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Do the lockdown-imposed changes in a wastewater treatment plant catchment's socio-demographics impact longitudinal temporal trends in psychoactive pharmaceutical use?

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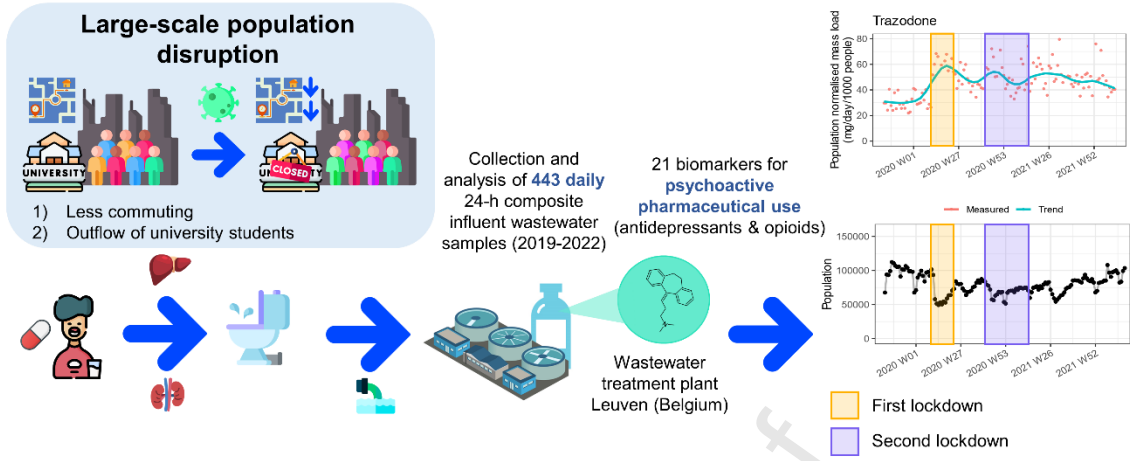
Keywords

Opioids; antidepressants; wastewater based epidemiology; COVID-19; mobile phone data; socio-demographics

Graphical abstract



Abstract

Wastewater-based epidemiology (WBE) includes the analysis of human metabolic biomarkers of xenobiotics in influent wastewater. WBE complements existing drug utilisation approaches and provides objective, spatio-temporal information on the consumption of pharmaceuticals in the general population. This approach was applied to 24-h composite influent wastewater samples from Leuven, Belgium. Daily samples were analysed from September 2019 to December 2019 (n=76), and on three days of the week (Monday, Wednesday, Saturday) from January 2020 to April 2022 (n=367). Sample analysis consisted of 96-well solid-phase extraction and liquid chromatography coupled to tandem mass spectrometry. Measured concentrations of 21 biomarkers for antidepressant and opioid use were converted to population-normalised mass loads (PNML) by considering the flow rate and catchment population. To capture population movements, mobile phone data was used. Amitriptyline, hydroxy-bupropion, norcitalopram, citalopram, normirtazapine, trazodone, O-desmethylvenlafaxine, codeine, 2-ethylidene 1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), methadone, morphine, O-desmethyltramadol, and tramadol were included in the temporal assessment since concentrations were above the lower limit of quantification. The PNML of most biomarkers increased (with 3-119%) throughout the sampling period. The population disruption during the COVID-19 pandemic led to a major change in the socio-demographics of the catchment area, resulting in temporal differences in the PNML of the different biomarkers. As such, higher PNML were observed during the different lockdown phases, which were characterized by the outflow of university students and a decreasing commuting in and out the catchment area. The effects of the fluctuating socio-demographics of the catchment population were further evidenced by the different week-weekend pattern of PNMLs over the course of the sampling campaign. Mean parent/metabolite ratios (i.e., citalopram/norcitalopram, tramadol/O-desmethyltramadol, venlafaxine/O-desmethylvenlafaxine, and methadone/EDDP) remained relatively stable throughout the entire sampling campaign (RSD% below 25% for all ratios, except for methadone/EDDP) and therefore were not affected by this population change.

1. Introduction

Drug Utilization Research (DUR) applies descriptive and analytical methods to quantify, understand and evaluate the different processes of drug utilization, including prescription, dispensing and consumption of pharmaceuticals and delivers insights into patterns, efficiency, quality and results of pharmaceutical use (World Health Organization, 2003). Currently, epidemiologic DUR information sources monitor pharmaceutical consumption through health interview surveys (HIS) and sales, billing, prescription and dispensing data (IQVIA, 2020; National Institute for Health and Disability Insurance (RIZIV), 2022; Sciensano, 2018). Even though HIS provide useful information on the determinants of pharmaceutical use, they also have some inherent limitations and challenges. Particularly, concealment and reporting bias are commonly associated with self-reported surveys, complicating the objective measurement of highly stigmatised and often concealed behaviour such as present in psychiatric disorders. Additionally, the infrequency of data reporting (i.e., not on a yearly basis), delay in data acquisition, and lack of spatial specificity are main limitations of these HIS. Furthermore, data on pharmaceutical sales, dispensing and prescriptions do not provide information about the actual amount of pharmaceuticals used in the population (Poluzzi et al., 2016; World Health Organization, 2003). Figure S1 visualizes trends in the use of psychoactive pharmaceuticals in Belgium based on different DUR data sources (National Institute for Health and Disability Insurance (RIZIV), 2022; Sciensano, 2018). In general, the number of opioid and antidepressants deliveries (i.e. the fraction of prescribed pharmaceuticals that were supplied to the patient) between January 2013 and May 2020 in Belgium has decreased with 1.4% and 3.6%, respectively. (National Institute for Health and Disability Insurance (RIZIV), 2022). On the other hand, results from the HIS revealed that the number of people who used psychoactive medication almost doubled from 1997 through 2018 (Sciensano, 2018). Due to incongruent epidemiological data between different DUR data sources, more up-to-date, complementary epidemiological information is needed to obtain the full picture of psychoactive pharmaceutical use in Belgium.

Influent wastewater (IWW) contains a wealth of information on lifestyle and public health aspects of local population groups (Boogaerts, Ahmed, et al., 2021; Daughton, 2001; Zuccato et al., 2008). Therefore, the analysis of IWW on human metabolic excretion products can be applied to measure a population's consumption of or exposure to different xenobiotics. Wastewater-based epidemiology (WBE) is based on the measurement of trace concentrations of these biomarkers in IWW. Within this approach, measured concentrations of human biomarkers are converted to population-normalized mass loads (PNML) by multiplying with the daily wastewater flow rate and dividing by the catchment population served by the wastewater treatment plant (WWTP) (Baker et al., 2014). Although the majority of WBE studies have focussed on monitoring recreational substances (e.g., illicit drugs,

alcohol, tobacco,…) in defined population groups (Baz-Lomba et al., 2016; Estévez-Danta et al., 2022; Gao et al., 2020; González-Mariño et al., 2020; Huizer et al., 2021; Thomas et al., 2012; van Nuijs et al., 2011), there has been a growing number of applications on pharmaceuticals that highlight the potential of WBE to reduce current knowledge gaps in DUR (Bade et al., 2020; Boogaerts, Ahmed, et al., 2021; Choi et al., 2019; Riva et al., 2020; Tscharke et al., 2016). However, the number of studies that measure psychoactive pharmaceuticals in IWW are limited and often only a small selection of compounds, locations and/or time points are being monitored (Boogaerts et al., 2019; Boogaerts, Quireyns, et al., 2021; Centazzo et al., 2019; Fattore et al., 2016; Fidan & Bakirdere, 2016; Krizman-Matasic et al., 2018; Rice et al., 2020; Silva et al., 2014; Subedi & Kannan, 2015).

