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Monitoring consumption of methadone and heroin in major Chinese cities by wastewater-based epidemiology

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A R T I C L E I N F O

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A B S T R A C T

Background: Methadone maintenance treatment (MMT) services have been used in China for treatment of heroin dependence. But no study has been conducted to assess the appropriateness of MMT distribution and the potential abuse of methadone in China. This study aims to do that through a nationwide estimation of methadone consumption in China via wastewater-based epidemiology and subsequently compare it with MMT data and level of heroin abuse.

Methods: Wastewater samples were collected from 53 wastewater treatment plants in 27 major cities that cover all geographic regions of China. Methadone and pure heroin consumptions were estimated based on influent concentrations of methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), morphine and codeine.

Results: Drug residues were detected in most samples. The ratio of EDDP/methadone was around 2 in influents and methadone and EDDP loads were strongly correlated, indicating that they originated from human consumption. Both influent methadone and EDDP loads in Southwest and Northwest China were significantly higher than those in other regions. The highest estimated consumptions of methadone and heroin in China were 22.0 ± 2.1 mg/1000 in./d and 263.9 ± 115.9 mg/1000 in./d, respectively. There was a significant positive correlation between methadone and heroin consumptions.

Conclusions: Consumption of methadone in China was primarily from MMT services. The use of methadone and heroin displayed a clear geographical pattern: it is higher in the western inland regions than in the eastern regions. This study has shown that the distribution of MMT services is reflective of the level of heroin abuse in different regions of China.

1. Introduction

Methadone is a synthetic, long acting, potent μ-opioid agonist (Monnelly et al., 2018). It is widely used for maintenance treatment of opioid dependency, particularly for heroin. In China, heroin is one of the most prevalent illicit drugs, with 0.955 million registered abusers in 2016 (OCNNCC, 2017). In order to treat people for heroin dependence in China, methadone clinics were established by the Chinese government in 2004 to provide methadone maintenance treatment services (Li et al., 2013). As a pilot work, there were only eight methadone clinics in five provinces of the country at the beginning. Up to 2006, more than one hundred methadone clinics were established, marking methadone maintenance treatment as a routine medical service in China. The consumption of methadone has increased rapidly over the past decade. Thus, understanding the relationship between the level of methadone use and heroin abuse across China as well as the geographical variation will provide more insights on the effectiveness of drug control and methadone maintenance treatment in the country.

Over the past decade, wastewater-based epidemiology (WBE) has become an alternative method to estimate community drug consumption. WBE studies have been successfully applied to estimate common illicit drug use such as cocaine, methamphetamine, amphetamine within and/or across countries and regions. Some of the results of the studies have been adopted by authorities as evidence for policy makers

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to formulate the drug control strategies (EMCDDA, 2016; ACIC, 2018). However, other addictive drugs such as methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) have not been paid enough attention although they were sometimes included in the multi-residue analysis methods.

WBE has also been frequently applied in China. Lai et al. (2013) performed the first WBE study in Hong Kong for a range of illicit drugs. Khan et al. (2014) and Li et al. (2014) applied the approach to estimate illicit drug use in four megacities (Beijing, Shanghai, Guangzhou and Shenzhen) of mainland China. In recent years, nationwide reconnaissance through WBE has been implemented to estimate methamphetamine, ketamine, heroin and new psychoactive substances use in China (Du et al., 2015, 2017; Xu et al., 2017; Gao et al., 2017). However, methadone has not yet been included in the above WBE campaigns.

The aim of this study was to obtain, for the first time, a snapshot picture of the level of methadone and heroin in major cities across China through WBE. Concentrations of methadone, its metabolite EDDP, morphine and codeine were measured in wastewater samples to estimate the mass loads and the drug consumption in the catchments. Geographical patterns of methadone and heroin use were examined by WBE data and the estimate through methadone maintenance treatments across China.

