

Research Paper



Assessing the potential of wastewater-based epidemiology to evaluate the impact of COVID-19 policy changes on stimulant use across 17 countries

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ARTICLE INFO

Keywords:

COVID-19 interventions

Modeling

Policy evaluation

Stimulants

Urban wastewater

ABSTRACT

Background and aims: A limited number of studies have employed wastewater-based epidemiology (WBE) to assess the impact of specific COVID-19 public health directives on stimulant consumption. This study investigates the potential of WBE as a complementary information source to support decision-making, by examining drug use changes during the pandemic.

Methods: WBE data on stimulant use from 2019 through 2022 was obtained from 17 countries covering a total of 47 wastewater treatment plants worldwide. The Oxford Coronavirus Government Response Tracker stringency index was used to standardize the severity of the COVID-19 interventions across different countries. A multiple linear regression model was fitted for the population-normalized mass loads of amphetamine, cocaine (through its metabolite benzoylecgonine), MDMA, and methamphetamine to investigate whether changes in COVID-19 restrictions influenced stimulant use, controlling for possible week-weekend and spatial effects.

Results: In most locations, WBE suggests that stimulant use was not significantly affected by the COVID-19 interventions, or even increased under the stricter measures. Methamphetamine use showed the largest decrease with increasing policy stringency, with a negative linear relationship found in 19% of cities, followed by MDMA (18%), cocaine (15%) and amphetamine (6%). Social gathering restrictions mainly impacted cocaine and MDMA use, while methamphetamine consumption declined most under stringent travel restrictions.

Conclusions: This study highlights the heterogeneous effects of the COVID-19 policy changes on stimulant use, even within countries. The ability of WBE to compile consecutive daily estimates proves to be particularly useful to assess the direct effect of specific policy changes on the consumption of different stimulants.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the associated coronavirus disease (COVID-19) affected many countries worldwide and overwhelmed many healthcare systems, resulting in large social and economic consequences. As of July 2024, the World Health Organization (WHO) has confirmed that there have been >750 million recorded cases of COVID-19 infections globally, and >7 million reported COVID-19 related deaths (World Health Organization (WHO) 2024). To curb the spread of the disease, many governments imposed a broad range of social restrictions in response to real-time changes in viral transmission, such as social distancing, cessation of special events, and full or partial lockdowns (EMCDDA, 2020; Dietze & Peacock, 2020). The profound alterations in societal and economic behaviors resulting from these measures may have impacted drug supply, distribution, and demand in diverse manners. Different measures were observed among countries in terms of the duration, intensity, and timing of travel restrictions, and social distancing measures. Due to the incongruent results between available data sources and the heterogeneity of the government mandates (Been et al., 2021; Gili et al., 2021; Manthey et al., 2021; Mariottini et al., 2021; Palamar et al., 2021), the potential impact of these policy changes on community-wide stimulant use should be further assessed using complementary approaches.

Over the last decade, wastewater-based epidemiology (WBE) has been successfully applied to deliver objective qualitative and quantitative information on stimulant use at the population scale and has proven its ability to monitor drug consumption trends in various regions worldwide (Bade et al., 2023; Chen et al., 2024; EMCDDA, 2024; Gonzalez-Marino et al., 2020; Salgueiro-Gonzalez et al., 2024). Within WBE, concentrations of human biomarkers related to different lifestyle-related and public health-related aspects (e.g., stimulants, pharmaceuticals) are measured in influent wastewater and converted into population-normalized mass loads (PNML, often expressed in mg/day/1000 inhabitants) by considering the total wastewater flow rate and the population size served by the wastewater treatment plant (WWTP) (Baker et al., 2014). This normalization allows the intra- and inter-country comparison between locations with different population equivalents and serves as a proxy for consumption.

WBE has been generally used as a complementary approach for monitoring substances of concern for public health, with strong advantages including cost-efficiency, high spatiotemporal resolution, large

population coverage, and fast turn-around times (O'Keeffe, 2021). Only a few monitoring programs have systematically applied WBE to evaluate the effects of specific government mandates on the use and/or exposure to different substances (Burgard et al., 2019; Rice et al., 2020; Tschärke et al., 2022; Verhagen et al., 2024). Before the start of the COVID-19 pandemic, the role of WBE in decision-making and government strategies was limited and there were only a few examples where WBE has been employed across different public health domains. Several important organizations (e.g., European Union Drug Agency (EUDA), Australian Crime Intelligence Commission, New Zealand Police) recognized WBE as a valuable complementary epidemiological information source to monitor the use of illicit and licit drugs (e.g., amphetamine, MDMA, fentanyl, oxycodone) in their drug reporting (Australian Crime Intelligence Commission, 2024; EMCDDA, 2024; Finish Institute for Health and Welfare, 2022; New Zealand Police, 2022). During the COVID-19 public health crisis, WBE played a significant role in evaluating temporal changes in the number of SARS-CoV-2 infections. Many government organizations acknowledged the capability of WBE to monitor trends in the number of SARS-CoV-2 infections at high spatio-temporal resolutions. WBE may also effectively survey the abundance of different variants and sublineages in influent wastewater (Ahmed et al., 2020; Centers for Disease Control and Prevention, 2022; Federal Office of Public Health, 2022; Government of the Netherlands, 2022; Health Protection Surveillance Centre, 2022; U.S. Food and Drug Administration, 2022). As illustrated by the Sewage CORE Group Europe (SCORE) monitoring program, such dedicated large scale wastewater programs could also aid substantially in identifying hotspots of illegal drug consumption, and in evaluating the effect of specific drug policy interventions (Boogaerts et al., 2022; Chen et al., 2024; Estevez-Danta et al., 2022; Reinstadler et al., 2021).

In this study, WBE data on amphetamine, cocaine (through its metabolite benzoylecgonine), methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) consumption was collected from 17 different countries worldwide to assess the impact of the severity of the pandemic-induced policy changes on stimulant usage trends. The aim was to use the COVID-19 pandemic as a case study to further explore the untapped potential of WBE as a complementary information source to support policy-making. The COVID-19 pandemic provides an opportunity to evaluate the effect of heterogeneous policy changes (i.e. to prevent COVID-19 spread) on stimulant use at the community level. To achieve this, WBE data from the 17 countries investigated is cross-referenced with the Oxford COVID-19 Government Response Tracker

(OxCGRt) stringency index and its subindices. Even though several WBE case studies have investigated the impact of the COVID-19 pandemic on stimulant use, this is one of the first studies to place these findings in an international context while simultaneously incorporating data from new sites.