WBE can be applied to monitor temporal patterns of pharmaceutical use or document interventions such as rescheduling (e.g., changing from over-the-counter to prescription only), sales-restrictions, and educational programs to influence prescription behaviour or consumer choice (Crowley et al., 2017; Golovko et al., 2014; Mackulak et al., 2016; Tscharke et al., 2016; Zhang et al., 2019). For example, a Chinese study reported a decline in antibiotic use following policy measures to prevent their prophylactic use during flu season in China (Zhang et al., 2019). WBE can also shed light on the temporal changes in the consumption patterns of pharmaceuticals during public health crises, such as the COVID-19 pandemic (Alygizakis et al., 2021b; Galani et al., 2021; Reinstadler et al., 2021; Tomsone et al., 2022; Yavuz-Guzel et al., 2022).

During the government-imposed lockdowns, the socio-demographics of the catchment population may be significantly different compared to the pre-pandemic period. Different WBE studies have proven the relationship between catchment specific sociodemographic parameters (e.g., age, socio-economic status,…) and per capita biomarker loads of different pharmaceuticals in these respective areas (Choi et al., 2019; Thomaidis et al., 2016). Additionally, the changes in demographic composition of a population over time can be measured using WBE (Thomaidis et al., 2016). For example, Thomaidis et al. observed a dramatic increase in the consumption of psychiatric pharmaceuticals (35-fold) and antidepressants (11-fold) during the economic crisis in Greece between 2010 and 2014 after the implementation of austerity measures. Changes in WWTP catchment socio-demographics might particularly occur during the COVID-19 pandemic since population movements are heavily impacted by the wide array of interventions including home confinement and social distancing.

The present study reveals temporal trends in the PNML of 14 biomarkers for opioid and antidepressant use (including both parent drugs and metabolites) from September 2019 through April 2022 in WWTP Leuven, Belgium. Particularly, this study investigates whether temporal trends

in the per capita biomarker mass loads are associated with demographic changes in the catchment population during the lockdown-imposed measures. Mobile phone data was used to estimate the *de facto* population numbers for calculation of the PNML. Additionally, this study aims to determine changes in the parent/metabolite ratios of 12 biomarkers for which both parent drugs and metabolites were measured during the sampling period. Finally, relative changes in PNML of the different biomarkers for psychoactive pharmaceutical use were compared with the temporal patterns in the number of pharmaceutical deliveries in the same geographical area.

2. Materials and methods

2.1. Sampling

Daily 24-h composite IWW samples were collected from the WWTP in Leuven, Belgium from September 2019 to December 2019 (n=76), and on three weekdays (Monday, Wednesday, Saturday) from January 2020 to April 2022 (n=367). This sampling strategy was chosen because preliminary data showed that the weekly mean of the PNML of the different biomarkers was similar to the 3-day average (data not shown), as was also suggested in other WBE studies (Bertels et al., 2022). The inclusion of a weekend day was of importance because of the differences in measured PNML between the weekends and the work week. In case of a missing IWW sample (e.g., due to a technical difficulty at the WWTP), another week- or weekend day was used instead to have a weekly average based on 3 measurements.

The autosampler device operated in a time-proportional manner at a high frequency (10 min) and at 4 °C to compile representative daily IWW samples to guarantee accurate average biomarker concentrations over a 24-h period (Ort et al., 2010). Upon sample collection at the WWTP, IWW samples were immediately frozen at -20 °C to ensure high-in sample stability during storage. Average hydraulic residence times in the wastewater system were less than 24 h and sewage temperature was in the range 11 °C to 24 °C. As visualized by Figure S2, the boundaries of WWTP Leuven not only capture the mid-size university city of Leuven, but also include twelve surrounding municipalities. The catchment area of WWTP Leuven harbors a substantial number of university students and changes in the use of psychoactive pharmaceuticals may be related to changing socio-demographics during the sampling period. A 2019 survey indicated that 47 252 students were enrolled at the university campus in Leuven, which corresponds with approximately 45% of the catchment population (KU Leuven, 2019). However, the *de facto* number of students will potentially be lower because not every enrolled student will be present each day in the catchment area. During the weekends, there is a major outflow of students from the catchment area, as reflected by the weekly changes in population numbers (see Figure 1). The same survey indicated that 90% of

students return home during the weekends. Therefore, the contribution of students during the weekends versus the workweek differs substantially. More information on the age demographics of the residents of the city of Leuven (excluding the university students) can be found in Figure S3 (STATBEL, 2022). Commuting patterns during the workweek versus the weekend might also be different.

2.2. Sample preparation and instrumental analysis

Sample preparation was done according to a previously validated method by *Boogaerts and Quireyns et al* capable of measuring 24 biomarkers of psychoactive pharmaceutical use (Boogaerts, Quireyns, Maes, et al., 2022). More information on the materials can be found in the Supplementary Information (S.2.). Briefly, 2 mL of IWW is acidified with 6 µL formic acid and, subsequently, spiked with an internal standard mixture. Solids are removed through centrifugation for 5 min at 10 000 *x g*. Sample extraction is done with a 96-well MCX solid phase extraction (SPE) procedure. Conditioning of the sorbent is performed with 500 µL of methanol and 500 µL of ultrapure water, both with 0.3% v/v formic acid. Then, 1.8 mL of the supernatant is loaded on the 96-well plate under vacuum. Washing is done consecutively with i) 500 µL ultrapure water with 0.3% formic acid, ii) 500 µL methanol with 0.3% formic acid and iii) 500 µL 30/70 v/v methanol/water. Subsequently, the sorbent is dried for 5 minutes under vacuum. Elution of the analytes is done with 200 µL of 5% v/v ammonia in methanol into a collection plate. The eluent is evaporated to dryness in a Biotage SPE Dry 96 device at 37 °C using nitrogen (2.5 L/min bottom, 50 L/min top). Reconstitution of the samples is done with 120 µL of 95/5 ultrapure water/methanol with 0.1% formic acid. Finally, the extracts are vortexed for 2.5 min at 1 500 *x g* and filtered with Agilent filtration plates (0.2 µm polypropylene, 96 well, 1 mL) into a 96-well injection plate ready to be analysed with liquid chromatography-tandem mass spectrometry (LC-MS/MS).

2.3. Back-calculations

Concentrations measured with LC-MS/MS were used to back-calculate PNML of the biomarkers for psychoactive pharmaceutical use (expressed in mg/day/1000 inhabitants), using daily wastewater flow rates (L/day) and population estimates based on mobile phone data using previously published methods (Boogaerts, Bertels, et al., 2022; Boogaerts, Quireyns, de prins, et al., 2022). Normalisation for wastewater flow and population size allows for comparisons of intake estimates between different time points. Daily measured PNML observations of the different biomarkers of interest were averaged by week (section 2.1). The equation for the estimation of the PNML is given in Equation 1:

Equation 1 Back-calculation to population-normalized mass loads

$$PNML\left({}^{mg}/_{day}\cdot 1000\ inhabitants\right)=\frac{concentration\left(\frac{ng}{L}\right)\cdot wastewater\ flow\left(\frac{L}{day}\right)}{population_{(Leuven)}}$$

The de facto population contributing to the sewage system was estimated based on passive mobile phone signalling records. Previous studies and reports showed that the use of an anthropogenic population proxy is highly advised to account for population fluctuations during the COVID-19 pandemic (Boogaerts, Quireyns, de prins, et al., 2022; Google, 2022; Reinstadler et al., 2021).

Daily population size numbers were acquired from Cropland, a partner of Orange (a mobile network provider), which also performed data analysis and validation. Their approach consisted of overlaying mobile phone masts with the catchment area. To estimate the population, mobile phone signals originating from the catchment area and present for longer than 2 h were included . When a mobile phone signal was absent for at least 3 hours it was excluded again. All records were filtered to exclude Internet of Things and machine-to-machine communications, and subsequently aggregated. In a next step, these records were extrapolated to population estimates by taking into account zone probability (98%), contact probability (98%), the number of persons per device (1.15 persons per device; taking into account people without a mobile device) and the market shares among local (18%) and non-national foreigners (33%). These extrapolation parameters were provided and externally validated by Cropland and are expected to be constant over time due to the size of the WWTP catchment. Additional details regarding the validation are not available due to proprietary and privacy constraints. Definitions of these extrapolation parameters can be found in the Supplementary Information (S 3.). A detailed description of this methodology can be found elsewhere (Boogaerts, Quireyns, de prins, et al., 2022).

