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Evaluation of pharmaceutical consumption between urban and suburban catchments in China by wastewater-based epidemiology

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ABSTRACT

Wastewater-based epidemiology (WBE) is amply used for estimating human consumption of chemicals, yet information on regional variation of pharmaceuticals and their environmental fate are scarce. Thus, this study aims to estimate the consumption of three cardiovascular, four non-steroidal anti-inflammatory pharmaceuticals (NSAIDs), and four psychoactive pharmaceuticals between urban and suburban catchments in China by WBE, and to explore their removal efficiencies and ecological risks. Eleven analytes were detected in both influent and effluent samples. The estimated consumptions ranged from <MDL-1510 mg/day/1000 inh for cardiovascular pharmaceuticals, 0.140–1980 mg/day/1000 inh for anti-inflammatory pharmaceuticals, and 0.135–177 mg/day/1000 inh for psychoactive pharmaceuticals, respectively. Consumption of most psychoactive pharmaceuticals were higher in urban than in suburban catchments, while higher consumption of carbamazepine was observed in suburban than in urban areas. Furthermore, PCA analysis revealed evident variation among sampling locations in China. Significantly positive correlation ($p < 0.05$, $r = 0.617$) was found between Log *Kow* and removal efficiencies of the analytes, indicating physicochemical property dependent removal in WWTPs. Ecological risk assessment exhibited moderate risks for metoprolol and venlafaxine to aquatic environment. Our study discloses significant regional variation in pharmaceutical consumption in China by WBE, which could provide basis for the establishment of well-calibrated environmental and public health policies.

1. Introduction

Pharmaceuticals are cataloged as emerging contaminants due to increasing concerns regarding adverse effects on ecosystem and human health (He et al., 2024). Cardiovascular and non-steroidal anti-inflammatory pharmaceuticals (NSAIDs) are extensively utilized pharmaceuticals worldwide. The number of cardiovascular disease patients in China has reached 330 million and will continue to rise (writing committee of the report on cardiovascular health and diseases in china, 2022), leading to a sustained increase in the consumption of cardiovascular pharmaceuticals. NSAIDs with approximately 35 million people worldwide used every day are one of the most widely consumed pharmaceuticals in the world, and it ranked as the second of China's total pharmaceuticals production (Yan et al., 2021; Yu et al., 2013). Additionally, more than one billion people worldwide were reportedly affected by substance dependence or mental disorders (Yañez et al., 2023; Charlson et al., 2019), which accounted for one-fifth of the total disease burden in 2020 (WHO, 2020), resulting in an increasing use of psychoactive pharmaceuticals (Davey et al., 2022). The China Mental Health Survey revealed that over 95 million people in China are suffering from depression (Lu et al., 2021). However, few study have investigated regional-specific consumption of pharmaceuticals especially for new psychoactive substances in China, and a better understanding of regional consumption is beneficial for governments to

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formulate relevant public health responses and environmental protection policies.

Wastewater-based epidemiology (WBE) was considered to be a useful tool for monitoring substance consumption or exposure of populations (Gracia-Lor et al., 2018; Kim and Oh, 2020). It has been successfully applied to evaluate consumptions of antibiotics (Gao et al., 2022; Wang et al., 2024), new psychoactive substances (Adhikari et al., 2023; Castiglioni et al., 2021), and tobacco (Zheng et al., 2023), as this approach with the characteristics of overcoming subjective factors of survey and allowing to back-estimate population-normalized consumption of substances based on analysis of human excreted residues in influent wastewater (Choi et al., 2018). Recently, WBE has been used in assessment of pharmaceuticals utilization where the estimated amounts by WBE were found comparable to production or prescription data (Huizer et al., 2021; Kim and Oh, 2020). So far, a few WBE studies have reported consumption of pharmaceuticals in China, e.g., Yan et al. (2021) investigated the occurrence of four NSAIDs in two sewage treatment plants in Guangzhou indicating lower mass load in China than in Europe and North America, Shao et al. (2023) determined psychoactive drugs in wastewater collected from wastewater treatment plants (WWTPs) in major cities in China. However, the existing WBE studies were mostly conducted in developed urban WWTPs. Information on pharmaceutical consumption in suburban catchments was still limited. This may lead to inaccurate estimates of pharmaceutical usage and environmental health risks due to the wide difference between urban and suburban areas. For example, Hou et al. (2023) found that the consumption of metoprolol by WBE varied with the prevalence of hypertension indicating regional specific pharmaceuticals usage. Gao et al. (2022) observed significant variations on consumption of antibiotics between urban and suburban catchments in China via WBE.

