

ORIGINAL RESEARCH

Assessment on the Impact on Human Health, Environment, Water and Soil by Disposing Household Expired Drugs: A Cross-Sectional Study in China

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Background: The household expired drugs disposal has been a huge public issue in many countries, including China, which may affect various side and toxic effects on human health and environment, water resources, and soil too. This paper explores the knowledge, attitude, and practice of Guangzhou city residents regarding household expired drugs and their effect on human health and provided the scientific pieces of evidence to carry out the long-term recovery mechanism for expired medicines.

Methods: An observational, cross-sectional study was conducted using a self-structured questionnaire. Descriptive analysis, including univariate and unconditional logistic regression models, was carried out to analyze the data.

Results: A total of 613 community residents with a 99.4% response rate enrolled for the study. More than half 60.2% of residents stated that expired drugs pollute the environment, soil, and water resources, where 81.2% of respondents knew that it would produce side effects or toxic effects. However, still, 71.6% of respondents disposed of directly into the trash bin or sink, and, only 24.8% had good practice that they use a designed recycling bin. Likewise, only 8.3% of respondents placed expired drugs into collection points nearly 3-5 times in a year, while 65.1% of participants never disposed of in the collection point, which found a worse practice.

Conclusion: Overall, the knowledge, attitude, and practice of Guangzhou residents regarding household expired drugs disposal were not ideal. To improve the resident's awareness about family expired drugs disposal, ensure the financial support for the recycling process, establish an accessible and acceptable recycling point, and introduce relevant laws and regulations for the long-term mechanism.

Keywords: household, expired drugs, knowledge, attitude, practice, collection point, Guangzhou, China

Introduction

Recent years pharmaceuticals companies have been substantially accelerating and manufacturing different pharmaceutical products globally to fulfill the population's demand for medications. This trend is predicted to extend continuously by year to year along with the population growth^{1,2} and at the same time families have been accumulating more spare drugs for future use in case of an emergency resulting that increasing the household expired drugs in the community.³

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A previous study stated that about 78.6% of households preserve spare drugs at home; among them, 94.8% of the residents mishandled those expired drugs.⁴ In this way, expired drugs have more prone to arise dangerous situation for their health if someone has taken unexpectedly, carelessly or mistakenly, also pollute the environment if expired drugs (household medical waste) throw out into the garbage or flushed down in the sink or the toilets.¹ Unused medications have brought an increased threat, eg, childhood poisoning (accident).⁵ Therefore, this issue should be solved by the stockholder, organization, or government itself by making a proper rule and regulations including accessible manner for the long-term mechanism.3

Although unavailable unified expired drugs recycling system in China, local cities or communities or state government have issued local regulations or regulatory documents for the recycling expired drugs.⁶ Even though, to date, residents do not know appropriately about how to deal with the expired drug. Thus, they throw away. Some countries have a particular system for the recycling, retreat, or proper handling of expired drugs.^{7–9} Although, the establishment of the expired drug recovery system and its long-term mechanism is still a social and debatable issue in developed as well as developing countries.

Therefore, with increasing storage of self-supplied household drugs and improper management of those drugs at home may transfer endanger to the family. Improper handling of expired drugs will pollute the environment. Likewise, obtaining illegal drugs through drug-dealers will cause common hidden dangers that affect the health and life of the residents. Securely disposal of family expired drugs has become a social problem. Short-term drug recovery activities have been carried out in some parts of China since 2005. Conversely, the overall situation is not satisfactory. 11

Previously conducted studies regarding the family expired drug disposal in different locations, eg, Dongcheng Districts, 12 Henan Xinxiang, 13 Tianjin, 14 Taizhou City, 6 Ruian City, in Guangdong Province, 11 suggested that there is still a lack of knowledge on the treatment of expired drugs among Guangzhou residents. The investigation on attitudes and behaviors regarding the above issue has not been well investigated for the improvement of their knowledge status. Therefore, this study is aimed to conduct a study to explore the knowledge, attitude, and practice regarding household expired

drugs disposal among the residents of Guangzhou City, which is the first evidence regarding family-expired drugs disposal in the study area.