Figure 1 illustrates the day-to-day variations in population size in the catchment area of Leuven. The relative pattern in population size shows decreases (up to 50%) in population size during the lockdown phases in Belgium (i.e. from 14 March 2020 through 8 June 2020 and from 19 October 2020 through 8 May 2021) and during the holiday periods (i.e. Christmas holidays, summer vacations at high schools and the university of Leuven). A week-weekend difference in the *de facto* population numbers was observed throughout the entire sampling campaign. A temporal change in PNML might occur due to several reasons including (i) temporal trends in consumption patterns; (ii) changes in population sizes and (iii) socio-demographic changes within the catchment population. The use of a dynamic population marker, such as mobile phone data, is necessary to account for the daily variations in the population present in the catchment area. After implementation of a dynamic population proxy, a temporal change in the PNML can be caused by differences in consumption

patterns, changes in the socio-demographic composition of the catchment area or a combination of both.

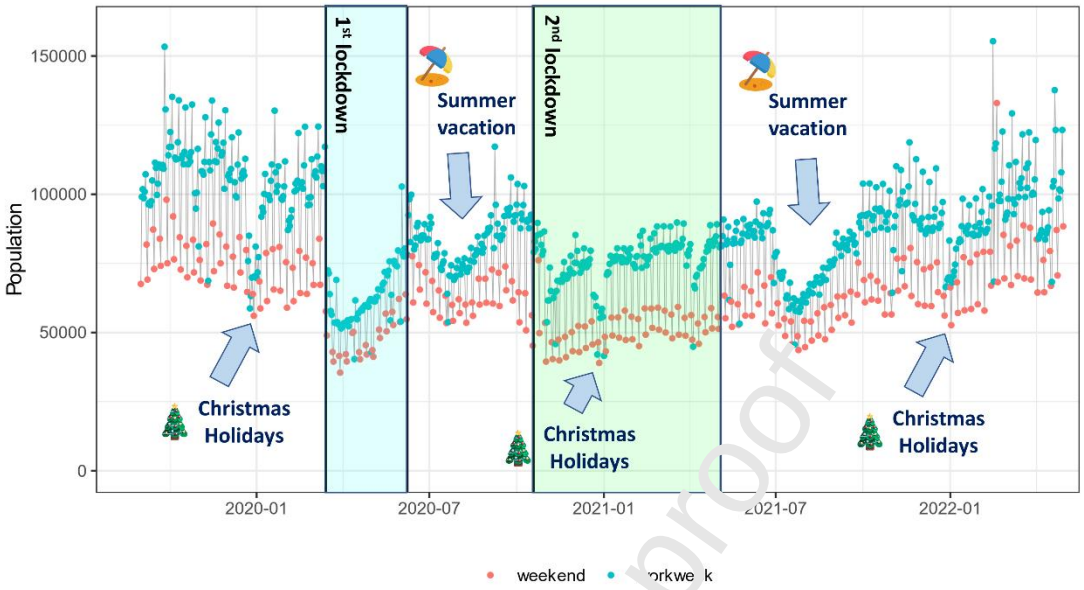


Figure 1 Daily population variations in the catchment area of wastewater treatment plant Leuven during the sampling campaign. Weekdays are visualized in blue; weekend days in red.

2.4. Time series analysis

An autocorrelation function was used to investigate seasonality, but no clear relationship was found between periodic time lags (e.g., seasonality and yearly). In order to assess seasonality, a first-order differencing was executed prior to the autocorrelation step to extract the longitudinal trend from the time series (i.e. the overall non-seasonal pattern). Since no seasonality was found, locally estimated scatterplot smoothing (LOESS) was used to plot the trend in the PNML of the psychoactive pharmaceutical biomarkers. The effect of different spans (between 0.2 and 0.8) was tested though a sensitivity analysis (Wildman, 2017). A span of 0.25 was the most appropriate for smoothing the trend. Imputation of missing data was not necessary because weekly data was available throughout the entire dataset. ARIMA models were applied to further document the temporal patterns in PNML of psychoactive pharmaceutical biomarkers, that were observed with the graphical analysis. Non-seasonal autoregressive integrated moving average (ARIMA) models comprise of a set of mathematical procedures (e.g. autoregression, differencing and moving averages) to convert non-stationary data into a stationary time series (Hyndman & Athanasopoulos, 2021). The ARIMA model consists of a non-seasonal (p,d,q) component build up of three parameters: i) p, the order of the autoregressive part (i.e. a linear combination of lagged values of the time series), ii) d, the degree of first differencing involved to obtain stationarity, and iii) q, the order of the moving average part (i.e. a linear combination of lagged model error terms). Minimization of the corrected Akaike Information

Criteria (AICc) was used for the optimization of the model. The *fable* package in R version 4.1.3 (R, Vienna, Austria) was employed to compute a suitable ARIMA model for each of the biomarkers (’O’Hara-Wild et al., 2021).

To investigate if there were any differences in the PNML between the workweek (Mon-Fri) and weekend (Sat-Sun), a one-sample Kolmogorov-Smirnov normality test was performed in first instance which indicated that a Wilcoxon signed pair rank test should be used in second instance to test for differences.

2.5. Data on pharmaceutical dispensing

Relative temporal trends in the PNML of the different biomarkers of interest were compared with relative trends in data on monthly pharmaceutical dispensing. These figures were obtained from the IFSTAT database which is compiled by the Institute for Pharmaco-Epidemiology in Belgium (IPHEB) (Belgian Institute for Pharmaco-Epidemiology (IPHEB), 2022). This database collects data on the dispensing of reimbursed pharmaceuticals in Belgian public pharmacies and covers 93% of all pharmaceutical deliveries in public pharmacies in Belgium. IFSTAT data was acquired from January 2019 through May 2022 for the broader district of Leuven. Pharmaceutical dispensing data adds valuable insights on the availability of pharmaceuticals, as expressed by the percentage of the prescribed pharmaceuticals that were actually supplied (e.g. tracked through submission to national health databases). It should be noted that the WWTP of the catchment area of Leuven only covers parts of this region (appendix S3). However, it was not possible to obtain data on pharmaceutical deliveries with the same spatial locality as the WBE data. Nevertheless, triangulation of both datasets can be done to get a better understanding on the use of psychoactive pharmaceuticals in the Leuven area. Data on the number of methadone deliveries could not be obtained as data on compounding is not covered by IFSTAT.

3. Results and Discussion

3.1. Temporal trends in psychoactive pharmaceutical use

Based on a preliminary screening of IWW in WWTP Leuven in October 2019 (Boogaerts, Quireyns, Maes, et al., 2022), 14 biomarkers for psychoactive pharmaceuticals were selected for temporal trend analysis, including 8 biomarkers for antidepressant use (i.e., amitriptyline, O-desmethylvenlafaxine, venlafaxine, trazodone, hydroxy-bupropion, trazodone, citalopram, norcitalopram and normirtazapine) and 6 biomarkers for opioid use (i.e., codeine, EDDP, methadone, morphine, O-desmethyltramadol (ODT) and tramadol). For the other biomarkers included in the analytical method, concentrations were below the lower limit of quantification

(LLOQ). The LLOQ is defined as the lowest concentration of an analyte that can still be quantified accurately and precisely. The methods of Boogaerts and Quireyns et al. that were applied for this preliminary screening contain a broad range of biomarkers of psychoactive pharmaceutical use, and cover the majority of antidepressants and opioids sold on the Belgian market (Boogaerts et al., 2019; Boogaerts, Quireyns, et al., 2021; Boogaerts, Quireyns, Maes, et al., 2022).