It is recognized that the active ingredients in pharmaceuticals, which are primarily designed to elicit a specific biological response, are known to have potential risk to the aquatic ecosystem (Merete et al., 2008). Studies have shown that many pharmaceuticals are less readily removed in typical wastewater biological treatment units (Behera et al., 2011; Kim and Oh, 2020). It is therefore crucial to assess removal efficiencies of large usage and new psychoactive pharmaceuticals in WWTPs due to the fact that degradation-resistant pharmaceuticals may enter aquatic environment through discharged water from WWTPs and their potential ecological risks on organisms (Archer et al., 2023). Many studies have reported higher removal efficiencies for large usage pharmaceuticals of, e.g., paracetamol and naproxen (>90%) (Park et al., 2017; Yang et al., 2017) whereas much lower removal efficiency was found for psychoactive pharmaceutical of carbamazepine (<30%) (Behera et al., 2011). Nevertheless, the occurrence and removal efficiencies of psychoactive pharmaceuticals (e.g., citalopram, temazepam, and venlafaxine) in WWTPs have rarely been investigated compared to cardiovascular pharmaceuticals and NSAIDs, though toxicological studies have confirmed adverse effects of citalopram and venlafaxine to freshwater organisms at environmentally relevant concentrations (Fong and Hoy, 2012).

This study aims to investigate the difference in the consumption of typical cardiovascular, NSAIDs, and psychoactive pharmaceuticals between urban and suburban areas in China by WBE, as well as their removal efficiencies in WWTPs and ecological risks. This may provide effective information for the prevention and control of pharmaceutical usage and pollution for the establishment of public health and environmental protection policies based on rural-urban differences in China.

2. Materials and methods

2.1. Chemicals and reagents

Methanol and hydrochloric acid were purchased from Merck (Shanghai, China) and Aladdin (Shanghai, China), respectively. Atenolol, benzafibrate, metoprolol, paracetamol, mefenamic acid, naproxen, diclofenac, carbamazepine, citalopram, temazepam, venlafaxine, and isotope standards (purity ≥98%) were purchased from Alta Scientific Co., Ltd. (Tianjin, China). The chemical properties of the pharmaceuticals can be found in Table S1. Atenolol-d_7, Benzafibrate-d_4, Metoprolol-d_4, Paracetamol-d_4, Mefenamic acid-d_4, Naproxen-d_4, Diclofenac-d_4, Carbamazepine-d_{10}, Citalopram-d_6, Temazepam-d_5, and Venlafaxine-d_4 were used as internal standards. Deionized water was produced by the Milli-Q Gradient A-10 system.

2.2. Sample collection

Daily (24 h) composite wastewater samples were collected from 8 wastewater treatment plants (WWTPs) in seven cities of China in 2021 (Fig. S1). Automatic samplers were used to collect time-proportional influents from all 8 WWTPs while 4 of the 8 WWTPs were selected to collect time-proportional effluents at the same sampling period with influents. Each WWTP was sampled for one consecutive week. Wastewater samples were acidified to pH = 2 onsite using 2 M hydrochloric acid, transported to the laboratory, and stored at −20 °C. The sampling WWTPs covered four developed urban catchments with megacities of Beijing, Shanghai, Guangzhou and Shenzhen. The other four WWTPs receive wastewater from suburban catchments in Jieyang, Tianshui (two WWTPs), and Wuzhou with lower per Capita gross domestic product than four developed cities. Detailed information of sampling locations and catchment characteristics are provided in Table S2.

2.3. Sample pretreatment and UPLC-MS/MS analysis

Solid phase extraction (SPE) was used to extract target pharmaceuticals from wastewater samples. Samples were thawed and filtered using 0.45 μM glass fiber filter membrane. Internal standards (10 ng) were added and extracted by Oasis HLB cartridges (6 cc, 150 mg). 6 mL of methanol and 6 mL of pH 2 Milli-Q water were used for conditioning before loading 100 mL filtered wastewater samples to the cartridges. The cartridges were rinsed with 6 mL Milli-Q water to remove possible salts, and then analytes were eluted with 12 mL methanol. The elutes were dried under gentle nitrogen gas flow, and transferred to 2 mL brown vials for further drying. The eluates were re-dissolved with 0.5 mL pH 2 Milli-Q water which translates to a 200 times concentrator factor.

