receive a practice called polypharmacy. However, identifying and addressing polypharmacy among older adults in rural areas is frequently challenging. This study aims to investigate the attitudes of patients with polypharmacy toward deprescribing in rural regions of Shandong Province, China, and to investigate the individual characteristics that influence their attitudes.

Method

Sample and Data Collection

We conducted a cross-sectional study recruited patients with multimorbidity in rural areas of Shandong Province, a coastal province in northern China with the largest elderly population in the country. In 2022, Shandong Province had 21.51 million residents aged 60 and above, representing for 21.15% of the total population. As one of the most populous provinces in China, Shandong is an exemplary setting for conducting deprescribing research.¹⁹ In November 2019, a multi-stage stratified random sampling method was conducted, selecting Jinan and Weifang cities as sample areas in Shandong Province. First, one county was randomly selected from each district of sample cities. Second, two towns were randomly selected from each county. Finally, four villages were randomly selected from each town, and 35 patients with multiple chronic diseases were randomly selected from each village.

Participants

Patients aged 18 years and older, with two or more chronic diseases, no cognitive impairments, and a willingness to participate in the investigation were deemed eligible. Those with cognitive impairments, mental disorders, or an inability to comprehend the questionnaire were excluded. When calculating the multimorbidity, this study included 14 types of chronic diseases defined by the China Health and Retirement Longitudinal Study: hypertension, dyslipidemia, diabetes, cancer, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, digestive disease, emotional or psychiatric problems, memory-related disease, arthritis and rheumatism, and asthma.²⁰ A total of 560 patients with

Variables and Measurement

entire questionnaire, resulting in the response rate of 94.82%.

The Patients' Attitudes Towards Deprescribing questionnaire was originally developed and validated in Australia and has been used in Denmark, Italy, and other countries.^{15,21} In this study, we selected the PATD questionnaire, which has been translated and validated in Chinese.¹³ The PATD questionnaire serve as a tool to describe individuals' attitudes, beliefs, and experiences regarding their medications, and willingness to stop using one or more of these medications.²² The questionnaire contains ten 5-point Likert scale questions and five multiple-choice questions. Three of the PATD questions were exclude as they focused on attitudes towards pharmacists and follow-up, which were not the point of our study. The deleted questions are as follows: (1) Have you ever tried to stop a regular medication (informing your doctor of the progress)? (2) If one of your regular medications was stopped, what follow-up would you like? (3) How comfortable would you be if a nurse was involved in stopping one or more of your regular medications and provided the follow-up (informing your doctor of the progress)? And the PATD questionnaire was developed as an exploratory tool with no scoring criteria, so removing three of the questions would not have affected the results.

In addition, we also collected sociodemographic data such as participants' age, gender, education level, marital status, financial assistance, and healthcare information including number of chronic diseases, number of medications taken, and the number of visits to medical institutions during the past 3 months. Prior to the formal study, we conducted training sessions for interviewers on administration the standardized questionnaire and the coding of responses. We ensured that the study's purpose was clearly explained to the patients and informed consent was obtained before the study started.

Statistical Analysis

Descriptive statistics were used to report the participants' characteristics and the distribution of the questionnaire. Similar to previous studies,¹⁴ we focused on two specific statements in the scale, as they reported an overview of individual attitudes toward deprescribing. These statements are "If my doctor said it was possible, I would be willing to stop one or more of my regular medications" (Question 4) and "I would like to reduce the number of medications I am taking" (Question 5), referred to as "willingness to stop" and "desire to reduce", respectively.⁹ A chi-square test was utilized to analyze the correlation between participant characteristics and their responses regarding "willingness to stop" and "desire to reduce." To conduct the analysis, the responses to the above two questions were converted into binary outcomes, which combined the "agree" and "strongly agree" into a single category of agreement and the remaining responses were classified as disagreement (unsure, disagree or strongly disagree). In the binary logistic regression model, "willingness to stop" and "desire to reduce", Number of chronic conditions, Number of prescribed medications, Polypharmacy, Pharmacy to buy medicine during the past 3 months, Hospitalization in the prior year, Medical Expenditure Sources) were determined as independent variables, with adjustment for demographic factors. Significance was set at p < 0.05. All analyses were performed using SPSS statistics version 27.0.

