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## Chinese physicians' attitudes toward eco-directed sustainable prescribing from the perspective of ecopharmacovigilance

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4 1 **Chinese physicians' attitudes toward eco-directed sustainable**  
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7 2 **prescribing from the perspective of ecopharmacovigilance**  
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35 10 **ABSTRACT**

36  
37 11 **Objective** Eco-directed sustainable prescribing (EDSP) is an effective upstream way to  
38  
39 12 reduce the environmental footprints of active pharmaceutical ingredients (APIs), a kind of  
40  
41 13 emerging contaminants, from the patients' excretion. EDSP is one of key steps in the  
42  
43 14 program of ecopharmacovigilance (EPV), a drug administration route on API pollution.  
44  
45 15 The study aimed to assess the attitudes of physicians prescribing medicines regarding  
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47 16 EDSP from the perspective of EPV.  
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50 17 **Design and setting** This cross-sectional study was conducted using a self-administered  
51  
52 18 questionnaire instruction delivered to 400 physicians in Hubei Province, China from March  
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54 19 to June, 2019. And 262 valid questionnaires were obtained.  
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57 20 **Results** Most physicians agreed the existence of APIs in environment, worried about the  
58  
59 21 potential environmental and ecological risks of API residues, supported the effectiveness  
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3 22 and necessity of EDSP under an EPV perspective in decreasing environmental exposure  
4  
5 23 of excreted APIs, and showed their willingness to participate in the EDSP practices.  
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7 24 Nevertheless, no respondent identified the environmental impacts as the aspects  
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9 25 regarding medicines affecting his(her) prescription decision, showed their self-satisfaction  
10  
11 26 with knowledge on EDSP and confidence toward EDSP. The most important barrier to the  
12  
13 27 effective implementation of EDSP was identified as “*poor awareness of EDSP and EPV*”.  
14  
15 28 And 97% responding physicians reported that they held the wait-and-see or conservative  
16  
17 29 attitudes towards EDSP practice. The biggest concerns in low-dose prescribing and  
18  
19 30 prescribing of drugs possessing environment-friendly excretion profiles, two EDSP  
20  
21 31 approaches, were “*It can not achieve ideal therapeutic efficacy, and might delay*  
22  
23 32 *treatment*” and “*Drug evaluation based on the excretion profile and pharmacokinetics is*  
24  
25 33 *too complicated and professional*”, respectively.

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27  
28 34 **Conclusions** Chinese physicians had positive attitudes towards EDSP from the  
29  
30 35 perspective of EPV. However, their environmental consciousness during prescribing and  
31  
32 36 the related education were insufficient. Some recommendations for implementing EDSP  
33  
34 37 from the perspective of EPV were proposed.  
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### 39 **Strengths and limitations of this study**

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44 40 ● To the best of our knowledge, this is the first study that explored the physicians’  
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46 41 perceptions and attitudes toward eco-directed sustainable prescribing (EDSP) from  
47  
48 42 the perspective of ecopharmacovigilance (EPV), a sustainable prescription approach  
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50 43 to minimize the environmental loads and risks of excreted active pharmaceutical  
51  
52 44 ingredient (API) residues from the source.  
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56  
57 45 ● Based on the survey results, we proposed some recommendations for further  
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59 46 implementing EDSP from the perspective of EPV in practice.  
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4 47 ● This study only enrolled physicians from one province in China, which might weaken  
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7 48 the generalizability of results.  
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## 49 INTRODUCTION

50 The occurrence of active pharmaceutical ingredients (APIs), a kind of emerging  
51 contaminants (ECs) without standard regulations, in the environment worldwide has  
52 become an issue of special importance.<sup>1-5</sup> As a critical part of modern life, pharmaceutical  
53 drugs are abundantly used in health-care practices around the world.<sup>5</sup> The  
54 environmental discharge of APIs in a continuous and unsupervised way as well as their  
55 inadequate removal during wastewater treatment processes have led to their detection in  
56 the various environmental matrices at levels of concern.<sup>2-5</sup> Considering their potent  
57 biological activities even at very low concentrations, API residues have been recognized  
58 to pose potential risks and hazards to the natural environment, ecology and human health  
59 due to long-term exposures.<sup>6-9</sup> Therefore, it is urgent to address this issue, aiming to  
60 minimize the environmental loads and risks of API residues.

61 Despite the fact that conventional and advanced end-of-pipe wastewater treatment  
62 optimizations have been proposed, studied and conducted from the perspective of  
63 environmental science, more effective, economic and better control activities for API  
64 pollutants emphasizing on input prevention are currently needed to eliminate pollution at  
65 the root source.<sup>6,10,11</sup> As a drug administration route on environment pollution caused by  
66 APIs, ecopharmacovigilance (EPV) is an emerging science of detection, evaluation,  
67 understanding and prevention the adverse effects of APIs in the environment.<sup>6, 11-18</sup> Based  
68 the fact that API pollution could be ultimately traced back to the use of medications in  
69 health-care practices, EPV focuses on the clinical application of active pharmaceutical  
70 management strategies to decrease the API emission from the sources and minimize the  
71 environmental footprint of the health-care industry.<sup>13,17</sup> The sources of APIs in  
72 environment include excretion from drug-consuming patients and animals, inappropriate  
73 deposition of expired or unwanted pharmaceutical products, manufacturing plant wastes,  
74 hospital wastes, *etc.*<sup>19-23</sup> Thereinto, patients' excretion in forms of parent APIs or active  
75 metabolites has been well-accepted to constitute the major contribution to most API  
76 pollutants in the environment, and the disposal of leftovers has been judged as the

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3 77 secondary source.<sup>10,24-26</sup> Therefore, the implementation of EPV should encourage the  
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5 78 effective control of these two routes of API entry to the environment. EPV-directed  
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7 79 pharmaceutical disposal management has been proposed and many guidelines for  
8  
9 80 discouraging inappropriate disposal of leftover and unwanted medicines have been  
10  
11 81 implemented in some areas around the world.<sup>13,24,25</sup> However, effective upstream ways to  
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13 82 reduce API releases to environment from the primary route (excretion) are still needed  
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15 83 under the principle of EPV.

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18 84 Since normal physiological excretion of APIs in drug-consuming patients cannot be  
19  
20 85 prevented, the optimized administration of pharmaceuticals ensuring satisfactory but not  
21  
22 86 too high pharmacologically active concentrations in patients might be a key protective  
23  
24 87 measure against excessive API entry to the environment from excretion.<sup>24,27-29</sup> Driven by  
25  
26 88 this idea, an approach termed eco-directed sustainable prescribing (EDSP) has been  
27  
28 89 recommended by Daughton<sup>24</sup> to reduce the environmental load of excreted APIs. As  
29  
30 90 prescribers are commonly confronted with more than one choice of drug treatment,<sup>30</sup>  
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32 91 EDSP provides a new and more established decision support system to include  
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34 92 environmental considerations in drug prescription. The term of EDSP is used to describe  
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36 93 the combination of two prescription optimization methods – reducing the usage or doses  
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38 94 of medications, and prescribing decisions basing on the excretion profiles of APIs. The  
39  
40 95 dose of drugs prescribed plays a paramount role on the quantities of APIs entering into  
41  
42 96 the environment.<sup>31</sup> Certainly, any reduction in API prescribing would lead to a proportional  
43  
44 97 reduction in excreted APIs released into wastewater.<sup>24,27,32</sup> Moreover, lower doses also  
45  
46 98 hold the potential to eliminate the subsequent need for disposal of leftovers, relieve  
47  
48 99 adverse events associated with drug overdose, improved patient/ physician  
49  
50 100 communication, avoid the accidental exposures as well as reduce health-care costs.<sup>24,27</sup>  
51  
52 101 On the other hand, EDSP places an additional emphasis on the metabolism and excretion  
53  
54 102 profiles of drugs rather than only the dose initially used by the patient. Within a same  
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56 103 therapeutic class, and with similar therapeutic efficacies, more extensively metabolizable  
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58 104 medicines which have more environment-friendly excretion profiles resulting in less  
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3 105 excretion of bioactive API residues would produce more negligible environmental  
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5 106 footprints, thus could be favored for EDSP.<sup>24,25</sup> EDSP has been endorsed by International  
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7 107 Pharmaceutical Federation <sup>33</sup> as a means to promoting the sustainable application of  
8  
9 108 drugs. More importantly, as a drug administration route to prevent the adverse effects of  
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11 109 APIs in the environment resulting from medical prescriptions, encouraging EDSP *i.e.*  
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13 110 improved and rational prescribing practices has been well-accepted as an indispensable  
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15 111 part during EPV implementation.<sup>12,16,17</sup>

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18 112 Theoretically, optimistic efficiencies of EDSP should and can minimize the entry of  
19  
20 113 APIs into the environment through excretion via urine and fecal material. However,  
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22 114 EDSP might conflict with long-accepted clinical prescribing guidelines and tenet, so the  
23  
24 115 translation of EDSP concept into clinical practice will mean to change the conventional  
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26 116 prescribing behavior of physicians, which would certainly be a major challenge.<sup>24,25,34</sup> It is  
27  
28 117 necessary to explore the attitudes of physicians as prescribers toward EDSP and the  
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30 118 willingness of physician participation.<sup>24</sup> The opinions toward EDSP held by physicians play  
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32 119 a pivotal role in determining its acceptability and future application. China is a populous  
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34 120 country where prescribing practices of physicians may have a significant impact on the  
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36 121 global environment. Therefore, the present study was carried out among Chinese  
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38 122 physicians prescribing medications in Hubei, a province locating in Central China, to  
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40 123 assess their perceptions about API pollution in environment and EPV, and most  
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42 124 importantly, their attitudes regarding EDSP from the perspective of EPV. The findings can  
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44 125 provide an insight into the potential opportunities and challenges for EDSP and EPV  
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46 126 implementation.

## 47 48 49 127 **METHODS**

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52 128 A descriptive, cross-sectional survey involving authorized physicians presently working at  
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54 129 government general hospitals in Hubei province, China, who were willing to participate in  
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56 130 the study, was undertaken to assess their perceptions about API pollution in environment  
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58 131 and EPV, in particular, their attitudes toward EDSP using a self-developed questionnaire.  
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60 132 The study was granted approval from the Ethics Committee of Wuhan University of

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3 133 Science and Technology, and was conducted for over a period of 4 months from March to  
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5 134 June, 2019.  
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8 135 The initial draft of survey questionnaire was developed using information from the  
9  
10 136 relevant published studies about API pollution in environment , EPV and EDSP. The  
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12 137 respondents were informed about the basic concepts of EPV and EDSP on the first page  
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14 138 of the questionnaire. And a total of 25 structured questions divided into three sections  
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16 139 were included in the survey questionnaire, which required about 10-15 minutes to  
17  
18 140 complete. The first section consisted of 5 questions about respondent physicians'  
19  
20 141 socio-demographic characteristics, including gender, age, education background,  
21  
22 142 specialty, and years of experience. The second section included 7 question items  
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24 143 designed to capture the perceptions toward API pollution in environment and EPV. A  
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26 144 5-point Likert-scale format was used in the data collection in this section (1: strongly  
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28 145 disagree, 2: disagree, 3: neutral, 4: agree, and 5: strongly agree). The third section of the  
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30 146 survey questionnaire included 13 items designed to assess the physicians' perceptions  
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32 147 and attitudes toward EDSP from the perspective of EPV.  
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35 148 Two specialists in the investigated field were asked to evaluate the clarity, content  
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37 149 validity, relevance, and conciseness of the items in the questionnaire. Then pretesting of  
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39 150 the questionnaire was done on a convenient sample of 20 physicians, who were not  
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41 151 included in the final survey, to examine the validity and acceptability of the questionnaire.  
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43 152 The overall Cronbach's alpha value was obtained as 0.788. Based on the comments and  
44  
45 153 suggestions on the content, quantity of questions and the questionnaire structure  
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47 154 provided by 2 specialists and 20 physicians from the pre-test stage, the final survey  
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49 155 questionnaire was prepared. The final questionnaire was developed in English as the  
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51 156 original language, then translated into Chinese and back into English.  
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54 157 The initial list of about 809 physicians distributed among 5 hospitals was used as the  
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56 158 target sampling frame. The sampling of the hospitals was a convenient one, determined  
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58 159 by the proximity of the hospital administrators to the authors. From this list, 400 physicians  
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60 160 were randomly selected for inclusion in this survey. The developed questionnaire was

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3 161 mailed to collect data from physicians *via* email addresses provided by the hospital  
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5 162 administrators. A confirmation email together with an explanatory letter about the  
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7 163 survey's purpose and objectives were firstly sent to the respondents. After returning  
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9 164 their confirmation letters, the responding physicians received copies of the electronic  
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11 165 questionnaire *via* email, and were requested to complete the questionnaire then return it  
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13 166 within next 3 days to the researchers. Two weeks after sending the questionnaire, a  
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15 167 follow-up reminder postcard was sent to the non-responder to increase the response  
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17 168 rate. Each respondent participated in the survey voluntarily. Those who were not willing to  
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19 169 participate in or did not return completed questionnaires within the stipulated time period  
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21 170 were excluded from this study.

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23  
24 171 The collected data were entered into SPSS20.0 for analysis. Results were presented  
25  
26 172 as numbers (percentages) for categorical variables, and mean (standard deviation (S.D.))  
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28 173 for quantitative variables. Any relationship between the categorical data was determined  
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30 174 using Chi-square test. Independent t test was applied to compare the mean perception  
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32 175 scores of the two groups. The differences between pair-wise groups were detected using  
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34 176 the one-way ANOVA with post hoc Tukey's HSD analysis for multiple comparisons.  
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36 177 Differences were statistically significant when the p value was less than 0.05.