The concentration of the analytes in the extracts was determined by a Waters I-Class Ultra-performance liquid chromatography (UPLC) coupled with a Waters TQ-S micro mass spectrometer. Separation was achieved using a BEH-C18 column (1.7 μm, 2.1 mm × 100 mm) and the column oven temperature was 35 °C. Mobile phase flow rate was 0.3 mL/min, mixing water (eluent A) and methanol (eluent B) both containing 0.2% v/v formic acid. The linear elution gradient program is as follow: 0–1.5 min (0% B), 1.5–3 min (0 → 40% B), 3–9 min (40 → 60% B), 9–12 min (60 → 80% B), 12–12.5 min (80 → 100% B), 12.5–18 (100% B), 18–19 min (100 → 0% B), 19–22.5 min (0% B). Positive mode electrospray ionization with multiple reaction monitoring modes was used for quantitative analysis. The injection volume was 5 μL. The source temperature was 500 °C and the ion spray voltage was 5 kV. The detailed instrumental parameters and retention times of analytes are provided in Table S3.

2.4. Back-estimation of pharmaceutical consumption

The population normalized pharmaceutical consumption was calculated using Equation (1).

$$\mathrm{Cons} = \frac{C \times \mathrm{F} \times CF}{P} \quad (1)$$

where Cons is the pharmaceuticals consumption (mg/day/1000 inh), C is the concentration (ng·L^{-1}) of each drug in influent wastewater, CF is the correction factors for each drug, F is the daily flow rate (L·d^{-1}), and P

is the population served by each WWTP. The correction factors for target compounds are summarized in Table S5. The population size (P) and the total flow rate (F) were provided by the authorities of the WWTPs (Table S2). Graphpad Prism (V9.1.0) and R language (R4.2.2) were used to map the plot and study the correlation between target pharmaceuticals consumption.

2.5. Calculation of removal efficiencies

The removal efficiencies of the studied drugs in the WWTPs were calculated based on Equation (2).

$$RE\ (\%) = \frac{Ci - C_e}{C_i} \times 100\% \quad (2)$$

where *RE* (%) refers to the removal efficiencies (%), C_i represents the influent concentrations, and C_e stands for the effluent concentrations of the drugs.

2.6. Ecological risk assessment

The effluents of the studied WWTPs were directly discharged into surface water, thus Risk Quotient (RQ) method was used to evaluate the ecological risks of the pharmaceuticals to the freshwater ecosystem. Potential risk levels were identified based on the RQ values: high risk, RQ $\geq$ 10; moderate risk, 1 $\leq$ RQ $\leq$ 10; low risk, 0.1 $\leq$ RQ $\leq$ 1; and insignificant risk, RQ $<$ 0.1 (Lu et al., 2023). RQs were calculated by Equation (3).

$$RQ = \frac{Ce}{PNEC} \quad (3)$$

where *Ce* is the effluent concentration (ng/L) of the pharmaceuticals, PNEC is the predicted no effect concentration (ng/L). The lowest PNECs for the pharmaceuticals obtained in tests of algae, daphnia, and fish that were available in the literature (Table S8) were used for the calculation of RQs.

2.7. Quality control

Method performance of all the target pharmaceuticals were assessed in Milli-Q water and matrix (pooled influents and effluents) samples. Quality control measures were implemented in the analysis (Table S4). No target drug was detected in the procedural blanks, and analytes present in the matrix samples were subtracted from matrix spiked samples. Calibration curves ($R^2 > 0.99$) were based on nine concentration levels ranging from 0.01 to 50 ng/mL. The accuracy of matrix spike samples ranged from 74 to 108% with duplicate samples of 2.3–10% precision. The recoveries of the analytes were 69~98%. Milli-Q water and calibration solutions were injected every 15 injections to check the possible carry-over and repeatability of the method. The limit of detection (LOD) and the limit of quantification (LOQ) were determined by a signal-to-noise ratio of 3 and 10, which were 0.02–2.3 and 0.06–7.0 ng/L, respectively.

3. Results and discussion

3.1. Occurrence of the pharmaceuticals in wastewater influent

All the 11 target pharmaceuticals were detected in both influent and effluent samples of the studied WWTPs, including 3 cardiovascular, 4 NSAIDs and 4 psychoactive drugs (Table 1 and S1). Atenolol, metoprolol, paracetamol, diclofenac, carbamazepine and venlafaxine were detected in all the influent samples (100%). Bezafibrate, naproxen, temazepam were frequently detected (DFs >70%), while citalopram (DF = 54.4%) and mefenamic acid (DF = 66.7%) were detected with a low detection frequency in influents.