Result

Characteristics of Participants

A total of 531 participants were enrolled in the study. The median age of the respondents was 69.5 years, and 59.1% were females. Among the participants, the majority were married (79.5%) and living with family members (84.4%), approximately 74.4% reported having elementary school education or lower. Nearly 60% of participants reported an annual income of less than RMB 10,000. When asked about the sources of their medical expenses, 61.6% indicated that they were able to cover their own medical expenses. Overall, all participants suffered from two or more chronic conditions, with a quarter of patients experiencing polypharmacy (24.5%). Moreover, 33% of the participants had been hospitalized in the previous year. Detail of the sociodemographic characteristics and health status are reported in Table 1.

 Table I Characteristics of the Enrolled Patients (n=531)

Characteristics	Value, n (%)
Gender	
Male	217 (40.9)
Female	314 (59.1)
Age (years)	
<55	21 (4.0)
55–64	114 (21.5)
65–74	250 (47.1)
≥75	146 (27.5)
Marital status	
Married	422 (79.5)
Single/divorced/widowed	109 (20.5)
Education level	
Primary school and lower	395 (74.4)
Junior high school	104 (19.6)
Senior high school and higher	32 (6.0)
Occupation	
Farmer	477 (89.8)
Other	54 (10.2)
Living alone	
Yes	83 (15.6)
No	448 (84.4)
Annual household income (CNY ^a)	
≤10,000	334 (62.9)
10,000–30,000	130 (24.5)
≥30,000	67 (12.6)
Number of chronic conditions	
2	224 (42.2)
3	191 (36.0)
4	76 (14.3)
≥5	40 (7.5)
Number of tablets or capsules taken daily	
<10	308 (58.0)
10–19	154 (29.0)
20–29	38 (7.2)
≥30	31 (5.8)
Polypharmacy	
Yes	130 (24.5)
No	401 (75.5)
Pharmacy to buy medicine during the past 3 months	
Yes	268 (50.5)
No	263 (49.5)
Visits to medical institutions during the past 3 months	
Yes	485 (91.3)
No	46 (8.7)

(Continued)

Characteristics	Value, n (%)
Hospitalization in the prior year	
Yes	175 (33.0)
No	356 (67.0)
Medical Expenditure Sources	
Own	327 (61.6)
From children or other	204 (38.4)

Table I (Continued).

Note: ^aA currency exchange rate of CNY I=US 0.14 is applicable.

Responses to the PATD Questionnaire

The responses to the first ten items of PATD questionnaire are presented in Table 2. There were 55.2% of participants agreed or strongly agreed that they would be willing to discontinue one or more medications if their doctor said it was possible. Half of the participants (52.9%) had the desire to reduce the number of medications they were taking, and 31.7% felt that they were taking excessive medications. In addition, 76.3% considered that they were comfortable with the number of drugs they were currently taking, and 6.6% felt they were taking medication that they no longer necessary. Approximately three-quarters of respondents (75.3%) reported that they could accept taking additional medications for their condition. The majority reported that they had a solid understanding of the therapeutic benefit of the medication (83.4%). Only 13.4% of participants indicated that the cost of the medication might influence their willingness to stop.

Table 3 indicates that 59.5% of participants felt that taking 5–10 pills was a lot. When asked to select the maximum number of tablets and capsules they could comfortably manage from a series of pictures, more than half (56.3%) selected the option depicting with 10 pills, suggesting that visual acceptance was generally consistent with theoretical responses.