## 37 38 39 178 **RESULTS**

### 40 41 42 179 **Respondents' Characteristics**

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45 180 By the end of the study period, 284 (71%) of 400 randomly selected Chinese physicians  
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47 181 had agreed to participate and responded to the survey, yielding 262 completed  
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49 182 questionnaires available for analysis (overall effective response rate: 66%). The  
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51 183 respondents' age ranged between 25 and 63 years with a mean of 43.6 (S.D.:12.3) years.  
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53 184 Table 1 presented the demographic information of respondents. The gender, age,  
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55 185 specialty, or years of experience distribution of physician respondents was approximately  
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57 186 equal. Majority of respondents (65%) held postgraduate qualifications, which was in  
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59 187 accordance with the popularization and advances of medical postgraduate education in  
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3 188 China.<sup>35</sup>  
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6 189 **Perceptions toward API pollution in environment and EPV**  
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9 190 EDSP has been well-accepted as an essential element of EPV practice in the control of  
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11 191 API pollution in environment.<sup>12,16,17</sup> Therefore, the perceptions toward API pollution and  
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13 192 EPV were collected from 262 physicians using 5-point Likert scales. Data shown in Table  
14  
15 193 2 revealed that the responding physicians' overall perception towards API pollution in  
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17 194 environment and EPV was positive. Most respondents (80%, 89%, 88% and 80%,  
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19 195 respectively) agreed or strongly agreed the entry of API residues into the environment  
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21 196 (Q1), their environmental and ecological adverse effects (Q2), the necessity to minimize  
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23 197 the entrance of APIs into the environment (Q3), as well as the importance of the  
24  
25 198 administration of medication use in health-care practices for the API pollution control (Q5).  
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27 199 As for the reverse-score item "*The control of API pollution is none of my business,*  
28  
29 200 *because it should be the responsibility of environmental experts and regulators.*"(Q4), only  
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31 201 4% respondents agreed, suggesting most physicians realized their own responsibility in  
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33 202 the control of API pollution. Then the physicians were asked about whether they agree  
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35 203 with EPV, an intervention emphasizing the control of upstream routes of APIs entry to the  
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37 204 environment (Q6-7). It was encouraging to find that 60% believed that "*EPV is an effective*  
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39 205 *tool to control the entrance of APIs into the environment*", and 64% claimed that they  
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41 206 would endorse and were very pleased to participate in. However, there were a  
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43 207 considerable portion (36-37%) of respondents felt undecided, suggesting their uncertainty  
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45 208 regarding EPV. The results of the univariate analysis using independent t or one-way  
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47 209 ANOVA test of the above variables in perceptions with regards to the respondents'  
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49 210 gender, age, education background, specialty, and years of experience groups were not  
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51 211 significant ( $p>0.05$ ).  
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53 212 **Perceptions and attitudes toward EDSP**  
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56 213 The emphasis of this survey was to determine the perceptions and attitudes of physicians  
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58 214 toward EDSP, an emerging prescribing concept as an environmentally better alternative in  
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3 215 the clinical use of medicines,<sup>24,25</sup> in order to support its usage, participation and feasibility.  
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5 216 As shown in Table 3, we firstly detect the possible factors affecting the physicians'  
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7 217 decision process for drug prescription (Q1). An overwhelming majority (94-100%) of  
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9 218 physicians supported that efficacy, safety or cost of medicines affected their prescription  
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11 219 decisions, which was in line with the well-accepted traditional rational prescription  
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13 220 principle, that is, that the selection of drugs should be based on efficacy, safety and  
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15 221 cost considerations.<sup>30,36</sup> However, none was environmentally conscious in their  
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17 222 prescribing. And the evaluation of pharmacokinetic property as the key basis for EDSP<sup>24</sup>  
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19 223 was incorporated into the prescribing process only by 22% respondents. Nevertheless, it  
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21 224 was encouraging that 65% physicians were aware of their responsibilities for reducing API  
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23 225 releases to environment, despite the fact that 31% were undecided (Q2). Almost all the  
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25 226 physician respondents had not previously heard of EDSP (Q3), however, the effectiveness  
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27 227 of EDSP in the control of the entrance of APIs into the environment was agreed or  
28  
29 228 strongly agreed by about half (53%) respondents (Q4).

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32 229 In view of two different 'front-of-pipe' approaches under the EDSP design,<sup>24,25,28,29</sup> we  
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34 230 explored the physicians' attitudes toward reducing the dosage or usage of medications  
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36 231 (low-dose prescribing), and basing prescribing decisions on drugs' excretion profiles  
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38 232 (prescribing of drugs possessing environment-friendly excretion profiles), respectively.  
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40 233 According to the theoretical analysis on the lower-dose prescribing,<sup>24,25,27</sup> a total of 8  
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42 234 possible benefits of low-dose prescribing had been summarized (Q5). Among them, 3  
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44 235 benefits related to the environmental issues (i.e. *Reducing the environmental loading of*  
45  
46 236 *API residues from patients' excretions, Eliminating the subsequent need and cost for*  
47  
48 237 *disposal of pharmaceutical leftovers, and Improving public trust—by reducing hidden and*  
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50 238 *unwelcomed exposure of humans to trace levels of numerous APIs via potable water and*  
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52 239 *contaminated foods.*) were supported by most physicians (92-98%). However, the item  
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54 240 "Improving therapeutic efficacy via minimizing off-target side-effects related to dosage,  
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56 241 and thus enhancing pharmaceutical compliance." was least recognized as the positive  
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58 242 outcome of low-dose prescribing. This finding was in accordance with the result that all  
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3 243 the respondents worried that the low-dose prescribing could not achieve ideal therapeutic  
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5 244 efficacy, and might delay treatment (Q6). On the other hand, the importance of prescribing  
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7 245 based on drugs' excretion profiles, the other element of EDSP, was agreed or strongly  
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9 246 agreed by a solid majority (75%) of respondents (Q7). However, being different from  
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11 247 findings from the same question posed for low-dose prescribing (Q6), few (13%)  
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13 248 respondents worried about the therapeutic efficacy of prescribing on drugs' excretion  
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15 249 profiles (Q8). Most (84%) physicians placed misgivings about the complexity and  
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17 250 professionalization of drug evaluation and EDSP design based on the excretion profile  
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19 251 and pharmacokinetics (Q8). In addition, the availability of the related data as well as the  
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21 252 long time period that will be taken to popularize in clinical practice were considered by  
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23 253 most respondents (73-99%) as physicians' concerns regarding these two ways to achieve  
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25 254 EDSP (Q6 and Q8).

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28 255 All the responding physicians were not satisfied with knowledge on EDSP (Q9), as  
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30 256 well as did not feel confident toward EDSP (Q10). Accordingly, about half (51%)  
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32 257 respondents would adopt a wait-and-see approach for EDSP. And 46% reported that they  
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34 258 would follow conservative EDSP strategies, such as promoting rational prescribing at  
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36 259 precise doses, avoiding overprescribing and mis-prescribing (Q11). The most important  
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38 260 perceived barrier to the effective implementation of EDSP under the perspective of EPV in  
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40 261 China was "*poor awareness of EDSP and EPV*", which was supported by 39%  
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42 262 respondents. And the item "*lack of available data related to EDSP under the perspective*  
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44 263 *of EPV*" was ranked as the second important barrier, which was supported by 37%  
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46 264 respondents (Q12). A majority of (78%) respondents claimed that, if EDSP is successfully  
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48 265 translated into clinical treatment, they would be very pleased to participate in the related  
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50 266 activities in their future practice(Q13).

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53 267 When assessing for differences in demographic factors (gender, age, education  
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55 268 background, specialty, and years of experience), we only found the responses from two  
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57 269 questions (Q1 and Q11) on perceptions and attitudes toward EDSP could be significantly  
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59 270 influenced by specialty. Compared to surgeons and physicians in other specialties, the  
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3 271 internal medicine physicians appeared to offer significantly more support that the  
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5 272 pharmacokinetics of medicines currently affected their prescription decisions (Q1), and  
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7 273 want to firstly choose the EDSP behaviors rather than take a wait-and-see approach  
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9 274 (Q11) ( $p < 0.01$ ). In particular, all 7 respondents who wanted to *implement the low-dose*  
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11 275 *prescribing or prescribe drugs possessing environment-friendly excretion profiles as much*  
12  
13 276 *as possible* were physicians working in the internal medicine specialties.

## 16 277 **DISCUSSION**

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19 278 It has been five years since the concept of EDSP was first proposed.<sup>24</sup> And the  
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21 279 indispensable role of EDSP in the practice of EPV, a promising source control strategy for  
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23 280 API pollution from the perspective of drug administration, has already been well  
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25 281 accepted in theory.<sup>12,16,17</sup> But unfortunately, this theoretically efficacious solution for the  
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27 282 environmental issues caused by excreted APIs is so far still on the conceptual level, and  
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29 283 its conceptualisation has been rarely applied to real cases, which also restricts the  
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31 284 empirical domain of EPV. In order to assure and promote the practical application of  
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33 285 EDSP and EPV, it is necessary to firstly explore the acceptance of these new concepts by  
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35 286 the involved stakeholders, which is prerequisite to subsequent behavioral change and  
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37 287 efficient participation.

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40 288 In China, the main prescribers were physicians within health-care systems. Of course,  
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42 289 physicians should be environmentally conscious in their prescribing, and prescribe those  
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44 290 drugs that might have minimal environmental impact.<sup>37</sup> Hubei province is one of the  
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46 291 national leaders in health-care industry and pharmaceutical consumption in China.<sup>18</sup> The  
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48 292 2018 China Health Statistical Yearbook reported that, in China, there were 64.4%  
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50 293 health workers were working in hospitals in 2017, with 81.0% of them in government  
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52 294 general hospitals.<sup>38</sup> Therefore, the physician samples included in this study were  
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54 295 randomly selected from 5 government general hospitals in Hubei province. Demographic  
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56 296 data based on gender, age, education background, specialty, and years of experience  
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58 297 indicated the surveyed physician samples were generally representative of Chinese  
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60 298 physicians.

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3 299 The survey data suggested that the environmental consciousness of Chinese  
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5 300 physicians during prescribing was insufficient, which was demonstrated by the finding that  
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7 301 no respondent identified the environmental impacts as the aspects regarding medicines  
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9 302 affecting his(her) prescription decision. The possible reason might be due to the utter lack  
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11 303 of the related education or training, which is in alignment with respondents'  
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13 304 self-satisfaction with knowledge on EDSP (100% were not satisfied) and respondents'  
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15 305 confidence toward EDSP (100% were not confident), considerable portions of  
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17 306 respondents who chose "undecided" option in many Likert-type attitude and perception  
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19 307 questions, as well as the conservative wait-and-see attitudes towards EDSP practice held  
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21 308 by physicians. And "poor awareness of EDSP and EPV" was conceived as the most  
22  
23 309 important barrier to the effective implementation of EDSP under the perspective of EPV.  
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25 310 Therefore, the environmental sustainability considerations should begin to be included in  
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27 311 the physicians' choice of prescription in China, and the long-established norms and  
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29 312 guidelines in the practice of clinical prescribing should be accordingly modified under the  
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31 313 principle of treating the environment and the patient as an interconnected, integral  
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33 314 whole.<sup>24</sup> There is a need to optimize the prescribing of drugs with a view to reducing  
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35 315 environmental exposure. Hospitals, medical centers and colleges could develop training  
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37 316 and educational programs to inform physicians prescribing medications and medical  
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39 317 students about APIs in environment, the environmental consciousness during  
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41 318 prescribing, the environmental impact of their professions, EPV and EDSP.

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44 319 However, it is encouraging that the responding physicians' overall attitudes and  
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46 320 perception concerning API pollution in environment as well as EDSP under an EPV  
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48 321 perspective were positive, which would shape the motivation for the future practice. In  
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50 322 recent years, along with the increasingly serious environmental pollution which has  
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52 323 attracted the particular attention of Chinese government, the environmental awareness  
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54 324 and initiatives of Chinese people have gradually been awakened.<sup>18</sup> Accordingly, most  
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56 325 Chinese physician respondents showed their concerns about the environment problems  
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58 326 caused by APIs. Using their professional knowledge on APIs, a majority of physicians



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3 327 agreed the existence, potential risks of APIs in environment, and the effectiveness of  
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5 328 EDSP under an EPV perspective in decreasing environmental exposure of excreted APIs  
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7 329 based on the description on the basic concepts of EPV and EDSP provided in the  
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9 330 questionnaire. Most respondents posed the eco-responsible attitudes and perceived their  
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11 331 own responsibility for the control of API pollution linked to medical prescriptions as well as  
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13 332 the implementation of EDSP under an EPV perspective, and importantly, expressed their  
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15 333 wiliness to participate in EDSP and EPV activities.

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18 334 In order to explore the possible factors influencing their future EDSP decision making,  
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20 335 this survey studied the perceive benefits and concerns of two EDSP approaches,  
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22 336 low-dose prescribing and prescribing of drugs possessing environment-friendly excretion  
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24 337 profiles, respectively. Despite the fact that the necessity and benefits of these two EDSP  
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26 338 approaches in the aspect of environmental protection were accepted by most responding  
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28 339 physicians, the biggest concerns in low-dose prescribing and prescribing of drugs  
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30 340 possessing environment-friendly excretion profiles were *“It can not achieve ideal*  
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32 341 *therapeutic efficacy, and might delay treatment”* and *“Drug evaluation based on the*  
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34 342 *excretion profile and pharmacokinetics is too complicated and professional”*, respectively.  
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36 343 Therefore, during the EDSP design from the perspective of EPV, special emphases  
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38 344 should be given to how to ensure the therapeutic efficacy of the “environment-friendly”  
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40 345 doses, and how to standardize and simplify the process of prescribing based on the drugs’  
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42 346 environment-friendly excretion profiles.

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45 347 Moreover, many physicians voiced their concerns about the availability of the related  
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47 348 information required in EDSP design. In China, no data system is currently available to  
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49 349 guide medical prescribing decisions in the clinical for selection of drugs having a low  
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51 350 probability of environmental risks and hazards. However, there is a Swedish model which  
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53 351 could be used as a reference.<sup>26,37</sup> Swedish Environmental Classification of  
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55 352 Pharmaceuticals developed by Stockholm County Council is a simple and straightforward  
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57 353 classification system for prescribing non environmentally- hazardous drugs, and has been  
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59 354 widely used and well accepted among Swedish medical doctors. This easy-to-understand  
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3 355 classification classifies APIs on the Swedish market according to environmental risks and  
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5 356 hazards of drugs in view of their persistence, bioaccumulation and toxicity data, and  
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7 357 suggests substitution by alternatives with a lower risk or hazard index. We proposed to  
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9 358 construct the similar classification system in China, so that physicians who wish to be  
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11 359 environmentally conscious in their prescribing could have a reference to allow them to  
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13 360 select the API with the lowest possible environmental impact with equivalent therapeutic  
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15 361 activity.

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18 362 Interestingly, as the major challenge for EDSP implementation which was worried  
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20 363 about by its advocate Daughton,<sup>24</sup> the issue “*changing the prescribing behavior of*  
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22 364 *physicians*” appeared to be regarded as a small matter by most physicians, because only  
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24 365 21% and 24% respondents chose the item “*It will change my prescribing habits, thus is*  
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26 366 *too troublesome*” as their concern regarding the low-dose prescribing and prescribing of  
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28 367 drugs possessing environment-friendly excretion profiles, respectively (Table3, Q6 and 8).  
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30 368 And only 6% physician respondents considered the item “*It conflicts with long-accepted*  
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32 369 *prescribing guidelines*” as the most major perceived barrier to the effective implementation  
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34 370 of EDSP (Table3, Q12). This results suggested the physicians were willing to change their  
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36 371 prescribing habits in order to make their due contributions to control the environmental  
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38 372 pollution by APIs.