Materials and methods

Oxford COVID-19 government response tracker stringency index

OxCGRt compiles a systematic series of cross-border, temporal measures of COVID-19 government responses starting from January 2020. It tracks national, or in some instances subnational (e.g., at a state level), government policies and interventions (Hale et al., 2021). Thanks to its global coverage (i.e. compiling data from over 180 countries) and granularity of policy detail, different composite indicators of OxCGRt have been widely applied to inform different scientific, economic and policy fields and to better understand the effects of governments' responses to COVID-19 across different populations and contexts (Hale et al., 2021; Ludwig-Walz et al., 2022; Reddy et al., 2023). Composite indicators include containment, health index (CHI), and government response index (GRI).

In this study, the OxCGRt was applied to further understand the effect of the COVID-19 policy changes on stimulant use during the pandemic period. In particular, the OxCGRt stringency index was employed to standardize the stringency of the policy interventions at (sub)national level, and enable an inter-country comparison among the severity of government restrictions on illicit drug consumption. The stringency index is the combination of nine different subindices: school and workplace closures, restrictions on social gatherings, public information campaigns, cancellation of public events, stay-at-home measures, closures of public transport, and domestic and international travel bans. The index is available on a daily basis by calculating the simple average of the normalized score of these nine metric functions. This results in a stringency index between 0 and 100, with higher scores associated with more stringent policy responses. This index was constructed for policies that apply to non-vaccinated people and those for vaccinated people. In this study, the weighted average of the non-vaccinated/vaccinated indices was obtained directly from Hale et al. (2021). They applied this weighting to account for differences in stringency index between both subsets of individuals, taking into account the proportion of the population that was vaccinated. Table S1 visualizes the different subindices of the stringency index and their possible values. More information on the calculation can be found in the study of Hale et al. (2021). For 2019, the stringency index was considered zero (i.e., no restrictions), similar to the pre-pandemic period in 2020. During the pre-pandemic period in 2019 and 2020, no COVID-19-related governmental measures were implemented, as the SARS-CoV-2 virus had not yet emerged. Therefore, a value of 0 appropriately reflects the absence of COVID-19-related policy restrictions captured by the index during this period.

Given the complexity and heterogeneity of the COVID-19 policy changes, deriving standardized local adjustments for the stringency index that would be comparable across all study locations was not feasible. Therefore, the national stringency index was applied as a proxy for policy stringency at the local scale. In the majority of countries, COVID-19 policy measures were implemented at the national level, supporting the applicability of the national stringency index. For countries where WBE data were collected from multiple cities, the same national stringency index was applied across all locations in the modeling approaches.

Data acquisition and chemical analysis

WBE data was acquired from different partners of the Sewage CORE Group Europe (SCORE). This network aims to standardize the

application of WBE across different laboratories and coordinate international wastewater surveillance campaigns (van Nuijs et al., 2018). This allows inter- and intra-country comparison of wastewater-based drug consumption estimates (Gonzalez-Marino et al., 2020). Sampling of influent wastewater was performed according to SCORE's best practice protocol (European Drug Agency, 2013). Influent wastewater was monitored in 17 different countries (i.e. Australia, Austria, Belgium, Canada, Chile, Cyprus, Finland, Greece, Italy, Latvia, Lithuania, the Netherlands, New Zealand, Portugal, Spain, the United Kingdom, and the United States), covering a total of 47 WWTPs. In each location, daily 24-h composite influent wastewater samples were collected from 2019 through 2022 during different time periods characterized by different COVID-19 policy interventions. Figure S1 and Table S2 give an overview of the different WWTPs and the corresponding sampling periods. As illustrated in Table S2, 24-h composite influent wastewater samples were collected either time-, volume- or flow-proportionally with frequent sampling intervals. Throughout this manuscript, country names are abbreviated to two letters using the ISO3166-1 alpha-2 classification. Even though differences in sample sizes were observed between the different study locations, WBE data was collected in each location relative to the COVID-19 policy changes, covering an appropriate range of stringency indices. This approach ensured an appropriate evaluation of the association between the stringency index and the zPNML of the different stimulants in each region. Figures S2-S8 show the distribution of datapoints during the sampling period for each OxCGRt subindex.

Each laboratory applied their in-house validated analytical methodologies for the determination of the stimulant biomarkers in influent wastewater (including amphetamine, benzoylecgonine, MDMA and methamphetamine). Cocaine use was measured through benzoylecgonine, its human metabolic excretion product. These analytical methods shared the following similarities: i) influent wastewater samples were spiked with isotope-labelled internal standards; ii) use of direct injection or solid-phase extraction as sample preparation step after removal of suspended solids; iii) compound identification and measurement using liquid-chromatography coupled to tandem mass spectrometry. Quality control (QC) was assured through external validation in the inter-laboratory SCORE exercise and in-house QC measures (van Nuijs et al., 2018). No correction factors were used to back-estimate the population normalized mass loads (PNML).

Statistical analysis: multiple linear regression models

In order to compare changes in stimulant use across WWTPs, Z-score normalization was performed by subtracting the mean PNML of the location from the daily value and dividing by the standard deviation. A multiple linear regression (MLR) model was fitted for the z-score normalized PNML of the different stimulants (zPNML, Equation 1) to evaluate the impact of temporal changes in the OxCGRt stringency index on stimulant use, accounting for possible effects of weekend (Sat-Sun) versus week (Mon-Fri) and location (Boogaerts et al., 2022). The model covered all available WBE data from each site across 2019–2022 (covering both the pre-pandemic period and the COVID-19 pandemic) with different sample sizes between WWTPs depending on data availability. Time periods for each location were selected based on their relevance for decision-making and availability of WBE data. In most WWTPs, the sample size was sufficiently high ($N \geq 3$ weeks) to ensure adequate statistical power. However, in a minority of WWTPs with a more limited number of observations, a non-significant effect could also be related to lower statistical power rather than the absence of an interaction. No analysis plan was pre-registered prior to statistical analysis. Data processing, statistical analysis, and visualization was performed with R (version 4.5.1) using the lme4 (version 1.1–37), multcomp (version 1.4–28) and multcompView packages (version 0.1–10) (R Core Team, 2022; Wickham et al., 2019).

$$\begin{aligned} \text{zPNML} &\sim \text{StringencyIndex} + \text{Location} + \text{weekWeekend} + \text{StringencyIndex} \\ &: \text{Location} + \text{weekWeekend} : \text{Location} + \text{StringencyIndex} \\ &: \text{weekWeekend} \end{aligned}$$

Equation 1. MLR model to estimate the effect of the stringency index on the z-score normalized population-normalized mass loads (zPNML) of different stimulants. The PNML in each location was normalized according to the location mean and standard deviation.