Question	Strongly Agree (n, %)	Agree (n, %)	Unsure (n, %)	Disagree (n, %)	Strongly Disagree (n, %)
I. I feel that I am taking a large number of medications.	21 (4.0)	147 (27.7)	20 (3.8)	325 (61.2)	18 (3.4)
2. I am comfortable with the number of medications that I am taking.	21 (4.0)	384 (72.3)	28 (5.3)	93 (17.5)	5 (0.9)
3. I believe that all my medications are necessary.	99 (18.6)	415 (78.2)	5 (0.9)	10 (1.9)	2 (0.4)
4. If my doctor said it was possible, I would be willing to stop one or more of my regular medications.	34 (6.4)	259 (48.8)	38 (7.2)	193 (36.3)	7 (1.3)
5. I would like to reduce the number of medications that I am taking.	30 (5.6)	251 (47.3)	46 (8.7)	198 (37.3)	6 (1.1)
6. I feel that I may be taking one or more medications that I no longer need.	0	35 (6.6)	53 (10.0)	405 (76.3)	38 (7.2)
7. I would accept taking more medications for my health conditions.	35 (6.6)	365 (68.7)	21 (4.0)	105 (19.8)	5 (0.9)
8. I have a good understanding of the reasons I was prescribed each of my medications.	83 (15.6)	360 (67.8)	9 (1.7)	66 (12.4)	13 (2.4)
9. Having to pay for fewer medications would play a role in my willingness to stop one or more of my medications.	4 (0.8)	67 (12.6)	13 (2.4)	349 (65.7)	98 (18.5)
10. I believe one or more of my medications is giving me side-effects.	19 (3.6)	118 (22.2)	21 (4.0)	313 (58.9)	59 (11.1)

Table 2 Patients' Attitudes Towards Deprescribing Based on the PATD Questionnaire

Note: Only select items were used from the PATD and not the whole PATD.

Question	Answer	n (%)
II. How many different tablets or capsules per day would you consider to be a lot?	5–10	316(59.5
	10–15	161(30.3
	15-20	41(7.7)
	20–25	8(1.5)
	>25	5(0.9)
12. What is the maximum number of tablets or capsules that you would be comfortable taking per day (pictorial response)?	≤5	105(19.8
	6–10	194(36.5
	11-15	144(27.1
	16-20	34(6.4)
	21–25	32(6.0)
	>25	22(4.1)

 Table 3 Results from Questions 11 to 12 of the Patients' Attitudes Towards Deprescribing Questionnaire

Note: Only select items were used from the PATD and not the whole PATD.

Characteristics Associated with Willingness to Stop

In the chi-square test, characteristics associated with attitudes towards deprescribing included education level, number of chronic conditions, number of prescribed medications, source of healthcare expenditure, polypharmacy, pharmacy to buy medicine during the past 3 months, and hospitalization in the prior year. However, certain correlations were no longer statistically significant in the binary logistic regression (Table 4).

	If My Doctor said It was Possible, I would be Willing to Stop One or More of My Regular Medications, OR (95% CI)		I Would Like to Reduce the Number of Medications that I am Taking, OR (95% CI)		
Characteristic	Unadjusted	Adjusted ^a	Unadjusted	Adjusted	
Education level					
Primary school and below	1.093 (0.509-2.349)	0.849 (0.372-1.937)	0.991 (0.467–2.107)	0.767 (0.340–1.731)	
Secondary school	0.685 (0.295-1.588)	0.576 (0.241-1.374)	0.498 (0.217–1.144)	0.422 (0.178–1.000)	
High school and beyond	Reference				
Number of chronic conditions					
2	2.839(1.262–6.382) ^b	3.038 (1.342–6.881) ^b	3.070 (1.372–6.870) ^b	3.350 (1.482–7.571) ^b	
3	1.850 (0.831-4.119)	1.991 (0.889-4.458)	2.409 (1.089–5.329) ^b	2.642 (1.184–5.897) ^b	
4	1.387 (0.571-3.372)	1.507 (0.616-3.690)	1.476 (0.609–3.577)	1.653 (0.675-4.044)	
≥5	Reference				
Number of prescribed medications					
<10	3.186 (1.189–8.539) ^b	2.994 (1.113–8.054) ^b	2.334 (0.914–5.959)	2.181 (0.848-5.609)	
10–19	3.009 (1.128-8.028)	2.845 (1.062-7.620)	2.103 (0.826–5.359)	1.982 (0.771–5.092)	
20–29	2.890 (0.926-9.014)	2.701 (0.854-8.542)	3.100 (1.036–9.282) ^b	2.846 (0.934-8.668)	
≥30	Reference				
Polypharmacy					
Yes	0.892 (0.549–1.452)	0.922 (0.564–1.508)	1.472 (0.907–2.389)	1.542 (0.944–2.520)	
No	Reference				

Table 4 Ordinal Logistic Regression Analysis of Factors Influencing Willingness to Stop Medication

(Continued)

Table 4 (Continued).