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41 373 In addition, we found there was a tendency among the internal medicine physicians  
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43 374 to have stronger intentions to attempt EDSP practice than physicians from other  
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45 375 specialties, which might be due to their better acquaintance with the pharmacokinetic  
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47 376 properties and excretion profile of drugs. There is thus the expectation that it is feasible to  
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49 377 first implement EDSP practice from the perspective of EPV in the internal medicine  
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51 378 department. Furthermore, nearly half responding physicians were inclined to adopt  
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53 379 rational prescribing as the EDSP behavior that they want to firstly choose. Rational  
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55 380 prescribing is a classical principle concept of drug selection of in the field of personalized  
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57 381 treatment or health-care.<sup>30</sup> Based on its high acceptability, further promoting rational  
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59 382 prescribing to control excess medication prescription is a good first approach to  
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3 383 implement EPV in the health-care system to reduce API pollution at the source. In fact,  
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5 384 recent emphasis of rational prescribing has been given to Personalized Health-care  
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7 385 through selection of optimal APIs and determination of individual dosages.<sup>26</sup> Personalized  
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9 386 adjustment of drug administration holds the potential for enhancing therapeutic outcomes,  
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11 387 while simultaneously reducing the environmental risks of APIs. Furthermore, considering  
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13 388 the faithfulness of physicians prescribing medicines to rational prescribing principles, it is  
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15 389 necessary to refine the rational prescribing concept through integrating the environmental  
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17 390 constituent into the prescribing decision, under the premise that this integration does not  
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19 391 jeopardize the quality of delivered health care. This upgraded rational prescribing principle  
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21 392 would guide physicians to include environmental sustainability considerations in their  
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23 393 practical choice of prescription.

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26 394 This study only enrolled physicians from one province in China, which might weaken  
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28 395 the generalizability of results. Further studies with larger samples should be conducted to  
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30 396 verify our findings.

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33 397 In conclusion, to the best of our knowledge, this is the first study that explored the  
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35 398 physicians' perceptions and attitudes toward EDSP from the perspective of EPV, a  
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37 399 sustainable prescription approach to minimize the environmental loads and risks of  
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39 400 excreted API residues from the source. The results suggested that the majority of Chinese  
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41 401 physicians had positive attitude towards EDSP from the perspective of EPV. Physicians  
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43 402 agreed the existence of APIs in environment, worried about the potential environmental  
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45 403 and ecological risks of API residues, supported the effectiveness and necessity of EDSP  
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47 404 under an EPV perspective in decreasing environmental exposure of excreted APIs, and  
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49 405 importantly, showed their willingness to participate in the EDSP practices. Nevertheless,  
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51 406 at present, the environmental consciousness of Chinese physicians during prescribing is  
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53 407 seriously insufficient, which was demonstrated by the finding that no respondent identified  
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55 408 the environmental impacts as the aspects regarding medicines affecting his(her)  
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57 409 prescription decision, showed their self-satisfaction with knowledge on EDSP and  
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59 410 confidence toward EDSP. The most important barrier to the effective implementation of  
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3 411 EDSP was identified as “*poor awareness of EDSP and EPV*”. And most responding  
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5 412 physicians reported that they held the wait-and-see or conservative attitudes towards  
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7 413 EDSP practice. Furthermore, the biggest concerns in low-dose prescribing and  
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9 414 prescribing of drugs possessing environment-friendly excretion profiles, two EDSP  
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11 415 approaches, were “*It can not achieve ideal therapeutic efficacy, and might delay*  
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13 416 *treatment*” and “*Drug evaluation based on the excretion profile and pharmacokinetics is*  
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15 417 *too complicated and professional*”, respectively. In addition, the availability of the related  
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17 418 information required in EDSP design was also taken into consideration. An unexpected  
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19 419 finding in this survey was that only few respondents were bothered by the issue that  
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21 420 EDSP changed the prescribing behavior of physicians, which was identified as the major  
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23 421 challenge for EDSP implementation by its advocate [Daughton \(2014a\)](#). This was in line  
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25 422 with the responding physicians’ eco-responsible attitudes toward API pollution in  
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27 423 environment. Moreover, we found that the internal medicine physicians might be more  
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29 424 initiative to engage in EDSP behaviors than physicians from other specialties.

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32 425 Based on the above findings, we concluded some recommendations for  
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34 426 implementing EDSP from the perspective of EPV:

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37 427 1. Introducing and strengthening the medical training and education about APIs in  
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39 428 environment, environmental consciousness during prescribing, the environmental impact  
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41 429 of their professions, EPV and EDSP.

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44 430 2. Further promoting rational prescribing to control excess medication prescription,  
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46 431 which is a good first approach to implement EPV in the health-care system.

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48  
49 432 3. Integrating the environmental constituent into the rational prescribing principles.

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51 433 4. Building the database to allow for acquiring the related information to prescribe non  
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53 434 environmentally-hazardous drugs, select the effective and “environment-friendly” doses,  
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55 435 understand the drugs’ environment-friendly excretion profiles, *etc.* And the Swedish  
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57 436 Environmental Classification of Pharmaceuticals could provide helpful sample materials.  
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3 437 5. Constructing the process model of EDSP from the perspective of EPV, in order to  
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5 438 ensure the quality, standardization and convenience of EDSP process.  
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8 439 6. Implementing EDSP practice from the perspective of EPV first in the internal  
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10 440 medicine department.  
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22 444 <sup>2</sup> Hubei Province Woman and Child Hospital, Wuhan 430070, China  
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25 445 **Contributors** JW conceived of the original idea for the study, designed the questionnaire,  
26  
27 446 obtained ethical approval, carried out the statistical analysis, drafted the paper and is  
28  
29 447 overall guarantor. SL contributed to the preparation of the data set and interpreted  
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31 448 results . BH contributed to the study design, interpretation of results and commented on  
32  
33 449 drafts of the paper.  
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45 454 **Patient consent** Not required.  
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48 455 **Ethics approval** The study was granted approval from the Ethics Committee of Wuhan  
49  
50 456 University of Science and Technology (19068).  
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53 457 **Data sharing statement** No additional data are available.  
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59 459 **References**  
60

- 1  
2  
3 460 1. Sato K, Watanabe H, Ikeda T, *et al.* Estimation of total prescription  
4  
5 461 weights of active pharmaceutical ingredients in human medicines based on  
6  
7 462 a public database for environmental risk assessment in Japan. *Regul Toxicol*  
8  
9 463 *Pharmacol* 2018;99:98-104.
- 10  
11  
12 464 2. Ahkola H, Tuominen S, Karlsson S, *et al.* Presence of active pharmaceutical  
13  
14 465 ingredients in the continuum of surface and ground water used in drinking water  
15  
16 466 production. *Environ Sci Pollut Res Int* 2017;24:26778-91.
- 17  
18  
19 467 3. Corra L. Chemical Pollutants of Pharmaceutical Origin Present in the Environment.  
20  
21 468 *J Health Pollut* 2018;8:180916.
- 22  
23  
24 469 4. Comber S, Gardner M, Sörme P, *et al.* Active pharmaceutical ingredients entering  
25  
26 470 the aquatic environment from wastewater treatment works: A cause for concern? *Sci*  
27  
28 471 *Total Environ* 2018;613-614:538-47.
- 29  
30  
31 472 5. Blair B, Zimny-Schmitt D, Rudd, MA. U.S. News Media Coverage of Pharmaceutical  
32  
33 473 Pollution in the Aquatic Environment: A Content Analysis of the Problems and  
34  
35 474 Solutions Presented by Actors. *Environ Manage* 2017;60:314-22.
- 36  
37  
38 475 6. He BS, Wang J, Liu J, *et al.* Eco-pharmacovigilance of non-steroidal  
39  
40 476 anti-inflammatory  
41  
42 477 drugs: Necessity and opportunities. *Chemosphere* 2017;181:178-89.
- 43  
44  
45 478 7. Frederic O, Yves P. Pharmaceuticals in hospital wastewater: their ecotoxicity and  
46  
47 479 contribution to the environmental hazard of the effluent. *Chemosphere* 2014;115:  
48  
49 480 31-9.
- 50  
51  
52 481 8. Niemuth NJ, Jordan R, Crago J, *et al.* Metformin exposure at environmentally  
53  
54 482 relevant concentrations causes potential endocrine disruption in adult male  
55  
56 483 fish. *Environ Toxicol Chem* 2015;34:291-6.

- 1  
2  
3 484 9. Meijide FJ, Da Cuña RH, Prieto JP, *et al.* Effects of waterborne exposure to the  
4  
5 485 antidepressant fluoxetine on swimming, shoaling and anxiety behaviours of the  
6  
7 486 mosquitofish *Gambusia holbrooki*. *Ecotoxicol Environ Saf* 2018;163:646-55.  
8  
9  
10 487 10. Kümmerer K, Dionysiou DD, Olsson O, *et al.* Reducing aquatic micropollutants  
11  
12 488 - Increasing the focus on input prevention and integrated emission management. *Sci*  
13  
14 489 *Total Environ* 2019;652:836-50.  
15  
16  
17 490 11. Wang J, He B, Yan D, *et al.* Implementing ecopharmacovigilance (EPV) from  
18  
19 491 a pharmacy perspective: A focus on non-steroidal anti-inflammatory drugs. *Sci Total*  
20  
21 492 *Environ* 2017;603-604:772-84.  
22  
23  
24 493 12. Holm G, Snape JR, Murray-Smith R, *et al.* Implementing ecopharmacovigilance  
25  
26 494 in practice: challenges and potential opportunities. *Drug Saf* 2013;36:533-46.  
27  
28  
29 495 13. Yu X, Hu X, Li S, *et al.* Attitudes and Practice Regarding Disposal for Unwanted  
30  
31 496 Medications among Young Adults and Elderly People in China from an  
32  
33 497 Ecopharmacovigilance Perspective. *Int J Environ Res Public Health* 2019;16(8).  
34  
35  
36 498 14. Medhi B, Sewal RK. Ecopharmacovigilance: an issue urgently to be addressed. *Indian*  
37  
38 499 *J Pharmacol* 2012;44:547-9.  
39  
40  
41 500 15. Silva LJ, Lino CM, Meisel LM, *et al.* Selective serotonin re-uptake inhibitors (SSRIs)  
42  
43 501 in the aquatic environment: an ecopharmacovigilance approach. *Sci Total Environ*  
44  
45 502 2012;437:185-95.  
46  
47  
48 503 16. Wang J, Zhao SQ, Zhang MY, *et al.* Targeted eco-pharmacovigilance for ketoprofen  
49  
50 504 in the environment: Need, strategy and challenge. *Chemosphere* 2018;194:450-62.  
51  
52  
53 505 17. Wang J, Zhang MY, Liu J, *et al.* Using a targeted ecopharmacovigilance  
54  
55 506 intervention to control antibiotic pollution in a rural aquatic environment. *Sci Total*  
56  
57 507 *Environ* 2019;696:134007.  
58  
59  
60

- 1  
2  
3 508 18. Liu J, Wang J, Hu XM. Knowledge, perceptions, and practice of  
4  
5 509 ecopharmacovigilance among pharmacy professionals in China. *Environ Monit*  
6  
7 510 *Assess* 2017;189:552.
- 8  
9  
10 511 19. Machado K C, Grassi MT, Vidal C, *et al.* A preliminary nationwide survey of the  
11  
12 512 presence of emerging contaminants in drinking and source waters in Brazil. *Sci Total*  
13  
14 513 *Environ* 2016;572:138-46.
- 15  
16  
17 514 20. Praveena SM, Shaifuddin SNM, Sukiman S, *et al.* Pharmaceuticals residues in  
18  
19 515 selected tropical surface water bodies from Selangor (Malaysia): Occurrence and  
20  
21 516 potential risk assessments. *Sci Total Environ* 2018;642: 230-40.
- 22  
23  
24 517 21. Sorensen JP, Lapworth DJ, Nkhuwa DC, *et al.* Emerging contaminants in urban  
25  
26 518 groundwater sources in Africa. *Water Res* 2015;72:51-63.
- 27  
28  
29 519 22. Sposito JCV, Montagner CC, Casado M, *et al.* Emerging contaminants in Brazilian  
30  
31 520 rivers: Occurrence and effects on gene expression in zebrafish (*Danio rerio*) embryos.  
32  
33 521 *Chemosphere* 2018;209: 696-704.
- 34  
35  
36 522 23. Yi X, Tran NH, Yin T, *et al.* Removal of selected PPCPs, EDCs, and antibiotic  
37  
38 523 resistance genes in landfill leachate by a full-scale constructed wetlands system.  
39  
40 524 *Water Res* 2017;121:46-60.
- 41  
42  
43 525 24. Daughton CG. Eco-directed sustainable prescribing: feasibility for reducing water  
44  
45 526 contamination by drugs. *Sci Total Environ* 2014;493:392-404.
- 46  
47  
48 527 25. Daughton CG. The Matthew Effect and widely prescribed pharmaceuticals lacking  
49  
50 528 environmental monitoring: case study of an exposure-assessment vulnerability. *Sci*  
51  
52 529 *Total Environ* 2014;466-467:315-325.
- 53  
54  
55 530 26. Straub JO. Reduction in the environmental exposure of pharmaceuticals through  
56  
57 531 diagnostics, Personalised Healthcare and other approaches. A mini review and  
58  
59 532 discussion paper. *Sustainable Chemistry and Pharmacy* 2016;3:1-7.
- 60



- 1  
2  
3 533 27. Blair BD. Potential Upstream Strategies for the Mitigation of Pharmaceuticals in  
4 the Aquatic Environment: a Brief Review. *Curr Environ Health Rep* 2016;3:153-160.  
5  
6  
7  
8 535 28. Daughton CG, Ruhoy IS. Green pharmacy and pharmEcovigilance: prescribing and  
9 the planet. *Expert Rev. Clin Pharmacol* 2011;4:211-32.  
10  
11  
12  
13 537 29. Daughton CG, Ruhoy IS. Lower-dose prescribing: minimizing "side effects" of  
14 pharmaceuticals on society and the environment. *Sci Total Environ* 2013;443:324-37.  
15  
16  
17  
18 539 30. Maxwell SR. Rational prescribing: the principles of drug selection. *Clin Med (Lond)*  
19 2016;16:459-64.  
20  
21  
22  
23 541 31. Ding B. Pharma industry 4.0: Literature review and research opportunities in  
24 sustainable pharmaceutical supply chains. *Process Safety and Environmental*  
25 *Protection* 2018;119:115-30.  
26  
27  
28  
29 544 32. Singer AC, Xu Q, Keller VDJ. Translating antibiotic prescribing into antibiotic  
30 resistance in the environment: A hazard characterisation case study. *PLoS*  
31 *One* 2019;14:e0221568.  
32  
33  
34  
35  
36 547 33. International Pharmaceutical Federation. Green pharmacy practice: taking  
37 responsibility for the environmental impact of medicines. The Hague, Netherlands:  
38 International Pharmaceutical Federation (FIP).2015.  
39  
40  
41  
42  
43 550 34. Balch J, Schoen JH, Patel PK. Should Physicians Consider the Environmental  
44 Effects of Prescribing Antibiotics? *AMA J Ethics* 2017;19:957-65.  
45  
46  
47  
48 552 35. Tian Y, Li C, Wang J, *et al.* Modified task-based learning program promotes  
49 problem-solving capacity among Chinese medical postgraduates: a mixed  
50 quantitative survey. *BMC Med Educ* 2017;17:153.  
51  
52  
53  
54  
55 555 36. Prakash B, Nadig P, Nayak A. Rational Prescription for a Dermatologist. *Indian J*  
56 *Dermatol* 2016;61:32-8.  
57  
58  
59  
60