Fixed effects included one continuous and two categorical variables: i) the OxCGRT stringency index (=Stringency Index, continuous), ii) the distinction between the weekdays and the weekend (=weekWeekend, categorical), whereby the weekend was defined as Saturday and Sunday, and iii) a location term (=Location, categorical) modelling the differences in stimulant use between the sampling locations. An interaction term (=Stringency Index:Location) was included in the model to test whether the effect of the stringency index on the zPNML differed between the locations. The MLR model was simplified in a stepwise backward way, beginning with the interaction terms. An F test was applied to test the significance of each parameter in the model, with a significance level of $\alpha=0.001$. In case of a significant Stringency index:Location interaction, the impact of the stringency index on the zPNML is not constant across the different locations. When a significant weekWeekend:Location interaction exists, the week-weekend effect was different across locations. In these cases, a separate model was fitted for each location. Contrastingly, when the Stringency index:Location interaction was non-significant, the effect of the stringency index is the same in all locations. We also attempted to evaluate models that compared impacts of the stringency index between weekends and weekdays through the Stringency Index:weekWeekend interaction term (Boogaerts et al., 2022). In the case of a significant Stringency Index:weekWeekend interaction, the impact of the stringency index on the zPNML of the different stimulants should be assessed separately for workweek and weekend days. The requirements for homoscedasticity were fulfilled for all stimulants across the different study locations. Additionally, the regression plots can be found in the Supplementary Information (S.4.) to assess linearity between Stringency Index and the zPNMLs.

Secondly, a similar statistical framework was used to evaluate the effect of the different subindices on the zPNML, as described by Equation 2. Separate MLR approaches with one subindex per model were constructed to assess the impact of specific policy changes on the zPNML of the different stimulants while avoiding potential issues arising from multicollinearity. In each MLR model, subindex C_n refers to the specified subset of interventions, with C_1 = school closures; C_2 = workplace closures; C_3 = cancellation of public events; C_4 = restrictions on gatherings; C_6 = stay-at-home measures; C_7 = domestic travel bans; and C_8 = international travel restrictions. Subindex C_5 , i.e. closure of public transport, was not assessed since it was constant in most WWTPs. Subindex H1, i.e., public information campaign, was also not considered for this analysis since it was not classified as a containment and closure indicator by OxGRT. This coding and associated nomenclature was adopted directly from Hale et al. (2021).

Figures S2-S8 visualize the distribution of datapoints for each subindex during the sampling period in each location. The codependency of the different subindices was not evaluated using these models (see Section 5).

$$\begin{aligned} \text{zPNML} &\sim \text{SubindexC}_n + \text{Location} + \text{weekWeekend} + \text{subindexC}_n:\text{location} \\ &+ \text{weekWeekend} \\ &: \text{Location} + \text{subindexC}_n:\text{weekWeekend} \end{aligned}$$

Equation 2. MLR model to estimate the effect of different subindices of the OxCGRT stringency index on the zPNML of different stimulants. The PNML in each location was normalized according to the location mean and standard deviation.

The reported associations between the stringency index and the

zPNML of the different stimulants should be interpreted at a local scale and should not be extrapolated to a national level, as local differences in population behavior, impact of the COVID-19 policy changes on stimulant use, and other contextual factors may result in heterogeneous effects across locations.

Results

Daily variations in stimulant use

For all stimulants, the weekWeekend:Location interaction was significant ($p < 0.001$) indicating that daily variations in stimulant use were different across locations. Therefore, separate models were fitted for each location.

Cocaine

Variations in the week-weekend effect on the zPNML of benzoylcegonine were observed across the different WWTPs (see Figure S9). In the absence of a statistically significant weekWeekend effect, stimulant use did not significantly differ between the workweek and weekend. When the weekWeekend term was statistically significant with a positive coefficient estimate, stimulant use was higher during the weekend compared to the workweek. In general, the error bars were also larger for the coefficients of week-weekend term because of lower proportion of datapoints in the weekend in some locations. In 32% of locations, no significant differences in cocaine consumption were found between the workweek and weekends. In the other 68% of WWTPs, cocaine use was on average higher during the weekend.

Amphetamine

WBE data were only reported in 32 of the studied WWTPs; in the remaining 16 WWTPs, no quantifiable data on amphetamine were available. A significant week-weekend effect was only found in 9% of WWTPs with higher use of amphetamine during the weekends (see Figure S10), including Innsbruck (AT), Helsinki (FI), and Tampere (FI). In the other WWTPs, amphetamine use remained stable throughout the week.

MDMA

In San Pedro de la Paz (CL), Castellón (ES), Palermo (IT) and Rome (IT), the measured concentrations of MDMA were negligible (below limit of quantification (LOQ) in the majority of samples) and, therefore, these WWTPs were not considered for this inter-country comparison. For MDMA, the week-weekend effect was significant in 41% of WWTPs with higher consumption observed during the weekend compared to the weekdays (see Figure S11). In AU, CY, ES, GB, GR, IT, LV, PT and US, the week-weekend term did not significantly impact the zPNML of MDMA in each location.

Methamphetamine

Methamphetamine concentrations were above the LOQ in only 37 WWTPs. In all locations, the time of the week did not have a significant effect on the zPNML of methamphetamine (see Figure S12). The use of methamphetamine remained the same during the workweek and weekend.

Effect of the OxCGRT stringency index on stimulant use

A significant interaction was found between the OxCGRT stringency index and the location ($p < 0.001$). For this reason, the zPNML of the different stimulants were assessed in each location separately and results were not combined. Exact p -values can be retrieved in Tables S3–6. Additionally, the interaction between the stringency index and week-weekend effect was non-significant for all stimulants with the lowest p -value observed for MDMA ($p = 0.007$), indicating that the model should not be separated for workweek and weekend days.