Methodology

Study Settings and Sample

A descriptive cross-sectional study conducted in Guangzhou, China. Guangzhou, also known as Canton, the capital city of Guangdong province is the most prosperous city in South China. According to the economic development, 11 administrative districts are in Guangzhou. A convenient sampling method was used to select the participants. Considering the representativeness from urban and rural areas, four districts selected for the study, eg, Tianhe District from high economic development level, Haizhu District from medium economic development level, Liwan District and Baiyun District for the moderate economic development and suburban areas represent the city's new urban area, old city, and the suburbs (Figure 1, Table S1).

The following approach was used to calculate the sample size. The knowledge rate of the expired drug was 50%, taking α =0.05, δ =±5%, p=0.5, and the sample size was n=384. Allowing for the investigation error and the validity of the questionnaire when the sample size is expanded by 50%, the sample size was 576 cases. The calculation formula is.

$$n = \left(\frac{Z_{\alpha/2}\sigma}{\delta}\right)^2 \times p(1-p)$$

Data Collection

The data was collected from different households and these were based on altered districts of Guangzhou city. An unanswered and unqualified questionnaires excluded before data analysis. The questionnaire was pre-tested among the participants for its validity and reliability before the final data collection (Supplementary Appendix). The project leader trained investigators uniformly. The informed consent sign was obtained from each participant after explaining the background, objective, data protection, and data privacy. After agreeing to the interview, the experienced project leaders conducted the interview. At the same time, we assured that all information was kept confidential.



Figure I Administrative map of Guangzhou districts, China, computed by authors.

Data Collection Instruments

A standardized self-designed questionnaire (written in Chinese) was used to collect the data, where the necessary information about the knowledge, attitude, and practice of expired drugs disposal included. We need to collect the large variety of opinions from the local communities. An individual face-to-face in-depth interview (IDI) also was conducted to know the views, experiences, beliefs, and motivations regarding knowledge, attitude, and practice of expired drugs disposal. Because an indepth interview offers the opportunity to capture the

views, experiences, beliefs, and motivations of descriptive information regarding the subject matter. This study was accompanied from February to March, 2016 with 26 general community residents in Guangzhou city, drug companies, and drug regulatory government departments (eg, six executive leaders in—charge of drug supervision in Guangdong Province and Guangzhou Municipal Food and Drug Administration, Eight pharmacy professionals from pharmacies (pharmaceutical factories), twelve community residents in Guangzhou), where, 15–25 minutes was for the interview.

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Table I Knowledge of Household Expired Drugs Disposal on Guangzhou Residents

Parameter	Responses	No of Cases	Percentage (%)
Attention towards expired date	Always pay attention before taking each medicine all the time	321	50.9
	Always pay attention before taking each medicine frequently	149	24.3
	Occasionally pay attention before taking the medicine	121	19.7
	Never pay attention before taking the medicine	31	5.1
Effective, harmful, or invalid	Invalid, harmful	497	81.1
	Invalid, harmless	49	8
	Effective and harmless	10	1.6
	Effective and harmful	56	9.1
Knowledge of cleaning up the medicine box	Know	89	14.5
	Know some	298	48.6
	Do not know	219	35.7
	No need	7	1.1
Hazard of expired drugs	Pollute the environment, including soil and water resources	369	60.2
	Cause waste of resources	369	60.2
	Continue to take it will produce side effects	498	81.2
	No harm	7	1.1
Efficacy of the expired drugs	Taking will affect your health	488	79.6
_	Reduced efficacy	92	15
	No effect	49	8
	The drug effect remains unchanged	4	0.7

Statistical Analysis

After coded and decoded, all collected data are entered into the data management software Epidata 3.0. Descriptive analysis carried out and continuously, the factors affecting the knowledge, attitude, and practice of family expired drugs disposal was analyzed by single factor univariate analysis chi-square test and the unconditional logistic regression analysis. Since our study was mainly focused on the knowledge on expired drugs collecting point, and return the expired drugs to the recycling point, we only included "Do you know the expired drug collection point" (knowing that the collection point = 0, do not know the collection point=1) as the dependent variable. Where, whether the monthly income per household was ≥5000 yuan, medical insurance, expired drugs clean up knowledge, disposal via household waste products, know the adverse effect of expired drugs, the number of people having drugs every month as an independent variable for one-way chisquare and logistic regression analysis. All the statistical tests were two-sided, and the significance assumed at a 0.05 level. All analyses were performed using SPSS software version-22.