- 1  
2  
3 557 37. Deblonde T, Hartemann P.Environmental impact of medical prescriptions: assessing  
4  
5 558 the risks and hazards of persistence, bioaccumulation and toxicity of  
6  
7 559 pharmaceuticals. *Public Health* 2013;127:312-7.  
8  
9  
10 560 38. The Ministry of Health of the People's Republic of China.The 2018 China health  
11  
12 561 statistical yearbook (in Chinese). Beijing: Peking Union Medical College Press. 2018.  
13  
14  
15 562  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
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For peer review only

563 **Table 1** Demographic information and knowledge score of Chinese physicians  
 564 participating in the study. (*n*=262)

Participant attribute	Number	% of respondents
<b>Gender</b>		
Male	124	47
Female	139	53
<b>Age</b>		
20-40 years	125	48
> 40 years	137	52
<b>Postgraduate training</b>		
Yes	170	65
No	92	35
<b>Job category</b>		
Internal medicine	102	39
Surgery	98	37
Others	62	24
<b>Years of experience</b>		
≤10	92	35
11-20	96	37
>20	74	28

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567 **Table 2** Chinese physicians' perceptions toward API pollution in environment and EPV.  
 568 (*n*=262)

Survey Question/Statement	Responses, number ( %)				
	Strongly agree	Agree	Undecided	Disagree	Strongly Disagree
Q1: APIs used in health-care practices could finally enter into the environment.	96(37)	113(43)	45(17)	8(3)	0(0)
Q2: API residues in environment could cause adverse effects on ecosystem, wildlife species, even human beings.	126(48)	108(41)	26(10)	2(1)	0(0)
Q3: It is necessary to minimize the entrance of APIs into the environment.	104(40)	125(48)	31(12)	2(1)	0(0)
Q4: The control of API pollution is none of my business, because it should be the responsibility of environmental experts and regulators.	5(2)	6(2)	73(28)	80(31)	98(37)
Q5: API pollution could be ultimately traced back to the use of medications in health-care practices.	113(43)	96(37)	50(19)	3(1)	0(0)
Q6: If there is an intervention emphasizing the control of upstream routes of API entry to the environment, I would endorse it, and be very pleased to cooperate in its implementation, if my participation is needed.	68(26)	99(38)	94(36)	1(0)	0(0)
Q7: According to the description on the basic concept of EPV provided on the first page of this questionnaire, I think EPV is an effective tool to control the entrance of APIs into the environment.	83(32)	74(28)	98(37)	5(2)	2(1)

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571 **Table 3** Assessment of Chinese physicians' perceptions and attitudes toward EDSP.572 (*n*=262)

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Survey Question/Statement	Response	Number	% of respondents
Q1: At present, the aspects regarding medicines affecting my prescription decision include: *	● Efficacy	262	100
	● Safety	258	98
	● Cost and economy	246	94
	● Convenience	188	72
	● Pharmacokinetics	57	22
	● Marketing and promoting	139	53
	● Environmental impacts	0	0
Q2: As prescribers, physicians bear a responsibility for reducing API releases to environment.	Strongly agree	86	33
	Agree	83	32
	Undecided	81	31
	Disagree	12	5
	Strongly disagree	0	0
Q3: Previous to this survey, I have heard of EDSP.	Yes	260	99
	No	2	1
Q4: According to the description on the basic concept of EDSP provided on the first page of this questionnaire, I think EDSP is an effective tool to control the entrance of APIs into	Strongly agree	54	21
	Agree	96	37
	Undecided	101	39
	Disagree	9	3

the environment.	Strongly disagree	2	1
Q5: I think the benefits of low-dose prescribing include:*	<ul style="list-style-type: none"> <li>● Reducing the environmental loading of API residues from patients' excretions.</li> </ul>	257	98
	<ul style="list-style-type: none"> <li>● Eliminating the subsequent need and cost for disposal of pharmaceutical leftovers</li> </ul>	240	92
	<ul style="list-style-type: none"> <li>● Reducing health-care expenditures for patients.</li> </ul>	104	40
	<ul style="list-style-type: none"> <li>● Improving therapeutic efficacy <i>via</i> minimizing off-target side-effects related to dosage, and thus enhancing pharmaceutical compliance.</li> </ul>	75	29
	<ul style="list-style-type: none"> <li>● Protecting public health by unintended poisonings by drugs (especially infants, toddlers, and children) resulted from inappropriate storage or disposal.</li> </ul>	238	91
	<ul style="list-style-type: none"> <li>● Reducing drug diversion and the profound problems with attendant abuse of certain drugs and misuse of others.</li> </ul>	215	82
	<ul style="list-style-type: none"> <li>● Improving public trust—by reducing hidden and unwelcomed exposure of humans to trace levels of numerous APIs via potable water and contaminated foods.</li> </ul>	242	92

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2				
3				
4		● Improving patient/ physician	89	34
5		communication.		
6				
7	Q6: My concerns regarding the	● It can not achieve ideal		
8	low-dose prescribing are:*	therapeutic efficacy, and	262	100
9		might delay treatment.		
10				
11		● The lowest effective dose		
12		with environmental safety is	259	99
13		not certain and available.		
14				
15		● It is a new prescribing		
16		concept, therefore, a long		
17		time will be taken to	207	79
18		popularize it in clinical		
19		practice.		
20				
21		● It will change my prescribing		
22		habits, thus is too	55	21
23		troublesome.		
24				
25				
26				
27				
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30				
31	Q7: It is necessary to emphasize on the	Strongly agree	79	30
32	metabolism and excretion of drugs			
33	rather than the initially ingested	Agree	123	45
34	dose by the patient, because the			
35	emission of APIs into the	Undecided	48	18
36	environment <i>via</i> sewers is dictated			
37	by the excretion profile and	Disagree	11	4
38	pharmacokinetics of the different			
39	types of pharmaceutical	Strongly disagree	1	0
40	compounds.			
41				
42				
43	Q8: My concerns regarding the	● It can not achieve ideal		
44	prescribing of drugs possessing	therapeutic efficacy, and	35	13
45	environment-friendly excretion	might delay treatment.		
46	profiles are:*			
47		● Under the EDSP design,		
48		drug evaluation based on		
49		the excretion profile and	219	84
50		pharmacokinetics is too		
51		complicated and		
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60				

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	professional.		
	<ul style="list-style-type: none"> <li>● There is no available accurate data on the excretion profile and pharmacokinetics of drugs.</li> </ul>	190	73
	<ul style="list-style-type: none"> <li>● It is a new prescribing concept, therefore, a long time will be taken to popularize it in clinical practice.</li> </ul>	211	81
	<ul style="list-style-type: none"> <li>● It will change my prescribing habits, thus is too troublesome.</li> </ul>	62	24
Q9: My self-satisfaction with knowledge on EDSP.	Agree	0	0
	Disagree	262	100
Q10: My confidence toward EDSP.	Agree	0	0
	Disagree	262	100
Q11: For now, the EDSP behavior that I want to firstly choose is:	<ul style="list-style-type: none"> <li>● None. I will take a wait-and-see approach.</li> </ul>	134	51
	<ul style="list-style-type: none"> <li>● I will promote rational prescribing at precise doses, avoid over-prescribing and mis-prescribing.</li> </ul>	121	46
	<ul style="list-style-type: none"> <li>● I will implement the low-dose prescribing.</li> </ul>	3	1
	<ul style="list-style-type: none"> <li>● I will prescribe drugs possessing environment-friendly excretion profiles as much as possible.</li> </ul>	4	2

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1				
2				
3				
4	Q12: I think the most major perceived	● Poor awareness of EDSP	101	39
5	barrier to the effective	and EPV.		
6	implementation of EDSP under the	● Lack of an administrative		
7	perspective of EPV in China is:	framework for EDSP under	50	19
8		the perspective of EPV.		
9		● Lack of available data		
10		related to EDSP under the	96	37
11		perspective of EPV.		
12		● It conflicts with		
13		long-accepted prescribing	15	6
14		guidelines.		
15				
16				
17				
18				
19				
20				
21				
22				
23	Q13: I am very pleased to participate in	Strongly agree	85	32
24	EDSP activities in my future	Agree	121	46
25	practice if it is successfully	Undecided	53	20
26	translated into clinical treatment.	Disagree	3	1
27		Strongly disagree	0	0
28				
29				
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574 \* Multiple responses were permitted, percentages do not add to 100%.

# Reporting checklist for quality improvement study.

Based on the SQUIRE guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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	Reporting Item	Page Number
<b>Title</b>		
	<a href="#">#1</a> Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patientcenteredness, timeliness, cost, efficiency, and equity of healthcare)	Page 1
<b>Abstract</b>		
	<a href="#">#0</a> Provide adequate information to aid in searching and indexing	Page 1-2
	<a href="#">2a</a>	
	<a href="#">#0</a> Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	Page 1-2
	<a href="#">2b</a>	

## 1 Introduction

2  
3  
4 Problem description [#3](#) Nature and significance of the local problem Page 3-5  
5  
6  
7

8  
9 Available knowledge [#4](#) Summary of what is currently known about the problem, Page 3-5  
10 including relevant previous studies  
11  
12

13 Rationale [#5](#) Informal or formal frameworks, models, concepts, and / or Page 5  
14 theories used to explain the problem, any reasons or  
15 assumptions that were used to develop the intervention(s),  
16 and reasons why the intervention(s) was expected to work  
17  
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19  
20

21 Specific aims [#6](#) Purpose of the project and of this report Page 5  
22  
23

## 24 Methods

25  
26  
27 Context [#7](#) Contextual elements considered important at the outset of Page 5-7  
28 introducing the intervention(s)  
29  
30

31  
32 Intervention(s) [#0](#) Description of the intervention(s) in sufficient detail that Page 5-7  
33 [8a](#) others could reproduce it  
34  
35

36  
37 Intervention(s) [#0](#) Specifics of the team involved in the work Page 6-7  
38 [8b](#)  
39  
40

41 Study of the [#0](#) Approach chosen for assessing the impact of the Page 6  
42 Intervention(s) [9a](#) intervention(s)  
43  
44  
45

46 Study of the [#0](#) Approach used to establish whether the observed Page 7  
47 Intervention(s) [9b](#) outcomes were due to the intervention(s)  
48  
49  
50

51 Measures [#1](#) Measures chosen for studying processes and outcomes of Page 6-7  
52 [0a](#) the intervention(s), including rationale for choosing them,  
53 their operational definitions, and their validity and reliability  
54  
55  
56

57 Measures [#1](#) Description of the approach to the ongoing assessment of Page 6-7  
58 contextual elements that contributed to the success,  
59

1		<a href="#">0b</a>	failure, efficiency, and cost	
2				
3	Measures	<a href="#">#1</a>	Methods employed for assessing completeness and	Page 6-7
4		<a href="#">0c</a>	accuracy of data	
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8	Analysis	<a href="#">#1</a>	Qualitative and quantitative methods used to draw	Page 7
9		<a href="#">1a</a>	inferences from the data	
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11				
12	Analysis	<a href="#">#1</a>	Methods for understanding variation within the data,	Page 6-7
13		<a href="#">1b</a>	including the effects of time as a variable	
14				
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16				
17	Ethical considerations	<a href="#">#1</a>	Ethical aspects of implementing and studying the	Page 5
18		<a href="#">2</a>	intervention(s) and how they were addressed, including,	
19			but not limited to, formal ethics review and potential	
20			conflict(s) of interest	
21				
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25	<b>Results</b>			
26				
27				
28		<a href="#">#1</a>	Initial steps of the intervention(s) and their evolution over	Page 7
29		<a href="#">3a</a>	time (e.g., time-line diagram, flow chart, or table), including	
30			modifications made to the intervention during the project	
31				
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33				
34		<a href="#">#1</a>	Details of the process measures and outcome	Page 7
35		<a href="#">3b</a>		
36				
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39		<a href="#">#1</a>	Contextual elements that interacted with the intervention(s)	Page 7
40		<a href="#">3c</a>		
41				
42				
43		<a href="#">#1</a>	Observed associations between outcomes, interventions,	Page 8-11
44		<a href="#">3d</a>	and relevant contextual elements	
45				
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48		<a href="#">#1</a>	Unintended consequences such as unexpected benefits,	Page 8-11
49		<a href="#">3e</a>	problems, failures, or costs associated with the	
50			intervention(s).	
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54		<a href="#">#1</a>	Details about missing data	Page 7
55		<a href="#">3f</a>		
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## Discussion

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3			
4	Summary	<a href="#">#1</a>	Key findings, including relevance to the rationale and
5		<a href="#">4a</a>	specific aims
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9	Summary	<a href="#">#1</a>	Particular strengths of the project
10		<a href="#">4b</a>	
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13	Interpretation	<a href="#">#1</a>	Nature of the association between the intervention(s) and
14		<a href="#">5a</a>	the outcomes
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18	Interpretation	<a href="#">#1</a>	Comparison of results with findings from other publications
19		<a href="#">5b</a>	
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23	Interpretation	<a href="#">#1</a>	Impact of the project on people and systems
24		<a href="#">5c</a>	
25			
26			
27	Interpretation	<a href="#">#1</a>	Reasons for any differences between observed and
28		<a href="#">5d</a>	anticipated outcomes, including the influence of context
29			
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31			
32	Interpretation	<a href="#">#1</a>	Costs and strategic trade-offs, including opportunity costs
33		<a href="#">5e</a>	
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37	Limitations	<a href="#">#1</a>	Limits to the generalizability of the work
38		<a href="#">6a</a>	
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41	Limitations	<a href="#">#1</a>	Factors that might have limited internal validity such as
42		<a href="#">6b</a>	confounding, bias, or imprecision in the design, methods,
43			measurement, or analysis
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47	Limitations	<a href="#">#1</a>	Efforts made to minimize and adjust for limitations
48		<a href="#">6c</a>	
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52	Conclusion	<a href="#">#1</a>	Usefulness of the work
53		<a href="#">7a</a>	
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57	Conclusion	<a href="#">#1</a>	Sustainability
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7b

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3 Conclusion #1 Potential for spread to other contexts Page 15-16

7c

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8 Conclusion #1 Implications for practice and for further study in the field Page 15-16

7d

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11  
12 Conclusion #1 Suggested next steps Page 15-16

7e

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17 **Other**  
18 **information**

19  
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21  
22 Funding #1 Sources of funding that supported this work. Role, if any, of Page 17  
23 8 the funding organization in the design, implementation,  
24 interpretation, and reporting  
25  
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28 None The SQUIRE 2.0 checklist is distributed under the terms of the Creative Commons Attribution  
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# BMJ Open

## Chinese physicians' attitudes toward eco-directed sustainable prescribing from the perspective of ecopharmacovigilance: a cross-sectional study

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1 Chinese physicians' attitudes toward eco-directed  
2 sustainable prescribing from the perspective of  
3 ecopharmacovigilance: a cross-sectional study

4  
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16  
17 **ABSTRACT**

18 **Introduction** Eco-directed sustainable prescribing (EDSP) is an effective upstream way  
19 to reduce the environmental footprints of active pharmaceutical ingredients (APIs), a kind  
20 of emerging contaminants, from the patients' excretion. EDSP is one of key steps in the  
21 program of ecopharmacovigilance (EPV), a drug administration route on API pollution.