Fig. 1 visualizes the $\log(p\text{-value})$ of the stringency index in each MLR model (Equation 1) on the zPNML of the different stimulants in each study location. The symbol indicates whether there is a positive (triangles) or negative (dots) linear relationship between the stringency index and the zPNML. A positive coefficient indicates that the mean zPNML increases with increasing stringency index values, while a negative coefficient implies that increases in severity of the policy changes are associated with lower values of the zPNML i.e. decrease in stimulant use. Higher absolute coefficients are associated with a larger impact of the stringency index on stimulant use. It is important to note that correlations between zPNML and the stringency index or its specific subindices do not necessarily imply causal relationships.

Cocaine

In 77% of WWTPs, there was no significant linear relationship between the stringency index and the zPNML. In 15% of WWTPs, a significant negative linear relationship was found between cocaine use (measured through benzoylecgonine) and the stringency index, with the lowest p -values observed in Innsbruck (AT), Limassol (CY) and Castellón (ES). On the contrary, a significant positive linear relationship was found between cocaine use and the stringency index in 9% WWTPs, with the most significant association found in Edmonton (CA), San Pedro de la Paz (CL), and Taupo (NZ). Even within specific countries, significant

variations were observed, further highlighting the heterogeneous effect of the COVID-19 policy changes on cocaine use. For example, in CY, a negative relationship was found in Limassol and Paphos, while a positive relationship was observed in Larnaca. At the same time, no significant relationship could be found in the other locations.

Amphetamine

A negative relationship was found between the stringency index and the zPNML of amphetamine in Innsbruck (AT), and Larnaca (CY). On the contrary, there was a positive relationship between both variables in Brussels (BE), Helsinki (FI), and Athens (GR). In 84% of WWTPs, the zPNML of amphetamine did not alter significantly when the stringency index changed.

MDMA

In San Pedro de la Paz (CL), Castellón (ES), Palermo (IT) and Rome (IT), the measured concentrations of MDMA were negligible (below limit of quantification (LOQ) in the majority of samples) and, therefore, these WWTPs were not considered for this inter-country comparison. No significant linear relationship was found in 77% of WWTPs. In ES, FI, GB, IT, LT, LV, NZ, PT, and US, the zPNML of MDMA remained unaffected by changes in the stringency index. In 18% of WWTPs, the zPNML of MDMA was negatively correlated with the stringency index, with the

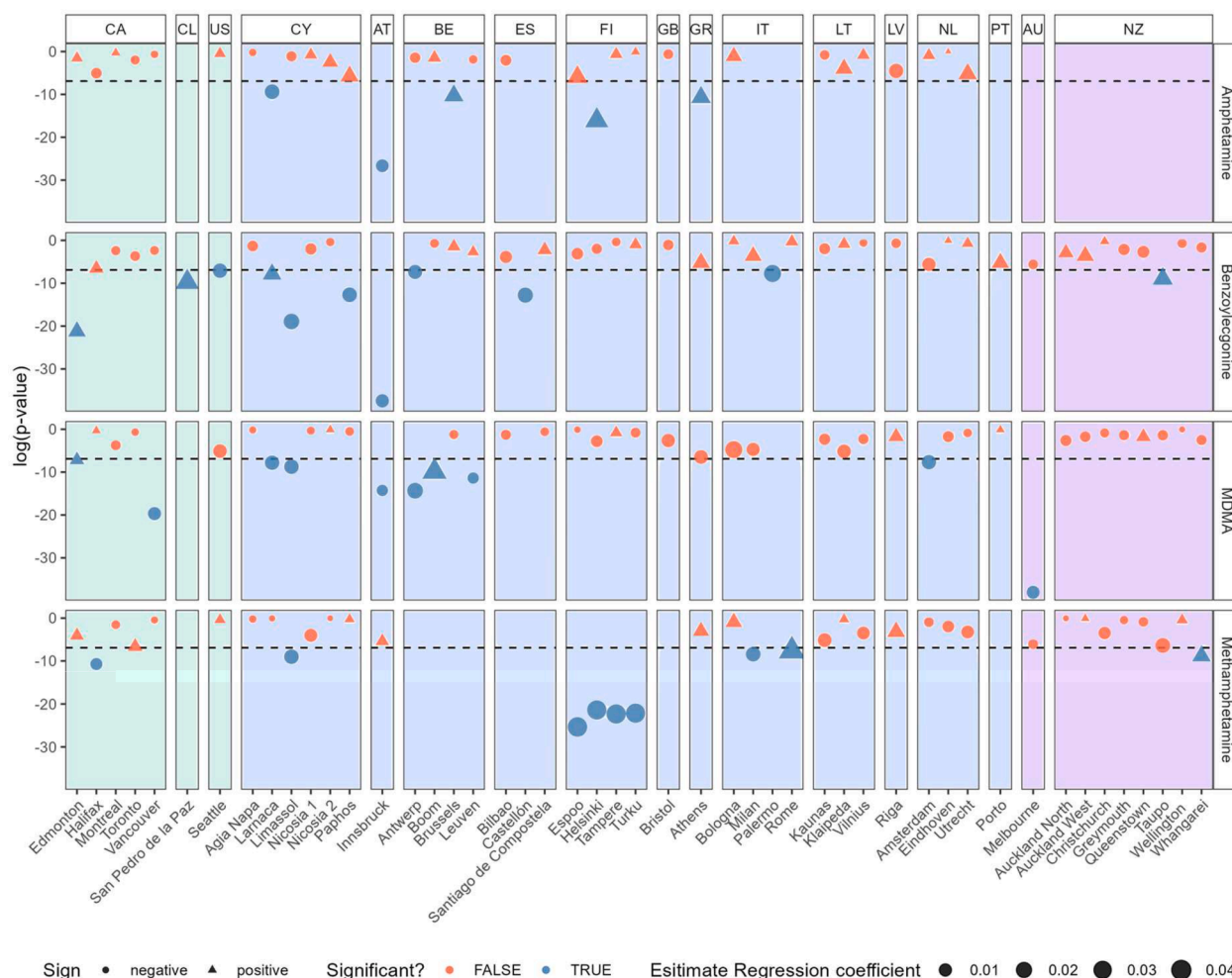


Fig. 1. Inter-country comparison of the significance of the impact of the stringency index on stimulant use. The dotted line represents the significance level $\log(0.001)$. Lower $\log(p\text{-values})$ are associated with higher levels of significance. The size of the symbols represents the absolute value of the estimates of the regression coefficients and the symbol the sign of the estimate. In case of a significant linear relationship between the stringency index and zPNML ($p < 0.001$), the dot is colored in blue. A positive regression coefficient means the average zPNML increases with increasing stringency index values, whereas a negative regression coefficient means that an increase in stringency index values is associated with a lower value of zPNMLs. Locations were grouped by geographical region: Americas (green), Europe (blue), Oceania (purple). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

most significant effect observed in Melbourne (AU), Vancouver (CA), and Antwerp (BE). Contrastingly, a positive relationship between the