2. Methods

2.1. Sample collection

Wastewater samples were collected from 27 major Chinese cities distributed in all seven geographic regions of China (Fig. 1). Twenty-five of the above cities are provincial capitals or equivalent to provincial capitals in terms of economic development and population sizes. Beijing and Shanghai are municipalities directly under the central government (Table S1). In total, 53 wastewater treatment plants participated in the sampling campaigns and there were two or more wastewater treatment plants participated in most sampled cities. The total population served by these wastewater treatment plants is 43 million (~3.1% of the population of China). For wastewater treatment plants from the same city, a numerical was added to the city, for example, Beijing-3 for the third wastewater treatment plant of Beijing and Qingdao-1 for the first wastewater treatment plant of Qingdao.

Due to limited resources, the sampling campaign was conducted from July to December of 2016 in most cities as described previously (Du et al., 2018) except that samples from Kunming were collected in May of 2017. Each wastewater treatment plant was sampled for three or four days, except for Changchun-1, Dalian-1, Dalian-2, Lhasa-1 where only one sample was collected (Table S1).

For influent samples, 24-h composite sample was collected using auto-sampler at the rate of 100 mL/h into a cooled sampling container. Auto-samplers (ISCO 3700/6712, Teledyne Technologies Inc., Lincoln, NE, USA; FC-9624, GRASP Science & Technology Co., LTD, Beijing; Sigma-SD900, HACH Inc., USA) were employed to collect time-proportional composite samples. After collection, the composite samples were adjusted to pH = 2 with hydrochloric and frozen immediately at −20℃ at each wastewater treatment plant and were shipped back to the laboratory in frozen state. Analysis was performed as soon as the samples were received at the laboratory. Details of sample collections and information of each wastewater treatment plant (flow rates and served inhabitants) are provided in Table S1.

2.2. Analysis

Standard solutions of methadone, EDDP, morphine, codeine and corresponding deuterated analogs (methadone-d9, EDDP-d9, morphine-