	,	as Possible, I would be or More of My Regular 5 CI)	I Would Like to Reduce the Number of Medications that I am Taking, OR (95% C		
Characteristic	Unadjusted	Adjusted ^a	Unadjusted	Adjusted	
Pharmacy to buy medicine during the past 3 months					
Yes No	1.364 (0.951–1.955) Reference	1.337 (0.928–1.926)	1.059 (0.741–1.514)	1.028 (0.686–1.542)	
Hospitalization in the prior year Yes No	0.632 (0.428–0.933) ^b Reference	0.636 (0.429–0.944) ^b	0.848 (0.577–1.245)	0.857 (0.581–1.265)	
Medical Expenditure Sources Own From children or other	0.595 (0.410–0.863) ^b Reference	0.639 (0.432–0.945) ^b	0.854 (0.591–1.234)	0.951 (0.645–1.402)	

Notes: ^aAdjusted for age, sex, Marital status, Occupation, Living alone. ^bSignificant association (P < 0.05). **Abbreviation**: OR. odd ratio.

The results presented in Table 4 show that participants with two chronic conditions (OR=3.038, 95% CI=1.342–6.881) exhibited a greater willingness to discontinue the medication compared with five or more chronic diseases. Participants taking fewer than 10 tablets (OR=2.994, 95% CI=1.113–8.054) and those taking 10–19 tablets (OR=2.845, 95% CI=1.062–7.620) had nearly three times the odds of willingness to cease medication compared to individuals taking more than 30 tablets. Additionally, those hospitalized for chronic diseases in the past year (OR=0.636, 95% CI=0.429–0.944) compared with those who were not, and those who had their own source of medical expenditure (OR=0.639, 95% CI=0.432–0.945) compare with those replying on their children and other sources, demonstrated lower odds of willingness to discontinue. Similarly, the odds of desiring to reduce were greater among participants with two chronic conditions (OR=3.350, 95% CI=1.482–7.571) and three diseases (OR=2.642, 95% CI= 1.184–5.897) compared to participants with 5 or more comorbidities. There was no significant association between education level, multiple medication use, living status, and pharmacy to buy medicine during the past 3 months with the willingness to reduce medication.

Discussion

This study showed that over half of participants with multimorbidity willing to have a medicine deprescribe if the physician agreed. Patients using the PATD questionnaire reported a willingness to discontinue their medication range from 70% to 95%, which is higher than the findings of our study.^{23–25} Nonetheless, some studies revealed that the actual willingness of patients to stop medication is not as elevated.^{26,27} A review paper showed that when advised to discontinue medications, only one-third of patients expressed acceptance of medication withdrawal.²⁸ These differences may be explained by the study populations and the type of medication being deprescribed. For example, 95% of individuals in Australia reported a willingness to have statins deprescribed,²⁴ while the acceptance of benzodiazepines cessation was below 20%.¹³ Previous studies revealed that populations from different countries have different attitudes towards deprescribing. The acceptance rates of deprescribing varied significantly between inpatients in Italy and community patients in Malaysia, at 89% and 67.7%, respectively.^{15,29} However, this study specifically investigates attitudes towards deprescribing among individuals living in rural areas, emphasizing the impact of cultural factors on the deprescribing.

The majority of participants reported that they felt comfortable with the number of medications they were currently taking. These contradictory statements (being willing to stop taking medication, but believing that their current medicines are appropriate) which are consistent with international research findings.^{30,31} This probably reflects the contradiction between people's reluctance to take their medications and the necessity to maintaining their current health status through medication in the Chinese cultural context. Another plausible explanation is that their reverence and reliance on their

physician. This also validates previous evidence from Singapore that physicians are perceived as authoritative figures in Asia.¹² Meanwhile, in rural China, medical services are predominantly provided by primary care physicians. Due to the inadequate healthcare services and a lack of systematic management of chronic diseases, the prevalence of potentially inappropriate medication among patients is common.¹⁸ The management of polypharmacy is directly related to medication safety for patients. As a result, it is imperative to enhance training in chronic disease management for healthcare providers and to encourage physicians to provide regular medication reviews and follow-ups, particularly for patients with multimorbidity.