3.1.1. Longitudinal trends

Figure 2 visualizes the longitudinal trends in the PNML of the different biomarkers for psychoactive pharmaceutical use that were obtained with the LOESS method. Comparable longitudinal patterns in the PNML of the different biomarkers were revealed. Overall, the PNML of all biomarkers increased (with 3.2-118.8% for all compounds between September 2019 and April 2022), with the exception of the PNML of ODT, which slightly decreased with 6.8%. The highest increase in PNML was reported for amitriptyline (+118.8%), followed by norcitalopram (+57.4%) and EDDP (+54.4%). An overview of the relative changes in the PNML of the different compounds between September 2019 and April 2022 can be found in Table S3. The application of ARIMA models also confirmed that the original time series of all biomarkers of interest showed non-stationarity (see Table S1).

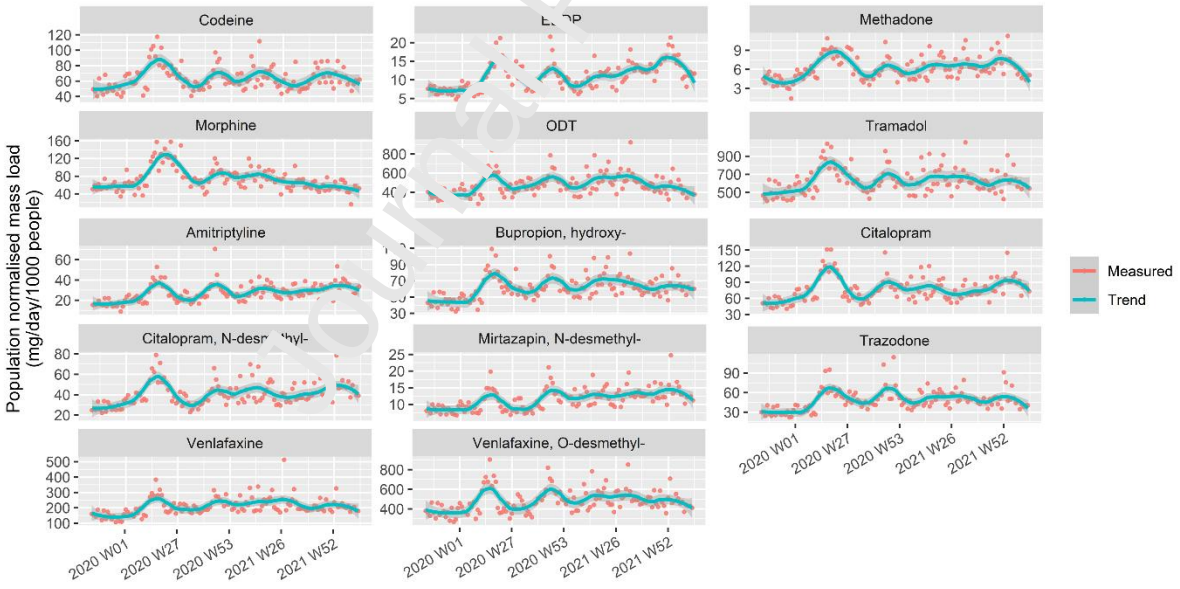


Figure 2 Longitudinal trends in the population-normalized mass loads of the different biomarkers for psychoactive pharmaceutical use. The trend was obtained with trend decomposition using LOESS. Abbreviations: EDDP = 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ODT = O-desmethyltramadol.

For all compounds, an increase in the PNML was observed during the first lockdown phase (i.e. March 14, 2020 through June 8, 2020) of the COVID-19 pandemic in Belgium. As indicated previously, the population and the linked socio-demographics (e.g., age, income level, educational

level) of the catchment area of WWTP Leuven changed substantially during this period, leading to changes in PNML. Therefore, changes in population composition should be taken into account when interpreting temporal WBE data. This is also reflected by the 50% decrease in the number of people present within the boundaries of the catchment area at the start of the first lockdown phase due to stay-at-home measures which resulted in a major reduction in commuting patterns in and out of Leuven, including the movement of university students. In another study from Boogaerts and Quireyns et al., similar decreases in population sizes were also found in the catchment areas of other WWTPs (including Antwerp-Zuid, Brussels-North and Boom) (Boogaerts, Quireyns, de prins, et al., 2022). Therefore, we hypothesize that this reduction is not only driven by a decrease in the number of students present in the catchment area, but also due to other changes in commuting patterns (e.g., reduction in the number of people coming to work due to stay-at-home measures). In this light, the changes in the PNML of the psychoactive pharmaceuticals during the lockdown periods could partially be explained by population changes in the catchment area (e.g., the absence of a large proportion of university students shifting the population to a proportionally older population that uses more opioids and antidepressants). During the lockdown phases, students were advised by the government to return home and no students were allowed on-site at the university campus (KU Leuven, 2020). People also had to work mainly from home and commuting was impacted by the governmental measures. During the second lockdown, the number of persons present in the catchment area of Leuven also decreased but not to the same extent of the first lockdown. It should be noted that the policy changes during the second lockdown were less stringent compared to the first lockdown (FPS Public Health, 2022) and commuting restored itself to some extent (Google, 2022). The second lockdown was mainly characterized with the closing of the catering industry and a restriction in the number of contact persons (i.e., 3 persons per contact) (FPS Public Health, 2022). The period between the first wave of COVID infections and second wave was characterized by an expansion in the number of contacts per person (i.e., up to 15) and the re-opening of the catering industry and culture sector.

As a result, it is possible that the socio-demographic features of the population within the catchment area during the COVID-19 crisis were characterized by different socio-demographic features (e.g., a larger contribution of an older population group compared to the pre-pandemic period). Figure S3 represents the age distribution of the population of the city of Leuven based on the official population registers from 2020 (STATBEL, 2022). During the academic year in 2019, this distribution was skewed by the influx of University students, resulting in the socio-demographics being predominantly driven by younger age groups. The use of prescription opioids and antidepressants in Belgium is strongly linked to higher age and polypharmacy in adult age groups (Belgian Institute for

Pharmaco-Epidemiology, 2016, 2018; van den Akker et al., 2019). It is important to note that the population shift is not only age-related, but other changes in socio-demographic attributes of the catchment population (e.g., gender, education, income level) can also lead to temporal changes in the PNML of psychoactive pharmaceutical. Other commuting patterns (e.g., people working from home instead of entering or leaving the catchment area) might also have impacted the socio-demographic composition of the catchment population. In general, the COVID-19 pandemic and it associated governmental measures led to a large-scale population disruption.

Figure 3 provides a comparison between the PNML based on static and dynamic (i.e., through mobile phone estimates) population data. This figure highlights the need for a dynamic population proxy in the WBE back-calculations. With static population data, temporal changes in the PNML of the psychoactive pharmaceuticals could also be the result of daily variations in the absolute number of people present in the WWTP catchment area. However, even with dynamic population data, it is not possible to determine whether differences in the PNML of the biomarkers of interest are the result of demographic changes (e.g., other type of users as a result of commuting) or actual consumption patterns. Until now, most WBE applications that investigated temporal changes in the use of substances and pharmaceuticals during the COVID-19 pandemic used fixed population equivalents in their back-calculations (Alygizakis et al., 2021a; Bade, Simpson, et al., 2021; Bade, Tscharke, et al., 2021; Been et al., 2021; Estévez-Danta et al., 2022; Love et al., 2022; Psichoudaki et al., 2023; Wang et al., 2020; Yavuz-Guzel et al., 2022). Only a few studies made efforts to refine WBE back-calculations based on dynamic population data (Boogaerts, Quireyns, de prins, et al., 2022; di Marcantonio et al., 2022; Galani et al., 2021; Hahn et al., 2022; Montgomery et al., 2021; Reinstadler et al., 2021; Tomsone et al., 2022). Most of these investigations applied metadata of the WWTP catchment area (e.g., chemical oxygen demand, biological oxygen demand, phosphorus, nitrogen, ammonium loads) to account for relative changes in population size (Been et al., 2014; Rico et al., 2017; Tscharke et al., 2019; van Nuijs et al., 2011). However, these hydrochemical parameters do not always fully correlate with the population size and are not always measured on a daily basis (Rico et al., 2017; Sim et al., 2023; Tscharke et al., 2019). Contrastingly, *Tomsone et al*. measured changes in population size by measuring daily concentrations of 5-hydroxy-indole acetic acid (5-HIAA), a endogenous serotonin metabolite (Tomsone et al., 2022). However, more research is needed to investigate the use of this population proxy because of the discrepancies with other studies. While some investigations found high correlations between the population size and 5-HIAA mass loads (Chen et al., 2014; Rico et al., 2017), others only reported weak to moderate correlations (Gudra et al., 2022; Hsu et al., 2022; Pandopulos et al., 2020). To our knowledge, Boogaerts and Quireyns et al. is the only study that applied mobile phone data as a dynamic population proxy for the refinement

of WBE back-calculations during the COVID-19 pandemic (Boogaerts, Quireyns, de prins, et al., 2022), even though its potential to measure relative changes in population size was already shown by *Baz-Lomba et al.* and *Thomas et al*. (Baz-Lomba et al., 2019; Thomas et al., 2017). The limited number of WBE studies that apply dynamic population proxies on a routine basis emphasizes the need for more research on this WBE methodological issue. This is of importance as failure to account for population movements leads to incorrect conclusions.