The influent concentration of metoprolol (range: 13.9–597 ng/L) measured in most of our studied catchments was higher than atenolol (8.40–64.8 ng/L) and bezafibrate (<MDL-15.3 ng/L) for cardiovascular drugs. Comparable level of metoprolol was found in Beijing (1.50–1680 ng/L) in a previous study (Hou et al., 2023). Paracetamol (1.10–4365 ng/L) and naproxen (<MDL-4201 ng/L) are the predominant compounds among target NSAIDs in influents. The paracetamol concentration in this study is higher than that in Hebei Province in China (0.30–21.1 ng/L) (Hou et al., 2020), but much lower than that in Australia (169 ng/mL, mean) (Hou et al., 2020). Comparable influent concentrations of psychoactive drugs, including carbamazepine (0.20–43.6 ng/L), venlafaxine (0.90–33.3 ng/L), Citalopram (<MDL-27.9 ng/L), and temazepam (<MDL-12.7 ng/L) were detected in the present study, which were lower than in the United States (99.1 ng/L, mean) (Bahlmann et al., 2014).

3.2. Regional variation on pharmaceutical consumption

The calculated consumptions of NSAIDs, cardiovascular and psychoactive drugs based on Equation (1) were shown in Fig. 1. Significant variations ($p < 0.05$, unpaired *t*-test) were found in specific pharmaceutical consumption between urban and suburban catchments. Higher population-normalized consumption of diclofenac, citalopram, temazepam and venlafaxine were observed in urban than in suburban areas, whereas consumptions of carbamazepine were higher in suburban than in urban areas. Previous studies have shown that the consumption of cardiovascular drugs is related to income, marital status, lifestyle and education (Rousis et al., 2022; Choi et al., 2019), which is consistent with our present study as the urban regions show higher cardiovascular drugs consumption than less-developed suburban areas due to the difference in the prevalence rate. It is reported that the incidence of epilepsy in rural areas is higher than that in urbans (Martinotti et al., 2015; Wagner et al., 2015), which could be the reason for the higher

Table 1
Occurrence and concentrations of the pharmaceuticals in the influent samples of the WWTPs.

Analytes	Detection Frequency (%)			Range (ng/L)		Median concentration (ng/L)		Mean Concentration (ng/L)	
	Total	Suburban	Urban	Suburban	Urban	Suburban	Urban	Suburban	Urban
Atenolol	100	100	100	12.2–62.1	8.40–64.8	30.70	23.0	35.1	30.8
Bezafibrate	70.2	70.4	75.0	<MDL-7.55	<MDL-15.3	3.18	3.65	3.27	5.37
Metoprolol	100	100	100	13.95–84.5	22.0–597	55.10	73.5	48.9	143
Paracetamol	100	100	100	0.20–2610	9.30–4360	29.8	641	516	898
Mefenamic acid	66.7	62.9	75.0	<MDL-303	<MDL-17.3	220	3.60	198	4.29
Naproxen	71.9	81.5	67.8	<MDL-4200	<MDL-1050	372	6.95	1240	129
Diclofenac	100	100	100	0.80–70.6	0.50–725	9.00	14.4	20.9	81.4
Carbamazepine	100	100	100	8.20–39.6	0.20–43.5	13.2	9.44	17.7	11.8
Citalopram	54.4	33.3	78.6	<MDL-2.30	<MDL-27.9	0.850	8.28	0.90	11.0
Temazepam	80.7	88.9	78.6	<MDL-2.55	<MDL-12.7	0.80	1.83	0.95	3.58
Venlafaxine	100	100	100	1.54–21.7	0.90–33.3	7.00	8.05	7.75	11.1

MDL: method detection limits.