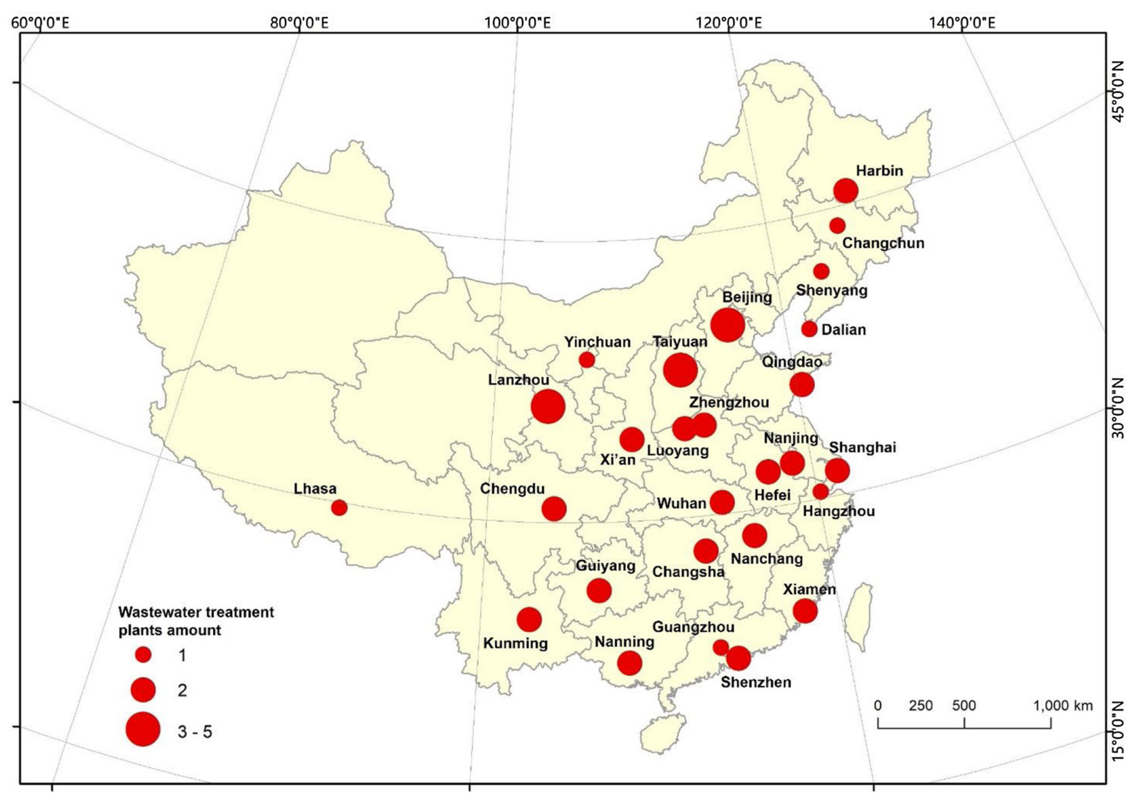

Fig. 1. Map of selected cities where wastewater samples were collected. The sizes of the circles represent the amount of sampled wastewater treatment plants. Xi'an, Lanzhou, and Yinchuan of Northwest China; Beijing and Taiyuan of North China; Shenyang, Changchun, Harbin and Dalian of Northeast China; Changsha and Wuhan, Zhengzhou and Luoyang of Central China; Shanghai, Nanjing, Hangzhou, Qingdao, Xiamen, Nanchang and Hefei of East China; Guangzhou, Shenzhen and Nanning of South China; Kunming, Chengdu, Guiyang and Lhasa of Southwest China.

Table 1
Statistics of methadone, EDDP, morphine and codeine concentrations in wastewater across China.

Chemicals	n	DF[a] (%)	Min ng/L	Median	Max	Mean ± STD
Methadone	208	82	< MDL	2.2	49.9	4.6 ± 6.8
EDDP	208	91	< MDL	4.3	108.0	10.5 ± 15.5
Morphine	208	84	< MDL	41.6	1168.0	86.4 ± 121.6
Codeine	208	99	< MDL	28.4	238.4	42.4 ± 37.9

[a] DF = Detection frequency.

d3 and codeine-d6) to be used as internal standards were all purchased from Cerilliant (Round Rock, TX, USA). Other reagents and materials can be found in Supplementary Material (Text S1).

Sample pretreatment and analysis followed the procedure described in our previous publication (Du et al., 2017) with minor modifications. The analytical method was subjected to strict quality control and quality assurance measures. The method detection limit (MDL), method quantification limit (MQL), recoveries and matrix effects were examined according to previous publication (Du et al., 2018) (Table S3). Details were described in the Supplementary Material (Text S1).

2.3. Mass load and consumption estimation

The daily mass load of each target compound per 1000 in.abitants (mg/1000 in./d) at a specific wastewater treatment plant was estimated by Eq. (1). Where C_i is the influent concentration of the target compound, F_{In} is the influent flow of the specific wastewater treatment plant (obtained from the staff in each respective plant), PS is the population served by the wastewater treatment plant (based on the census data of the wastewater treatment plant service areas).

$$Load = \frac{C_i(ng/L) \times F_{In}(L/d)}{\frac{PS}{1000}} \times \frac{1}{10^6}\left(\frac{mg}{ng}\right) \tag{1}$$

The consumption (mg/1000 in./d) of methadone was estimated by the following equation:

$$Consumption_{MTD} = Load_{MTD} \times \frac{MW_{MTD}}{MW_{EDDP}} \times \frac{1}{EF_{MTD}} \tag{2}$$

$Load_{MTD}$ is daily mass load of methadone at a specific wastewater treatment plant, MW_{MTD} is the molecular weight of methadone, MW_{EDDP} is the molecular weight of EDDP, and EF_{MTD} is excretion fraction of a given dose of methadone excreted as main metabolite (EDDP) through urine.

The consumption (mg/1000 in./d) of pure heroin was estimated based on the influent concentrations of both morphine and codeine using the procedure described in a previous paper (Du et al., 2017). Detailed description can be found in Text S2.

Uncertainties involved in the above estimation process have been discussed in previous studies (Li et al., 2014; Du et al., 2017).