Fig. 2. (A): Inter-country comparison of the significance of the impact of the different subindices on stimulant use. (B): Intra-country comparison in Belgium with detailed step-by-step guide on interpreting the differences. The orange line represents the significance level $\log(0.001)$. Lower $\log(p\text{-values})$ are associated with higher levels of significance. The color of the symbols represents the different subindices, the size of the symbols represents the absolute value of the estimates and the symbol the sign of the estimate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

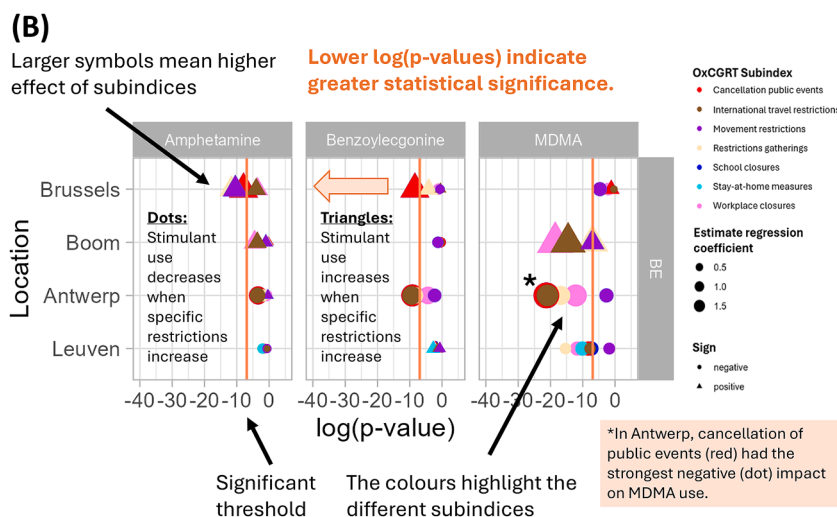


Fig. 2. (continued).

stringency index and the zPNML was only found in Boom (BE) and Edmonton (CA).

Methamphetamine

In 75% of studied WWTPs, there was no significant linear relationship between the stringency index and the zPNML (see Fig. 1 and Table S6). A negative linear relationship between the stringency index and zPNML was found in 19% of WWTPs, while a positive relationship was observed in only 5% of WWTPs (e.g. Rome and Whangarei). There was a large decrease in the use of methamphetamine in FI in each location (i.e., Espoo, Helsinki, Tampere, and Turku), when the stringency of the COVID-19 measures increased. Similar to the other stimulants, intra-country differences in the effect of the stringency of the measures on methamphetamine use were also found.

Effect of different OxCGRT subindices on stimulant use

In this section, the effect of specific COVID-19 interventions on the use of different stimulants was assessed through the use of different OxCGRT subindices. As stated in the study limitations, the heterogeneity of the dataset can also impact the outcomes of this MLR analysis, with a higher level of uncertainty observed in WWTPs with smaller sample sizes. However, the sample sizes in the included WWTPs were sufficient to perform the statistical analysis and the changes in the zPNML can primarily be attributed to the effect of specific policy interventions. The sample size was evaluated for each subindex individually, as visualized by the distribution of data points in Figures S2-S8. For some locations, the number of datapoints were more limited compared to others (e.g., CL, CY, GR, GB, IT), resulting in higher uncertainty for the coefficients for the subindices.

The interaction between the different subindices and the week-weekend effect was non-significant for all compounds and subcategories ($p < 0.001$), except for the interaction between the international travel restrictions and week-weekend effect of benzoylcegonine ($p = 0.0001$). To avoid further model stratification and preserve an interpretable statistical framework across stimulants and subindices, the model was not split into week and weekend days.

Cocaine

Fig. 2 visualizes the log(p-value) of the different subindices in each MLR model (Equation 2) on the zPNML of the different stimulants in each study location. The size of the symbols represents the absolute value of the estimates for the respective subindices. Important to note is that the sizes should only be used to compare the same subindex across

WWTPs. Intra- and inter-country differences were found for the impact of the different subindices on cocaine use (see also Figures S14-S20). International travel restrictions had the strongest negative relationship with zPNML of benzoylcegonine affecting 25% of the study WWTPs, followed by cancellation of public events (25%), restrictions on social gatherings (21%) and workplace closures (21%). The zPNML of benzoylcegonine was positively correlated with any subindex in $\leq 10\%$ of WWTPs. Specific information on estimate sizes can be found in Section S.2.

Amphetamine

Similar to cocaine, the MLR models highlighted significant intra- and inter-country differences between the effect of the different subindices and the zPNML of amphetamine (see Fig. 2 and Figures S21-27). Amphetamine use remained stable during the COVID-19 pandemic in $>60\%$ of WWTPs, but decreased when public events were cancelled in 16% of WWTPs. Cancellation of public events, restrictions on social gatherings, and school closures also resulted in a decrease in amphetamine use in 16% of WWTPs. Contrastingly, amphetamine use increased in 19% of WWTPs when restrictions on social gathering were implemented, highlighting different responses to governmental mandates across different sites.

MDMA

Intra- and inter-country differences were observed in the effect of the different subindices on the zPNML of MDMA (see Fig. 2 and Figures S28-S34). School closures and cancellation of public events showed the best association with a decrease in MDMA use (18% of WWTPs), followed by restrictions on gatherings (16%) and international travel restrictions (16%). In $>75\%$ of WWTPs, specific COVID-19 policies did not correlate with significant change in MDMA use. The zPNML of MDMA was positively correlated with any subindex in $\leq 7\%$ of WWTPs.

Methamphetamine

For methamphetamine, spatial variations in the impact of the subindices on the zPNML were also observed (Fig. 2 and Figures S35-41). International travel restrictions negatively impacted the zPNML of methamphetamine in 24% of WWTPs, followed by cancellation of public events (22%), and school closures (19%). Methamphetamine use remained stable in $>70\%$ of WWTPs when more severe measures went into effect. In $\leq 11\%$ of WWTPs, the zPNML of methamphetamine was positively correlated with any subindex.