22 **Objective** To assess the attitudes of physicians prescribing medicines regarding EDSP

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3 23 from the perspective of EPV.  
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6 24 **Design** A cross-sectional study conducted from March to June, 2019.  
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8 25 **Setting** 5 government general hospitals in Hubei Province, China.  
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11 26 **Participants** 405 physicians were randomly selected, and 262 valid questionnaires were  
12  
13 27 obtained.  
14

15  
16 28 **Outcome measures** A self-developed questionnaire, which inquired about participant  
17  
18 29 characteristics, perceptions and attitudes toward API pollution, EPV and EDSP from an  
19  
20 30 EPV perspective, was e-mailed to collect data from physicians.  
21

22  
23 31 **Results** Most physicians agreed the existence of APIs in environment, worried about the  
24  
25 32 potential environmental and ecological risks of API residues, supported the effectiveness  
26  
27 33 and necessity of EDSP under an EPV perspective in decreasing environmental exposure  
28  
29 34 of excreted APIs, and showed their willingness to participate in the EDSP practices.  
30  
31 35 Nevertheless, no respondent identified the environmental impacts as the aspects  
32  
33 36 regarding medicines affecting his(her) prescription decision, none was satisfied with  
34  
35 37 knowledge on EDSP and showed confidence toward EDSP. The most important barrier to  
36  
37 38 the effective implementation of EDSP was identified as "*poor awareness of EDSP and*  
38  
39 39 *EPV*". Most responding physicians (97%) reported that they held the wait-and-see or  
40  
41 40 conservative attitudes towards EDSP practice. The biggest concerns in *low-dose*  
42  
43 41 *prescribing and prescribing of drugs possessing environment-friendly excretion profiles,*  
44  
45 42 two EDSP approaches, were the possible negative impact on therapeutic outcomes, and  
46  
47 43 too complicated and professional drug evaluation process, respectively.  
48

49 44 **Conclusions** Chinese physicians had positive attitudes towards EDSP from the  
50  
51 45 perspective of EPV. However, their environmental consciousness during prescribing and  
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53 46 the related education were insufficient.  
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## Strengths and limitations of this study

- To the best of our knowledge, this is the first study that explored the physicians' perceptions and attitudes toward eco-directed sustainable prescribing (EDSP) from the perspective of ecopharmacovigilance (EPV), a sustainable prescription approach to minimize the environmental loads and risks of excreted active pharmaceutical ingredient (API) residues at their sources.
- Based on the survey results, we proposed some recommendations for further implementing EDSP from the perspective of EPV in practice.
- The main limitation of this study is the sampling bias.

## 58 INTRODUCTION

59 The occurrence of active pharmaceutical ingredients (APIs), a kind of emerging  
60 contaminants (ECs) without standard regulations, in the environment worldwide has  
61 become an issue of special importance.<sup>1-5</sup> As a drug administration route on environment  
62 pollution caused by APIs, ecopharmacovigilance (EPV) is an emerging science of  
63 detection, evaluation, understanding and prevention the adverse effects of APIs in the  
64 environment.<sup>6-14</sup> In recent years, an approach termed eco-directed sustainable prescribing  
65 (EDSP),<sup>15</sup> which was proposed to prevent the adverse effects of APIs in the environment  
66 resulting from medical prescriptions, has been well-accepted as an indispensable part  
67 during EPV implementation.<sup>8,12,13</sup> However, EDSP might conflict with long-accepted  
68 clinical prescribing guidelines and tenet. It is necessary to explore the attitudes of  
69 prescribers toward EDSP.<sup>15</sup>

70 As a critical part of modern life, pharmaceutical drugs are abundantly used in  
71 health-care practices around the world.<sup>5</sup> The environmental discharge of APIs in a  
72 continuous and unsupervised way as well as their inadequate removal during wastewater  
73 treatment processes have led to their detection in the various environmental matrices at  
74 levels of concern.<sup>2-5</sup> Considering their potent biological activities even at very low  
75 concentrations, API residues have been recognized to pose potential risks and hazards to  
76 the natural environment, ecology and human health due to long-term exposures.<sup>6,16-18</sup>  
77 Therefore, it is urgent to address this issue, aiming to minimize the environmental loads  
78 and risks of API residues. Based the fact that API pollution could be ultimately traced back  
79 to the use of medications in health-care practices, EPV focuses on the clinical application  
80 of active pharmaceutical management strategies to decrease the API emission at the  
81 sources and minimize the environmental footprint of the health-care industry.<sup>9,13</sup> The  
82 sources of APIs in environment include excretion from drug-consuming patients and  
83 animals, inappropriate deposition of expired or unwanted pharmaceutical products,  
84 manufacturing plant wastes, hospital wastes, *etc.*<sup>19-23</sup> Thereinto, patients' excretion in

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2  
3 85 forms of parent APIs or active metabolites has been well-accepted to constitute the major  
4  
5 86 contribution to most API pollutants in the environment.<sup>15,24-26</sup>  
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8 87 Since normal physiological excretion of APIs in drug-consuming patients cannot be  
9  
10 88 prevented, the optimized administration of pharmaceuticals ensuring satisfactory but not  
11  
12 89 too high pharmacologically active concentrations in patients might be a key protective  
13  
14 90 measure against excessive API entry to the environment from excretion.<sup>15,27-29</sup> Driven by  
15  
16 91 this idea, EDSP was recommended by Daughton<sup>15</sup> to reduce the environmental load of  
17  
18 92 excreted APIs. As prescribers are commonly confronted with more than one choice of  
19  
20 93 drug treatment,<sup>30</sup> EDSP provides a new and more established decision support system to  
21  
22 94 include environmental considerations in drug prescription. The term of EDSP is used to  
23  
24 95 describe the combination of two prescription optimization methods – *low-dose prescribing*  
25  
26 96 and *prescribing of drugs possessing environment-friendly excretion profiles*. The dose of  
27  
28 97 drugs prescribed plays a paramount role on the quantities of APIs entering into the  
29  
30 98 environment.<sup>31</sup> Certainly, any reduction in API prescribing would lead to a proportional  
31  
32 99 reduction in excreted APIs released into wastewater.<sup>15,27,32</sup> Moreover, lower doses also  
33  
34 100 hold the potential to eliminate the subsequent need for disposal of leftovers, relieve  
35  
36 101 adverse events associated with drug overdose, improved patient/ physician  
37  
38 102 communication, avoid the accidental exposures as well as reduce health-care costs.<sup>15,27</sup>  
39  
40 103 On the other hand, EDSP places an additional emphasis on the metabolism and excretion  
41  
42 104 profiles of drugs rather than only the dose initially used by the patient. Within a same  
43  
44 105 therapeutic class, and with similar therapeutic efficacies, more extensively metabolizable  
45  
46 106 medicines which have more environment-friendly excretion profiles resulting in less  
47  
48 107 excretion of bioactive API residues would produce more negligible environmental  
49  
50 108 footprints, thus could be favored for EDSP.<sup>15,25</sup> EDSP has been endorsed by International  
51  
52 109 Pharmaceutical Federation<sup>33</sup> as a means to promoting the sustainable application of  
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54 110 drugs.  
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57 111 However, the translation of EDSP concept into clinical practice will mean to change  
58  
59 112 the conventional prescribing behavior of physicians, which would certainly be a major  
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3 113 challenge.<sup>15,25,34</sup> The opinions toward EDSP held by prescribers play a pivotal role in  
4  
5 114 determining its acceptability and future application. China is a populous country where  
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7 115 prescribing practices of physicians may have a significant impact on the global  
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9 116 environment. In order to explore the attitudes of prescribers toward EDSP and their  
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11 117 willingness of participation, the present study was carried out among Chinese physicians  
12  
13 118 prescribing medications in Hubei, a province locating in Central China, to assess the  
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15 119 physicians' attitudes toward EDSP from the perspective of EPV and obtained some  
16  
17 120 interesting findings. This is an innovative subject and may contribute to policy  
18  
19 121 development.

## 122 **METHODS**

### 123 **Study design**

124 A descriptive, cross-sectional survey involving authorized physicians presently working at  
125 government general hospitals in Hubei province, China, who were willing to participate in  
126 the study, was undertaken to assess their perceptions about API pollution in environment  
127 and EPV, in particular, their attitudes toward EDSP using a self-developed questionnaire.  
128 The study was granted approval from the Ethics Committee of Wuhan University of  
129 Science and Technology, and was conducted for over a period of 4 months from March to  
130 June, 2019.

### 131 **Study population**

132 The initial list of about 809 physicians distributed among 5 hospitals was used as the  
133 target sampling frame. The sampling of the hospitals was a convenient one, determined  
134 by the proximity of the hospital administrators to the authors. From this list, 405 physicians  
135 were randomly selected for inclusion in this survey using an 2:1 proportion.

136 The sample size was determined by considering the availability of subjects and the  
137 feasibility of enrolling physicians. A review of existing literature <sup>35-38</sup> indicated a sample  
138 size of 200-400 physicians would be adequate to ensure data analysis and  
139 generalisability of responses.

## 140 **Questionnaire development**

141 A self-developed questionnaire was used in this study, since there is no standardized  
142 material for testing attitudes about EDSP. The initial draft of survey questionnaire was  
143 developed using information from the relevant published studies regarding to API pollution  
144 in environment,<sup>1-5,1,16-26</sup> EPV<sup>6-14</sup> and EDSP<sup>15,25,27-29</sup> after performing a thorough literature  
145 review. The initial questions were devised, developed and refined for clarity by all authors  
146 during several in-person group discussions.

147 The respondents were informed about the basic concepts of EPV and EDSP on the  
148 first page of the questionnaire. A total of 25 structured questions divided into three  
149 sections were included in the survey questionnaire, which required about 10-15 minutes  
150 to complete. The first section consisted of 5 questions about respondent physicians'  
151 socio-demographic characteristics, including gender, age, education background,  
152 specialty, and years of experience. The second section included 7 question items  
153 designed to capture the perceptions toward API pollution in environment and EPV. A  
154 5-point Likert-scale format was used in the data collection in this section (1: strongly  
155 disagree, 2: disagree, 3: neutral, 4: agree, and 5: strongly agree). The third section of the  
156 survey questionnaire included 13 items designed to assess the physicians' perceptions  
157 and attitudes toward EDSP from the perspective of EPV.

158 Two specialists in the investigated field were asked to evaluate the clarity, content  
159 validity, relevance, and conciseness of the items in the questionnaire. For validation of the  
160 questionnaire, pretesting of the questionnaire was done on a convenient sample of 20  
161 physicians, who were not included in the final survey, to examine the validity and  
162 acceptability of the questionnaire. After discussion and minor modification, the final survey  
163 questionnaire was approved with overall and separate Cronbach's alpha values, and  
164 Kaiser-Meyer-Olkin (KMO) measures >0.700. The final questionnaire was developed in  
165 English as the original language, then translated into Chinese and back into English.

## 166 **Data collection**

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3 167 The developed questionnaire was mailed to collect data from physicians *via* email  
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5 168 addresses provided by the hospital administrators. A confirmation email together with an  
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8 169 explanatory letter about the survey's purpose and objectives were firstly sent to the  
9  
10 170 respondents. After returning their confirmation letters, the responding physicians received  
11  
12 171 copies of the electronic questionnaire *via* email, and were requested to complete the  
13  
14 172 questionnaire then return it within next 3 days to the researchers. Two weeks after  
15  
16 173 sending the questionnaire, a follow-up reminder postcard was sent to the non-responder  
17  
18 174 to increase the response rate. Each respondent participated in the survey voluntarily. All  
19  
20 175 questionnaires were check by J.W. and S.L to ensure data quality. Those who were not  
21  
22 176 willing to participate in or did not return completed questionnaires within the stipulated  
23  
24 177 time period were excluded from this study.

### 178 **Statistical analysis**

179 The collected data were entered into SPSS20.0 for analysis. Results were presented  
180 as numbers (percentages) for categorical variables, and mean (standard deviation (S.D.))  
181 for quantitative variables. Reliability and validity of the questionnaire were assessed using  
182 Cronbach's alpha coefficient and Bartlett's test of sphericity/KMO measures, respectively.  
183 Any relationship between the categorical data was determined using Chi-square test or  
184 Fisher's exact test. Independent t test was applied to compare the mean perception  
185 scores of the two groups. The differences between pair-wise groups were detected using  
186 the one-way ANOVA with post hoc Tukey's HSD analysis for multiple comparisons.  
187 Differences were statistically significant when the *p* value was less than 0.05.

### 188 **Patient and public involvement**

189 Patients and the public were not involved in the design and conception of this study.

## 190 **RESULTS**

### 191 **Respondents' Characteristics**

192 By the end of the study period, 284 (71%) of 405 randomly selected Chinese physicians



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3 193 had agreed to participate and responded to the survey, yielding 262 completed  
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5 194 questionnaires available for analysis (overall effective response rate: 65%). The  
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7 195 respondents' age ranged between 25 and 63 years with a mean of 43.6 (S.D.:12.3) years.  
8  
9 196 Table 1 presented the demographic information of respondents. The gender, age,  
10  
11 197 specialty, or years of experience distribution of physician respondents was approximately  
12  
13 198 equal. Majority of respondents (65%) held postgraduate qualifications, which was in  
14  
15 199 accordance with the popularization and advances of medical postgraduate education in  
16  
17 200 China.<sup>39</sup>

### 201 **Reliability and validity of the questionnaire**

202 The overall Cronbach's alpha and KMO values were obtained as 0.788 and 0.716,  
203 respectively. For the reliability of separate items of *API pollution in environment*, *EPV* and  
204 *EDSP*, the Cronbach's alpha values were 0.801, 0.792 and 0.865. The result for Bartlett's  
205 test of sphericity was  $\chi^2_{(190)}=938.8$  and was statistically significant ( $p < 0.001$ ), suggesting  
206 a factorable intercorrelation matrix. For the construct validity of separate items of *API*  
207 *pollution in environment*, *EPV* and *EDSP*, KMO measures were 0.741, 0.789 and 0.712 ,  
208 respectively.