2.4. Consumption in methadone maintenance treatment

Data of methadone consumption in methadone maintenance treatment were collected from the cities Kunming and Shenzhen. The data were supplied by Workgroup of Kunming Methadone Maintenance Treatment and Clean Syringe Exchange and Workgroup of Guangdong Detoxification Medicine Maintenance Treatment.

2.5. Statistical analysis

Normality was examined through the Kolmogorov-Smirnov (K-S) test before other analyses. Pearson correlation analysis was used to assess the correlation between methadone and EDDP loads, morphine and codeine loads, methadone and heroin consumptions. The significance of geographical variation of mass loads and consumptions were assessed via one-way ANOVA. Student-t test was employed for comparing the differences of consumptions in weekdays and weekends, and differences between estimated methadone consumptions and therapeutic methadone. All statistical analyses were performed using SPSS 20 (IBM Co., USA), with a p-value below 0.05 meaning the difference is statistically significant.

3. Results

3.1. Influents concentrations of biomarkers

Concentrations of methadone and EDDP in influent samples ranged from < MDL to 49.9 ng/L (mean ± STD, 4.6 ± 6.8 ng/L) and < MDL to 108.0 ng/L (mean ± STD, 10.5 ± 15.5 ng/L), with detection frequencies of 82% and 91%, respectively (Table 1). There were 7 wastewater treatment plants with the mean EDDP concentrations > 20 ng/L (Lanzhou-2, Lanzhou-3, Lanzhou-4, Xi'an-1, Kunming-1, Kunming-2 and Guiyang-1) indicating a high level of methadone consumption in the catchment (Table S4). The wastewater treatment plant with highest mean methadone and EDDP concentrations is Lanzhou-2 (32.7 ± 17.5 ng/L and 63.7 ± 38.8 ng/L) while methadone and EDDP were not detected in the influents of Harbin-1, Harbin-2, Changchun-1, Shenyang-1, Dalian-1 and Lhasa-1 (Table S4). Mean ratio of EDDP/methadone was 2.24 ± 0.86 in influent samples. The detection frequencies of morphine and codeine were 84% and 99% in influent samples, with concentrations ranging from 41.6 to 1168.0 ng/L (mean ± STD, 86.4 ± 121.6 ng/L) and 28.4 to 238.4 ng/L (mean ± STD, 42.4 ± 37.9 ng/L), respectively (Table 1). There was only one wastewater treatment plant (Lhasa-1) with both the morphine and codeine concentrations below MDL in influents (Table S4). The highest mean morphine and codeine concentrations were also found at Lanzhou-2 (528.6 ± 448.8 ng/L and 141.5 ± 77.7 ng/L). Mean ratio of morphine/codeine was 2.34 ± 1.86 in influent samples, and it was much higher than that in European countries (Östman et al., 2014; Vuori et al., 2014).

3.2. Daily loads of methadone, EDDP, morphine and codeine

The daily per capita loads of methadone and EDDP (major human metabolite of methadone) at sampled wastewater treatment plants varied from wastewater treatment plant to wastewater treatment plant, ranging from < 0.1 to 8.9 ± 4.8 mg/1000 in./d for methadone and < 0.1 to 17.4 ± 10.6 mg/1000 in./d for EDDP (Fig. 2, Table S5). The highest mean methadone load was found at Lanzhou-2 (8.9 ± 4.8 mg/1000 in./d), followed by Lanzhou-4 (5.1 ± 1.6 mg/1000 in./d). Mean methadone loads in the others wastewater treatment plants were below 5 mg/inh/d. The highest mean EDDP load was also found at Lanzhou-2 (17.4 ± 10.6 mg/1000 in./d), followed by Xi'an-1 (13.5 ± 4.1 mg/1000 in./d) and Kunming-2 (11.7 ± 3.6 mg/1000 in./d). Statistically significant positive correlation was found between influent methadone and EDDP loads ($p < 0.05$) (Fig. 2).