3.1.2. Periodic trends

Table S2 gives an overview of the differences between the workweek (Mon-Fri) and weekend (Sat-Sun) during the different time periods, including the pre-pandemic period in 2019, the first lockdown (i.e. March 14, 2020 through June 8, 2020) and second lockdown (i.e. October 19, 2020 through May 8, 2021). A week-weekend pattern in the PNML was observed for all compounds during the pre-pandemic period and second lockdown (with the exception of amitriptyline), with the highest PNML observed during the weekends (see Figure 4 and Figure S5). It is important to mention that the socio-demographic features of the catchment population substantially change between the workweek and the weekend, because many students leave the catchment area on Friday to go home for the weekend. From surveys it's known that approximately 90% of the housing students return home (see Figure 1). Additionally, the observed daily differences in the PNML could also be explained by a synergetic effect of other commuting patterns, with more people entering the catchment area during the workweek. During the first lockdown phase, the week-weekend pattern of the PNML of some biomarkers (e.g., amitriptyline, norcitalopram, normirtazapine, ODT, ODV, trazodone, venlafaxine) remained stable ($p>0.05$) (see Figures S5). This further confirms that the COVID-19 pandemic and its accompanied social measures led to a shift in the socio-demographic features of the population within the catchment area. For example, students were advised to return to their homes during the first lockdown phase and commuting in and out of the catchment area was minimized by the different COVID-19 restrictions (e.g., stay-at-home measures, remote work,…). Commuting patterns during the second lockdown were less heavily impacted by the governmental measures compared to the first lockdown.

Differences in the within-week variations in the PNML highlight the relationship between the PNML of the psychoactive pharmaceuticals and the socio-demographics of the catchment area population (Figure 4). In this light, the application of a dynamic population proxy, such as mobile phone data, was necessary to account for these within-week variations in population size. The present study showed that the weekend population was consistently lower compared to the workweek population throughout the entire sampling campaign, as visualized by Figure 1. During the workweek, there is a

higher number of people present in the catchment due to commuting and influx of University students. Figure 1 also shows that the transient population movement is larger during the second lockdown in comparison with the first lockdown.

Other than the weekly variations, no significant periodic patterns (e.g. monthly, yearly,…) were observed within the time series with the autocorrelation function (as illustrated in Figure S4). Different frequencies (weekly, monthly, quarterly) resulted in negligible contribution of the periodic component to the overall PNML. However, approximately two and a half years of sampling were included and, at the time of the study period, a large socio-demographic disruption occurred which might disturb specific seasonal changes. This indicates that the PNML of the different biomarkers for psychoactive pharmaceutical use is mainly driven by the longitudinal trend component. These results were also confirmed by the use of the ARIMA models. Table S1 represents the different parameters obtained when applying ARIMA on the time series of the weekly PNML of the different biomarkers. A non-seasonal ARIMA model was obtained for all analytes of interest. The diagnostics of the different ARIMA models can be found in the Supplementary Information (Figure S7-20). The weekly variations in the PNML further indicate the need for an accurate population proxy in WBE studies.

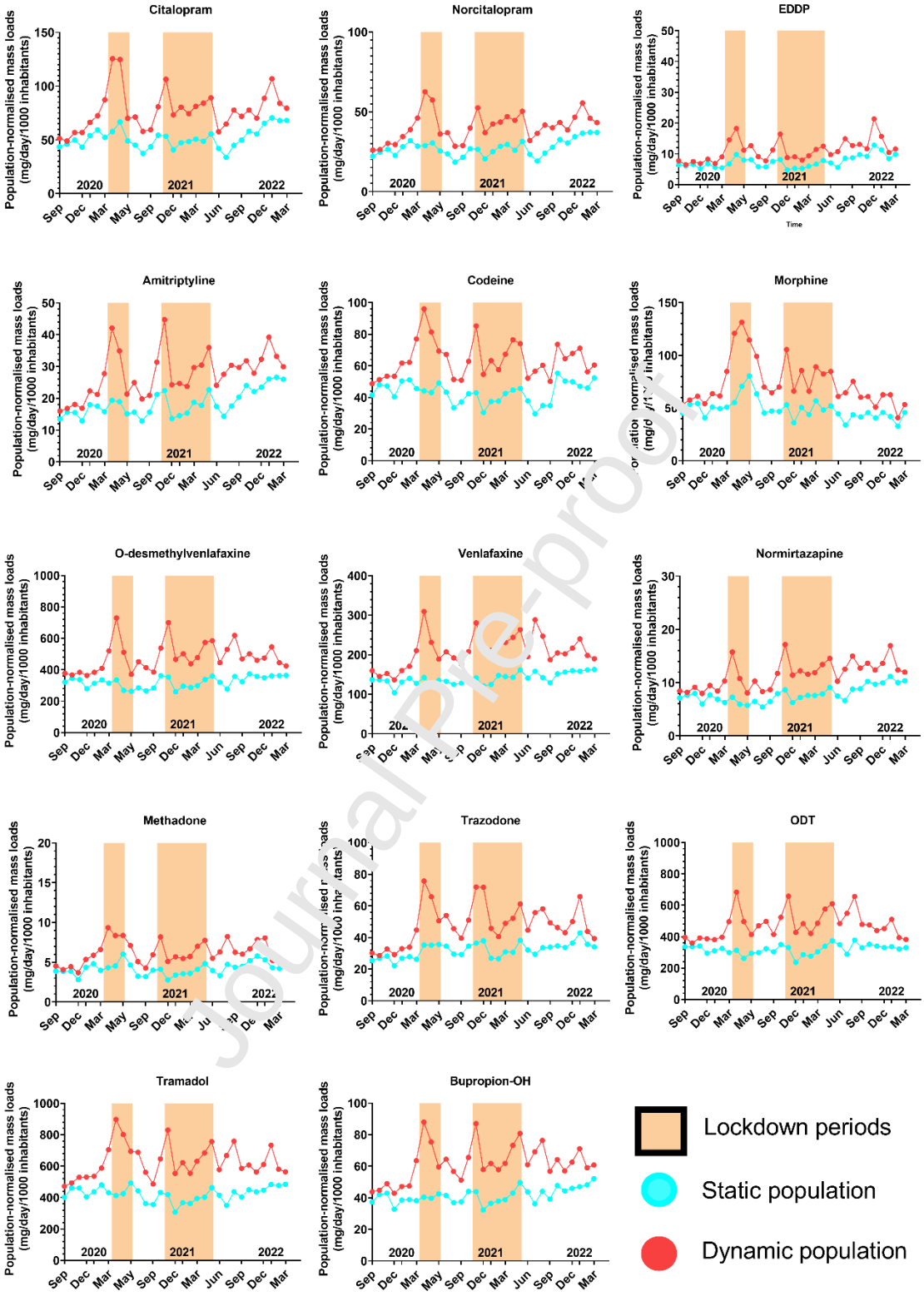


Figure 3 Comparison of population-normalized mass loads of biomarkers for psychoactive pharmaceutical use using static (in blue) and dynamic (in red) population sizes. The orange bars represent the lockdown periods. Abbreviations: EDDP = 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ODT = O-desmethyltramadol.