Furthermore, we analyzed qualitative data, such as verbal, record, notes and, transcription of in-depth interviews. Then, we made separate notes of each participant in MS word file according to the research question. Similarly, we applied some symbols or codes for each participant to recognize it easily, such as 01/*01, etc, and categorized accordingly. We saved all respondent's information. Then, finally we summarized and combined the paragraphs and wrote the analysis report.

Results

Among 617 community residents, only 613 were valid with the response rate of 99.4%, where 26 more participates were selected for an in-depth interview. Likewise, about 47% (n=288) respondents had a monthly income between 2000 and 4999 Yuan (\$308–769), followed by 29.9% (n=183) had 5,000 to 9999 Yuan (\$769–1538), and 13.7% (n=84) respondents had more than 10,000-Yuan (\$1539) income per month (Table S2).

Table 1 shows the knowledge about expired drugs disposal among Guangzhou residence, which was found inadequate. Only 14.5% (n=89) respondents knew about timely cleaning the medicine box, while 48.6% (n=289)

had improper knowledge. Regarding the attention of the expiration date of drugs, 50.9% (n=312) respondents had always paid attention every time before taking medicine. Majority 81.2% (n=498) of residents had reasonable knowledge that if continue taking expired drugs, then it will produce toxic effects in the body (Table 2).

Table 2 explains the influencing factors of expired drugs disposal among the respondents and results showed that district, family's monthly income, family's medical insurance, the awareness of cleaning the medicine box, family expired drugs knowledge, disposal via household waste products, expired drugs have toxic effects, and cause environmental pollution too was statistically significant (Table 2). Furthermore, unconditional logistic regression analysis results showed that knowledge about clean up the medicine box found the statistically significant (OR=0.17, of 95% CI 0.085–0.340, P=0.001) influencing factor (Table S3) for expired drug disposal.

This study result showed that nearly half 47% (n=288) respondents served expired drugs to the collecting point if it is nearby home/residence, where only 25.1% (n=154) respondents stated that the distance does not matter (Table 3). In single-factor univariate analysis result showed that the monthly income of the family and medical insurance were statistically significant influencing factors, while in multi-factor logistic regression analysis showed that more than >5000 \(\pmonth{\text{F}}\) monthly income of residents (OR=2.47, of 95% CI 1.753-3.494, P=0.001) and medical insurance (OR=0.59, of 95% CI, 0.409-0.850) were positive contributing factors to change the attitude of respondents towards expired drugs disposal (Tables S4 and S5). This study identified more than half 59.7% (n=366) respondents agreed that expired drugs should be handled by the government itself, where 27.2% (n=167) believed that it is the responsibility of pharmaceuticals companies (Table 3).

Table 4 shows that about 31.8% (n=195) respondents always take medicine within the time of validity period; however, approximately 65.1% (n=399) indicated that they never dispose of expired drugs in collecting point resulting that majority of the respondent's 71.6% (n=439) dispose of expired drugs via household waste, while only 24.8% (n=152) through expired drugs into the designated recycling bin (Table 4).

In-depth interview, more than half of the residents believed that the main reason for the expiration of the drugs at home was that respondents did not finish or take all medicines which were prescribed by doctors. About half of the respondents thought that they are requesting to the doctor for more medicines for future consumption such as cold and anti-inflammatory purpose. However, few respondents insisted that medicines expired due to a lack of proper storage place.

Additionally, most of the interviewees assumed that the reasonable way for "recycling of household expired drugs" set up, which should be located in the crowded residence place as much as possible. They also thought that it should be located in the neighborhood committee, community health service station, and near the pharmacy. Most of the respondents alleged that the recycling expenses should be borne by the government itself, where the drug administration managers (5/6) also considered that the "family expired drug recycling work" is paid by the government, and one respondent (1/6) thought that the cost should be paid by the pharmaceutical companies. In the interview, most of the residents throw expired drugs directly into the garbage, knowing that it is harmful to the health because they did not know that expired drugs either should be recycled. The in-depth interview identified that the lack of relevant policies and regulations on expired drug disposal in the study area. Moreover, respondents emphasized more to publicity, about recycling place because they did not know where the recycling point is. The recycling practice of residents was not ideal.