The average influent loads of methadone and EDDP were 1.0 ± 1.3 mg/1000 in./d and 2.5 ± 3.1 mg/1000 in./d (population-weighted average ± STD) in all 53 wastewater treatment plants. These loads were much lower (nearly one or two order of magnitude) than the loads reported in wastewater from other countries, such as Croatia (Krizman-Matasic et al., 2019), UK (Baker and Kasprzyk-Hordern, 2011), Italy (Castiglioni et al., 2006; Cosenza et al., 2018), France (Nefau et al., 2013), Switzerland (Berset et al., 2010), Spain (Martínez Bueno et al., 2011), Australia (Bade et al., 2018; Thai et al., 2016) and the USA (Foppe et al., 2018; Skees et al., 2018). The values were similar with those in Slovakia (Mackul'ak et al., 2016), Belgium (van Nuijs et al., 2011) and Sweden (Östman et al., 2014).

For morphine and codeine, the mean loads in influents at sampled wastewater treatment plants were ranging from < 0.2 mg/1000 in./d to

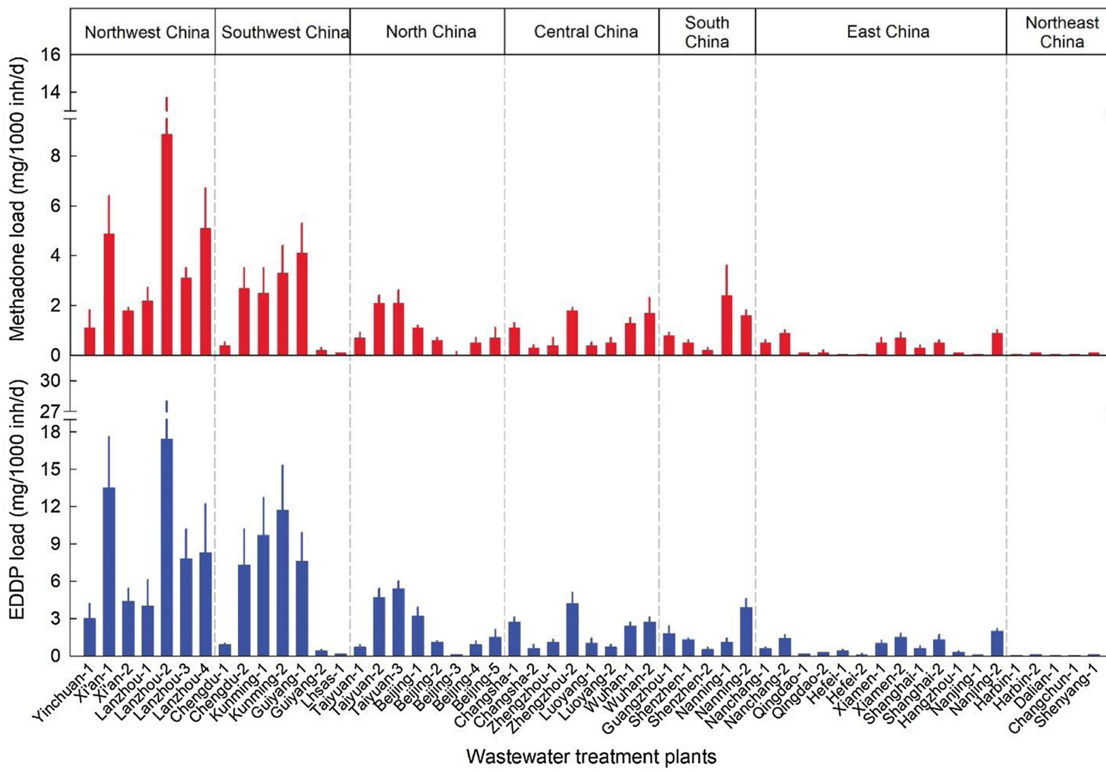

Fig. 2. Influent mean loads of methadone and EDDP at the wastewater treatment plants across China.