Having adequate information is a crucial prerequisite for participating in medical decision-making.²⁶ Related studies have shown that individuals with higher education levels exhibit a greater capacity to engage in their medication management and also more open to medication discontinuation.¹² Those with lower educational attainment may struggle to access adequate medical information and tend to rely on their physician's prescriptions. In our study, three-quarters of participants had only elementary school education or less, which may explain their lower acceptance of discontinue medication. A recent survey indicated that only approximately 10% of the population understood the term "deprescribing". Most patients are not familiar with the concept of deprescribing and still adhere to the conventional culture of persistent medication use.³² On the other hand, individuals with low levels of education may be more positive about deprescribing. As they have a low awareness of the necessity to take medication for maintaining their current health status, and generally harbor a dislike for taking medications.^{29,33} Consequently, the healthcare sector also needs to create targeted interventions that improve the acceptance of deprescribing among rural patients with multiple chronic conditions.

Furthermore, patients' attitudes toward deprescribing may be influenced by their perceptions of their current medication regimens. Although all participants were taking multiple medications, merely one-third felt they were taking too many medications. One study indicated that patients who concurred with this sentiment were more likely to consider medication cessation.³⁴ The reasons contributing to the willingness to embrace deprescribing among participants in our study appear to be varied and need to be further analyzed. It is essential to enhance patients' awareness of deprescribing and to encourage them to discuss their concerns about medications with their physicians.

Meanwhile, patients' socioeconomic status was associated with the willingness to deprescribing. Interestingly, the willingness to medication cessation was higher among those whose medical expenses were covered by their children or other sources, as opposed to those who covered their own expenses. This may be related to participants' reluctance to impose a financial burden on their children.³⁵ In contrast to accepted beliefs,⁹ participants' willingness to discontinue medication decreased as the dosage increased in this study. This phenomenon may be attributed to older adults' more pragmatic attitude toward stopping medication,¹⁶ as they are often willing to take more medication if deemed necessary for their health.³⁶ In fact, 75.3% of respondents considered that their willingness to taking more medication for their well-being. This also validates that patients who have been hospitalized for chronic conditions in the last year diminished willingness to discontinue their medications due to concern about their health status. Similarly, participants with more comorbidities were less willing to reduce their medication. A study that observed individuals over the aged 65 yielded comparable findings.³⁷ This association may be attributed to patients with poorer health status being more reliant on their physicians. Consistent with previous studies, no significant association was found between willingness to discontinue or reduce medication and factors such as age, polypharmacy, or annual household income.³⁸

There are several limitations to this study. First, the PATD questionnaire was developed as an exploratory tool, lacking scoring system to calculate overall factor scores.³⁹ Second, the findings are exclusively representative of respondents' attitudes towards medication cessation in rural Shandong, which may affect generalizability. Moreover, patient self-reported data are inevitably associated with response and social desirability bias. Lastly, we only analyzed the effect of medication quantity on attitudes toward deprescribing, without further analyzing whether the type of medication influenced participants' perspectives. Future research should investigate whether the specific type of medication influences patients' willingness to discontinue, and conduct qualitative studies to understand longitudinal changes in attitudes towards deprescribing.

Conclusion

This study indicated that more than half of patients with multimorbidity were willing to discontinue one or more medications, if their doctor agreed, while half of the patients desire to reduce medications they were taking. Factors such

as the number of chronic conditions, medication doses, and sources of medical expenditures may influence patients' attitudes toward deprescribing. These findings necessitate that physicians in rural area enhance their engagement with patients and actively promote awareness of medication cessation and the potential harms of inappropriate medication use.

Data Sharing Statement

The data sets analyzed during this study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Center for Health Management and Policy Research, Shandong University (Reference ID: ECSHCMSDU20170401). All participants filled out the informed consent form. This study methodology was carried out in accordance with relevant guidelines and regulations and is in line with the declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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