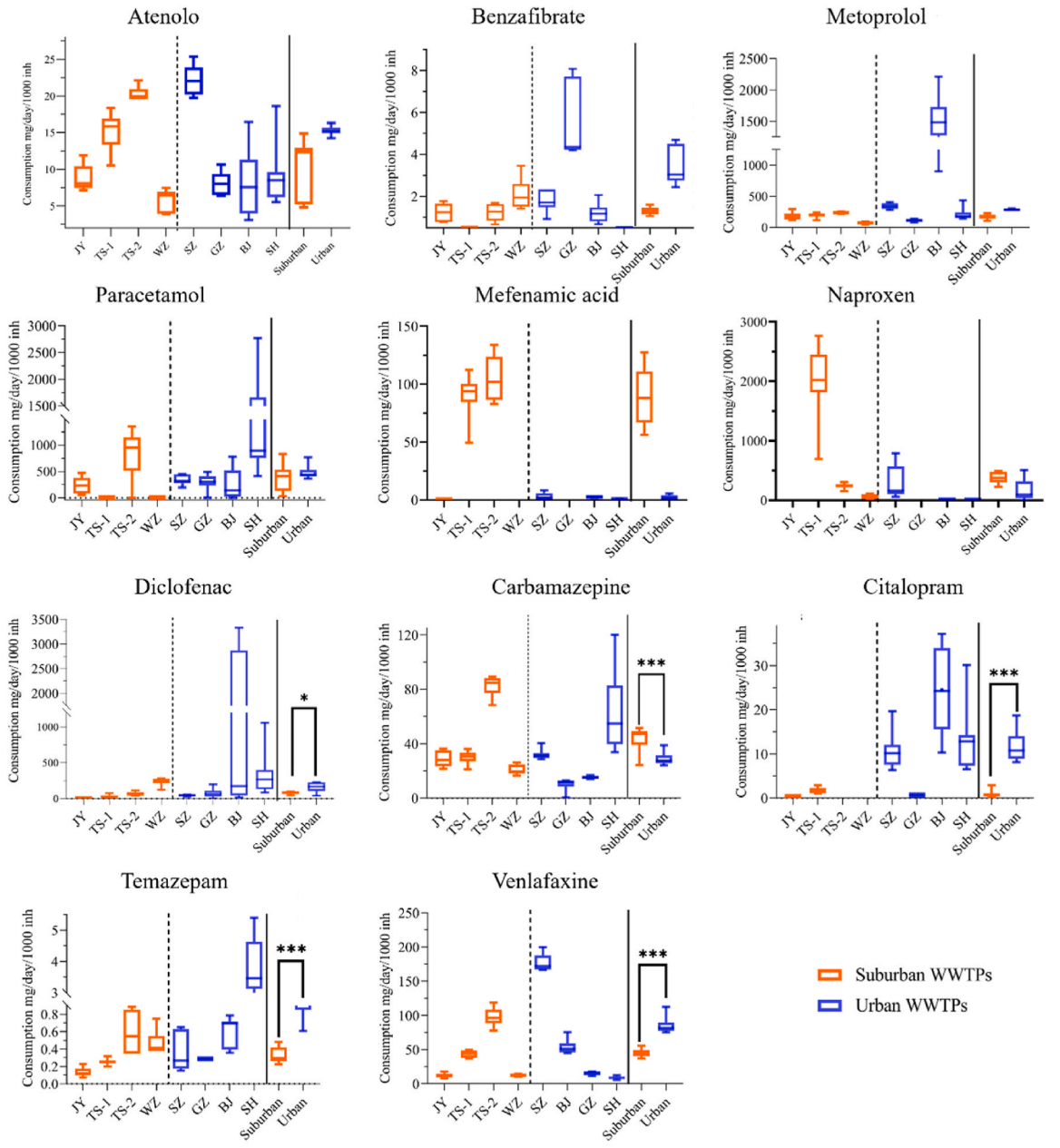

Fig. 1. Pharmaceutical consumption (5th-95th percentile) between urban and suburban catchments. Mean values of pharmaceutical consumptions between urban and suburban areas are shown on the right side of the solid line. *, *** represent $p < 0.05$, 0.01, respectively.

consumption of carbamazepine in suburban catchments. Interestingly, our present study found higher consumption of citalopram and venlafaxine in urban than in suburban areas. Elevated morbidity of depressive disorder in urban than in rural residents may contribute to this finding (Sun et al., 2021), which draw attention to the mental health of residents in metropolitan cities.

To further understand variations of the pharmaceuticals among sampling WWTPs, principal component analysis (PCA) was performed using influent concentrations of drugs with DFs >50%. The first two principal components (PC1 and PC2) explained 50% of the total variability. Factor score plot (Fig. 2A) exhibited that the sampling WWTPs could be separated into four clusters. GZ, WZ, JY, and SZ mainly in the first quadrant represent WWTPs located in south China, while TS1 and TS2 are catchments in northeast China. BJ and SH in the second and third quadrant stand for WWTPs located in north and east China, respectively (Fig. S1). This finding suggested obvious regional variations on pharmaceutical consumption. As shown in loadings plot (Fig. 2B), the first quadrant of benzafibrate is consistent with the highest level in GZ; metoprolol, diclofenac and citalopram located in the second quadrant approaching to BJ; temazepam and paracetamol in the third quadrant related to SH; naproxen and mefenamic acid in the fourth quadrant correspond to the highest consumptions in TS1 and TS2, providing further evidence to the observed regional difference among catchments.