Discussion

This study found that the overall knowledge about expired drugs disposal among Guangzhou residence was low such as only 14.5% of respondent timely cleaned up the medicine box, while 48.6% had still improper knowledge. A previously conducted study also stated that respondents did not frequently check out the medicine box. 16 Although, to check out the expiry date of the pharmaceutical products and provide the proper guidelines about drugs before dispensed is a responsibility of all health workers and pharmacists. 17,18 The present study found that 60.2% of respondents believed that expired drugs might produce environmental pollution, soil and water resource too, consistent result observed (41.8%) in the previous study of Bound et al. 19 However, awareness about the dangerous situation or fear of expired drugs effect can significantly increase via media exposure. In this study, almost 81.2% of residents had reasonable knowledge about if continuously consuming expired drugs then it will be adverse (toxic) effects in the body, almost similar finding 81.1% revealed by the earlier study

Table 2 Influencing Factors of Household Expired Drug Disposal Knowledge in Guangzhou Residents

Variables	No. of Cases n (%)		X ² Value	P-value
	Recycling Point	Non-Recycling Point		
Tianhe District	5 (3.6)	135 (96.4)	64.574	<0.0001
Haizhu District	31 (23.1)	103 (76.9)		
Baiyun District	6 (8.0)	69 (92.0)		
Liwan District	87 (36.1)	54 (63.9)		
Monthly income of the family (yuan)				
<2000 Yuan (\$07.8)	16 (29.1)	39 (70.9)	8.135	0.043
2000~4999 (\$308–769.4)	68 (24.7)	207 (75.3)		
5000~9999 (\$769–1538.9)	35 (19.8)	142 (80.2)		
>10000 (\$1539.1)	10 (12.0)	73 (88.0)		
Family members:				
≤3	55 (20.7)	211 (79.3)	0.400	0.527
>3	74 (22.8)	250 (77.2)		
Whether the family take medicine every month:				
Yes	2 (23.4)	95 (76.6)	0.213	0.627
No	100 (21.5)	366 (78.5)		
Covered by medical insurance				
Yes	98 (24.3)	306 (75.7)	4.296	0.042
No	31 (16.7)	155 (83.3)		
Expired drugs Clean-up knowledge:				
Know	42 (47.7)	46 (52.3)	60.472	<0.000
Know some	69 (24.6)	211 (75.4)		
Do not know	17 (7.9)	198 (92.1)		
No need	I (I4.3)	6 (85.7)		
Do you know the collection point?:				
Yes	129 (35.2)	237 (64.8)	101.043	<0.0001
No	0 (0)	224 (100)		
Dispose via household waste products:				
Yes	61 (17.3)	292 (82.7)	10.809	0.001
No	68 (28.7)	169 (71.3)		
Knowledge about its side effects:				
Yes	83 (17.3)	396 (82.7)	30.672	<0.000
No	46 (41.4)	65 (58.6)		
Knowledge about polluting the environment:	07 (24 7)	245 (75.2)	4.153	0.045
Yes	87 (24.7)	265 (75.3)	4.153	0.043
No	42 (17.6)	196 (82.4)		
Effectiveness/Harmfulness of Expired drugs	104 (00.5)	272 (77.0)	4.705	
Invalid and Harmful	106 (22.2)	372 (77.8)	4.733	0.192
Ineffective	12 (25.0)	36 (75.0)		
Effective and harmless	4 (40.0)	6 (60.0)		
Effectively harmful	7 (13.0)	47 (87.0)		