144.4 ± 122.6 mg/1000 in./d and < 0.2 mg/1000 in./d to 41.7 ± 4.8 mg/1000 in./d, respectively (Fig. S2, Table S5). The highest mean loads of morphine and codeine occurred in Lanzhou-2 (144.4 ± 122.6 mg/1000 in./d) and Nanchang-2 (41.7 ± 4.8 mg/ 1000 in./d), respectively. In most wastewater treatment plants, morphine loads were greater than that of codeine. The average influent loads of morphine and codeine were 23.5 ± 28.5 mg/inh/d and 12.7 ± 10.3 mg/inh/d (population-weighted average ± STD) across the country. These loads were lower than many countries such as UK (Baker et al., 2014), Sweden (Östman et al., 2014), Spain (Boleda et al., 2009), Australia (Lai et al., 2013), Canada (Yargeau et al., 2014), etc. There was a significantly positive correlation between morphine and codeine loads, which is consistent with our previous study (Du et al., 2017). There were no significant differences between the average morphine and codeine loads and the values in our previous study in 2014 and 2015 (Du et al., 2017) ($p <$ 0.05). Minor variation of morphine and codeine loads compared to data of 2014–2015 (Du et al., 2017) indicates a relatively stable level of heroin consumption in recent years in China. This finding was consistent with the minor variation of heroin seizures in 2014 (9.3 t) and 2016 (8.8 t) (OCNNCC, 2015, 2017).

3.3. Consumptions of methadone and heroin

We used the major human metabolite of methadone to estimate the methadone consumption. The excretion rate of EDDP (55%) was applied (Thai et al., 2016). Average methadone consumption in major Chinese cities ranged from < 0.2 mg/1000 in./d to 22.0 ± 2.1 mg/ 1000 in./d (population-weighted average ± STD) (Fig. 3, Table S6). There were 5 cities with the average methadone consumption above 10 mg/1000 in./d: Kunming (22.0 ± 2.1 mg/1000 in./d), Lanzhou (17.3 ± 9.6 mg/1000 in./d), Xi'an (14.1 ± 8.3 mg/1000 in./d), Guiyang (12.8 ± 5.6 mg/1000 in./d) and Chengdu (11.2 ± 5.9 mg/ 1000 in./d). All these cities were located in the Southwest and Northwest China, indicating overall high use of methadone in these two regions. The average consumptions in Yinchuan, Taiyuan, and Nanning were between 5 to 7 mg/1000 in./d, and the other cities with consumptions below 5 mg/ 1000 in./d.

As a major metabolite of heroin, morphine was used to estimate its consumption. However, as showed in Eq. S1 to S4 in the Supplementary Material, we had to subtract the morphine measured in wastewater by the amount of morphine originated from prescription of morphine and codeine as well as from heroin product (as impurities). As such the heroin consumption was set as zero when negative estimates were obtained. The population-weighted average consumption of pure heroin ranged from 0 (Changchun, Nanjing and Lhasa) to 263.9 ± 115.9 mg/ 1000 in./d (Chengdu) in major cities of China (Fig. 3, Table S6). Chengdu had the highest consumption, followed by Lanzhou (241.1 ± 85.7 mg/1000 in./d). In total, there were 3 cities (Kunming, Guiyang and Xi'an) with consumptions between 100 mg/1000 in./d to 200 mg/1000 in./d, and the consumptions were below 100 mg/ 1000 in./d in the others.

4. Discussion

4.1. Sources of biomarkers in influents

The ratio of EDDP/methadone measured across wastewater treatment plants is relatively stable around 2, which is similar to that reported by Thai et al. (2016, 2019). This ratio indicated that those drug residues in wastewater samples highly likely originated from human consumption. Significant correlation between influent methadone and EDDP loads again confirmed that methadone and EDDP found in wastewater of cities in China are from human metabolism of methadone rather than direct disposal (Fig. 2). The high ratio of morphine/codeine in across wastewater treatment plants (Fig. S1) also confirm that morphine found in wastewater was predominantly from street heroin use, as reported in our previous study (Du et al., 2017).

