ELSEVIER

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

International Journal of Drug Policy 104 (2022) 103679

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Temporal monitoring of stimulants during the COVID-19 pandemic in Belgium through the analysis of influent wastewater

Tim Boogaerts[a,1,*], Maarten Quireyns[a,1], Maarten De prins[a], Bram Pussig[b], Hans De Loof[c], Catharina Matheï[b], Bert Aertgeerts[b], Virginie Van Coppenolle[d], Erik Fransen[e], Adrian Covaci[a], Alexander L.N. van Nuijs[a,*]

[a] Toxicological Centre, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
[b] Academisch Centrum voor Huisartsengeneeskunde, Department of Public Health and primary Care, KU Leuven, Kapucijnenvoer 7, 3000 Leuven, Belgium
[c] Laboratory of Physiopharmacology, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
[d] Cropland, Willem van Laarstraat 86, 2600 Berchem, Belgium
[e] StatUa Core facility, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

ARTICLE INFO

Keywords:
Wastewater-based epidemiology
Stimulants
Temporal analysis
COVID-19 interventions
Lockdown
Consumption

ABSTRACT

Background and aims: Wastewater-based epidemiology (WBE) is a complementary epidemiological data source to monitor stimulant consumption. The aims were to: (i) study intra- and inter-year temporal changes in stimulant use in Belgium during the first wave of the COVID-19 pandemic; and (ii) evaluate the effect of COVID-19 restrictive measures on stimulant consumption.

Methods: The study population corresponded to the catchments of four wastewater treatment plants corresponding with four Belgian cities (i.e., Antwerp-Zuid, Boom, Brussels, Leuven). Daily 24-h composite influent wastewater samples collected over one week in September 2019 and March through June 2020 during the first wave of the COVID-19 pandemic were analyzed for biomarkers of amphetamine, cocaine, methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA). Measured concentrations were converted to population-normalized mass loads by considering the daily flow rate and the catchment population size. Mobile network data was used to accurately capture population movements in the different catchment areas. Temporal changes were assessed with multiple linear regression models, and the effect of the COVID-19 interventions on stimulant consumption were investigated.

Results: An increase in amphetamine use was observed in three cities during governmental restrictions, with highest consumption predominantly during lockdown. Similarly, cocaine consumption was higher after the pandemic started, with highest consumption noted during the lockdown period in Boom and Leuven. Consumption of MDMA was similar in Antwerp-Zuid, Brussels and Leuven throughout the entire sampled period. In Boom, the highest consumption was observed during the full lockdown period.

Conclusions: The present study shows the potential of WBE to assess the impact of stringent lockdown measures on stimulant use in Belgium. This paper shows that strong restrictive measures did not have a profound effect on stimulant consumption.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic triggered the need for various governmental measures to curb the spread of the virus, such as physical distancing, stay-at-home measures, curfew, and closing of all non-essential activities. These interventions could potentially result in reduced treatment, prevention, and harm-reduction campaigns in terms of substance use and reduced supply of substances (Dietze & Peacock, 2020; EMCDDA, 2020b, 2020a). The introduction of these strict restrictions influenced the movement and gatherings of individuals, potentially limiting social opportunities to consume substances. It could be considerably more difficult for people to have access to their usual drug supply (EMCDDA, 2020a). However, a digitalization of the drug market might counteract this, ensuring con-

* Corresponding authors.
E-mail addresses: Tim.Boogaerts@uantwerpen.be (T. Boogaerts), Alexander.vannuijs@uantwerpen.be (A.L.N. van Nuijs).
[1] Joint first author.

https://doi.org/10.1016/j.drugpo.2022.103679

0955-3959/© 2022 Elsevier B.V. All rights reserved.

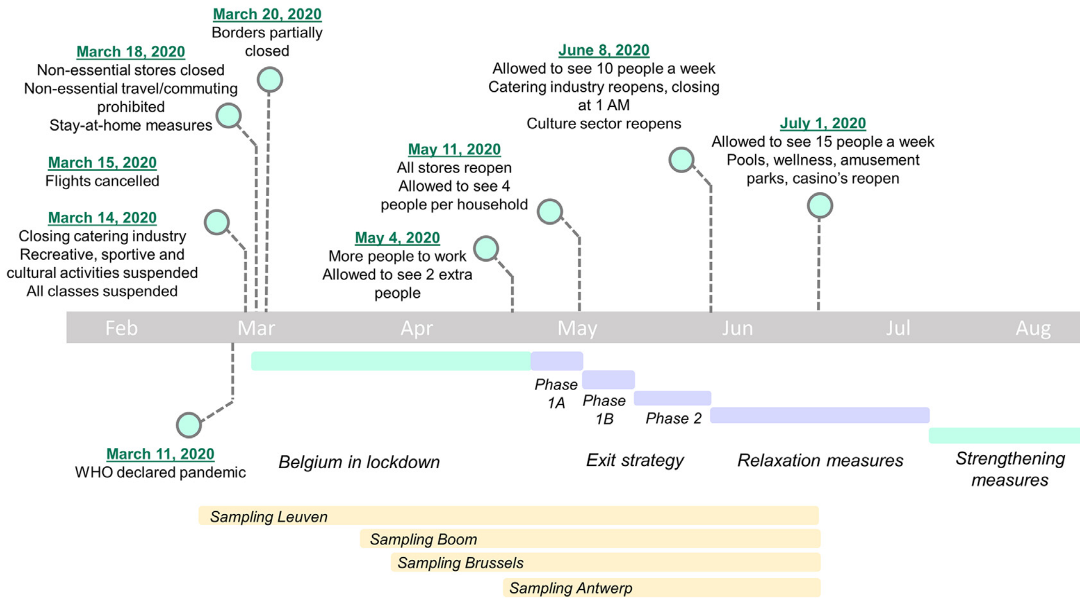

Fig. 1. Timeline of the Belgian COVID-19 measures (FPS Public Health, 2022). Strengthening of the measures is indicated with a green bar; relaxation of the measures with a blue bar. Yellow bars represent the sampling periods for each location.

tinuity in the availability of illegal substances (EMCDDA, 2020a). Furthermore, the coronavirus disease 2019 (COVID-19) could also have implications on the population's mental health status (Brooks et al., 2020), potentially resulting in the use of substances due to psychological and social discomfort (Rehm et al., 2020).

Preliminary findings of the European Monitoring Centre for Drugs and Drug Addiction's (EMCDDA) mixed-method trendspotter study suggest an overall decrease of drug use in Europe in the beginning of the COVID-19 pandemic, with cocaine and 3,4-methylenedioxymethamphetamine (MDMA) mostly affected due to closure of the night-time economy and home confinement (EMCDDA, 2020a, 2020b). However, this study only provides a brief snapshot of illicit drug use and related harms among known people who use drugs during the beginning of the pandemic. Additionally, the state of play with respect to the impact of the COVID-19 crisis on illegal drug consumption appears to be heterogeneous across different European countries and variable by drug type (Been et al., 2021; EMCDDA, 2020a). The heterogenic nature of the implementation of the COVID-19 pandemic countermeasures is also reflected by the contrasting findings between different data sources (Gili et al., 2021; Manthey et al., 2021; Mariottini et al., 2021; Palamar et al., 2021).

In Belgium, a first lockdown was initiated on the 14th of March 2020 (i.e., closing of all bars, restaurants and nightlife), prior to a full lockdown on the 18th of March 2020 (i.e., closure of all non-essential activities) (FPS Public Health, 2022), as illustrated in Fig. 1. These restrictions were followed on the 4th of May 2020 with the initiation of a first exit strategy, after a decrease in the number of new COVID-19 cases (FPS Public Health, 2022). According to the online Health Survey COVID-19 of Sciensano (i.e., the Belgian Scientific Institute for Public Health), with known drug users, fewer individuals used illicit drugs during this period in 2020 compared to 2018 (Sciensano, 2020). A decrease in consumption was reported by 32.3% of people who use illicit drugs, compared to 23.5% for which drug use increased (Sciensano, 2020). It has to be mentioned that the interview method in 2020 changed from computer assisted personal interviews to online surveys, potentially excluding certain population groups (e.g., people with limited internet access) which could result in concealment and reporting bias. Additionally, this small subset of individuals with known drug use might not be representative for the entire population. In order to obtain a more objective view on the drug consumption, complementary epidemiological information is necessary to investigate potential temporal changes introduced by the COVID-19 interventions.