Consumption of cardiovascular drugs, including metoprolol, atenolol, and benzafibrate in the present study (Fig. 1), are consistent with most previous studies in China (Hou et al., 2023), but lower than in developed countries, e.g., Australia, France, and German (Thiebault et al., 2017; Oertel et al., 2023). Similar results were also found for NSAIDs (Yan et al., 2021; Hou et al., 2020; Thomas and Foster, 2010). Consumption of psychoactive drugs in the present study is generally lower than or comparable to that of developed countries. Consumption of venlafaxine and carbamazepine varied from 8.72 mg/day/1000 inh in

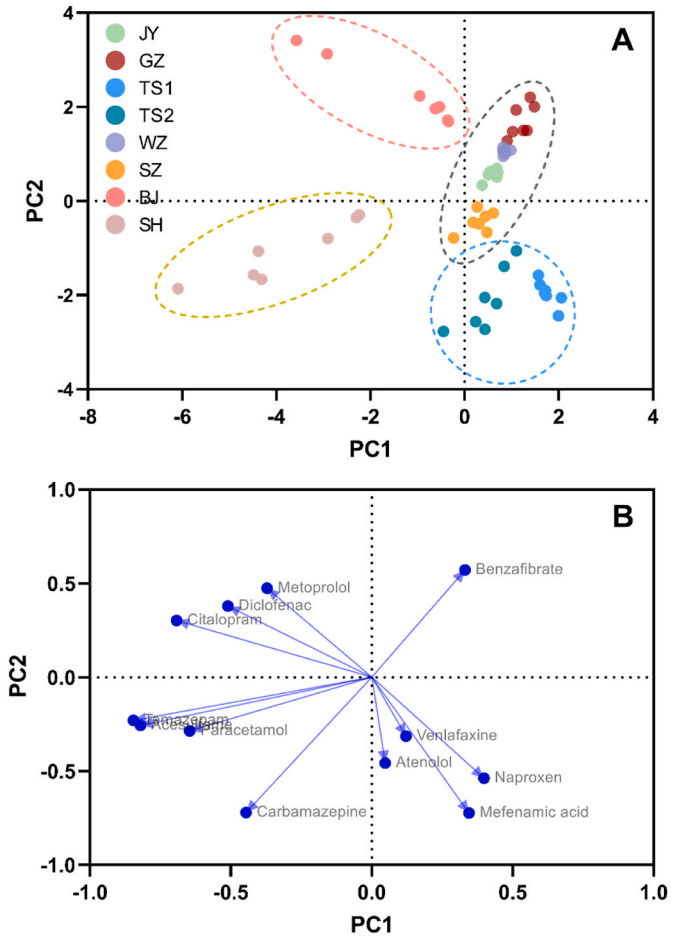

Fig. 2. Principal component analysis results of the studied pharmaceuticals. The figure legends represent the factor scores (A) and factor loadings (B).

Shanghai to 177 mg/day/1000 inh in Shenzhen and from 15.4 mg/day/1000 inh in Beijing to 82.6 mg/day/1000 inh in TS-2, respectively, which were comparable to that in China (Shao et al., 2023), Australia (Wang et al., 2017), and United States (Skees et al., 2018). Consumption of citalopram and temazepam were found from 0.450 mg/day/1000 inh in Jieyang to 24.5 mg/day/1000 inh in Beijing and from 0.135 mg/day/1000 inh in Jieyang to 3.64 mg/day/1000 inh in Shanghai, respectively, which were lower than the United States (Skees et al., 2018; Adhikari et al., 2023). Comparisons on the consumption of the target pharmaceuticals globally are summarized in Table S7. Collectively, the consumption of NSAIDs, cardiovascular, and psychoactive drugs in China is mostly lower than or comparable to that of developed countries, though significant variations existed among sampling regions.

3.3. Removal efficiencies

The removal efficiencies (RE%) of the drugs were calculated as the ratio of the difference between influent and effluent concentrations and the influent concentration. Four of 8 catchments were selected in this study for the removal efficiencies calculation, as automatic samplers were equipped for both influents and effluents in the 4 WWTPs. The treatment process used in the 4 WWTPs includes screening, anoxic and aerobic biological degradation, and disinfection (Table S2). The removal efficiencies for each WWTP are shown in Fig. S2A. The removal efficiency of the target pharmaceuticals ranged from −81.2% to 97.9% (Table 2). High removal efficiency was only observed for paracetamol (RE = 96.3–97.9%), while naproxen (RE = 63.7–82.4%) and

Table 2
Influent and effluent concentrations (ng/L) and removal efficiencies (%) of the pharmaceuticals.