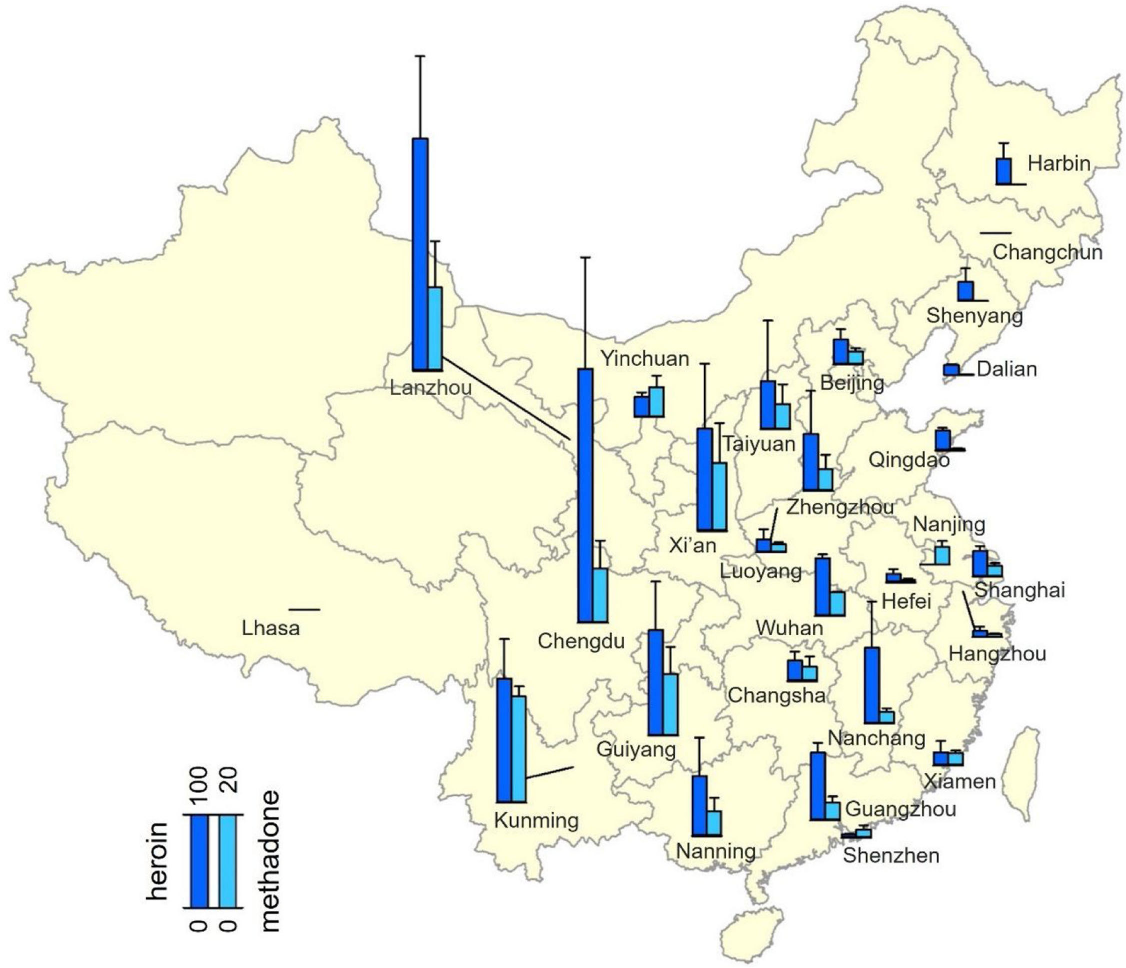

Fig. 3. Average consumption of methadone and heroin (mg/1000 in./d, population-weighted average) in major cities of mainland China.