### 209 **Perceptions toward API pollution in environment and EPV**

210 The perceptions toward API pollution and EPV were collected from 262 physicians using  
211 5-point Likert scales. Data shown in Table 2 revealed that the responding physicians'  
212 overall perceptions towards API pollution in environment and EPV was positive. Most  
213 respondents (80%, 89%, 88% and 80%, respectively) agreed or strongly agreed the entry  
214 of API residues into the environment (Q1), their environmental and ecological adverse  
215 effects (Q2), the necessity to minimize the entrance of APIs into the environment (Q3), as  
216 well as the importance of the administration of medication use in health-care practices for  
217 the API pollution control (Q5). As for the reverse-score item indicating the control of API  
218 pollution is not physicians' responsibility (Q4), only 4% respondents agreed, suggesting  
219 most physicians realized their own responsibility in the control of API pollution. Then the  
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3 220 physicians were asked about whether they agree with EPV, an upstream intervention for  
4  
5 221 controlling API entry to the environment (Q6-7). It was encouraging to find that 60%  
6  
7 222 believed that EPV is an effective tool to control API entry to the environment, and 64%  
8  
9 223 claimed that they would endorse and be very pleased to participate in. However, there  
10  
11 224 were a considerable portion (36-37%) of respondents felt undecided, suggesting their  
12  
13 225 uncertainty regarding EPV. The results of the univariate analysis using independent t or  
14  
15 226 one-way ANOVA test of the above variables in perceptions with regards to the  
16  
17 227 respondents' gender, age, education background, specialty, and years of experience  
18  
19 228 groups were not significant ( $p>0.05$ ).

### 229 **Perceptions and attitudes toward EDSP from the perspective of EPV**

230 Possible factors affecting the physicians' decision process for drug prescription

231 As shown in Table 3, an overwhelming majority (94-100%) of physicians supported that  
232 efficacy, safety or cost of medicines affected their prescription decisions (Q1), which was  
233 in line with the well-accepted traditional rational prescription principle, that is, that the  
234 selection of drugs should be based on efficacy, safety and cost considerations.<sup>30,40</sup>  
235 However, none was environmentally conscious in their prescribing. As the key basis for  
236 EDSP<sup>15</sup>, the evaluation of pharmacokinetic property was incorporated into the prescribing  
237 process only by 22% respondents. Nevertheless, it was encouraging that 65% physicians  
238 were aware of their responsibilities for reducing API releases to environment, despite the  
239 fact that 31% were undecided (Q2). Almost all the physician respondents had not previous  
240 heard of EDSP (Q3), however, the effectiveness of EDSP in the control of the entrance of  
241 APIs into the environment was agreed or strongly agreed by about half (53%)  
242 respondents (Q4).

243 Physicians' attitudes toward *low-dose prescribing and prescribing based on drugs'*  
244 *excretion profiles*, two EDSP approaches

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3 245 *Low-dose prescribing* is one of two different 'front-of-pipe' approaches under the EDSP  
4 design.<sup>15,25,28,29</sup> According to its theoretical analysis,<sup>24,25,27</sup> a total of 8 possible benefits of  
5 246 *low-dose prescribing* had been summarized (Q5). Among them, 3 benefits related to the  
6 247 environmental issues (i.e. reducing the API environmental loading from patients'  
7 248 excretions, reducing pharmaceutical leftovers, and improving public trust) were supported  
8 249 by most physicians (92-98%). However, the improvement on therapeutic efficacy was  
9 250 least recognized as the positive outcome of *low-dose prescribing*. This finding was in  
10 251 accordance with the result that all the respondents worried that the *low-dose prescribing*  
11 252 could not achieve ideal therapeutic efficacy, and might delay treatment (Q6).  
12 253

13 254 On the other hand, the importance of *prescribing based on drugs' excretion profiles*,  
14 255 the other element of EDSP, was agreed or strongly agreed by a solid majority (75%) of  
15 256 respondents (Q7). However, being different from findings from the same question posed  
16 257 for *low-dose prescribing* (Q6), few (13%) respondents worried about the therapeutic  
17 258 efficacy of *prescribing on drugs' excretion profiles* (Q8). Most (84%) physicians placed  
18 259 misgivings about the complexity and professionalization of drug evaluation and EDSP  
19 260 design based on the excretion profile and pharmacokinetics (Q8).  
20 261

21 262 In addition, the availability of the related data as well as the long time period that will  
22 263 be taken to popularize in clinical practice were considered by most respondents (73-99%)  
23 264 as physicians' concerns regarding these two ways to achieve EDSP (Q6 and Q8).  
24 265

#### 25 264 Physicians' attitudes toward EDSP

26 265 All the responding physicians were not satisfied with knowledge on EDSP (Q9), as well as  
27 266 did not feel confident toward EDSP (Q10). Accordingly, about half (51%) respondents  
28 267 would adopt a wait-and-see approach for EDSP. Furthermore, 46% reported that they  
29 268 would follow conservative EDSP strategies, such as promoting rational prescribing at  
30 269 precise doses, avoiding overprescribing and mis-prescribing (Q11). The most important  
31 270 perceived barrier to the effective implementation of EDSP under the perspective of EPV in  
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1  
2  
3 271 China was “*poor awareness of EDSP and EPV*”, which was supported by 39%  
4  
5 272 respondents. The lack of available data related to EDSP under the perspective of EPV  
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7 273 was ranked as the second important barrier, which was supported by 37% respondents  
8  
9 274 (Q12). A majority of (78%) respondents claimed that, if EDSP is successfully translated  
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11 275 into clinical treatment, they would be very pleased to participate in the related activities in  
12  
13 276 their future practice(Q13).

#### 17 18 277 Group comparisons

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21 278 When assessing for differences in demographic factors (gender, age, education  
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23 279 background, specialty, and years of experience), we only found the responses from two  
24  
25 280 questions (Q1 and Q11) on perceptions and attitudes toward EDSP could be significantly  
26  
27 281 influenced by specialty. Compared to surgeons and physicians in other specialties, the  
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29 282 internal medicine physicians appeared to offer significantly more support that the  
30  
31 283 pharmacokinetics of medicines currently affected their prescription decisions (Q1), and  
32  
33 284 want to firstly choose the EDSP behaviors rather than take a wait-and-see approach (Q11)  
34  
35 285 ( $p<0.01$ ). In particular, all 7 respondents who wanted to implement the *low-dose*  
36  
37 286 *prescribing* or *prescribe drugs possessing environment-friendly excretion profiles* as much  
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39 287 as possible were physicians working in the internal medicine specialties.

#### 41 42 288 **DISCUSSION**

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45 289 It has been more than five years since the concept of EDSP was first proposed.<sup>15</sup> The  
46  
47 290 indispensable role of EDSP in the practice of EPV, a promising source control strategy for  
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49 291 API pollution from the perspective of drug administration, has already been well  
50  
51 292 accepted in theory.<sup>8,12,13</sup> But unfortunately, this theoretically efficacious solution for the  
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53 293 environmental issues caused by excreted APIs is so far still on the conceptual level, and  
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55 294 its conceptualisation has been rarely applied to real cases, which also restricts the  
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57 295 empirical domain of EPV. In order to assure and promote the practical application of  
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59 296 EDSP and EPV, it is necessary to firstly explore the acceptance of these new concepts by  
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3 297 the involved stakeholders, which is prerequisite to subsequent behavioral change and  
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5 298 efficient participation.  
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8 299 In China, the main prescribers were physicians within health-care systems. Of course,  
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10 300 physicians should be environmentally conscious in their prescribing, and prescribe those  
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12 301 drugs that might have minimal environmental impact.<sup>41</sup> Hubei province is one of the  
13  
14 302 national leaders in health-care industry and pharmaceutical consumption in China.<sup>14</sup> The  
15  
16 303 2018 China Health Statistical Yearbook reported that, in China, there were 64.4%  
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18 304 health workers were working in hospitals in 2017, with 81.0% of them in government  
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20 305 general hospitals.<sup>42</sup> Therefore, the physician samples included in this study were  
21  
22 306 randomly selected from 5 government general hospitals in Hubei province. Demographic  
23  
24 307 data based on gender, age, education background, specialty, and years of experience  
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26 308 indicated the surveyed physician samples were generally representative of Chinese  
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28 309 physicians.  
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30 310 The emphasis of this survey was to determine the perceptions and attitudes of  
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32 311 physicians toward EDSP, an emerging prescribing concept as an environmentally better  
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34 312 alternative in the clinical use of medicines.<sup>15,25</sup> But EDSP has been well-accepted as an  
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36 313 essential element of EPV practice in the control of API pollution in environment.<sup>8,12,13</sup>  
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38 314 Therefore, the perceptions toward API pollution and EPV were first studied. The results  
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40 315 from Table 2 showed the positive overall perception of responding physicians towards API  
41  
42 316 pollution in environment and EPV. Accordingly, it is encouraging that the responding  
43  
44 317 physicians' overall attitudes and perceptions concerning API pollution in environment as  
45  
46 318 well as EDSP under an EPV perspective were positive (Table 3), which would shape the  
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48 319 motivation for the future practice. In recent years, along with the increasingly serious  
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50 320 environmental pollution which has attracted the particular attention of  
51  
52 321 Chinese government, the environmental awareness and initiatives of Chinese people  
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54 322 have gradually been awakened.<sup>14</sup> Accordingly, most Chinese physician respondents  
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56 323 showed their concerns about the environment problems caused by APIs. A majority of  
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58 324 physicians agreed the existence, potential risks of APIs in environment, and the  
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3 325 effectiveness of EDSP under an EPV perspective in decreasing environmental exposure  
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5 326 of excreted APIs. Most respondents posed the eco-responsible attitudes and perceived  
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7 327 their own responsibility for the control of API pollution linked to medical prescriptions as  
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9 328 well as the implementation of EDSP under an EPV perspective, and importantly,  
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11 329 expressed their wiliness to participate in EDSP and EPV activities.  
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14 330 Our survey data suggested that the environmental consciousness of Chinese  
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16 331 physicians during prescribing was insufficient, which was demonstrated by the finding that  
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18 332 no respondent identified the environmental impacts as the aspects regarding medicines  
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20 333 affecting his(her) prescription decision. The possible reason might be due to the utter lack  
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22 334 of the related education or training, which is in alignment with respondents'  
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24 335 self-satisfaction with knowledge on EDSP (100% were not satisfied) and respondents'  
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26 336 confidence toward EDSP (100% were not confident), considerable portions of  
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28 337 respondents who chose "undecided" option in many Likert-type attitude and perception  
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30 338 questions, as well as the conservative wait-and-see attitudes towards EDSP practice held  
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32 339 by physicians. "Poor awareness of EDSP and EPV" was conceived as the most important  
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34 340 barrier to the effective implementation of EDSP under the perspective of EPV. Therefore,  
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36 341 the environmental sustainability considerations should begin to be included in the  
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38 342 physicians' choice of prescription in China, and the long-established norms and guidelines  
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40 343 in the practice of clinical prescribing should be accordingly modified under the principle of  
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42 344 treating the environment and the patient as an interconnected, integral whole.<sup>24</sup> There is a  
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44 345 need to optimize the prescribing of drugs with a view to reducing environmental exposure.  
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47 346 In order to explore the possible factors influencing their future EDSP decision making,  
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49 347 this survey studied the perceive benefits and concerns of two EDSP approaches,  
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51 348 *low-dose prescribing* and *prescribing of drugs possessing environment-friendly excretion*  
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53 349 *profiles*, respectively. Despite the fact that the necessity and benefits of these two EDSP  
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55 350 approaches in the aspect of environmental protection were accepted by most responding  
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57 351 physicians, the biggest concerns in *low-dose prescribing* and *prescribing of drugs*  
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59 352 *possessing environment-friendly excretion profiles* were the possible negative impact on  
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3 353 therapeutic outcomes, and too complicated and professional drug evaluation process,  
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5 354 respectively. Therefore, during the EDSP design from the perspective of EPV, special  
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7 355 emphases should be given to how to ensure the therapeutic efficacy of the  
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9 356 “environment-friendly” doses, and how to standardize and simplify the process of  
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11 357 prescribing based on the drugs’ environment-friendly excretion profiles.

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14 358 Moreover, many physicians voiced their concerns about the availability of the related  
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16 359 information required in EDSP design. In China, no data system is currently available to  
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18 360 guide medical prescribing decisions in the clinical for selection of drugs having a low  
19  
20 361 probability of environmental risks and hazards. However, there is a Swedish model which  
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22 362 could be used as a reference.<sup>26,41</sup> Swedish Environmental Classification of  
23  
24 363 Pharmaceuticals developed by Stockholm County Council is a simple and straightforward  
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26 364 classification system for prescribing non environmentally- hazardous drugs, and has been  
27  
28 365 widely used and well accepted among Swedish medical doctors. This easy-to-understand  
29  
30 366 classification classifies APIs on the Swedish market according to environmental risks and  
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32 367 hazards of drugs in view of their persistence, bioaccumulation and toxicity data, and  
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34 368 suggests substitution by alternatives with a lower risk or hazard index. We proposed to  
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36 369 construct the similar classification system in China, so that physicians who wish to be  
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38 370 environmentally conscious in their prescribing could have a reference to allow them to  
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40 371 select the API with the lowest possible environmental impact among the candidates with  
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42 372 equivalent therapeutic activities.