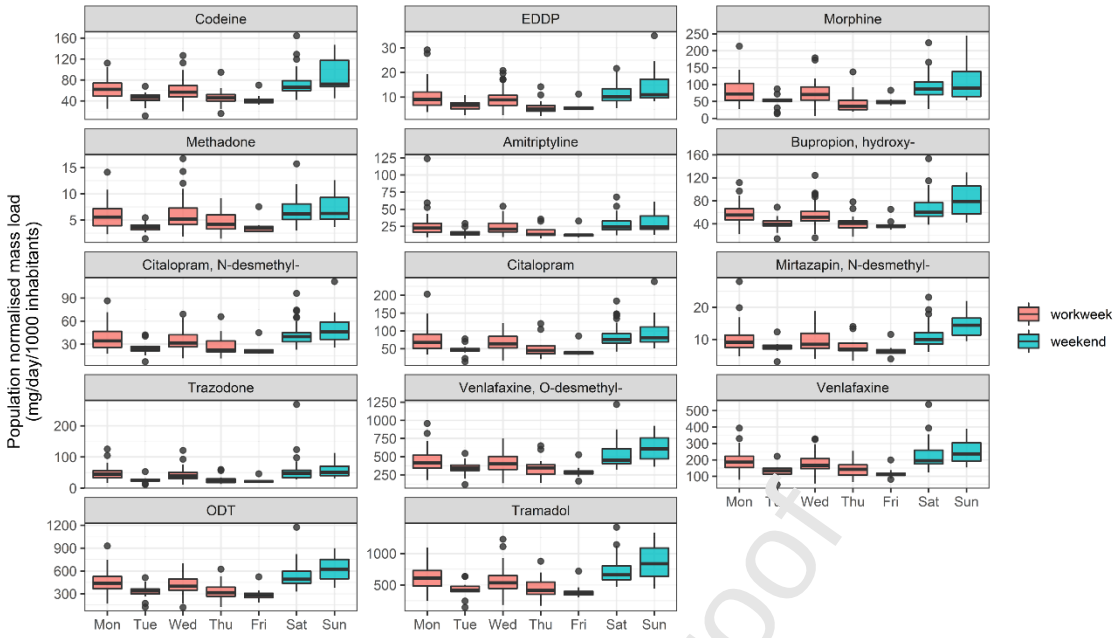


Figure 4 Weekly variations in population-normalized mass loads of psychoactive pharmaceuticals during the pre-pandemic period (i.e. 4 September 2019 through 31 December 2019). Abbreviations: EDDP = 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ODT = O-desmethyltramadol.

3.2. Parent/Metabolite Ratios

Table 1 Comparison of the measured parent/metabolite ratios with other WBE studies. Abbreviations: EDDP = 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ODT = O-desmethyltramadol.

Parent/Metabolite	P:M ratio (mean± SD)	Measured P:M ratio range in other studies	Reference
Citalopram/Norcitalopram	1.9 ± 0.2	1.3-1.7	(Boogaerts et al., 2019)
Tramadol/ODT	1.3 ± 0.2	0.3-0.9	(Rúa-Gómez & Püttmann, 2012)
Codeine/Morphine	0.91 ± 0.38	0.22-5.5	(Baker et al., 2014; Baker & Kasprzyk-Hordern, 2011b; Bijlsma et al., 2014; Boleda et al., 2007, 2009; González-Mariño et al., 2010; Lai et al., 2011; Martínez Bueno et al., 2011; Östman et al., 2014; Senta et al., 2013)
Venlafaxine/O-desmethylvenlafaxine	0.44 ± 0.06	0.2-0.5	(Boogaerts et al., 2019; Rúa-Gómez & Püttmann, 2012)
Methadone/EDDP	0.58 ± 0.13	0.25-1.2	(Boogaerts, Quireyns, et al., 2021; Thai et al., 2016)

Even though the population was drastically disrupted due to the COVID-19 pandemic, the parent/metabolite ratio (P:M ratio) of most compounds remained relatively stable within the sampling period. For citalopram/norcitalopram, tramadol/O-desmethyltramadol, venlafaxine/O-desmethylvenlafaxine and methadone/EDDP, the relative standard deviation (%RSD) of the measured P:M ratio was lower than 25%. However, a %RSD of 30% was reported for the codeine/morphine ratio, but a larger variation was expected given that multiple substances, including morphine, codeine and heroin, metabolize to morphine and/or codeine. Major differences

in the P:M ratio of codeine/morphine were also found in other WBE studies. The variations in the composition of the catchment population during the sampling period did not result in large variances in the P:M ratios (see Figure 5). For example, a shift in P:M ratio was not observed during the lockdown periods. In other words, the decrease in population size did not result in significant deviations from the overall mean P:M ratio. Such deviations could potentially occur in smaller catchment populations because of the high inter-individual differences in metabolism and excretion. Overall, the reported P:M ratios were also in line with other studies, as illustrated in Table 1. The mean P:M ratio of citalopram/norcitalopram and tramadol/O-desmethyltramadol was slightly higher in this study in comparison to other WBE studies. However, O-desmethyltramadol, citalopram and norcitalopram were only measured in a handful of studies with only limited sample sizes. The stable temporal pattern in the P:M ratio indicates that the biomarker loads found in this study are most likely the result from consumption rather than direct disposal of the parent drug.

3.3. Relative trends in measured population-normalized mass loads versus data on pharmaceutical dispensing

Figure 6 overlays the relative changes in PNML (i.e., by dividing the monthly PNML with the mean) with the percent differences in pharmaceutical deliveries in the district of Leuven (i.e., by dividing the monthly daily defined doses with the mean) to compare psychoactive pharmaceutical use between both data sources. Back-calculations to daily defined doses based on WBE measurements were not performed since the aim of this study was not to compare the absolute pharmaceutical consumption estimates between both DUR information sources, but rather to investigate relative temporal changes. Overall, relative trends in pharmaceutical dispensing proved to be more stable compared to the temporal changes in the PNML of the different biomarkers for psychoactive pharmaceutical use, as illustrated by Figure 6 and Table S3. This was also reflected by the differences between the %RSD between WBE (i.e., %RSD ranged between 22.3 to 35.5%) and data on pharmaceutical dispensing (i.e., RSD <24.4% for all pharmaceuticals). The effect direction (i.e. being either increasing, decreasing or stable) was the same for bupropion, mirtazapine and trazodone, while discrepancies were found for citalopram, codeine, morphine, tramadol and venlafaxine. While the PNML of the corresponding biomarkers increased (between 3.2 and 118.8%), a slight decrease (ranging between -36.4 and -2.0%) was observed with data on pharmaceutical dispensing. Differences in temporal patterns between WBE data and data on pharmaceutical dispensing may arise from several factors. WBE estimates also reflect import, export, and diversion of pharmaceuticals to other geographical areas. Dispensed pharmaceuticals might not actually be consumed by patients. Additionally, the locality between the location of consumption and excretion

might be different due to commuting. This could be especially the case for the city of Leuven that is characterised by the in- and efflux of a lot of visitors (e.g., commuters,…).

Moreover, population movements and socio-demographics were highly influenced by the social measures introduced to curb the spread of SARS-CoV-2 and, thus, not the same across the entire sampling campaign. Additionally, the WWTP catchment area does not correspond fully with the boundaries of the district of Leuven. The triangulation of WBE data and data on pharmaceutical dispensing showed that the use of most psychoactive pharmaceuticals slightly increased, while a stable temporal pattern was found for others. Contrastingly, a decreasing longitudinal trend was found for morphine based on data on pharmaceutical dispensing, while a 3.2% increase was found with WBE. Morphine loads measured in IWW could also be the result of heroin use, but it was not possible to confirm this with a specific biomarker for heroin. Data on pharmaceutical dispensing only reflects legal use of pharmaceuticals, while WBE could also deliver information on illegal consumption.