4.2. Geographical variation of methadone and heroin use in China

The methadone and EDDP loads of sampled wastewater treatment plants in all seven regions of China followed normal distributions (K-S test, $p > 0.05$). One-way ANOVA reveals that methadone and EDDP loads in wastewater display a clear geographical pattern ($p < 0.05$). The methadone and EDDP loads in Northwest China and Southwest China were significantly higher than North China, Central China, South China, East China and Northeast China (Fig. 2). East China and Northeast China had the lowest methadone and EDDP loads. In general, methadone and EDDP loads decreased from the west to the east of the country, although there was an exception for Lhasa (in Southwest China). The findings were similar in morphine and codeine loads (K-S test, $p > 0.05$; One-way ANOVA, $p < 0.05$), with higher loads in the western inland regions than in the eastern regions (Fig. S1). These results indicated the fact that both methadone and heroin are more prevalently in west regions of China. This geographical pattern of methadone and heroin use are mainly attribute to opioids input from the “Golden Crescent” and “Golden Triangle” areas to Northwest and Southwest China. Differences in average daily methadone dose levels, purity of street heroin, and ways of drug use (such as injecting and smoking) in different cities could be also causing the geographical pattern. In addition, the cities with the highest/lowest methadone or heroin consumption indicated that there was relatively high/low methadone or purity of heroin dose level.

4.3. Comparison of MTD and heroin consumptions

A significant positive correlation ($p < 0.05$) between the consumptions of methadone and pure heroin in China can be derived from the results of this study (Fig. 3). This correlation implies that more methadone was used for treatment of heroin dependence where the heroin use was more prevalent, which in turn indicates a good response (based on the correlation between methadone and heroin consumption) of public health system toward heroin dependence problem in cities across China. In addition, data of methadone consumptions from methadone maintenance treatment clinics were collected and compared with WBE data in Kunming and Shenzhen. The total consumptions of methadone maintenance treatment were 3,380,091 mg in May 2017 at the urban areas of Kunming (4.88 million inhabitants) and 609,680 mg in December 2016 in Shenzhen (11.91 million inhabitants), which equate to 23.1 mg/1000 in./d in Kunming and 1.7 mg/1000 in./d in Shenzhen. According to the WBE estimates, methadone consumption of Kunming was 22.0 ± 2.1 mg/1000 in./d and that at of Shenzhen was 1.7 ± 0.9 mg/1000 in./d, which matched very well with the data from methadone maintenance treatment clinics mentioned above. The result indicated that methadone and EDDP found in influent wastewater, no matter high or low, were predominantly from methadone maintenance treatment source rather than the abuse of methadone in the two cities. This finding was further supported by the lack of detection of methadone and EDDP in both Harbin and Lhasa where there was no methadone clinic (Heilongjiang and Tibet provinces). Additionally, methadone is rarely seized by Chinese law enforcement authorities (OCNNCC, 2017), indicating that methadone is not prevalent on the illicit drug market. But, it didn't mean that the methadone dose level was high enough to prevent withdrawal, or the patients withdrawn from methadone. Meanwhile, the result couldn't indicate that there was no diversion or supplemental supplies of methadone available, or no patients go looking for other sources to prevent withdrawal in other Chinese cities.

5. Conclusions

In summary, as the first study to report concentrations of methadone and EDDP in wastewater on a national scale in China, this paper fills a data gap in the understanding of methadone use in China. The results of this study suggested that methadone, EDDP, morphine and codeine in wastewater of the majority of cities in China comes from human consumption of methadone and heroin. Consumption of methadone was primarily from methadone maintenance treatment in most major Chinese cities. The average consumptions of methadone and heroin in China ranging from < 0.2 to 22.0 ± 2.1 mg/1000 in./d and from 0 to 263.9 ± 115.9 mg/1000 in./d, respectively. Methadone and heroin consumptions in Northwest and Southwest China were much higher than that in other regions.

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Contributors

Peng Du and Xiqing Li conceived the study. Peng Du, Ya Bai, Zilei Zhou and Zeqiong Xu conducted the sampling campaign and analysis. Jing Wang and Congbin Zhang collected the data of methadone consumptions in methadone maintenance treatment (Kunming and Shenzhen). Peng Du performed the data analysis and generated the figures and tables. Peng Du, Phong K. Thai, Xiqing Li, Xuan Zhang, Congbin Zhang, Jing Wang and Fanghua Hao wrote and reviewed the manuscript.

Declaration of Competing Interest

Authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.06.034.

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