Analytes	Influent (ng/L)	Effluent (ng/L)	Removal efficiencies (%)
Atenolol	32.90	52.19	−58.65
Bezafibrate	4.38	1.63	62.68
Metoprolol	96.90	67.63	30.21
Paracetamol	714.35	14.53	97.97
Mefenamic acid	91.07	61.31	32.67
Naproxen	725.91	128.16	82.35
Diclofenac	50.09	69.07	−37.89
Carbamazepine	14.75	24.40	−65.47
Citalopram	8.05	5.96	25.92
Temazepam	2.18	1.87	14.17
Venlafaxine	9.36	16.97	−81.20

benzafibrate (62.7–78.7%) were removed >60% in all the WWTPs, indicating effectively removed by biological treatment process. Atenolol (RE = −58.7 ~ −16.4%), diclofenac (RE = −37.9 ~ −4.07%), carbamazepine (RE = −65.5 ~ −23.8%), and venlafaxine (RE = −81.2 ~ −26.5%) exhibited low removal efficiencies for all the WWTPs. Similar results were found in previous studies (Ashfaq et al., 2017; Niemi et al., 2020).

It is reported that the physicochemical properties of the chemicals, characteristics of the WWTP, and microbial degradability of the drug are related to the removal efficiency of the pharmaceutical in WWTPs (Barra Caracciolo et al., 2015). We found significantly positive correlation ($p < 0,05$, $r = 0.617$) between Log *Kow* values and removal efficiencies of the pharmaceuticals except for paracetamol (Fig. S2B), indicating pharmaceuticals with lower log *Kow* are less readily removed in WWTPs. Similar correlation was also found by Kim and Oh (2020). Previous study (Behera et al., 2011) interpreted that chemicals with log *Kow* values < 3 are not likely sorbed to suspended particulate matter, which is consistent with our present study, as lower removed drugs of atenolol and venlafaxine have the lowest log *Kow* (0.16 and 0.43) among target pharmaceuticals. In addition, low removal efficiencies could also be attributed to chemical structure and microbial toxicity. For example, chlorine in the structure increases the persistence of diclofenac because the strong electronegativity of chlorine ions lead to strong intermolecular forces and not easy to break (Kimura et al., 2005); Almeida et al. (2014) found that carbamazepine has toxic effect on aquatic microorganisms making it difficult for biochemical units to work. Inversely, higher removal efficiencies of paracetamol and naproxen in the present study could be due to poor resistance to biological degradation, easy sorption to particulate matter, and retransformation of metabolites during biological treatment process (Sun et al., 2016; Yang et al., 2017; Oliveira et al., 2015). Meanwhile, operating conditions for the water treatment processes are the main reasons contributing to the varied removal efficiencies of the drugs among WWTPs, and even the observed negative removal efficiencies. Many studies have reported varied removal efficiencies for different treatment processes (Yadav et al., 2017), e.g., Kim and Oh (2020) found negative removal efficiencies for psychoactive pharmaceuticals. It was speculated that the negative removal efficiency could be associated with deconjugation of glucuronide and sulfate conjugated metabolites, as well as changes in adsorption behavior to particles (Jones et al., 2005; Papageorgiou et al., 2016). The exact factors influencing removal efficiencies of pharmaceuticals in WWTPs are not yet well understood. Nevertheless, removal efficiencies for the operating conditions of WWTPs are essential in identifying the potential ecological risks posed by discharged pharmaceuticals in effluents which requires further studies.

3.4. Ecological risk assessment

The lowest PNEC values for the target pharmaceuticals on algae, daphnia, and fish that were retrieved from available literature are

summarized in Table S8. The RQs of each pharmaceutical in all the sampling sites were calculated based on the effluent concentrations and corresponding PNECs. The RQs of most drugs in the sampling WWTPs were <1, indicating generally low ecological risk (Fig. 3). Atenolol, benzafibrate, paracetamol, and naproxen exhibited negligible risk (RQs <0.1) in all the sampling effluents. Carbamazepine, mefenamic, and temazepam showed potential low risks in several effluents. The RQs for metoprolol, diclofenac, citalopram, and venlafaxine ranged from 0.1 to 10, indicating low or moderate risks in all the studied catchments. It should be noted that moderate risks were found for metoprolol and venlafaxine in the WWTPs of GZ, SZ (south China), and TS2 (north-west China), implying a wide range of elevated risks. These results are consistent with previous studies (Kisielius et al., 2023; Lu et al., 2023; Rapp-Wright et al., 2023) for the low or moderate risks of the pharmaceuticals occurred. Considering the high DFs (100%) and relatively low removal efficiencies, our present study calls for attention to the ecological risks of venlafaxine and metoprolol in the aquatic environment.