Over the past decade, wastewater-based epidemiology (WBE) became a well-established method for delivering complementary information on spatio-temporal consumption patterns of illicit drugs (European Monitoring Centre for Drugs and Drug Addiction, 2019; Gonzalez-Marino et al., 2020). WBE comprises the measurement of trace concentrations of human metabolic excretion products in influent wastewater (IWW) to investigate human consumption and exposure to xenobiotics at the population level (see Fig. 2) (Zuccato et al., 2008). Previous studies have shown the applicability of WBE to analyze other lifestyle-related biomarkers (e.g., alcohol, tobacco and food biomarkers) (Baz-Lomba et al., 2016; Boogaerts et al., 2016; Choi et al., 2019; Lai et al., 2018) and health-related biomarkers (e.g., environmental pollutants, pharmaceuticals, personal care products, endogenous substances, etc.) (Ahmed et al., 2020; Been et al., 2017; Boogaerts et al., 2019; Daughton, 2018; Rousis et al., 2017). Measured concentrations (ng/L to µg/L range) of human biomarkers in raw influent are converted to population-normalized mass loads (PNML) (mg/day/1000 inhabitants) by multiplying with daily wastewater flow rates (L/day) and dividing by the population in the catchment area at a given day (Baker et al., 2014). Earlier studies illustrate that WBE is suitable to measure temporal changes in drug consumption during the COVID-19 public health crisis, continuously and with a higher spatio-temporal resolution compared to other epidemiological information sources (Australian Crime Intelligence Commision, The University of Queensland & The University of South Australia, 2021; Bade et al., 2021; Been et al., 2021; Reinstadler et al., 2021; Wang et al., 2020). Additionally, Thomaidis et al. already showed the potential of WBE to measure temporal differences during a period in which there was a severe economic downturn accompanied with the introduction of several austerity policies (Thomaidis et al., 2016). For this reason, WBE could deliver valuable information to governments and health institutions for the optimization and management of harm-reduction, prevention and treatment strategies targeting illegal drug consumption and drug markets. Although WBE delivers valuable information on consumer patterns at the population level, it cannot provide information on the socio-demographic features of people who use drugs and on the drivers of drug use during these turbulent times. This highlights the need for var-

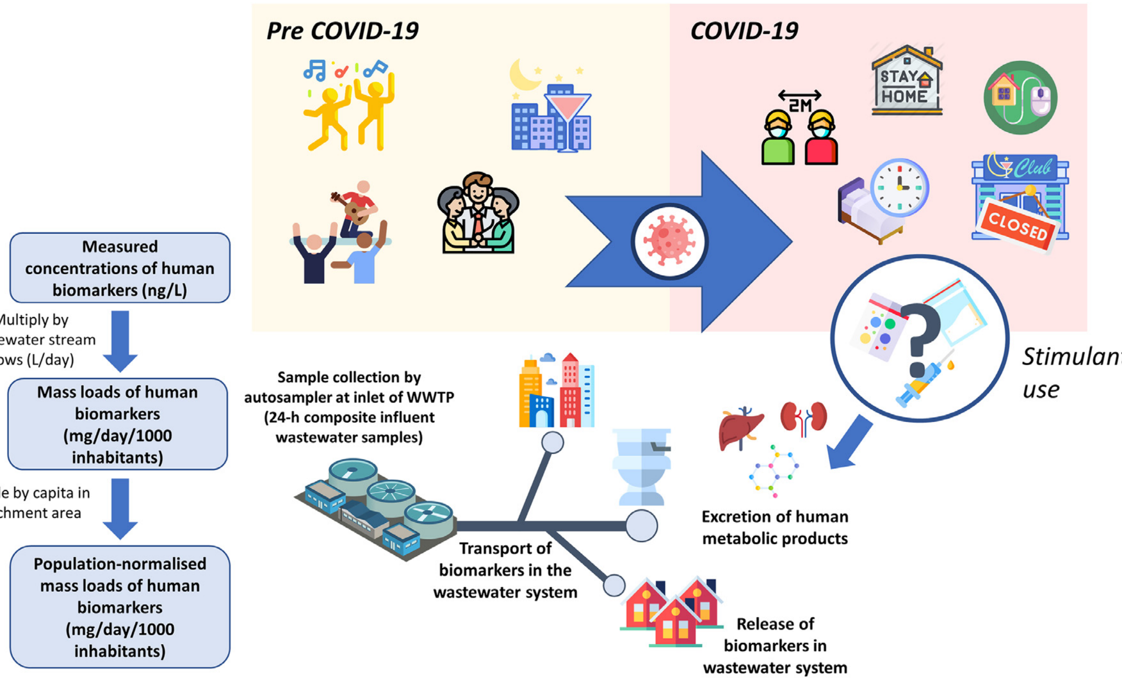

Fig. 2. Schematic overview of WBE as a complementary tool to evaluate the effect of the COVID-19 measures on stimulant consumption.

Table 1
Sampling campaign information. Population served, sampling period, and method of sampling collection method by WWTP.

WWTP (Abbr.)	City	Percentage of Belgian population	Sampled period	Sampling method
Antwerp-Zuid (AZ)	Antwerp	1.76 %	23-SEP-2019 to 29-SEP-2019 04-MAY-2020 to 30-JUN-2020	Time-proportional
Boom (BOO)	Boom	0.28 %	23-SEP-2019 to 29-SEP-2019 03-APR-2020 to 29-JUN-2020	Time-proportional
Brussel-Noord (BRU)	Brussels	8.30 %	23-SEP-2019 to 29-SEP-2019 14-APR-2020 to 30-JUN-2020	Volume-proportional
Leuven (LEU)	Leuven	0.96 %	23-SEP-2019 to 29-SEP-2019 09-MAR-2020 to 30-JUN-2020	Time-proportional

ious complementary epidemiological information sources to further assess the impact of the COVID-19 implications on substance use.

This study aims to monitor temporal trends in stimulant use (i.e., amphetamine, cocaine, methamphetamine and MDMA) at the population level in four different cities in Belgium (i.e., Antwerp, Boom, Brussels and Leuven) during the COVID-19 pandemic and to compare the consumption with baseline consumption observed in 2019. Different covariates were accounted for including week/weekend pattern.

Method

Sampling and analysis

Sampling

Daily 24-h composite influent wastewater samples (500 mL) were collected from four Belgian wastewater treatment plants (WWTPs), covering approximately 11.3% of the Belgian population. Samples were collected in a time- or volume proportional manner (Table 1). In case of time-proportional sampling, a high frequency (<20 min) was used to compose daily representative IWW samples to ensure that average biomarker concentrations were captured accurately over a 24-h period (Ort et al., 2010). IWW aliquots were immediately frozen after sample collection and stored at -20°C until analysis to prevent transformation of human biomarkers during storage. Wastewater temperature ranged between 11 and 24°C. Average residence time was less than 24 h in all four locations. Samples from 2019 were acquired during a week with no special events reported (23 September 2019 through 29 September 2019), providing a baseline for stimulant consumption before the introduction of the COVID-19 measures. This week was sampled previously for the 2019 monitoring campaign of the sewage analysis core group Europe (SCORE) (Gonzalez-Marino et al., 2020). Sample collection in 2020 was done during the *lockdown* (14 March 2020 through 4 May 2020), *exit strategy* (4 May 2020 through 8 June 2020) and the *relaxations* period (8 June 2020 through 30 June 2020).

Sample preparation and instrumental analysis

Extraction of amphetamine, benzoylecgonine, methamphetamine and MDMA in wastewater was performed according to previously validated bioanalytical methods (van Nuijs et al., 2009). Information on reagents and materials can be found in the supplementary information (S.1). The use of cocaine was measured through its metabolite benzoylecgonine. SPE was used to purify and concentrate human biomarkers in IWW. Quantification was done by liquid chromatography coupled to triple quadrupole mass spectrometry. A detailed description of the standard operating procedure is given in the Supplementary Information. Performance criteria (i.e., accuracy, precision, matrix effects,…) of this analytical procedure met the requirements for bioanalytical method validation provided by the European Medicines Agency guidelines (Committee for Medicinal Products for Human Use (CHMP), 2011). Six-level linear calibration curves with final concentrations ranging between 1 and 3000 ng/L were constructed for the analytes under investigation using isotope-labelled internal standards (IS) for quantification (i.e., mixture of amphetamine-D_8, benzoylecgonine-D_3, methamphetamine-D_{11} and MDMA-D_5). A weighting factor of $1/x$ or $1/x^2$ was applied based on the native biomarker concentrations found in wastewater to improve the accuracy of the method. A weighting of $1/x^2$ was considered more appropriate for biomarkers with measured concentrations at the lower end of the calibration curve, whereas $1/x$ was used for higher concentrations. For biomarker identification, the qualifier/quantifier (q/Q) ratio must not differ more than ±15% and the relative retention time (RRt, i.e., ratio of retention time of analyte to that of the IS) must not differ more than 2.5%. Quality control was performed through annual participation in the interlaboratory SCORE exercise and in-house QA/QC measures (van Nuijs et al., 2018).

Mobile network data: a dynamic population proxy

Fixed population equivalents have been applied to standardize biomarker mass loads in the vast majority of WBE studies executed to date (Gonzalez-Marino et al., 2020). These fixed numbers do not consider that the population is mobile and contribute to the overall level of uncertainty (up to 55%) associated with the WBE approach (Castiglioni et al., 2013; Thomas et al., 2017). This is problematic since apparent changes in PNML may be due to a change in consumption, differing number of consumers, and/or changes in the catchment population. This is especially complicated when large socio-economic disruptions exist, such as those observed during the COVID-19 pandemic (Thomaidis et al., 2016). For this reason, a dynamic population marker is needed to account for fluctuations in population numbers during the COVID-19 pandemic.

As evidenced by Baz-Lomba et al. and Thomas et al., mobile network data was used to better estimate the *de facto* population contributing to the sewage system and to refine the back-calculation of the PNML (Baz-Lomba et al., 2019; Thomas et al., 2017). These studies have shown the applicability of mobile network data to take population movements accurately into account. For this reason, no further comparison with static population data was made.

Mobile stations (e.g., mobile phones) presence can be inferred from their periodical connection to mobile masts employed by the mobile network operator (signaling records). Radio cells coverage (i.e., transmission antennas) were matched with the boundaries of the WWTP catchment area. Signaling events (e.g., network authentication, location update, sending and receiving data, etc.) are related to a particular radio cell and accordingly the location of the mobile station (Ricciato et al., 2020). All signalization records within the catchment area are compiled and further filtered to exclude machine-to-machine and Internet of Things communications (e.g., cars, scooters, payment terminals, etc.) to minimize overestimation. The population was further extrapolated based on several factors, such as zone probability, contact probability and market share (appendix S.3).

Anonymized aggregated data from mobile network operator, Orange Belgium (Cropland, Antwerp, Belgium), was acquired to temporally estimate the population in each catchment area. The mean daily number of people present in the catchment area was used to normalize mass loads for daily variations in population size numbers. Mobile device signals present for more than 2 h in the catchment area, were included in the population estimate. A visit terminated when a mobile device signal was absent for 3 h. Mobile network-based analytics were acquired corresponding with the sampling period (i.e., Sept. 2019, Mar. to Jun. 2020), encompassing the IWW sampling of each WWTP catchment area). A previously established population study from Baz-Lomba et al. was used as a framework for the implementation of mobile data in this work (Baz-Lomba et al., 2019).