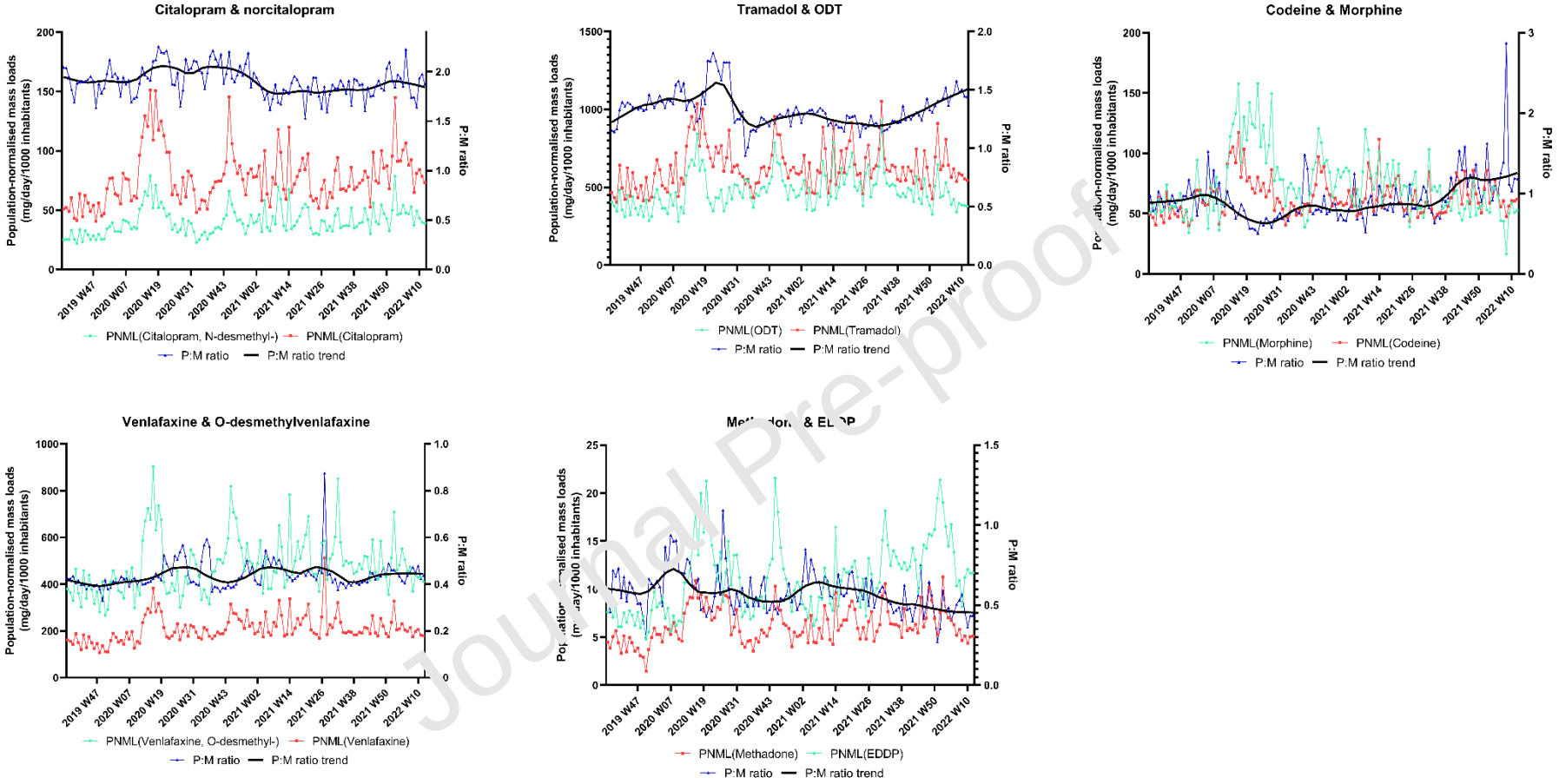
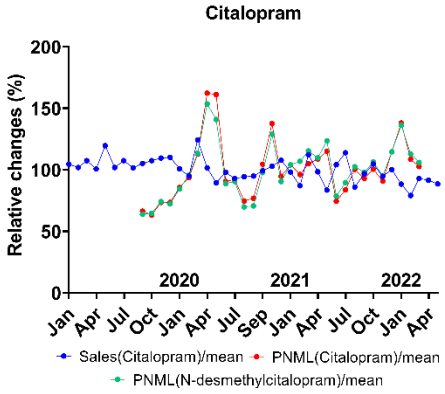
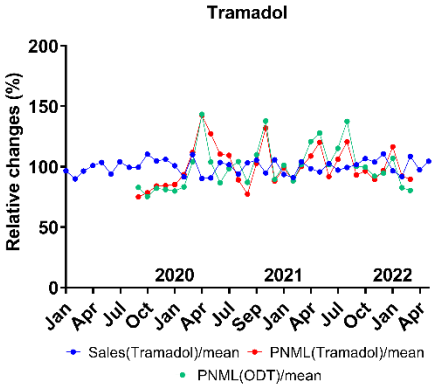
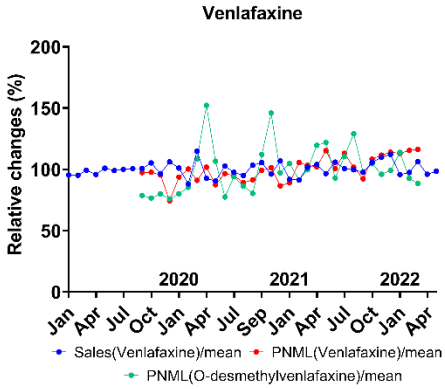
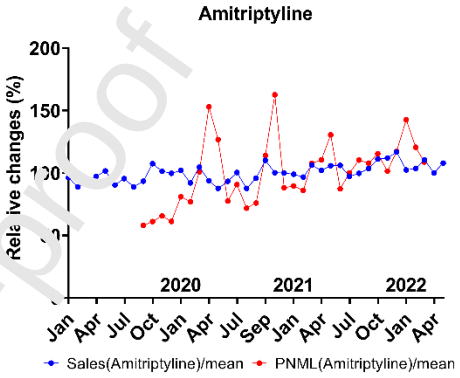


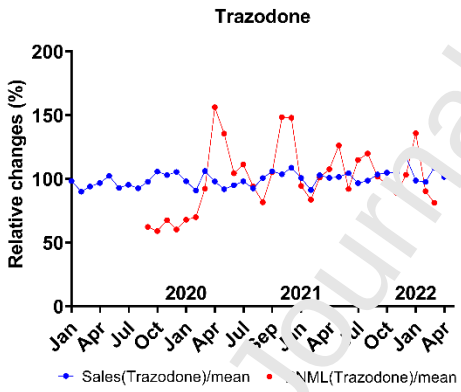
Figure 5 Temporal trends in the parent/metabolite ratios of different biomarkers for psychoactive pharmaceutical use. Abbreviations: EDDP = 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ODT = O-desmethyltramadol.