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45 373 Interestingly, as the major challenge for EDSP implementation which was worried  
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47 374 about by its advocate Daughton,<sup>15</sup> the issue “changing the prescribing behavior of  
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49 375 physicians” appeared to be regarded as a small matter by most physicians, because only  
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51 376 21% and 24% respondents chose this item as their concern regarding the *low-dose*  
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53 377 *prescribing* and *prescribing of drugs possessing environment-friendly excretion profiles*,  
54  
55 378 respectively (Table3, Q6 and 8). Only 6% physician respondents considered the item “*It*  
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57 379 *conflicts with long-accepted prescribing guidelines*” as the most major perceived barrier to  
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59 380 the effective implementation of EDSP (Table3, Q12). This results suggested the  
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3 381 physicians were willing to change their prescribing habits in order to make their due  
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5 382 contributions to control the environmental pollution by APIs.  
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8 383 In addition, we found there was a tendency among the internal medicine physicians  
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10 384 to have stronger intentions to attempt EDSP practice than physicians from other  
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12 385 specialties, which might be due to their better acquaintance with the pharmacokinetic  
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14 386 properties and excretion profile of drugs. There is thus the expectation that it is feasible to  
15  
16 387 first implement EDSP practice from the perspective of EPV in the internal medicine  
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18 388 department. Furthermore, nearly half responding physicians were inclined to adopt  
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20 389 rational prescribing as the EDSP behavior that they want to firstly choose. Rational  
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22 390 prescribing is a classical principle concept of drug selection of in the field of personalized  
23  
24 391 treatment or health-care.<sup>30</sup> Based on its high acceptability, further promoting rational  
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26 392 prescribing to control excess medication prescription is a good first approach to  
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28 393 implement EPV in the health-care system to reduce API pollution at the sources. In fact,  
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30 394 recent emphasis of rational prescribing has been given to Personalized Health-care  
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32 395 through selection of optimal APIs and determination of individual dosages.<sup>26</sup> Personalized  
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34 396 adjustment of drug administration holds the potential for enhancing therapeutic outcomes,  
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36 397 while simultaneously reducing the environmental risks of APIs.  
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38  
39 398 The main limitation of this study is the sampling bias. This study only enrolled  
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41 399 physicians from one province in China, which might weaken the generalizability of results.  
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43 400 Moreover, the sample size was not determined by precision analysis technique. Further  
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45 401 studies with larger samples should be conducted to verify our findings.  
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47 402 In conclusion, to the best of our knowledge, this is the first study that explored the  
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49 403 physicians' perceptions and attitudes toward EDSP, a sustainable prescription approach  
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51 404 to minimize the environmental loads and risks of excreted API residues at their sources.  
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53 405 The results suggested that the majority of Chinese physicians had positive attitude  
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55 406 towards EDSP. Respondents agreed the existence of APIs in environment, worried about  
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57 407 the potential environmental and ecological risks of API residues, supported the  
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59 408 effectiveness and necessity of EDSP, importantly, showed their willingness to participate  
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3 409 in the EDSP practices. Nevertheless, at present, the environmental consciousness of  
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5 410 Chinese physicians during prescribing is seriously insufficient, which is demonstrated by  
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7 411 the finding that no respondent identified the environmental impacts as the aspect  
8  
9 412 regarding medicines affecting his(her) prescription decision, none was satisfied with  
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11 413 knowledge on EDSP and showed confidence toward EDSP. The most important barrier to  
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13 414 the effective implementation of EDSP was identified as “*poor awareness of EDSP and*  
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15 415 *EPV*”. Accordingly, most responding physicians reported that they held the wait-and-see  
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17 416 or conservative attitudes towards EDSP practice. Furthermore, the biggest concerns in  
18  
19 417 *low-dose prescribing and prescribing of drugs possessing environment-friendly excretion*  
20  
21 418 *profiles*, two EDSP approaches, were the possible negative impact on therapeutic  
22  
23 419 outcomes, and too complicated and professional drug evaluation process, respectively. In  
24  
25 420 addition, the availability of the related information required in EDSP design was also taken  
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27 421 into consideration. An unexpected finding in this survey was that only few respondents  
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29 422 were bothered by the issue that EDSP changed the prescribing behavior of physicians,  
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31 423 which was identified as the major challenge for EDSP implementation by its advocate  
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33 424 Daughton <sup>15</sup> This was in line with the responding physicians’ eco-responsible attitudes  
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35 425 toward API pollution in environment. Moreover, we found that the internal medicine  
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37 426 physicians might be more initiative to engage in EDSP behaviors than physicians from  
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39 427 other specialties.

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42 428 Based on the above findings, we concluded some recommendations for  
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44 429 implementing EDSP from the perspective of EPV:

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46 430 1. Introducing and strengthening the related medical training and education.  
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48 431 Hospitals, medical centers and colleges could develop training and educational programs  
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50 432 to inform physicians prescribing medications and medical students about APIs in  
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52 433 environment, the environmental consciousness during prescribing, the environmental  
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54 434 impact of their professions, EPV and EDSP.

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57 435 2. Further promoting rational prescribing to control excess medication prescription,  
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59 436 which is a good first approach to implement EPV in the health-care system based on the  
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3 437 survey finding on the respondent physicians' preferred EDSP behaviors.  
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6 438 3. Integrating the environmental constituent into the rational prescribing principles.  
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8 439 Considering the faithfulness of physicians prescribing medicines to rational prescribing  
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10 440 principles, this upgraded rational prescribing principle would guide physicians to include  
11  
12 441 environmental sustainability considerations in their practical choice of prescription.  
13

14 442 4. Building the database to allow for acquiring the related information to prescribe non  
15  
16 443 environmentally-hazardous drugs, select the effective and "environment-friendly" doses,  
17  
18 444 understand the drugs' environment-friendly excretion profiles, etc. The Swedish  
19  
20 445 Environmental Classification of Pharmaceuticals could provide helpful sample materials.  
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23 446 5. Constructing the process model of EDSP from the perspective of EPV, in order to  
24  
25 447 ensure the quality, standardization and convenience of EDSP process.  
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28 448 6. Implementing EDSP practice from the perspective of EPV first in the internal  
29  
30 449 medicine department.  
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35 451 **Contributors** JW conceived of the original idea for the study, designed the questionnaire,  
36  
37 452 obtained ethical approval, carried out the statistical analysis, drafted the paper and is  
38  
39 453 overall guarantor. SL contributed to the preparation of the data set and interpreted results .  
40  
41 454 BH contributed to the study design, interpretation of results and commented on drafts of  
42  
43 455 the paper.  
44

45  
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49  
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51

52 459 **Competing interests** None declared.  
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54  
55 460 **Patient consent** Not required.  
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57  
58 461 **Ethics approval** The study was granted approval from the Ethics Committee of Wuhan  
59  
60 462 University of Science and Technology (19068).

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3 463 **Data sharing statement** No additional data are available.  
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8 465 **References**  
9

- 10 466 1. Sato K, Watanabe H, Ikeda T, *et al.* Estimation of total prescription  
11  
12 467 weights of active pharmaceutical ingredients in human medicines based on  
13  
14 468 a public database for environmental risk assessment in Japan. *Regul Toxicol*  
15  
16 469 *Pharmacol* 2018;99:98-104.  
17  
18 470 2. Ahkola H, Tuominen S, Karlsson S, *et al.* Presence of active pharmaceutical  
19  
20 471 ingredients in the continuum of surface and ground water used in drinking water  
21  
22 472 production. *Environ Sci Pollut Res Int* 2017;24:26778-91.  
23  
24 473 3. Corra L. Chemical Pollutants of Pharmaceutical Origin Present in the Environment.  
25  
26 474 *J Health Pollut* 2018;8:180916.  
27  
28 475 4. Comber S, Gardner M, Sörme P, *et al.* Active pharmaceutical ingredients entering  
29  
30 476 the aquatic environment from wastewater treatment works: A cause for concern? *Sci*  
31  
32 477 *Total Environ* 2018;613-614:538-47.  
33  
34 478 5. Blair B, Zimny-Schmitt D, Rudd, MA. U.S. News Media Coverage of Pharmaceutical  
35  
36 479 Pollution in the Aquatic Environment: A Content Analysis of the Problems and  
37  
38 480 Solutions Presented by Actors. *Environ Manage* 2017;60:314-22.  
39  
40 481 6. He BS, Wang J, Liu J, *et al.* Eco-pharmacovigilance of non-steroidal anti-inflammatory  
41  
42 482 drugs: Necessity and opportunities. *Chemosphere* 2017;181:178-89.  
43  
44 483 7. Wang J, He B, Yan D, *et al.* Implementing ecopharmacovigilance (EPV) from  
45  
46 484 a pharmacy perspective: A focus on non-steroidal anti-inflammatory drugs. *Sci Total*  
47  
48 485 *Environ* 2017;603-604:772-84.  
49  
50 486 8. Holm G, Snape JR, Murray-Smith R, *et al.* Implementing ecopharmacovigilance  
51  
52 487 in practice: challenges and potential opportunities. *Drug Saf* 2013;36:533-46.  
53  
54 488 9. Yu X, Hu X, Li S, *et al.* Attitudes and Practice Regarding Disposal for Unwanted  
55  
56 489 Medications among Young Adults and Elderly People in China from an  
57  
58 490 Ecopharmacovigilance Perspective. *Int J Environ Res Public Health* 2019;16(8).  
59  
60

- 1  
2  
3 491 10. Medhi B, Sewal RK. Ecopharmacovigilance: an issue urgently to be addressed. *Indian*  
4 *J Pharmacol* 2012;44:547-9.  
5 492  
6  
7 493 11. Silva LJ, Lino CM, Meisel LM, *et al.* Selective serotonin re-uptake inhibitors (SSRIs)  
8 in the aquatic environment: an ecopharmacovigilance approach. *Sci Total Environ*  
9 494 2012;437:185-95.  
10 495  
11  
12 496 12. Wang J, Zhao SQ, Zhang MY, *et al.* Targeted eco-pharmacovigilance for ketoprofen  
13 in the environment: Need, strategy and challenge. *Chemosphere* 2018;194:450-62.  
14 497  
15  
16 498 13. Wang J, Zhang MY, Liu J, *et al.* Using a targeted ecopharmacovigilance  
17 intervention to control antibiotic pollution in a rural aquatic environment. *Sci Total*  
18 499 *Environ* 2019;696:134007.  
19 500  
20  
21 501 14. Liu J, Wang J, Hu XM. Knowledge, perceptions, and practice of  
22 ecopharmacovigilance among pharmacy professionals in China. *Environ Monit*  
23 502 *Assess* 2017;189:552.  
24 503  
25  
26 504 15. Daughton CG. Eco-directed sustainable prescribing: feasibility for reducing water  
27 contamination by drugs. *Sci Total Environ* 2014;493:392-404.  
28 505  
29  
30 506 16. Niemuth NJ, Jordan R, Crago J, *et al.* Metformin exposure at environmentally  
31 relevant concentrations causes potential endocrine disruption in adult male  
32 fish. *Environ Toxicol Chem* 2015;34:291-6.  
33 507  
34  
35 508 17. Meijide FJ, Da Cuña RH, Prieto JP, *et al.* Effects of waterborne exposure to the  
36 antidepressant fluoxetine on swimming, shoaling and anxiety behaviours of the  
37 mosquitofish *Gambusia holbrooki*. *Ecotoxicol Environ Saf* 2018;163:646-55.  
38 509  
39  
40 510 18. Kümmerer K, Dionysiou DD, Olsson O, *et al.* Reducing aquatic micropollutants  
41 - Increasing the focus on input prevention and integrated emission management. *Sci*  
42 511 *Total Environ* 2019;652:836-50.  
43 512  
44  
45 513 19. Machado K C, Grassi MT, Vidal C, *et al.* A preliminary nationwide survey of the  
46 presence of emerging contaminants in drinking and source waters in Brazil. *Sci Total*  
47 514 *Environ* 2016;572:138-46.  
48 515  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
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- 1  
2  
3 518 20. Praveena SM, Shaifuddin SNM, Sukiman S, *et al.* Pharmaceuticals residues in  
4 selected tropical surface water bodies from Selangor (Malaysia): Occurrence and  
5 519 potential risk assessments. *Sci Total Environ* 2018;642: 230-40.  
6  
7 520  
8  
9 521 21. Sorensen JP, Lapworth DJ, Nkhuwa DC, *et al.* Emerging contaminants in urban  
10 groundwater sources in Africa. *Water Res* 2015;72:51-63.  
11 522  
12  
13 523 22. Sposito JCV, Montagner CC, Casado M, *et al.* Emerging contaminants in Brazilian  
14 rivers: Occurrence and effects on gene expression in zebrafish (*Danio rerio*) embryos.  
15 524  
16  
17 525 *Chemosphere* 2018;209: 696-704.  
18  
19 526 23. Yi X, Tran NH, Yin T, *et al.* Removal of selected PPCPs, EDCs, and antibiotic  
20 resistance genes in landfill leachate by a full-scale constructed wetlands system.  
21 527  
22  
23 528 *Water Res* 2017;121:46-60.  
24  
25 529 24. Frederic O, Yves P. Pharmaceuticals in hospital wastewater: their ecotoxicity and  
26 contribution to the environmental hazard of the effluent. *Chemosphere* 2014;115:  
27 530  
28  
29 531 31-9.  
30  
31 532 25. Daughton CG. The Matthew Effect and widely prescribed pharmaceuticals lacking  
32 environmental monitoring: case study of an exposure-assessment vulnerability. *Sci*  
33 533  
34  
35 534 *Total Environ* 2014;466-467:315-325.  
36  
37 535 26. Straub JO. Reduction in the environmental exposure of pharmaceuticals through  
38 diagnostics, Personalised Healthcare and other approaches. A mini review and  
39 536  
40  
41 537 discussion paper. *Sustainable Chemistry and Pharmacy* 2016;3:1-7.  
42  
43 538 27. Blair BD. Potential Upstream Strategies for the Mitigation of Pharmaceuticals in  
44 the Aquatic Environment: a Brief Review. *Curr Environ Health Rep* 2016;3:153-160.  
45 539  
46  
47 540 28. Daughton CG, Ruhoy IS. Green pharmacy and pharmEcovigilance: prescribing and  
48 the planet. *Expert Rev. Clin Pharmacol* 2011;4:211-32.  
49 541  
50  
51 542 29. Daughton CG, Ruhoy IS. Lower-dose prescribing: minimizing "side effects" of  
52 pharmaceuticals on society and the environment. *Sci Total Environ* 2013;443:324-37.  
53 543  
54  
55 544 30. Maxwell SR. Rational prescribing: the principles of drug selection. *Clin Med (Lond)*  
56 2016;16:459-64.  
57 545  
58  
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- 546 31. Ding B. Pharma industry 4.0: Literature review and research opportunities in  
547 sustainable pharmaceutical supply chains. *Process Safety and Environmental*  
548 *Protection* 2018;119:115-30.
- 549 32. Singer AC, Xu Q, Keller VDJ. Translating antibiotic prescribing into antibiotic  
550 resistance in the environment: A hazard characterisation case study. *PLoS*  
551 *One* 2019;14:e0221568.
- 552 33. International Pharmaceutical Federation. Green pharmacy practice: taking  
553 responsibility for the environmental impact of medicines. The Hague, Netherlands:  
554 International Pharmaceutical Federation (FIP).2015.
- 555 34. Balch J, Schoen JH, Patel PK. Should Physicians Consider the Environmental  
556 Effects of Prescribing Antibiotics? *AMA J Ethics* 2017;19:957-65.
- 557 35. Bashiri FA, Al Shalawi AA, Hamad MH, *et al.* Assessment of physicians knowledge  
558 and attitudes in the management of febrile seizures. *Neurosciences (Riyadh)*  
559 2018;23:314–9.
- 560 36. Vogt F, Seidl F, Santarpino G, *et al.* Healthcare IT Utilization and Penetration among  
561 Physicians: Novel IT Solutions in Healthcare - Use and Acceptance in Hospitals. *Eur*  
562 *Surg Res* 2018;59:100–13.
- 563 37. Azuri J, Nashef S. Primary Care Physicians' Characteristics and Attitudes on  
564 Smoking Cessation. *Am J Health Behav* 2016;40:578–84.
- 565 38. Provenzano DA, Kamal KM, Giannetti V. Evaluation of Primary Care Physician  
566 Chronic Pain Management Practice Patterns. *Pain Physician* 2018;21:E593–602.
- 567 39. Tian Y, Li C, Wang J, *et al.* Modified task-based learning program promotes  
568 problem-solving capacity among Chinese medical postgraduates: a mixed  
569 quantitative survey. *BMC Med Educ* 2017;17:153.
- 570 40. Prakash B, Nadig P, Nayak A. Rational Prescription for a Dermatologist. *Indian J*  
571 *Dermatol* 2016;61:32-8.
- 572 41. Deblonde T, Hartemann P. Environmental impact of medical prescriptions: assessing  
573 the risks and hazards of persistence, bioaccumulation and toxicity of  
574 pharmaceuticals. *Public Health* 2013;127:312-7.