Table 3 Attitudes of Guangzhou Residents on Family Expired Drugs

Variables	Responses	No of Cases	Percentage (%)
Attitude towards Collection point distance and	No matter how far away from home	154	25.1
delivery	If collection point is too far from home, you will not be served	127	20.7
	If it is close to home, it will be served	288	47
	Will not serve	44	7.2
Attitude to encouraging measures	Issue a drug discount card	287	46.8
	Give a small gift	154	25.1
	Safety medication booklet	170	27.7
	Other incentives	47	7.7
Attitude of the recycling methods of expired	In recycling box according to hazard nature	166	27.1
drugs	Designed recycle point or Recycle Bin	343	56
	Personal visit and recycling the garbage	75	12.2
	Sent back to the factory and replaced by new	68	11.1
Attitude of Recycling point setting	Community health station	214	34.9
	Neighborhood committee	173	28.2
	Pharmacy	256	41.8
	Other	20	3.3
Attitude of Recycling funds bear department	Government	366	59.7
	Pharmaceutical companies	167	27.2
	Pharmacy	38	6.2
	Does not matter	66	10.8
Effectiveness of recycling measures	National legislation becomes a social responsibility and obligation	254	41.4
	Material encouragement	251	40.9
	Strengthen publicity and guidance	360	58.7
	Set up as many collection points as possible	351	57.3
	Trade-in old for new	266	43.4
Views on recycling work	Introduce relevant policies to avoid pollution	351	57.3
	Introduce relevant policies to avoid waste	248	40.5
	Self-addressed according to individual circumstances	73	11.9
	No need	10	1.6

of Bound et al, 20 and this finding also supports by the study of Bhayana et al. 21

This study found that family's monthly income, family's medical insurance coverage, the awareness of cleaning the medicine box, expired drugs produce toxic effects and pollute environment, statistically were significant influencing factors of knowledge regarding expired drug disposal. The expired drugs clean-up knowledge was positively associated with knowledge of respondents, which considered that "knowing the knowledge of expiring drug cleanup" tends to be close to put the family expired drug at the collection point. Therefore, it has been considered that the in-depth promotion of family

expired drugs cleaning knowledge is a contributing factor to the recovery of family expired drugs.

An essential and the significant debatable issue regarding who is responsible for collecting and recycling of expired drugs, in this regard, about 59.7% of respondent agreed that it should be handed by the government itself, where 27.2% supposed that it is the responsibility of pharmaceuticals companies. However, the primary responsibility of disposing of expired drugs should be a task of the government itself with an appropriate rule, regulations, and policy revealed by²² Al-Shareef et al, which is somehow applying in the Chinese community too. This present study found that 11.1% of respondent returned expired drugs to factory or

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Table 4 Practice of Expired Drugs Disposal by Guangzhou City Residents

Variables	Responses	No. of Cases	Percentage (%)
Whether to take the drug in order of the validity	Always	195	31.8
	Often	173	28.2
	Occasionally	155	25.3
	Never	90	14.7
Frequency of expired drugs dispose into the collection point in	Always (5 times or more)	22	3.6
a year	Often (3–5 times)	51	8.3
	Occasionally (I-2 times)	141	23
	Never	399	65.1
Frequency of expired drugs cleaning up	Always cleaning up (1–2 months)	65	10.6
	Frequently cleaning up (3-6 months)	166	27.1
	Occasionally cleaning up (7-12 months)	317	51.7
	Never cleaning up (more than 12 months)	65	10.6
Cleaning-up expired drugs	Put it into the designated recycling bin or collection point	152	24.8
	Throw it away as trash	439	71.6
	Reluctant to throw it away, continue to store or	12	2
	take		-
	Other treatment methods	10	1.6
Type of drugs stored	0 types	20	3.3
,, ,	I–3 types	139	22.7
	4–6 types	230	37.5
	7–10 types	109	17.8
	More than 10 types	115	18.8
Frequency of reserving drugs	Always reserving drugs	244	39.8
. , 5 6	Frequently reserving drugs	183	29.9
	Occasionally reserving small amounts of drugs	177	28.9
	No drugs reserved	9	1.5
Type of the drugs reserved	Drugs for common diseases	500	81.6
•	Drugs for external use	398	64.9
	Drugs for health protection	161	23.6
	Drugs for first-aid	198	32.3
			1
	Drugs for chronic disease	154	25.1

pharmacy and replaced by the new one, where only 10% returned to the Central Drug Store in Kuwait,²³ indicating that Guangzhou residence had a quite right attitude compared with previous studies of Al-Shareef et al.²² Tong et al,²⁵ indicated that only 1.4% and 2% of respondents returned expired drugs to a pharmacy in the USA and Saudi Arabia. Expired drugs "take-back" and "mailbag" programs have well known in several countries where pharmacies and pharmacists have substantial roles in the collection and recycling process.^{5,23} However, so far, this facility is not well-practiced in China.