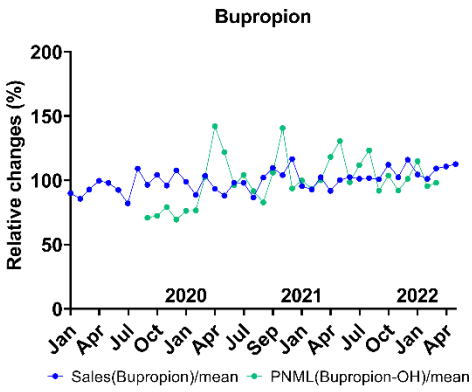


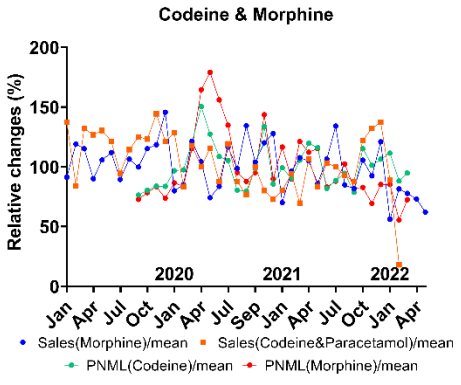












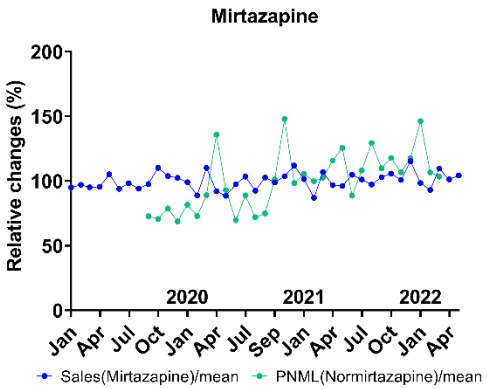


Figure 6 Comparison of the relative differences between wastewater-based epidemiology (WBE) figures and data on pharmaceutical dispensing in the district of Leuven. Abbreviations: EDDP = 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; ODT = O-desmethyltramadol.

4. Study limitations

The results in this study may not be generalizable to a national level since the population served by WWTP Leuven only covers 1% of the Belgian population and consist for large parts of university students. Additionally, the socio-demographics of the catchment population was significantly different during the disruption caused by the COVID-19 pandemic compared to the pre-pandemic period. Therefore, an increase in PNML could be associated with a larger proportion of people consuming, a similar proportion of people consuming more, or a combination of both. In this light, the result of the present show that the use of a dynamic population proxy is vital to interpret the changes in PNML correctly. Even though mobile phone data proved to be valuable to correct for relative changes in population size, more research is needed to evaluate its capability to estimate absolute population numbers on a daily base. In particular, more research is needed on the uncertainty associated with the extrapolation of mobile device signals to population size estimates. The limited number of WBE studies that apply dynamic population proxies on a routine basis emphasizes the need for more research on this methodological issue. This is of importance as failure to account for population dynamics leads to incorrect conclusions.

In addition, it is possible that specific events and/policy changes resulted in a synergetic or antagonistic effect on the use of psychoactive pharmaceuticals and the interpretation of temporal trends might be complicated by such heterogenic effects (Calina et al., 2021). Starting from January 2020, three datapoints per week were used for the calculation of the average weekly PNML. Variations in PNML of the included days could deviate from the true weekly mean. However, data showed that this approach was valid to capture the weekly average PNML accurately. The applicability of alternative sampling strategies should be further explored for temporal trend analysis and policy evaluation.

Additionally, there were some variations in the storage times of the IWW samples. Aliquots collected in 2019 were stored for a longer time compared to the samples from the later years. Differences in in-sample stability at -20 °C might also introduce variability in the PNML over the course of the sampling period. In-sewer stability for several of the biomarkers of interest has been studied in various other publications. However, it remains difficult to find a consensus about a suitable approach that fully mimics the sewer conditions, and thus various authors reported different set-ups (e.g., biofilm-free, rising main sewer and gravity sewer reactors) and conditions (different temperature, pH, biofilm content and duration), which makes comparison between investigations

difficult (Choi et al., 2020; Gao et al., 2019; van Nuijs et al., 2012). A literature review by McCall et al. presented variable (i.e., discrepancies in reported results) in-sewer stability for methadone, EDDP and morphine (Baker & Kasprzyk-Hordern, 2011a; McCall et al., 2016). In contrast, oxycodone and codeine were stable in-sewer (< 20% transformation) (Gao et al., 2019; McCall et al., 2016). Additionally, Choi et al. measured stable in-sewer conditions for venlafaxine and citalopram (Choi et al., 2020).

For some analytes, sorption to solid particulate matter (SPM) and/or biofilm can also contribute to the overall uncertainty, especially for biomarkers with high log K_{ow} values (>3) (Baker & Kasprzyk-Hordern, 2011b; Campos-Mañas et al., 2022; Ramin et al., 2017). In this light, *Baker et al.* showed that adsorption to SPM was substantial for some biomarkers for antidepressant and opioid use, including fluoxetine, norfluoxetine, dosulepin, fentanyl, nortriptyline, amitriptyline, methadone, EDDP and nortramadol (Baker & Kasprzyk-Hordern, 2011b). Daily variations in the concentration of SPM (expressed in mg/L) can be present which could in turn affect temporal changes in observed PNML.

Furthermore, uncertainties can arise from the direct discharge of unused drugs, the formation from other chemicals, or conjugated drugs (Bettington et al., 2018; Guirguis, 2010). The former is especially an issue if the parent compound is used as biomarker (Petrie et al., 2015). However, no aberrant PNML were observed during the entire sampling campaign and measured PNML are most likely the result of consumption rather than direct disposal.

5. Conclusions

This case study shows the potential of WBE to measure temporal changes in the use of psychoactive pharmaceuticals in specific locations at high temporal resolution. To our knowledge, this is one of the first studies that investigated the use of opioids and antidepressants continuously for a period of more than 2 years. The use of mobile phone data for refinement of WBE back-calculations was necessary to interpret temporal trends in psychoactive pharmaceutical use accurately. The population disruption during the COVID-19 pandemic led to a major change in the socio-demographics of the WWTP catchment area, resulting in temporal differences in the reported PNML of the biomarkers for psychoactive pharmaceutical use. For example, higher PNML were observed during the first and second lockdown phase, which were characterized by the absence of large numbers of University students and a decrease in commuting in and out the catchment area. The effects of the changing demographic features of the catchment population on measured PNML were further revealed by the variations in the week-weekend pattern between the pre-pandemic and lockdown periods. Although changes in the population socio-demographics are a well-known

limitation of WBE, its effects may be underrepresented or even underestimated in previous WBE studies that investigated xenobiotic use during large-scale population disruptions. The P:M ratios of the different compounds remained relatively stable throughout the entire sampling period, indicating that measured PNML are likely the result from regular consumption. The population decrease during both lockdown phases did not result in major changes in P:M ratios. Overall, the PNML of most psychoactive pharmaceuticals increased during the sampling campaign. No significant reoccurring seasonal patterns were found in the use of psychoactive pharmaceuticals, but only two and a half years were included and the time period was characterized by a large socio-demographic disruption.

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Author contributions

Tim Boogaerts **–** Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing – original draft, writing – review & editing, visualization; ***Maarten Quireyns*** **–** Conceptualization, methodology, validation, formal analysis, investigation, data curation, visualization, writing – review & editing; ***Hans De Loof*** **–** Conceptualization, methodology, supervision, writing – review & editing; ***Xander Bertels*** **–** Methodology, validation, formal analysis, writing – review & editing; ***Natan Van Wichelen*** **–** Methodology, investigation, writing – review & editing; ***Bram Pussig*** **–** Resources, writing – review & editing; ***Jan Saevels*** **–** Resources, writing – review & editing; ***Lies Lahousse*** **–** methodology, validation, formal analysis, writing – review & editing; ***Pauline Bonmariage*** **–** Resources, writing – review & editing; ***Wouter Hamelinck*** **–** Resources, writing – review & editing; ***Bert Aertgeerts*** **–** Resources, writing – review & editing; ***Adrian Covaci*** **–** Conceptualization, methodology, resources, writing – review & editing, supervision, project administration, funding acquisition; ***Alexander L.N. van Nuijs*** **–** Conceptualization, methodology, resources, writing – review & editing, supervision, project administration, funding acquisition;

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Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- In-depth analysis of wastewater-derived use estimates from 134 consecutive weeks;
- The use of psychoactive pharmaceuticals increased with 3-119% from 2019 through 2022;
- Population-normalized mass loads are affected by dynamic socio-demographics and population size;
- In WBE, a dynamic population marker is needed to account for population changes in the catchment area.