Discussion

In the majority of WWTPs, stimulant use was not significantly affected by the COVID-19 interventions or even continued to rise when more stringent measures were present. The MLR models showed that the use of methamphetamine decreased to the largest extent when the stringency of the policy increased, with a negative relationship found in 19% of WWTPs. Similarly, a negative effect size was observed for MDMA in 18% of WWTPs, for cocaine in 15% and for amphetamine in 6%. While the use of methamphetamine has been established in Central Europe, AU, CA, NZ, and the US for years (Australian Crime Intelligence Commission, 2024; Chappell et al., 2022; Gonzalez-Marino et al., 2020), this substance only emerged during the late 2010s on the Western European drug market. Therefore, the methamphetamine trends in Western European countries should be interpreted within this growing market (European Monitoring Centre for Drugs and Drug Addiction, 2021). Table 1 identifies additional eligible WBE studies resulting from a narrative literature review along with their main outcomes.

The statistical analysis highlighted variations in the effect of stringency index on the zPNML among the different stimulants, but also intra- and inter-country differences for specific stimulants. For example, restrictive measures led to a decrease in methamphetamine use in all Finnish WWTPs, while cocaine and MDMA consumption remained stable in the majority of WWTPs. On the other hand, amphetamine use increased in Helsinki, when more stringent measures were present. Gunnar and Kankaanpää showed that the changes in amphetamine and methamphetamine use could also be attributed to normal market fluctuations between both substances (Gunnar and Kankaanpää, 2019), and not be solely attributed to the COVID-19 restrictions (EMCDDA, 2024). A joint report between law enforcement and the Finnish Institute for Health and Welfare from June 2020 also confirmed that amphetamine remained the most dominant stimulant in the metropolitan area (Police of Finland, 2020). In addition, MDMA use decreased in Melbourne (AU) when more stringent COVID-19 measures were in place, while their effect on its consumption was limited in most WWTPs in NZ. It should also be emphasized that COVID-19 restrictions were designed to protect the population from viral transmission and not to mitigate drug use. In Melbourne, the effect of increased stringency had the most significant impact on the use of MDMA, which could potentially be attributed to its decline in availability prior to the full stay-at-home measures or gradual increase on restrictions on social gatherings and public events resulting in declined demand (Chen et al., 2024). A decrease in MDMA use with increasing stringency measures was also observed in other AU regions, including the Australian Capital Territory, New South Wales, Queensland, Tasmania, South Australia, Victoria, and Western Australia, as shown in Figure S51. Intra-country differences in stimulant use were also found for the US in response to the COVID-19 policy changes. While a decrease in COC use was reported in Seattle when the OxCGRT stringency index increased as a result of the lockdown measures, its consumption increased in a Northeastern University town and in communities in Tennessee and Kentucky (Luo et al., 2023).

The demand of stimulants in nightlife settings, primarily MDMA and cocaine, could potentially have decreased in the short term by the closure of this sector and cancellation of festivals, especially in regions with a large share of clubs and cafes. Our results for cocaine and MDMA show that 16–25% of WWTPs were negatively affected by the closure of public events (subindex C3) and restrictions on social gatherings (subindex C4), while amphetamine and methamphetamine were impacted to a lower extent. This suggests that people continued to use stimulants even during home confinement, or that people who use drugs disregarded stay-at-home measures in these areas. In <9% of study WWTPs, a significant week-weekend pattern was found for amphetamine and methamphetamine, while weekend increases were observed for cocaine and MDMA in respectively 31 and 41% of WWTPs. This finding further supports the observation of the European Web Survey on Drugs that cocaine and MDMA are associated to a higher extent with

nightlife settings compared to amphetamine and methamphetamine (EUDA, 2025). According to the European Web Survey on Drugs 2024, 51% of respondents who used amphetamine and 44% of those who used methamphetamine reported they used the drug to stay awake. On the other hand, >75% of respondents who used MDMA or cocaine powder reported that they used the drug to get high or for fun (EUDA, 2025).

The mixed outcomes between countries could be explained not only by the geographical variations in the COVID-19 restrictions and relaxations, but also by confounding variables such as drug market disruptions, demand changes, population habits and movement variations. The supply-demand dynamics affecting stimulant use likely changed during the COVID-19 period (EMCDDA, EUROPOL, 2020). Demand may have changed due to the reduced social gatherings, or the increased stressors people experienced at the time. Supply could have been impacted by mobility-related changes brought by limited/banned local and international travel, both in source and destination countries or regions (EMCDDA, EUROPOL, 2020). However, a cautious statement based on our results could be made that drug trafficking, supply and distribution strategies and patterns in stimulant use adapted quickly in the majority of locations to overcome the COVID-19 restrictions (EMCDDA, 2020; EMCDDA, EUROPOL, 2020). According to the 2020 joint report from the EUDA and EUROPOL, the production of synthetic drugs, including amphetamines, continued in the main production zones in BE and NL (EMCDDA, EUROPOL, 2020), as reflected by the amount of illicit laboratories dismantled and reporting of dump sites across this region. In CY, the COVID-19 restrictions did not have a significant impact on the use of amphetamine and methamphetamine in the majority of WWTPs. As indicated by Psychoudaki et al. (2023), local production and supply of amphetamines in CY could compensate to some extent for the decreased imported amounts (Psychoudaki et al., 2023).

Additionally, cocaine traffic to Europe using maritime shipping was seemingly not altered by the different restrictions, as evidenced by the frequent seizure of large shipments at main European ports during the pandemic (EMCDDA, EUROPOL, 2020). Our findings show that the use of cocaine remained largely unaffected by the international travel restrictions in the majority of European WWTPs. The quick adaptation of criminal networks to the situation could also be reflected by the increase in cocaine trafficking by post and parcel services largely driven by the darknet markets (EMCDDA, EUROPOL, 2020). It is also possible that large stocks of cocaine were already available in European countries. It should be noted that subindices C7 and C8 were largely linked to the travel restrictions for passengers, but transport of goods was not influenced to the same extent by the COVID-19 restrictions. Contrastingly, the international travel restrictions were negatively associated with cocaine use in NZ, indicating that cocaine traffic might have been disrupted during the pandemic.