- 1  
2  
3 575 42. The Ministry of Health of the People's Republic of China. The 2018 China health  
4  
5 576 statistical yearbook (in Chinese). Beijing: Peking Union Medical College Press. 2018.  
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For peer review only

578 **Table 1** Demographic information and knowledge score of Chinese physicians  
 579 participating in the study. (*n*=262)

Participant' characteristics	Respondents No. (%)
<b>Gender</b>	
Male	124 (47)
Female	139 (53)
<b>Age</b>	
20-40 years	125 (48)
> 40 years	137 (52)
<b>Postgraduate training</b>	
Yes	170 (65)
No	92 (35)
<b>Job category</b>	
Internal medicine	102 (39)
Surgery	98 (37)
Others	62 (24)
<b>Years of experience</b>	
≤10	92 (35)
11-20	96 (37)
>20	74 (28)



581 **Table 2** Chinese physicians' perceptions toward API pollution in environment and EPV.  
 582 (*n*=262)

Survey Question/Statement	Respondents No. (%)				
	Strongly agree	Agree	Undecided	Disagree	Strongly Disagree
Q1: APIs used in health-care practices could finally enter into the environment.	96(37)	113(43)	45(17)	8(3)	0(0)
Q2: API residues in environment could cause adverse effects on ecosystem, wildlife species, even human beings.	126(48)	108(41)	26(10)	2(1)	0(0)
Q3: It is necessary to minimize the entrance of APIs into the environment.	104(40)	125(48)	31(12)	2(1)	0(0)
Q4: The control of API pollution is none of my business, because it should be the responsibility of environmental experts and regulators.	5(2)	6(2)	73(28)	80(31)	98(37)
Q5: API pollution could be ultimately traced back to the use of medications in health-care practices.	113(43)	96(37)	50(19)	3(1)	0(0)
Q6: If there is an upstream intervention for controlling API entry to the environment, I would endorse it, and be very pleased to participate in its implementation.	68(26)	99(38)	94(36)	1(0)	0(0)
Q7: Based on the description of EPV given on the first page of this questionnaire, I think EPV is an effective tool to control API entry to the environment.	83(32)	74(28)	98(37)	5(2)	2(1)

583

584 **Table 3** Assessment of Chinese physicians' perceptions and attitudes toward EDSP.  
 585 ( $n=262$ )

Survey Question/Statement	Response	Respondents No.(%)
Q1: At present, the aspects regarding medicines affecting my prescription decision include: *	● Efficacy	262 (100)
	● Safety	258 (98)
	● Cost and economy	246 (94)
	● Convenience	188 (72)
	● Pharmacokinetics	57 (22)
	● Marketing and promoting	139 (53)
	● Environmental impacts	0 (0)
Q2: As prescribers, physicians bear a responsibility for reducing API releases to environment.	Strongly agree	86 (33)
	Agree	83 (32)
	Undecided	81 (31)
	Disagree	12 (5)
	Strongly disagree	0 (0)
Q3: Previous to this survey, I have heard of EDSP.	Yes	260 (99)
	No	2 (1)
Q4: According to the description on the basic concept of EDSP provided on the first page of this questionnaire, I think EDSP is an effective tool to control the entrance of APIs into the environment.	Strongly agree	54 (21)
	Agree	96 (37)
	Undecided	101 (39)
	Disagree	9 (3)
	Strongly disagree	2 (1)
Q5: I think the benefits of <i>low-dose prescribing</i> include:*	● Reducing the environmental loading of API residues from patients' excretions.	257 (98)
	● Eliminating the subsequent need and cost for disposal of pharmaceutical leftovers	240 (92)
	● Reducing health-care expenditures for patients.	104 (40)
	● Improving therapeutic efficacy <i>via</i> minimizing off-target side-effects related to dosage, and	75 (29)

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1		thus enhancing	
2		pharmaceutical	
3		compliance.	
4		● Protecting public health by	
5		unintended poisonings by	
6		drugs (especially infants,	238 (91)
7		toddlers, and children)	
8		resulted from	
9		inappropriate storage or	
10		disposal.	
11		● Reducing drug diversion	
12		and the profound	215 (82)
13		problems with attendant	
14		abuse of certain drugs and	
15		misuse of others.	
16		● Improving public trust—by	
17		reducing hidden and	
18		unwelcomed exposure of	
19		humans to trace levels of	242 (92)
20		numerous APIs <i>via</i>	
21		potable water and	
22		contaminated foods.	
23		● Improving patient/	89 (34)
24		physician communication.	
25		● It can not achieve ideal	262 (100)
26		therapeutic efficacy, and	
27		might delay treatment.	
28		● The lowest effective dose	
29		with environmental safety	259 (99)
30		is not certain and	
31		available.	
32		● It is a new prescribing	
33		concept, therefore, a long	207 (79)
34		time will be taken to	
35		popularize it in clinical	
36		practice.	
37		● It will change my	55 (21)
38		prescribing habits, thus is	
39		too troublesome.	
40	Q6: My concerns regarding the	Strongly agree	79 (30)
41	<i>low-dose prescribing</i> are:*		
42		Agree	123 (45)
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54	Q7: It is necessary to emphasize on		
55	the metabolism and excretion of		
56	drugs rather than the initially		
57	ingested dose by the patient,		
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4	because the emission of APIs into	Undecided	48 (18)
5	the environment <i>via</i> sewers is		
6	dictated by the excretion profile	Disagree	11 (4)
7	and pharmacokinetics of the		
8	different types of pharmaceutical	Strongly disagree	1 (0)
9	compounds.		
10			
11	Q8: My concerns regarding the	● It can not achieve ideal	
12	<i>prescribing of drugs possessing</i>	therapeutic efficacy, and	35 (13)
13	<i>environment-friendly excretion</i>	might delay treatment.	
14	<i>profiles are:*</i>	● Under the EDSP design,	
15		drug evaluation based on	
16		the excretion profile and	219 (84)
17		pharmacokinetics is too	
18		complicated and	
19		professional.	
20		● There is no available	
21		accurate data on the	
22		excretion profile and	190 (73)
23		pharmacokinetics of	
24		drugs.	
25		● It is a new prescribing	
26		concept, therefore, a	
27		long time will be taken to	211 (81)
28		popularize it in clinical	
29		practice.	
30		● It will change my	
31		prescribing habits, thus is	62 (24)
32		too troublesome.	
33			
34	Q9: My self-satisfaction with	Agree	0 (0)
35	knowledge on EDSP.	Disagree	262 (100)
36			
37	Q10: My confidence toward EDSP.	Agree	0 (0)
38		Disagree	262 (100)
39			
40	Q11: For now, the EDSP behavior that	● None. I will take a	
41	I want to firstly choose is:	wait-and-see approach.	134 (51)
42		● I will promote rational	
43		prescribing at precise	
44		doses, avoid over-	121 (46)
45		prescribing and mis-	
46		prescribing.	
47		● I will implement the	
48		low-dose prescribing.	3 (1)
49		● I will prescribe drugs	
50			4 (2)
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	possessing environment-friendly excretion profiles as much as possible.	
Q12: I think the most major perceived barrier to the effective implementation of EDSP under the perspective of EPV in China is:	<ul style="list-style-type: none"> <li>● Poor awareness of EDSP and EPV. 101 (39)</li> <li>● Lack of an administrative framework for EDSP under the perspective of EPV. 50 (19)</li> <li>● Lack of available data related to EDSP under the perspective of EPV. 96 (37)</li> <li>● It conflicts with long-accepted prescribing guidelines. 15 (6)</li> </ul>	
Q13: I am very pleased to participate in EDSP activities in my future practice if it is successfully translated into clinical treatment.	<p>Strongly agree 85 (32)</p> <p>Agree 121 (46)</p> <p>Undecided 53 (20)</p> <p>Disagree 3 (1)</p> <p>Strongly disagree 0 (0)</p>	

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586 \* Multiple responses were permitted, percentages do not add to 100%.

# Reporting checklist for quality improvement study.

Based on the SQUIRE guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SQUIRE reporting guidelines, and cite them as:

Ogrinc G, Davies L, Goodman D, Batalden P, Davidoff F, Stevens D. SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence): revised publication guidelines from a detailed consensus process

	Reporting Item	Page Number
<b>Title</b>		
	<a href="#">#1</a> Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patientcenteredness, timeliness, cost, efficiency, and equity of healthcare)	Page 1
<b>Abstract</b>		
	<a href="#">#0</a> <a href="#">2a</a> Provide adequate information to aid in searching and indexing	Page 1-2
	<a href="#">#0</a> <a href="#">2b</a> Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions	Page 1-2

## 1 Introduction

2			
3			
4	Problem	<a href="#">#3</a>	Nature and significance of the local problem
5	description		Page 3-5
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8			
9	Available	<a href="#">#4</a>	Summary of what is currently known about the problem,
10	knowledge		including relevant previous studies
11			Page 3-5
12			
13	Rationale	<a href="#">#5</a>	Informal or formal frameworks, models, concepts, and / or
14			theories used to explain the problem, any reasons or
15			assumptions that were used to develop the intervention(s),
16			and reasons why the intervention(s) was expected to work
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21	Specific aims	<a href="#">#6</a>	Purpose of the project and of this report
22			Page 5
23			

## 24 Methods

25			
26			
27	Context	<a href="#">#7</a>	Contextual elements considered important at the outset of
28			introducing the intervention(s)
29			Page 5-7
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31			
32	Intervention(s)	<a href="#">#0</a>	Description of the intervention(s) in sufficient detail that
33		<a href="#">8a</a>	others could reproduce it
34			Page 5-7
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36			
37	Intervention(s)	<a href="#">#0</a>	Specifics of the team involved in the work
38		<a href="#">8b</a>	
39			Page 6-7
40			
41	Study of the	<a href="#">#0</a>	Approach chosen for assessing the impact of the
42	Intervention(s)	<a href="#">9a</a>	intervention(s)
43			Page 6
44			
45			
46	Study of the	<a href="#">#0</a>	Approach used to establish whether the observed
47	Intervention(s)	<a href="#">9b</a>	outcomes were due to the intervention(s)
48			Page 7
49			
50			
51	Measures	<a href="#">#1</a>	Measures chosen for studying processes and outcomes of
52		<a href="#">0a</a>	the intervention(s), including rationale for choosing them,
53			their operational definitions, and their validity and reliability
54			Page 6-7
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56			
57	Measures	<a href="#">#1</a>	Description of the approach to the ongoing assessment of
58			contextual elements that contributed to the success,
59			Page 6-7

	<a href="#">0b</a>	failure, efficiency, and cost	
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3	Measures	<a href="#">#1</a> Methods employed for assessing completeness and	Page 6-7
4		<a href="#">0c</a> accuracy of data	
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8	Analysis	<a href="#">#1</a> Qualitative and quantitative methods used to draw	Page 7
9		<a href="#">1a</a> inferences from the data	
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12	Analysis	<a href="#">#1</a> Methods for understanding variation within the data,	Page 6-7
13		<a href="#">1b</a> including the effects of time as a variable	
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16			
17	Ethical	<a href="#">#1</a> Ethical aspects of implementing and studying the	Page 5
18	considerations	<a href="#">2</a> intervention(s) and how they were addressed, including,	
19		but not limited to, formal ethics review and potential	
20		conflict(s) of interest	
21			
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25	<b>Results</b>		
26			
27			
28		<a href="#">#1</a> Initial steps of the intervention(s) and their evolution over	Page 7
29		<a href="#">3a</a> time (e.g., time-line diagram, flow chart, or table), including	
30		modifications made to the intervention during the project	
31			
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34		<a href="#">#1</a> Details of the process measures and outcome	Page 7
35		<a href="#">3b</a>	
36			
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39		<a href="#">#1</a> Contextual elements that interacted with the intervention(s)	Page 7
40		<a href="#">3c</a>	
41			
42			
43		<a href="#">#1</a> Observed associations between outcomes, interventions,	Page 8-11
44		<a href="#">3d</a> and relevant contextual elements	
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48		<a href="#">#1</a> Unintended consequences such as unexpected benefits,	Page 8-11
49		<a href="#">3e</a> problems, failures, or costs associated with the	
50		intervention(s).	
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54		<a href="#">#1</a> Details about missing data	Page 7
55		<a href="#">3f</a>	
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## Discussion

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4	Summary	<a href="#">#1</a>	Key findings, including relevance to the rationale and
5		<a href="#">4a</a>	specific aims
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9	Summary	<a href="#">#1</a>	Particular strengths of the project
10		<a href="#">4b</a>	
11			
12			
13	Interpretation	<a href="#">#1</a>	Nature of the association between the intervention(s) and
14		<a href="#">5a</a>	the outcomes
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18	Interpretation	<a href="#">#1</a>	Comparison of results with findings from other publications
19		<a href="#">5b</a>	
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22			
23	Interpretation	<a href="#">#1</a>	Impact of the project on people and systems
24		<a href="#">5c</a>	
25			
26			
27	Interpretation	<a href="#">#1</a>	Reasons for any differences between observed and
28		<a href="#">5d</a>	anticipated outcomes, including the influence of context
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31			
32	Interpretation	<a href="#">#1</a>	Costs and strategic trade-offs, including opportunity costs
33		<a href="#">5e</a>	
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37	Limitations	<a href="#">#1</a>	Limits to the generalizability of the work
38		<a href="#">6a</a>	
39			
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41	Limitations	<a href="#">#1</a>	Factors that might have limited internal validity such as
42		<a href="#">6b</a>	confounding, bias, or imprecision in the design, methods,
43			measurement, or analysis
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47	Limitations	<a href="#">#1</a>	Efforts made to minimize and adjust for limitations
48		<a href="#">6c</a>	
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52	Conclusion	<a href="#">#1</a>	Usefulness of the work
53		<a href="#">7a</a>	
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57	Conclusion	<a href="#">#1</a>	Sustainability
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7b

Conclusion

#1

Potential for spread to other contexts

Page 15-16

7c

Conclusion

#1

Implications for practice and for further study in the field

Page 15-16

7d

Conclusion

#1

Suggested next steps

Page 15-16

7e**Other  
information**

Funding

#1

Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting

Page 17

8

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