Statistical analysis

A multiple linear regression model (MLR) was fitted for the PNML of the different stimulants (Eq. (1)) to investigate whether the period of the COVID-19 pandemic (i.e., *pre-lockdown*, *lockdown*, *exit strategy* and *relaxations*) influenced the use of the substances, accounting for possible effects of weekend versus week and location. In other words, this model was applied to investigate the intra- and inter-year changes in illicit drug use simultaneously. No analysis plan was pre-registered before statistical analysis. A flowchart for statistical testing was given in Fig. S1. PNML can be considered as a proxy for the use of the parent compound. Since the aim of this study was to investigate temporal changes, no further back-calculations to doses were performed (Boogaerts et al., 2021; Jones et al., 2014).

Eq. (1) MLR model for the estimation of the PNML

$$PNML \sim Period + weekWeekend + period : weekWeekend + location + period : location \quad (1)$$

Fixed effects included three categorical predictors: i) the period of the COVID-19 pandemic, modeling differences in PNML between *pre-lockdown*, *lockdown*, *exit strategy* and *relaxations*, ii) the difference between week and weekend, whereby the weekend was defined as Saturday and Sunday, and iii) a location effect modeling the difference between the four cities where samples were collected. To test for possible effect modification, two interaction terms were included, respectively between the period and the week/weekend effect and between the period and the location. The period:location interaction was included to test whether periodic changes were different in the locations under investigation. The interaction period:weekWeekend investigates whether the differences in PNML between the periods, are the same across week and weekend. This regression model was simplified in a stepwise backward way, starting with the interaction terms. In this study, a Chi-Square test was applied to test the significance of the different parameters in the MLR. The significance level was set at 0.05.

In case of significance of the period:location interaction, there is a difference in temporal changes in the PNML between the different locations. Thus, the analysis was split by location, according to the MLR model in Eq. (2) fitting a separate model for each location.

Eq. (2) MLR model for the estimation of the PNML applied when filtered by location

$$PNML \sim Period + weekWeekend + period : weekWeekend \quad (2)$$

In the next step, the significance of the period:weekWeekend interaction was tested to investigate whether temporal changes occurred in the amplitude of the week/weekend effect during the COVID-19 pandemic. If this interaction proved to be significant, the MLR model in Eq. (2) was further split separated into two separate models (Eq. (3)) for the week and weekend respectively, since a significant period:weekWeekend interaction indicates that period changes are not uniform between week and weekend. On the other hand, this interaction was removed from the model in case of non-significance, indicating that differences in PNML between the four periods were the same across week and weekend. In this latter case, Eq. (4) was used for further testing. In the end, the same MLR model was applied across all biomarkers under investigation based on the significance of the interactions. For the final model, the pairwise differences in PNML between the four locations were tested using a Tukey post-hoc analysis with Tukey correction for multiple hypothesis testing.

Eq. (3) MLR model for the estimation of the PNML applied when filtered by location and weekWeekend

$$PNML \sim Period \quad (3)$$

Eq. (4) MLR model for the estimation of the PNML when filtered by location

$$PNML \sim Period + weekWeekend \quad (4)$$

An identical MLR strategy was applied for the population estimates, based on mobile phone data, to investigate whether there were significant fluctuations between the periods of the COVID-19 pandemic and between different locations. In this case, the dependent parameter PNML was replaced by the population estimate. The same fixed effects were investigated to estimate the population equivalent, as illustrated in Eq. (5).

Eq. (5) Multiple linear regression model for the estimation of population equivalents

$$Population\ equivalent \sim Period + weekWeekend + period : weekWeekend + location + period : location \quad (5)$$

Results

Concentrations of methamphetamine were low to negligible in the different locations and for this reason methamphetamine was not included in the temporal analysis. An interaction was found for all compounds between the period of the COVID-19 pandemic and the location ($p < 0.001$ in all cases). For this reason, PNML were investigated for each location separately and results were not combined. In addition, the period:weekWeekend interaction was not significant for all compounds, meaning that the same week/weekend pattern was observed across the different stages of the first wave of the COVID-19 pandemic. In this case, the MLR in Eq. (4) was applied for further testing. Exact p-values can be found in Supplementary Tables S4-7.

Inter-year differences in stimulant use

To assess inter-year temporal trends, baseline stimulant consumption in 2019 (i.e., before the start of the pandemic) was compared to the different stages of the COVID-19 crisis.

Amphetamine

As indicated by Fig. 3, significant differences in PNML of amphetamine were observed between the sampling period in September 2019 and the different stages of the COVID-19 pandemic. An increase in PNML compared to previous year was observed in Antwerp for both *relaxation* and *exit strategy* periods ($p= 0.002$ and $p<0.001$, respectively), in Boom for the *lockdown* period ($p<0.001$), in Brussels for the *lockdown* ($p<0.001$) and *exit strategy* period ($p<0.001$), and in Leuven consumption remained stable.

These findings suggest that the consumption of amphetamine in the different Belgian communities in 2020 increased or remained stable compared to 2019. However, only one week of sampling was included in September 2019 to determine baseline consumption. It should be noted that the findings of 2020 were in line with the results from the annual sewage monitoring campaign, which reports a slight increase in baseline stimulant use in Western-European countries.

Cocaine

Fig. 4 shows that the PNML of benzoylecgonine significantly increased in 2020 compared to 2019 for Antwerp in the *relaxation* (p 0.017) and *exit strategy* (p 0.002) period, for Boom in the *lockdown* (p 0.021) period, for Brussels in all periods (*lockdown*, p 0.016; *exit strategy*, $p < 0.001$; and *relaxation*, $p < 0.001$), and in Leuven for both the *lockdown* ($p < 0.001$) and *exit strategy* (p 0.021) period. These findings indicate that the use of cocaine increased or remained stable even after the introduction of the COVID-19 interventions to diminish the spread of SARS-CoV-2 such as closure of the night-time economy and home confinement measures.

MDMA

An increase compared to 2019 was noted during the lockdown period in Boom ($p = 0.011$), but for all other locations and periods consumption remained stable (Fig. 5). Previous reports have shown that the use of MDMA is mostly associated with social gatherings and the nightlife industry (EMCDDA, 2020a). These findings, however, suggest that the use of MDMA remained stable throughout the lockdown even when the COVID-19 measures, such as physical distancing and stay-at-home measures, heavily restricted the use of MDMA in this social context.

Intra-year differences in stimulant use

In this section, differences in stimulant use were investigated with regards to the interventions during the first wave of the COVID-19 pandemic in Belgium (i.e. within 2020). Changes in stimulant use were examined to determine the short-term implications of this socio-economic disruption on drug use behavior at the population scale.

Amphetamine

A significant week/weekend effect was observed in all locations ($p < 0.001$, higher consumption during the weekends), except for Boom ($p = 0.2$) (see Fig. 3). In this location, there was no difference between week and weekend consumption of amphetamine and this pattern was observed during each period of the COVID-19 pandemic. Intra-year differences in PNML of amphetamine were found in all locations of interest, as illustrated in Fig. 3. Observed PNML of amphetamine in Boom and Brussels were significantly higher during the *lockdown* period compared to the *relaxation* period ($p < 0.001$ in both cases). In addition, a higher amphetamine use was observed in Boom and Leuven in the *lockdown* period compared to the *exit strategy* ($p < 0.001$ in both cases). In Antwerp, there was a higher PNML in the *relaxation* period compared to the *exit strategy* ($p = 0.008$).

The overall use of amphetamine during the initial *lockdown* period appears to be stable or significantly higher in the different locations compared to the other periods aligned by the COVID-19 measures. It should, however, be noted that for some locations limited or no data could be obtained during the lockdown period (i.e., Antwerp and Brussels).

Cocaine

Intra-year temporal changes in cocaine use were observed in Boom, Brussels and Leuven (see Fig. 4), but remained stable in Antwerp during the COVID-19 pandemic. However, it should be noted that no sampling was done for Antwerp during the lockdown phase. Cocaine use was higher in Boom, Brussels and Leuven during the *lockdown* compared to the *exit strategy*. Additionally, cocaine use did differ significantly between the *exit strategy* and the *relaxation* period in Brussels ($p = 0.024$) with a higher use observed during the *exit strategy*. In Leuven, the measured PNML of benzoylecgonine were also significantly higher in the *lockdown* period compared to the *relaxation* period ($p = 0.006$). Similar to amphetamine, cocaine use remained stable or even increased during the initial phases of the COVID-19 pandemic. These findings indicate that there was limited effect of the stringent measures during the COVID-19 crisis on the consumption of cocaine.

MDMA

A significant week/weekend pattern was observed in all locations ($p < 0.001$ for all locations) except for Boom ($p = 0.09$), as illustrated by Fig. 5. This is in line with other WBE studies that observe substantially higher consumption during the weekend compared to the week. In Boom, stable use of MDMA during the week was observed during all different stages of the first wave of the COVID-19 pandemic. Significant differences in MDMA consumption were only observed in Boom, with a higher consumption during the *lockdown* compared to the *exit strategy* and *relaxations* period ($p < 0.001$ in both cases). The use of MDMA remained stable throughout the first wave of the COVID-19 pandemic in the other locations.

Implementation of mobile phone data

Fig. 6 illustrates the population dynamics during the different stages of the first lockdown of the COVID-19 pandemic in Belgium. This figure highlights the need for accurate and timely population size numbers to normalize mass loads to reliably interpret temporal changes in illicit drug consumption patterns.