A key methodological consideration in this study is the assumption of a linear association between the OxCGRT stringency index and zPNML of stimulants. The MLR framework tests whether increases in policy stringency are associated with proportional increases or decreases in stimulant use. However, behavioural and market responses to public health restrictions are unlikely to follow strictly linear dynamics. Drug consumption may exhibit threshold effects (e.g., abrupt changes once nightlife venues close), delayed responses due to supply-chain disruptions, temporary reductions followed by rapid adaptation, or rebound effects after restrictions are eased. Similarly, the stringency index aggregates multiple interventions that were often implemented simultaneously, potentially producing stepwise rather than gradual behavioural shifts. Therefore, a non-significant linear coefficient does not necessarily imply absence of an effect, but rather absence of a monotonic linear relationship. Future work could apply generalized additive models, segmented regression, distributed lag models, or interrupted time-series approaches to explicitly explore potential non-linear and lagged responses. Incorporating such flexible modelling strategies may provide additional insight into the temporal dynamics of stimulant markets during large-scale policy disruptions. It is also important to note that the

Table 1

Overview of all WBE investigations that evaluate the effect of COVID-19 policy changes on stimulant use. AMP = amphetamine; BE = benzoylecgonine; MDMA = 3,4-methylenedioxymethamphetamine; METH = methamphetamine.

Year	Study	Biomarkers	Number of WWTPs [ISO code]	Number of samples (time period)	Main findings
2021	Been et al. (2021)	11-Nor-9-carboxy- Δ^9 -tetrahydrocannabinol, amphetamine, benzoylecgonine, cocaine, MDMA, methamphetamine	7 [EU]	294 (2015–2020)	- Heterogeneous effects of lockdown-imposed measures on illicit drug use in different countries - Changes in weekly patterns were observed
2021	Reinstadler et al. (2021)	24 illicit drugs and pharmaceuticals	1 [AT]	327 (2016–2020)	- During the lockdown period, changes in the consumption of illicit drugs and pharmaceuticals for short-term application were observed - These changes were linked to the closure of hospitality industry and event cancellation
2021	Alygizakis et al. (2021)	Wide-scope target and suspect screening of 11 286 compounds (targeted analysis for stimulants)	1 [GR]	22 (2019–2020)	- MDMA decreased significantly during the lockdown, potentially as a result of the stay-at-home measures and nightlife closures - Amphetamine, cocaine and methamphetamine use increased during the lockdown phase, highlighting that people who use drugs maintained access to these stimulants despite the strict measures
2021	Bade et al. (2021)	Alcohol, cannabis, cocaine, MDMA, methamphetamine	20 [AU]	3041 (2016–2020)	- Decrease in the use stimulants and alcohol during the lockdown phase - Decrease in week/weekend ratios for cocaine, MDMA and alcohol during the lockdown
2021	Montgomery et al. (Montgomery, Bowers and Subedi, 2021)	29 illicit drugs and pharmaceuticals	2 [US]	80 (2020)	- During the first 2 months of the public health crisis, there was an increase in stimulant use in both WWTPs - Higher consumption of methamphetamine in rural communities
2022	Boogaerts et al. (2022)	Amphetamine, benzoylecgonine, methamphetamine	4 [BE]	362 (Sep 2019; Mar 2020–Jun 2020)	- The use of amphetamine, cocaine and MDMA remained stable in 2020 during the first wave of the COVID-19 pandemic compared to 2019 - Mobile phone mobility data showed a 30–50% decrease in the number of people present in the catchment area during the lockdown period
2022	Love et al. (2022)	Amphetamine, cocaine, cannabis, MDMA, methamphetamine	2 [IS]	126 (2017–2020)	- The use of amphetamine, methamphetamine and cannabis increased during COVID-19 pandemic, while the use of cocaine decreased - The use of MDMA remained stable compared to the pre-pandemic period
2022	Di Marcantonio et al. (2022)	Methamphetamine, benzoylecgonine, cocaine, lincomycin, trimethoprim, sulfamethoxazole, sulfadiazine, carbamazepine, ketoprofen, caffeine	2 [IT]	84 (2019–2020)	Increase in the use of cocaine during the COVID-19 restrictions
2022	Estevez-Danta et al. (2022)	Amphetamine, benzoylecgonine, cocaine, cotinine, ethyl sulphate, MDMA, methamphetamine, THC–COOH, trans-3'-hydroxycotinine	4 [ES] 2 [PT]	194 (2019; Mar 2020 – Jul 2020)	- No significant changes were found in the PNML compared to previous years, except for benzoylecgonine. Benzoylecgonine increased in Porto and Santiago de Compostela, while it decreased in Castellon - Contradictory conclusions were found between different epidemiological data sources
2022	Hahn et al. (2021)	Amphetamine, caffeine, cocaine, MDMA, Methamphetamine, nicotine, and THC	1 [BR]	347 (Mar 2020–Mar 2021)	- Decrease in stimulant use during the COVID-19 pandemic, probably resulting from stay-at-home recommendations and reduced access - A negative correlation between MDMA use and human mobility
2023	Verhagen et al. (2023)	Benzoylecgonine, cotinine, MDMA, methamphetamine and noroxycodone	43 [AU]	501 (2019–2020)	- Cocaine and MDMA use was higher in 2020 in half of the locations when compared to 2019 - Methamphetamine use decreased in half of the sites by >25% from 2019 compared to 2020 - Cocaine consumption showed clear differences between the level of remoteness of the catchment areas
2023	Psichoudaki et al. (2023)	Amphetamine, benzoylecgonine, MDMA and methamphetamine	6 [CY]	300 (2019–2022)	During home confinement, the use of amphetamine and methamphetamine did not decrease. As drug availability was limited over time, a strong decrease in their consumption was reported post-lockdown. The social measures have led to a decrease in the use of cocaine and MDMA. Re-opening of activities resulted in a significant increase in their use
2023	Luo et al. (2023)	Amphetamine, benzoylecgonine, MDMA and methamphetamine and 10 priority opioids	1 [US]	46 (Sep 2018–Aug 2020)	There was a notable decrease in the use of amphetamine, cocaine and MDMA was observed in April 2020

(continued on next page)

Table 1 (continued)