This study found that majority of the respondent's 71.6% dispose of expired drugs via household waste, which tendency is quite similar 79.1% with the previous study of Fatma Al-Shareef et al,²² conducted in Saudi Arabia, and 87% in the USA. Likewise, direct throwing into trash or bin has identified as the most common means of disposal way in many countries, eg, the USA, the UK, Serbia, Kuwait,²³ Saudi Arabia, Pakistan, India.^{2,20,22,23,25} Additionally, the next commonly used method for expired drugs is identified as flushing down into the toilet or sink directly.²⁵ The potential disparities regarding disposal of

expired drugs vary according to demographic characteristics, health-seeking behavior, and existing law and legislation of that particular state.²⁶

Likewise, this study found several issues, such as relevant policies and programs of expired drugs, insufficient publicity of recycling point, low number of collection points, weak awareness about the recycling process, and low enthusiasm to recycle it. Fewer studies regarding expired drugs disposal and the cost of the recycling process, which is too high are the main lacking factors of disposal and recycling household expired drugs in Guangzhou city. To solve these issues, the government itself, stockholders, and other organizations as well as the health community needed to make a co-operation and look forward to a long-term solution. A previous study also suggested that the government should make a proper design a subsidy policy to return and recycle expired drugs and establish proper expired drugs collection points in the community.3

Expired drugs are different from regular garbage. There was no such system to provide compensation for expired drugs. At present, the recycling of expired drugs in China has not been supported by the State Government. The pharmaceutical companies in China have borne the cost of expired drug recycling. The ongoing work has been facing significant economic burdens.²⁷ Due to the relatively high economic pressure on the harmless destruction of expired drugs, about 90% of pharmaceutical companies have not recycled expired household drugs. The large company, eg, GPHL, has been recycling expired drugs, even though they find it is difficult to maintain such high destruction costs, which may become a bottleneck restricting their continued public welfare.²⁸

The strength of this study is that results provide essential information for the next planning and improving health education intervention and mass media campaign to improve the KAP of Guangzhou residents. Despite that, this study has some limitations. First, this is a cross-sectional study design, which limits the generalizability of the findings. Second, we obtained the information using a self-structured questionnaire; therefore, the responses of participants were prone to be information bias.

Conclusion

The awareness regarding household expired drugs disposal of Guangzhou residents was relatively low. The most common method of household expired drugs disposal was through trash or bin via household waste products because most of the respondents did not know the collecting/recycling point. Such knowledge, attitude, and practice stand possible threats to the population which needed to be solved. Their collection point or recycling point should be disseminated via mass media exposure alongside the legislation, policies, and programs and applied subsequently to make such changes towards expired drugs disposal. Further brief educational interventions should be carried out to improve the resident's knowledge, attitude, and practice regarding expired drugs disposal.

Recommendation

As per our study findings, and knowledge, we have made the following recommendations:

- 1. The best way to dispose of expired or unused drugs is to drop off in the expired drugs collection center.
- If there is no such facility for collection counter nearby then immediately flush this potentially dangerous medicine into the toilet (only flushable list items).
- There are few drugs that cannot be flush, such medicines can result in death from even a single dose if it has taken inappropriately.
- 4. Always keep safe those drugs from children, adults, or pet in the home, that can accidentally or intentionally ingest, touch, misuse, or abuse and can be dangerous for everyone's life.
- Review the instructions of the medicines or prescription of doctor or contact to health professional such as a pharmacist, doctor to find out the proper way to dispose expired medicines.
- Read the specific instructions carefully for sprays, lozenges, ointment, and inhaler to discard into the trash at home, and if possible then check with the nearest pharmacist about collection center and disposal system.
- Check with the community health center or health care management team of the local community or hospital about how, where, and what is the best way to dispose of the expired drugs.
- 8. Start awareness champion about drug take-back program, flushing medicines, disposable medicines in household trash, flushing drugs, and environmental pollution, etc by advertising media, poster, pamphlet, health education to the community.

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Make a healthy public policy regarding expired drug disposal and promote it to utilize properly.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval had been approved by the Ethics Committee of the School of Public Health, Sun Yat-Sen University, Guangzhou, China. The ethical approval number is 053-2018. The written and verbal sign was taken with each respondent in an informed consent form at the beginning of each survey.

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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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