As discussed in section 2.4., a similar MLR was applied to investigate whether there were any temporal changes in the catchment population. The interaction between the location and the period proved to be significant, meaning that a different effect of the period was observed in each location. In Brussels, there was also an interaction between the period of the COVID-19 pandemic and the week/weekend effect, indicating that a different week/weekend pattern in population fluctuations was observed at different timepoints during the COVID-19 pandemic. For this reason, the MLR in Eq. (3) was applied in which popula-

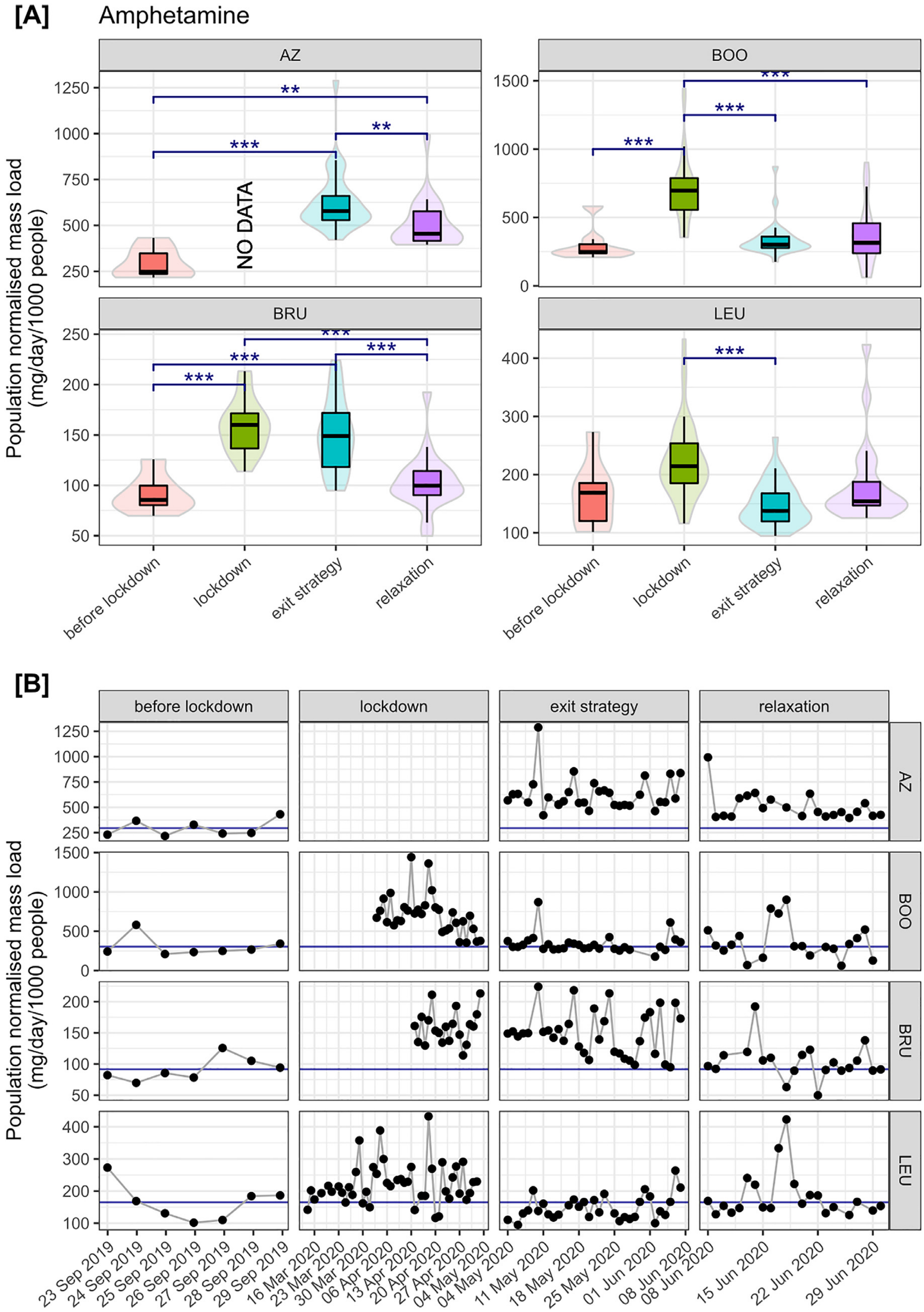

Fig. 3. (A) Boxplots of the population-normalized mass loads of amphetamine in the different locations and time periods. Statistical differences (Tukey Contrasts) between periods are highlighted with an asterisk. Significance levels: * p<0.05, ** p<0.01, *** p<0.001. (B) Intra- and inter-year changes in amphetamine consumption with regards to the COVID-19 pandemic. The pre-lockdown period represents one week of sampling during Sep 2019. The mean consumption of the before lockdown period is indicated with a horizontal blue line. Abbreviations: Antwerp-Zuid (AZ), Boom (BOO), Brussels (BRU), and Leuven (LEU).

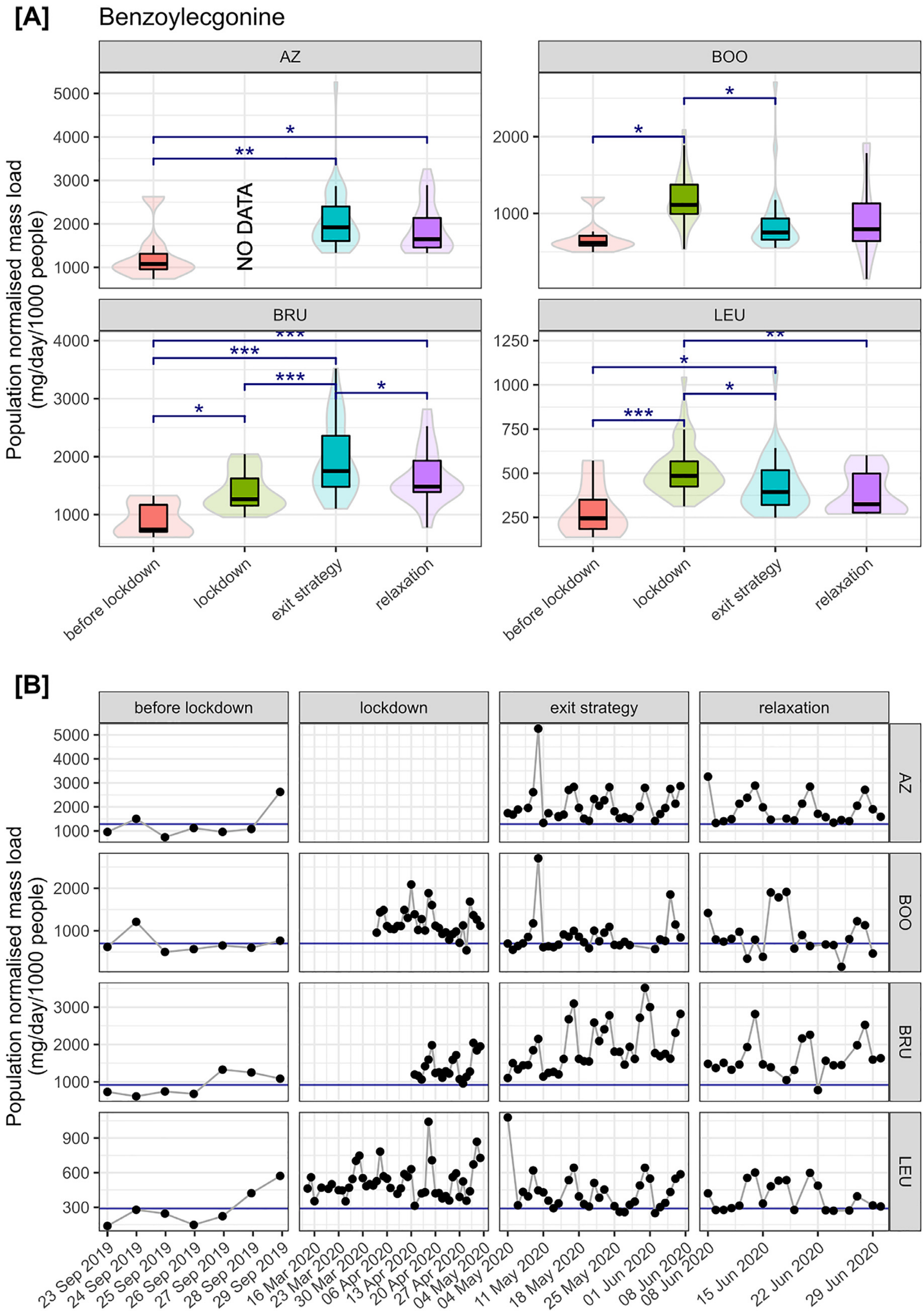

Fig. 4. (A) Boxplots of the population-normalized mass loads of benzoylecgonine in the different locations and time periods. Statistical differences (Tukey Contrasts) between periods are highlighted with an asterisk. Significance levels: * p<0.05, ** p<0.01, *** p<0.001. (B) Intra- and inter-year changesin population-normalized mass loads of benzoylecgonine with regards to the COVID-19 pandemic. The pre-lockdown period represents one week of sampling during Sep 2019. The mean consumption of the before lockdown period is indicated with a horizontal blue line. Abbreviations: Antwerp-Zuid (AZ), Boom (BOO), Brussels (BRU), and Leuven (LEU).