3.5. Comparison with national production statistics

We compared our WBE estimations with production-derived estimates for paracetamol, naproxen, carbamazepine, diclofenac, venlafaxine and citalopram (Table S9). The production-derived estimate of diclofenac was within the range of WBE estimations. Lower WBE estimations of paracetamol, naproxen, carbamazepine, and citalopram were found than production statistics. This may be attributed to that not all the produced pharmaceuticals were consumed. Moreover, low prescription adherence and the degradation of these pharmaceuticals during sewer transport and uncertain around the excretion factor may contribute to the results as well (Gao et al., 2022). Otherwise, the WBE estimated consumption of venlafaxine was one order of magnitude higher than the production derived estimate. Variation in seasonal consumption with higher usage during the studied period may partly explain the observation (Tomsone et al., 2022). Additionally, since the production statistic of venlafaxine was generated in 2016 (Shao et al., 2023), it is possibly that the consumption of venlafaxine increased rapidly in recent years (Lu et al., 2023). It should be noted that the present study investigated typical urban and suburban WWTPs which could not represent the whole country of China, thus caution should be exercised when comparing the WBE estimates with production-derived estimates.

3.6. Limitations

In this study, regional-specific consumption of typical pharmaceuticals in China were investigated by WBE, but there are still some limitations. Firstly, the present study evaluated parent pharmaceuticals with no metabolite included, and the stability of the pharmaceuticals in the sewer was not adequately assessed, which may contribute to the large inconsistence with production derived estimates, as parent pharmaceuticals may also originate from, e.g., disposal and production. Secondly, WBE results are susceptible to served population. The served population in this study was employed at the optimal population estimate for wastewater treatment plant operators. However, due to the rapid population growth in megacities such as Beijing and Shenzhen, there is uncertainty in the estimation of accurate served population. Finally, the number of sampling limits. Although this study compared regional variation in the consumption of pharmaceuticals, the limited sampling of each area may result in uncertainty for the data.

4. Conclusions

In this study, regional variation on pharmaceutical consumption was investigated in China by WBE. The estimated consumptions for psychoactive pharmaceuticals were much lower than cardiovascular and NSAIDs. There were differences in pharmaceutical consumption between urban and suburban areas. Consumption of most psychoactive pharmaceuticals were higher in urban than suburban populations, while carbamazepine was more used in suburban than in urban areas. Additionally, this study indicated regional-specific pharmaceutical usage patterns in China, which could provide scientific data for the improvement of environmental and public health policies.

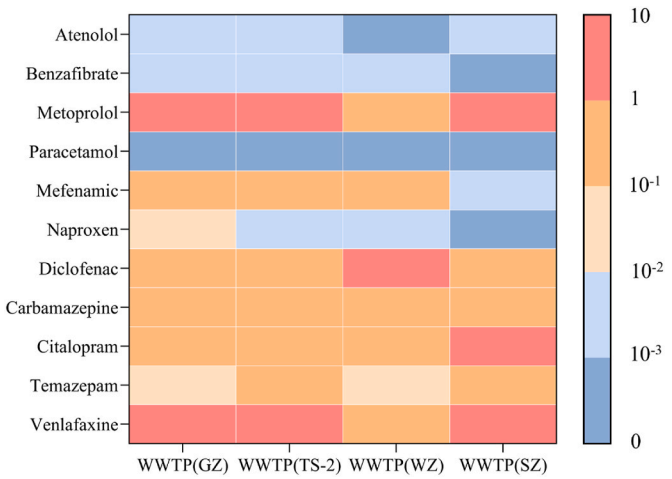

Fig. 3. RQs of the pharmaceuticals in effluent of WWTPs.

CRediT authorship contribution statement

Zongrui Li: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Jincheng Li:** Writing – original draft, Software, Investigation, Formal analysis, Data curation. **Yongxia Hu:** Writing – review & editing, Funding acquisition, Formal analysis. **Yile Yan:** Formal analysis, Data curation. **Shaoyu Tang:** Formal analysis, Data curation. **Ruixue Ma:** Methodology, Investigation. **Liangzhong Li:** Supervision, Resources, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.118544.

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