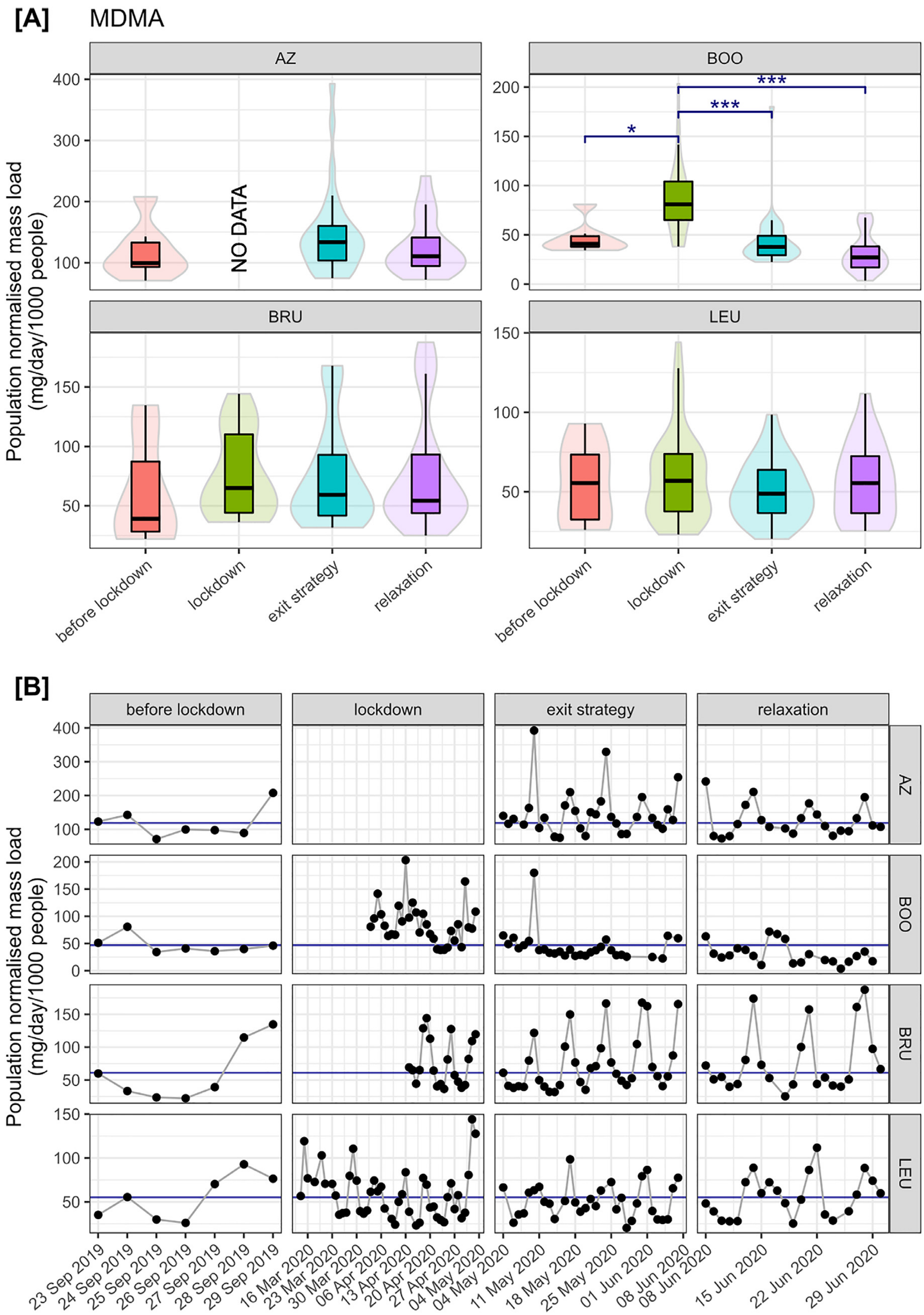

Fig. 5. (A) Boxplots of the population-normalized mass loads of MDMA in the different locations and time periods. Statistical differences (Tukey Contrasts) between periods are highlighted with an asterisk. Significance levels: * p<0.05, ** p<0.01, *** p<0.001. (B) Intra- and inter-year changes in MDMA consumption with regards to the COVID-19 pandemic. The pre-lockdown period represents one week of sampling during Sep 2019. The mean consumption of the before lockdown period is indicated with a horizontal blue line. Abbreviations: Antwerp-Zuid (AZ), Boom (BOO), Brussels (BRU), and Leuven (LEU).

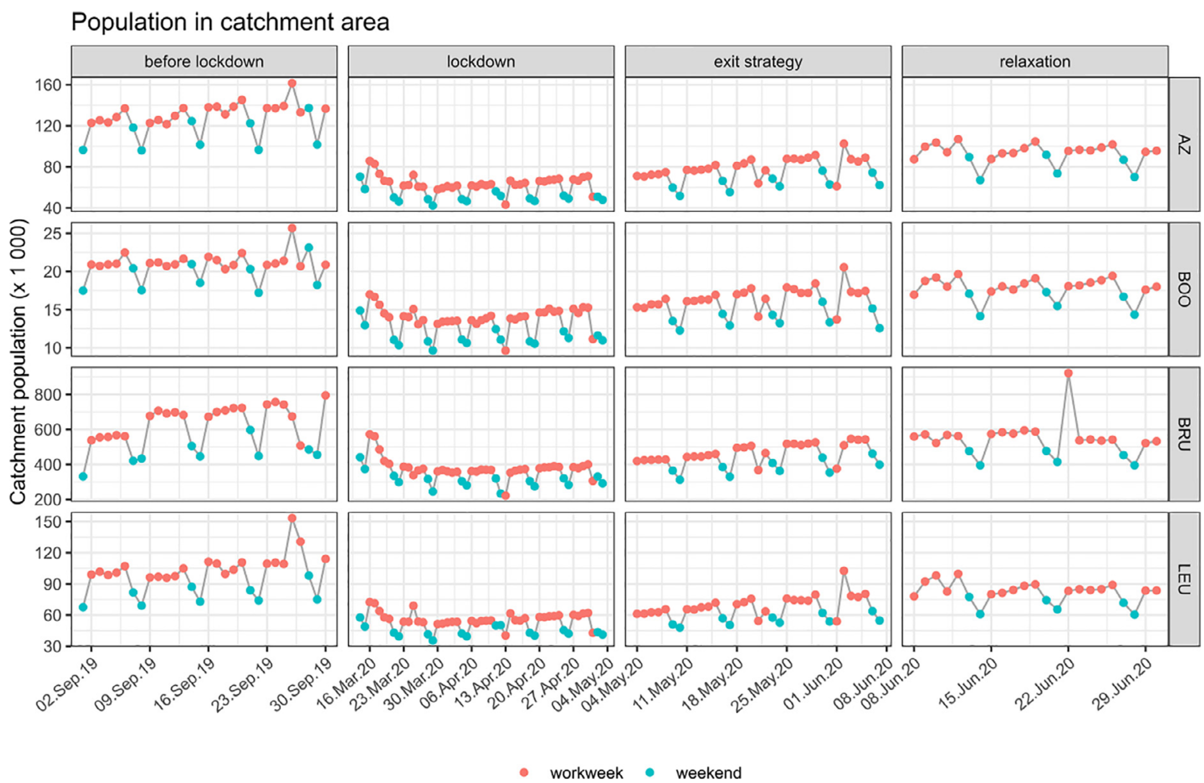

Fig. 6. Population dynamics based on mobile phone data during the first lockdown of the COVID-19 pandemic. Locations were labelled as follows: AZ = Antwerp-Zuid, BOO = Boom, BRU = Brussels, and LEU = Leuven.

tion numbers were considered individually for week and weekend days in each location. The results of this investigation are summarized in Table S8

In Antwerp, Boom and Leuven, there was a significant difference ($p < 0.05$) in population numbers during the different periods of the entire sampling period (i.e., *pre-lockdown, lockdown, exit strategy, relaxations*) for both week and weekend days. In Brussels, there was no significant difference in the number of people present in the catchment area during the weekend between the *pre-lockdown* period and the *relaxation period* ($p = 0.84$). Additionally, the population number in the weekends during the *relaxation* period and *exit strategy* was not significantly different ($p = 0.21$) in this location. For the remaining periods, significant differences in the population number were found during the week and weekend in Brussels. Population equivalents were the lowest during the *lockdown* period in all locations, probably due to the social measures heavily impacting movement of individuals inside and outside the catchment area (e.g., less commuting, tourism, …).

Discussion

Stimulant use

At this moment, limited information is available on the effect of the COVID-19 interventions on substance use. The results found in this study are in contrast with the results of different survey reports since the use of stimulants remained stable or even increased in 2020 compared to 2019. In addition, the investigation of the intra-year temporal changes showed that the PNML of amphetamine and benzoylecgonine was higher during the *lockdown* compared to the *exit strategy* and/or *relaxations* period in some locations. The use of MDMA remained stable throughout stages of the first wave of the COVID-19 pandemic with exception of Boom where higher consumption was measured during the *lockdown* period. These findings suggest that stimulant use in Belgium might have been less impacted by the limited social opportunities to use them. These findings may also indicate that people continue to use stimulants during home confinement. Additionally, it is also possible that users of these drugs disproportionately disregard home confinement.

Most epidemiological studies report a decline in the use of stimulants during the initial phase of the pandemic, mostly resulting from the implementation of confinement and physical distancing measures (Ali et al., 2021; EMCDDA, 2020b, 2020c; EMCDDA & EUROPOL, 2020; Gili et al., 2021; Manthey et al., 2021; Palamar et al., 2021; Price et al., 2021), with later lifting of restrictions associated with a recovery to previous levels (European Monitoring Centre for Drugs and Drug Addiction, 2021a) According to the EMCDDA, the use of cocaine and MDMA seems to be the most affected by COVID-19 restrictions. However, most of the information available is compiled from online surveys with known individuals who use drugs, making it difficult to generalize the results of this subsample to the general population which contains also occasional users (Ali et al., 2021; Manthey et al., 2021; Palamar et al., 2021; Price et al., 2021). The adverse social effects of the COVID-19 measures, such as social isolation and anxiety, could potentially be a driver for first time drug usage. In addition, these questionnaires often employ different surveying methods compared to their pre-pandemic counterparts. In order to fill in some of the knowledge gaps, WBE could deliver valuable complementary information on the implications of the COVID-19 pandemic on the consumption of illegal drugs at population scale (Australian Crime Intelligence Commision et al., 2021; Been et al., 2021; Reinstadler et al., 2021). For instance, Been et al. and Reinstadler et al. clearly demonstrate the heterogenic effects the COVID-19 measures had on substance use in Europe (Been et al., 2021; Reinstadler et al., 2021). In some cities, such as Amsterdam, Milan and Innsbruck, a decline in PNML appears to be the case. However, in other European cities, stimulant use remained stable compared to 2019. These mixed outcomes could partially be explained by the complex geographical differences in the COVID-19 interventions in the different countries, but also by the underlying changes in the drug markets as a response to the current restrictions.

The EMCDDA reported that demand or opportunity to use common party drugs reduced due to the halted nightlife venues and festivals. The COVID-19 restrictions appear to have disrupted the availability of drugs to varying extent in EU countries and drug-using populations (Palamar et al., 2021), however overall the drug market has been resilient (European Monitoring Centre for Drugs and Drug Addiction, 2021b). The geographical location of Belgium within the European landscape could potentially explain the continued use of illicit drugs in this country. Belgium is one of the main entry points and distribution hubs for cocaine in Europe (EMCDDA & EUROPOL, 2020). EUROPOL reported no change in the number of cocaine seizures in Belgium in April 2020, indicating limited short-term effects of the COVID-19 interventions on the trafficking of cocaine to Europe (EMCDDA & EUROPOL, 2020). At the same time, 73% of cocaine seized from Jan to mid-May 2020 at Columbia ports was destined for Belgium (EMCDDA & EUROPOL, 2020). In this light, different national focal points also indicate that illicit drug flows may not be influenced, mainly because the cross-border passage of legal and commercial good transport has continued. Similarly, aviation and maritime cargo shipping has not seen the same widespread disruption compared to individual passenger transport (EMCDDA & EUROPOL, 2020). In general, a shift in wholesale transport was noted, with more export using intermodal containers and commercial supply chains (European Monitoring Centre for Drugs and Drug Addiction, 2021b). Together these data could potentially indicate that the supply of cocaine to the EU during the pandemic remained unaffected by the different COVID-19 interventions.

Similar to cocaine, no change was reported in the availability of amphetamine and MDMA in Belgium at the consumer level. The lack of inter-year differences in amphetamines use may also be partially explained by their domestic production. According to EUROPOL, the main synthetic drug production hubs in Belgium and the Netherlands remained operational and the production of amphetamine and MDMA does not appear to be influenced by the COVID-19 interventions (EMCDDA & EUROPOL, 2020), with uncovering of synthetic production sites remaining stable during last six months of 2020 (European Monitoring Centre for Drugs and Drug Addiction, 2021b). EUROPOL also indicates that organized crime groups may become more resilient in altering their business models to this complex and rapidly changing context: further exploring secure communication channels, adapting transportation models, trafficking routes, and new concealment methods. Although street dealing in some cities was seriously affected by the movement restrictions and increased law enforcement, distribution might have been mitigated more to online channels and delivery service models (EMCDDA & EUROPOL, 2020; European Monitoring Centre for Drugs and Drug Addiction, 2021b). The findings of this study potentially suggest that changes in drug use need to be considered in a wider context of drug availability, markets, and distribution mechanisms. Possibly, individuals will be able to maintain their existing patterns of drug consumption when supply chains and distribution channels continue to function.

Additionally, there have been reports of the use of drugs by people at home and the occurrence of 'streaming parties' as a substitute for physical social gatherings (EMCDDA, 2020b; Palamar & Acosta, 2021). Furthermore, media reports have suggested that illegal parties outside urban areas associated with drug use have taken place during the lockdown period (ATV, 2020; EMCDDA, 2020b). It is also notable that a quarter of respondents in EMCDDA's online surveys reported an increase in drug consumption with main reasons being boredom and anxiety (EMCDDA, 2020b).

Mobile data to refine back-calculations

The estimation of the population in a catchment area significantly affects uncertainty. Traditionally, in WBE, static population numbers have regularly been used. To determine the static population, the census data, the design capacity, or hydrochemical parameters of the WWTP are often considered. However, the design capacity and biochemical oxygen demand is not only dependent on the contributing population to a catchment, but is also affected by expected future expansion, industrial WW discharge, etc. Census data on the other hand may not reflect the amount of people contributing on a certain day (e.g., home-work travel) (Thomas et al., 2017). Castiglioni et al and Thomas et al indicate that the uncertainty with static population numbers can yield up to 55% (Castiglioni et al., 2013; Thomas et al., 2017). By not considering dynamic population fluctuations incorrect interpretations of WBE data could be made. To date, dynamic population estimates have been investigated in WBE applications (Baz-Lomba et al., 2019; Been et al., 2014; Lai et al., 2015; Thomas et al., 2017; Yu et al., 2021), however, to our knowledge only Reinstadler et al. used a dynamic population proxy to estimate population fluxes during the COVID-19 pandemic (Reinstadler et al., 2021).

In the present study, mobile device-based population numbers were used to account for fluctuations in the population size. The estimated population size is closer to the actual number of people contributing, and furthermore temporal trends are better reflected (Thomas et al., 2017) than the commonly used static population in WBE publications, especially in the case of a disruption in population mobility.

The results of this study clearly demonstrate the temporal differences in population estimates during the first wave of the COVID-19 pandemic. This further indicates the need for refinement of WBE back-calculations based on accurate population numbers. This also demonstrates that the use of static population data for the back-calculation of PNML may not be applicable during similar large-scale population disruptions.

Study limitations

The sampling campaign encompassed four urban cities covering 11.3 % of the Belgian population. The results of this analysis might not be representative for rural areas in Belgium. Due to logistics, the start of sample collection differs by location resulting in a different number of data points between periods and locations. Results obtained are not generalizable to the entire Belgian population, but our findings are valuable in the global picture of substance use during the COVID-19 disruption.

Limited data was available for inter-year comparison, one week in September 2019 was compared with at least nine weeks starting from March 2020. The sampled week in 2019 was chosen because it does not include any special events (holidays, festivals, etc.) and thus is representative as baseline consumption. Contrastingly, the sampling period in 2020 also contained national holidays with higher reported consumption levels, which complicates the comparison between 2019 and 2020 data. Seasonality in the consumption of stimulants potentially influences the interpretation of the results as well. For example, seasonal variability for cocaine and MDMA were noted in earlier studies (Ort et al., 2014; Tscharke et al., 2016). Further research should be directed to estimate the impact of seasonal variability of stimulant consumption.

The statistical model was constructed using conventional workweek/weekend days (Mon-Fri, and Sat-Sun) to compare workweek-weekend trends. This does not completely reflect the actual excretion pattern. The half-life of the compounds under investigation is individually variable and long, often exceeding multiple days (Abraham et al., 2009; de la Torre et al., 2004; Shimomura et al., 2019). For example, Humphries et al. observed weekly cycles for amphetamine, cocaine, and MDMA with a peak on Monday and a through around Thu-Fri (Humphries et al., 2016). From a WBE perspective, more pharmacokinetic research is needed to further distinguish week/weekend consumption. Additionally, there were slight changes in the weekly cycle between the different periods (Fig. S2). A change from traditional weekend use is possible as measures in certain periods (e.g., *lockdown*) may have impacted access to the habituated place of consumption.

WBE relies on the premise that the demographic population contributing to a WWTP remains relatively constant. For example, an increase in PNML may be the result of a larger proportion of people consuming, a smaller proportion of people consuming more, or a combination of both. It is well known that the type of drug consumed, and amount of drug taken, is very different amongst different demographics. During the government-imposed lockdown, the demography of the population contributing to a WWTP may be significantly different to pre-lockdown.

Furthermore, uncertainties are introduced from quantitative chemical analysis to the back-calculation of PNML; related to chemical analysis, sampling, drug stability and excretion, estimation of population size, etc. A validated method and common protocol are followed to reduce the analytical uncertainties. Laboratory performance is ensured through multi-year participation in an external quality control study (van Nuijs et al., 2018). To account for fluctuations in the population size, mobile device-based population numbers were used.

Flow-proportional sampling is the recommended sampling method (Ort et al., 2010). However, for technical reasons, volume- or time-proportional sampling modes were applied in this study. High sampling frequencies were applied to compile the daily IWW samples and to accurately capture average biomarker concentrations over the 24-h period.

It should also be noted that a small proportion of amphetamine could be legally prescribed for treatment of attention deficit and hyperactivity disorder (ADHD). However, amphetamine is only given to very specific patients in Belgium when treatment with methylphenidate is clinically unsatisfactory (BCFI: Chapter 10 Nervous System: 10.4. Treatment of ADHD and narcolepsy, 2022). For this reason, the high PNML measured in IWW are mainly the result of recreational amphetamine use. Additionally, the measurement of parent drugs (i.e., amphetamine, MDMA, and methamphetamine) could be influenced by direct disposal in the sewer system. However, the dumping of parent drug usually results in aberrant PNML that deviate from the historical pattern (Boogaerts et al., 2021; Emke et al., 2014). In this study, no such outliers in the PNML were found, which indicates that the measured PNML are most likely the result of consumption.

Conclusions

There was no decrease in stimulant use in 2020 during the COVID-19 pandemic compared to the pre-pandemic period in four Belgian cities. In addition, consumption of stimulants was unchanged, or higher during the full *lockdown* period compared to *exit strategy* and *relaxation* period. We hypothesize that accessibility of drugs by individual persons was not severely impacted. This could primarily be explained by Belgium's geographical location and the fact that the supply and distribution channels within the illicit drug market were not heavily disrupted, as indicated in different EMCDDA reports.

The results of this study clearly highlight the potential of WBE to monitor the effects of different policy changes considering the on-going public health crisis on the use of stimulants. Thanks to its high temporal resolution, WBE could be employed as a complementary epidemiological indicator to measure the extent of short-term effects of the COVID-19 pandemic on substance use. A major advantage of WBE during the turbulent times of this nationwide socio-economic disruption is that this approach captures the general population objectively and more convenient compared to the early health interview surveys reports. Furthermore, it does not focus on specific subsets of the population (i.e., known individuals who use drugs). In context of the heterogenic effects of the COVID-19 restrictions across different communities, WBE could also be employed for area-based assessments for policy makers. This study also emphasizes the need for triangulation of different epidemiological information sources to monitor the use of substances, as discrepancies were found between the different epidemiological indicators.

Declarations of 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.

Acknowledgements

In living memory of Prof. Dr. Cathy Matheï (1965-2021). The authors would like to thank the WWTP personnel from Aquafin and Aquiris for their support in the sampling. This study was funded by the European Union's Justice Programme—Drugs Policy Initiatives, EuSeME (project number: 861602), and Research Scientific Foundation Flanders (FWO, project number: G060920N).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2022.103679.

References

Abraham, T. T., Barnes, A. J., Lowe, R. H., Kolbrich Spargo, E. A., Milman, G., Pirnay, S. O., & Huestis, M. A. (2009). Urinary MDMA, MDA, HMMA, and HMA excretion following controlled MDMA administration to humans. *Journal of Analytical Toxicology, 33*(8), 439–446. 10.1093/jat/33.8.439.

Ahmed, F., Tscharke, B., O'Brien, J., Thompson, J., Samanipour, S., Choi, P., & Thomas, K. (2020). Wastewater-based estimation of the prevalence of gout in Australia. *Science of the Total Environment, 715*, Article 136925. 10.1016/j.scitotenv.2020.136925.

Ali, F., Russell, C., Nafeh, F., Rehm, J., LeBlanc, S., & Elton-Marshall, T. (2021). Changes in substance supply and use characteristics among people who use drugs (PWUD) during the COVID-19 global pandemic: A national qualitative assessment in Canada. *International Journal of Drug Policy, 93*, Article 103237. 10.1016/j.drugpo.2021.103237.

ATV. (2020). Still lockdownparties in Antwerp - mayor intervenes [Dutch]. Retrieved from https://atv.be/nieuws/nog-altijd-lockdownfeestjes-burgemeester-grijpt-in.

Australian Crime Intelligence Commision, The University of Queensland, & The University of South Australia. (2021). National wastewater drug monitoring program: Report 13. Retrieved from https://www.acic.gov.au/publications/national-wastewater-drug-monitoring-program-reports/report-13-national-wastewater-drug-monitoring-program.

Bade, R., Simpson, B. S., Ghetia, M., Nguyen, L., White, J. M., & Gerber, C. (2021). Changes in alcohol consumption associated with social distancing and self-isolation policies triggered by COVID-19 in South Australia: A wastewater analysis study. *Addiction, 116*(6), 1600–1605. 10.1111/add.15256.

Baker, D. R., Barron, L., & Kasprzyk-Hordern, B. (2014). Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part A: Chemical analysis and drug use estimates. *Science of the Total Environment, 487*, 629–641. 10.1016/j.scitotenv.2013.11.107.

Baz-Lomba, J. A., Di Ruscio, F., Amador, A., Reid, M., & Thomas, K. V. (2019). Assessing alternative population size proxies in a wastewater catchment area using mobile device data. *Environmental Science & Technology, 53*(4), 1994–2001. 10.1021/acs.est.8b05389.

Baz-Lomba, J. A., Salvatore, S., Gracia-Lor, E., Bade, R., Castiglioni, S., Castrignanò, E., & Thomas, K. (2016). Comparison of pharmaceutical, illicit drug, alcohol, nicotine and caffeine levels in wastewater with sale, seizure and consumption data for 8 European cities. *BMC Public Health, 16*(1), 1035. 10.1186/s12889-016-3686-5.

BCFI: Chapter 10 Nervous System: 10.4. Treatment of ADHD and narcolepsy. (2022). *Gecommentarieerd geneesmiddelenrepertorium*. Maloteaux. Retrieved from https://www.bcfi.be/nl/chapters/11?matches=Dexamfetamine%7CLisdexamfetamine%7Cdexamfetamine%7CLisdexamfétamine&frag=8318.

Been, F., Bastiaensen, M., Lai, F. Y., van Nuijs, A. L. N., & Covaci, A. (2017). Liquid chromatography-tandem mass spectrometry analysis of biomarkers of exposure to phosphorus flame retardants in wastewater to monitor community-wide exposure. *Analytical Chemistry, 89*(18), 10045–10053. 10.1021/acs.analchem.7b02705.

Been, F., Emke, E., Matias, J., Baz-Lomba, J. A., Boogaerts, T., Castiglioni, S., & Bijlsma, L. (2021). Changes in drug use in European cities during early COVID-19 lockdowns – A snapshot from wastewater analysis. *Environment International, 153*, Article 106540. 10.1016/j.envint.2021.106540.

Been, F., Rossi, L., Ort, C., Rudaz, S., Delémont, O., & Esseiva, P. (2014). Population normalization with ammonium in wastewater-based epidemiology: Application to illicit drug monitoring. *Environmental Science & Technology, 48*(14), 8162–8169. 10.1021/es5008388.

Boogaerts, T., Ahmed, F., Choi, P., Tscharke, B., O'Brien, J., De Loof, H., & van Nuijs, A. L. N. (2021). Current and future perspectives for wastewater-based epidemiology as a monitoring tool for pharmaceutical use. *Science of the Total Environment, 789*, Article 148047. 10.1016/j.scitotenv.2021.148047.

Boogaerts, T., Covaci, A., Kinyua, J., Neels, H., & van Nuijs, A. L. N. (2016). Spatial and temporal trends in alcohol consumption in Belgian cities: A wastewater-based approach. *Drug and Alcohol Dependence, 160*, 170–176. 10.1016/j.drugalcdep.2016.01.002.

Boogaerts, T., Degreef, M., Covaci, A., & van Nuijs, A. L. N. (2019). Development and validation of an analytical procedure to detect spatio-temporal differences in antidepressant use through a wastewater-based approach. *Talanta, 200*, 340–349. 10.1016/j.talanta.2019.03.052.

Boogaerts, T., Jurgelaitiene, L., Dumitrascu, C., Kasprzyk-Hordern, B., Kannan, A., Been, F., & van Nuijs, A. L. N. (2021). Application of wastewater-based epidemiology to investigate stimulant drug, alcohol and tobacco use in Lithuanian communities. *Science of the Total Environment, 777*, Article 145914. 10.1016/j.scitotenv.2021.145914.

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: Rapid review of the evidence, *395*(10227), 912–920. 10.1016/S0140-6736(20)30460-8.

Castiglioni, S., Bijlsma, L., Covaci, A., Emke, E., Hernández, F., Reid, M., & Zuccato, E. (2013). Evaluation of uncertainties associated with the determination of community drug use through the measurement of sewage drug biomarkers. *Environmental Science & Technology, 47*(3), 1452–1460. 10.1021/es302722f.

Choi, P., Tscharke, B., Samanipour, S., Hall, W. D., Gartner, C. E., Mueller, J. F., & O'Brien, J. W. (2019). Social, demographic, and economic correlates of food and chemical consumption measured by wastewater-based epidemiology. *Proceedings of the National Academy of Sciences of the United States of America, 116*(43), 21864–21873. 10.1073/pnas.1910242116.

Committee for Medicinal Products for Human Use (CHMP). (2011). Guideline on bioanalytical method validation.

Daughton, C. G. (2018). Monitoring wastewater for assessing community health: Sewage Chemical-Information Mining (SCIM). *Science of the Total Environment, 619–620*, 748–764. 10.1016/j.scitotenv.2017.11.102.

de la Torre, R., Farré, M., Navarro, M., Pacifici, R., Zuccaro, P., & Pichini, S. (2004). Clinical pharmacokinetics of amfetamine and related substances: Monitoring in conventional and non-conventional matrices. *Clinical Pharmacokinetics, 43*(3), 157–185. 10.2165/00003088-200443030-00002.

Dietze, P. M., & Peacock, A. (2020). Illicit drug use and harms in Australia in the context of COVID-19 and associated restrictions: Anticipated consequences and initial responses. *Drug and Alcohol Review, 39*(4), 297–300. 10.1111/dar.13079.

EMCDDA. (2020a). EMCDDA trendspotter briefing: Impact of COVID-19 on patterns of drug use and drug-related harms in Europe. Retrieved from https://www.emcdda.europa.eu/publications/ad-hoc-publication/impact-covid-19-patterns-drug-use-and-harms_en.

EMCDDA. (2020b). EMCDDA trendspotter briefing - Impact of COVID-19 on drug services and help-seeking in Europe. Retrieved from https://www.emcdda.europa.eu/publications/ad-hoc/impact-of-covid-19-on-drug-services-and-help-seeking-in-europe_en.

EMCDDA. (2020c). EMCDDA update on the implications of COVID-19 for people who use drugs and drug service providers. Lisbon. Retrieved from https://www.emcdda.europa.eu/publications/topic-overviews/catalogue/covid-19-and-people-who-use-drugs_en.

EMCDDA, & EUROPOL. (2020). EU drug markets: Impact of COVID-19. Lisbon. Retrieved from https://www.emcdda.europa.eu/publications/joint-publications/eu-drug-markets-impact-of-covid-19_en.

Emke, E., Evans, S., Kasprzyk-Hordern, B., & de Voogt, P. (2014). Enantiomer profiling of high loads of amphetamine and MDMA in communal sewage: A Dutch perspective. *Science of the Total Environment, 487*, 666–672 (1st International Multidisciplinary Conference on Detecting Illicit Drugs in Wastewater: Testing the Waters). 10.1016/j.scitotenv.2013.11.043.

European Monitoring Centre for Drugs and Drug Addiction. (2019). European drug report 2019: Trends and development. Luxembourg. Retrieved from http://www.emcdda.europa.eu/system/files/publications/4541/TDAT17001ENN.pdf_en.

European Monitoring Centre for Drugs and Drug Addiction. (2021a). European drug report 2021: Trends and developments. Luxembourg. Retrieved from https://www.emcdda.europa.eu/system/files/publications/13838/TDAT21001ENN.pdf.

European Monitoring Centre for Drugs and Drug Addiction. (2021b). Impact of COVID-19 on drug markets, use, harms and drug services in the community and prisons. Lisbon. Retrieved from https://www.emcdda.europa.eu/publications/ad-hoc-publication/impact-covid-19-drug-markets-use-harms-and-drug-services-community-and-prisons_en.

FPS Public Health. (2022). Coronavirus COVID-19: What are the current measures? Retrieved from https://www.info-coronavirus.be/en/faq/.

Gili, A., Bacci, M., Aroni, K., Nicoletti, A., Gambelunghe, A., Mercurio, I., & Gambelunghe, C. (2021). Changes in drug use patterns during the COVID-19 pandemic in Italy: Monitoring a vulnerable group by hair analysis. *International Journal of Environmental Research and Public Health, 18*(4), 1967. 10.3390/ijerph18041967.

Gonzalez-Marino, I., Baz-Lomba, J. A., Alygizakis, N. A., Andres-Costa, M. J., Bade, R., Bannwarth, A., & Ort, C. (2020). Spatio-temporal assessment of illicit drug use at large scale: Evidence from 7 years of international wastewater monitoring. *Addiction, 115*(1), 109–120. 10.1111/add.14767.

Humphries, M. A., Bruno, R., Lai, F. Y., Thai, P. K., Holland, B. R., O'Brien, J. W., & Mueller, J. F. (2016). Evaluation of monitoring schemes for wastewater-based epidemiology to identify drug use trends using cocaine, methamphetamine, MDMA and methadone. *Environmental Science & Technology, 50*(9), 4760–4768. 10.1021/acs.est.5b06126.

Jones, H. E., Hickman, M., Kasprzyk-Hordern, B., Welton, N. J., Baker, D. R., & Ades, A. E. (2014). Illicit and pharmaceutical drug consumption estimated via wastewater analysis. Part B: Placing back-calculations in a formal statistical framework. *Science of the Total Environment, 487*(100), 642–650. 10.1016/j.scitotenv.2014.02.101.

Lai, F. Y., Anuj, S., Bruno, R., Carter, S., Gartner, C., Hall, W., & Ort, C. (2015). Systematic and day-to-day effects of chemical-derived population estimates on wastewater-based drug epidemiology. *Environmental Science & Technology, 49*(2), 999–1008. 10.1021/es503474d.

Lai, F. Y., Gartner, C., Hall, W., Carter, S., O'Brien, J., Tscharke, B. J., & Mueller, J. F. (2018). Measuring spatial and temporal trends of nicotine and alcohol consumption in Australia using wastewater-based epidemiology. *Addiction, 113*(6), 1127–1136. 10.1111/add.14157.

Manthey, J., Kilian, C., Carr, S., Bartak, M., Bloomfield, K., Braddick, F., & Rehm, J. (2021). Use of alcohol, tobacco, cannabis, and other substances during the first wave of the SARS-CoV-2 pandemic in Europe: A survey on 36,000 European substance users. *Substance Abuse Treatment, Prevention, and Policy, 16*(1), 36. 10.1186/s13011-021-00373-y.

Mariottini, C., Ojanperä, I., & Kriikku, P. (2021). Increase in drugs-of-abuse findings in post-mortem toxicology due to COVID-19 restrictions-First observations in Finland. *Drug Testing and Analysis, 13*(4), 867–870. 10.1002/dta.2982.

Ort, C., Eppler, J. M., Scheidegger, A., Rieckermann, J., Kinzig, M., & Sörgel, F. (2014). Challenges of surveying wastewater drug loads of small populations and generalizable aspects on optimizing monitoring design. *Addiction, 109*(3), 472–481. 10.1111/add.12405.

Ort, C., Lawrence, M. G., Reungoat, J., & Mueller, J. F. (2010). Sampling for PPCPs in wastewater systems: Comparison of different sampling modes and optimization strategies. *Environmental Science & Technology, 44*(16), 6289–6296. 10.1021/es100778d.

Palamar, J. J., & Acosta, P. (2021). Virtual raves and happy hours during COVID-19: New drug use contexts for electronic dance music partygoers. *International Journal of Drug Policy, 93*, Article 102904. 10.1016/j.drugpo.2020.102904.

Palamar, J. J., Le, A., & Acosta, P. (2021). Shifts in drug use behavior among electronic dance music partygoers in New York during COVID-19 social distancing. *Substance Use & Misuse, 56*(2), 238–244. 10.1080/10826084.2020.1857408.

Palamar, J. J., Le, A., Carr, T. H., & Cottler, L. B. (2021). Shifts in drug seizures in the United States during the COVID-19 pandemic. *Drug and Alcohol Dependence, 221*, Article 108580. 10.1016/j.drugalcdep.2021.108580.

Price, O., Man, N., Bruno, R., Dietze, P., Salom, C., Lenton, S., & Peacock, A. (2021). Changes in illicit drug use and markets with the COVID-19 pandemic and associated restrictions: Findings from the Ecstasy and Related Drugs Reporting System, 2016-2020. *Addiction, 117*(1), 182–194. 10.1111/add.15620.

Rehm, J., Kilian, C., Ferreira-Borges, C., Jernigan, D., Monteiro, M., Parry, C. D. H., & Manthey, J. (2020). Alcohol use in times of the COVID 19: Implications for monitoring and policy. *Drug and Alcohol Review, 39*(4), 301–304. 10.1111/dar.13074.

Reinstadler, V., Ausweger, V., Grabher, A.-L., Kreidl, M., Huber, S., Grander, J., & Oberacher, H. (2021). Monitoring drug consumption in Innsbruck during coronavirus disease 2019 (COVID-19) lockdown by wastewater analysis. *Science of the Total Environment, 757*, Article 144006. 10.1016/j.scitotenv.2020.144006.

Ricciato, F., Lanzieri, G., Wirthmann, A., & Seynaeve, G. (2020). Towards a methodological framework for estimating present population density from mobile network operator data. *Pervasive and Mobile Computing, 68*, Article 101263. 10.1016/j.pmcj.2020.101263.

Rousis, N. I., Gracia-Lor, E., Zuccato, E., Bade, R., Baz-Lomba, J. A., Castrignanò, E., & Castiglioni, S. (2017). Wastewater-based epidemiology to assess pan-European pesticide exposure. *Water Research, 121*, 270–279. 10.1016/j.watres.2017.05.044.

Sciensano. (2020). COVID-19 health survey. Retrieved from https://www.sciensano.be/en/biblio/eerste-covid-19-gezondheidsenquete-eerste-resultaten.

Shimomura, E. T., Jackson, G. F., & Paul, B. D. (2019). *Chapter 17 - Cocaine, crack cocaine, and ethanol: A deadly mix* (pp. 215–224). Academic Press.. A. B. T.-C. I. in A. and D. of A. T. (Second E. Dasgupta (Ed.). 10.1016/B978-0-12-815607-0.00017-4.

Thomaidis, N. S., Gago-Ferrero, P., Ort, C., Maragou, N. C., Alygizakis, N. A., Borova, V. L., & Dasenaki, M. E. (2016). Reflection of socioeconomic changes in wastewater: Licit and illicit drug use patterns. *Environmental Science & Technology, 50*(18), 10065–10072. 10.1021/acs.est.6b02417.

Thomas, K. V., Amador, A., Baz-Lomba, J. A., & Reid, M. (2017). Use of mobile device data to better estimate dynamic population size for wastewater-based epidemiology. *Environmental Science & Technology, 51*(19), 11363–11370. 10.1021/acs.est.7b02538.

Tscharke, B. J., Chen, C., Gerber, J. P., & White, J. M. (2016). Temporal trends in drug use in Adelaide, South Australia by wastewater analysis. *Science of the Total Environment, 565*, 384–391. 10.1016/j.scitotenv.2016.04.183.

van Nuijs, A. L. N., Lai, F. Y., Been, F., Andres-Costa, M. J., Barron, L., Baz-Lomba, J. A., & Ort, C. (2018). Multi-year inter-laboratory exercises for the analysis of illicit drugs and metabolites in wastewater: Development of a quality control system. *TrAC Trends in Analytical Chemistry, 103*, 34–43. 10.1016/j.trac.2018.03.009.

van Nuijs, A. L. N., Tarcomnicu, I., Bervoets, L., Blust, R., Jorens, P. G., Neels, H., & Covaci, A. (2009). Analysis of drugs of abuse in wastewater by hydrophilic interaction liquid chromatography-tandem mass spectrometry. *Analytical and Bioanalytical Chemistry, 395*(3), 819–828. 10.1007/s00216-009-3017-0.

Wang, S., Green, H. C., Wilder, M. L., Du, Q., Kmush, B. L., Collins, M. B., & Zeng, T. (2020). High-throughput wastewater analysis for substance use assessment in central New York during the COVID-19 pandemic. *Environmental Science: Processes & Impacts, 22*(11), 2147–2161. 10.1039/D0EM00377H.

Yu, H., Shao, X.-T., Liu, S.-Y., Pei, W., Kong, X.-P., Wang, Z., & Wang, D.-G. (2021). Estimating dynamic population served by wastewater treatment plants using location-based services data. *Environmental Geochemistry and Health, 43*(11), 4627–4635. 10.1007/s10653-021-00954-7.

Zuccato, E., Chiabrando, C., Castiglioni, S., Bagnati, R., & Fanelli, R. (2008). Estimating community drug abuse by wastewater analysis. *Environmental Health Perspectives, 116*(8), 1027–1032. 10.1289/ehp.11022.