Year	Study	Biomarkers	Number of WWTPs [ISO code]	Number of samples (time period)	Main findings
2023	Oertel et al. (2023)	Amphetamine, benzoylecgonine, cocaine, cotinine, MDMA and methamphetamine	15 [DE]	860 (2020–2021)	• In Dresden and Chemnitz, methamphetamine use increased during lockdown 1, but decreased starting from the summer 2020 • Stimulant use differed in general during the onset of the pandemic, but later restrictions had a more limited impact
2024	Ceolotto et al. (2024)	Amphetamine, benzoylecgonine, cocaine, caffeine, cocaine, diclofenac, MDMA, methamphetamine, naproxen, nicotine and tramadol	4 [UK]	545 (Apr 2020 – Mar 2022)	• Cocaine use decreased during the national lockdown, followed by an increase in consumption • Spatial variations were observed in the effect of the COVID-19 interventions on stimulant use • Illicit drug use increased after the third national lockdown (amphetamine +8%, benzoylecgonine +39%) when restrictions were eased, and social and recreation activities restarted
2024	Chen et al. (2024)	Benzoylecgonine, MDMA, methamphetamine	1 [AU]	660 (Jan 2020 – Dec 2021)	• Methamphetamine use increased before the start of the first lockdown and decreased after its end. A stable temporal trend was observed during the second lockdown and steeply increased after it terminated • Cocaine use decreased at the start of the first lockdown and increased at the end the second lockdown • MDMA use decreased after the start of the first lockdown and remained stable during 2020 and 2021

absence of a statistically significant association in a given WWTP does not necessarily imply that stimulant use was unaffected by COVID-19 interventions. Statistical non-significance may reflect limited sample size, reduced variability in the stringency index during the sampling window, or unmeasured confounding factors masking underlying behavioural changes. Moreover, rapid market adaptation or short-term disruptions may not be captured by a linear association across the full study period. Therefore, the interpretation of stable trends should be made cautiously and in the context of analytical and structural constraints inherent to multi-site retrospective analyses.

Increased cocaine prices and decreases in its availability were reported in multiple European countries (e.g., CY, FR, ES) at the onset of the pandemic (EMCDDA, EUROPOL, 2020). In other countries, cocaine prices and availability remained mostly unaffected by the COVID-19 pandemic (e.g. in BE and NL). Heterogeneous price and availability trends were also observed for synthetic drugs such as amphetamine, MDMA and methamphetamine (EMCDDA, EUROPOL, 2020). These underlying drug market changes in response to the pandemic could also potentially explain the heterogeneous effect of the stringency index on the zPNML of these stimulants in different WWTPs. For example, unaffected drug prices and no shortages in the availability of cocaine in BE and NL in 2020 could potentially explain why their use remained mostly unchanged by the stringency of the measures in the majority of WWTPs.

The results of this study clearly demonstrate that WBE can measure short-term changes in stimulant use, which may have changed based on policy changes affecting either supply or demand. The mixed results could partially be described by the complex spatial variations in the COVID-19 policies in the different countries (or even jurisdictions within countries), but also by the underlying trends in the illicit drug markets in response to these measures. In some locations, the equilibrium of local drug markets might have been significantly disrupted by the social restrictions, while its operability was less impacted in other areas (EMCDDA, EUROPOL, 2020). The inter-country variations in the impact of the stringency index on stimulant use could potentially also be explained by the different periods of sample collection relative to the COVID-19 policy changes. To counter this, a broad range of time periods were selected by the contributing laboratories in order to cover a wide range of different OxCGRT stringency index values. Similar restrictions were enforced in different countries during the initial phases of the

COVID-19 pandemic, as evidenced by similar OxCGRT stringency indices (see Figure S50). At the onset of the pandemic, many countries shared a high degree of commonality with most initially imposing stricter restrictions, followed by easing the restrictions. However, there was a variation in the intensity and geographical coverage of these policies. As the months that restrictions were in place grew, OxCGRT reported a growing divergence in the stringency of the different measures, as visualized in Figure S50. The public health crisis was complex and unfolded differently in each WWTP. This is reflected in the different effects observed on stimulant use between WWTPs, with no clear common trends observed.

It should also be acknowledged that WBE reflects aggregated community-level consumption and does not provide information on individual-level behaviours, user subgroups, or distributional changes within the population, limiting causal inference regarding specific demographic or behavioural shifts.

Our results show that WBE could potentially further support policymaking by measuring the short-term effects of specific policy changes on stimulant use with high spatiotemporal resolution. Its unique feature to compile consecutive daily estimates proves to be particularly useful to evaluate the direct effect of specific policy changes on stimulant use. For example, stimulant use and the underlying drug markets were impacted in different ways by the individual COVID-19 restrictions, such as the cancellation of public events, restrictions on gatherings, domestic and international travel bans, etc. The mixed effects across the study locations underscore the added value of WBE for city- or community-level assessments, enabling policy-makers to finetune interventions to local contexts. Compared to traditional survey-based methods, WBE provides a scalable and cost-efficient approach to monitor entire urban populations, particularly useful in resource-constrained settings.

Study limitations

In this study we evaluated the difference between WBE from multiple locations and the location-matched OxCGRT indices and subindices. There are a few key limitations of this study relating to the OxCGRT and WBE data. Firstly, there may be a lag time between a policy change and a measurable effect in population use of stimulants, which may differ between locations, substances, and over time. This study heavily relies

on the accuracy of the OxCGRT measurements and the OxCGRT trackers. Their measurements or pre-established categories may not fit for purpose in every study location (e.g. observed discrepancies in Spain and Portugal) (Hale et al., 2021). The OxCGRT trackers are also national measurements and cannot fully compensate for differences at the city scale, especially in large jurisdictions with many heterogeneous sub-units. We included subnational information on the OxCGRT at state scale for AU and US to obtain more reliable inter-country comparisons. Finally, the OxCGRT only takes into account the number and degree of policy interventions, without measuring how strictly these measures were enforced, implemented, and adhered to by the population. Differences in compliance of the measures by the population are therefore not recorded or accounted for (Hale et al., 2021). However, the OxCGRT remains the most suitable method as there are no other standardization methods for the severity of the COVID-19 policy changes available globally.

Statistical non-significance could also be related to the limited sample sizes in specific locations and the impact of potential confounding variables, including behavioural and contextual factors such as population mobility, socio-economic differences, and drug market changes. These potential confounders could not be systematically incorporated into the statistical models due to the lack of sufficiently detailed and standardized datasets across the study locations.

As for the WBE data, the lack of dynamic population data during the COVID-19 pandemic in PNML calculations is an important limitation. Population movements and habits were heavily disrupted by the SARS-CoV-2 countermeasures, such as social distancing and national lockdowns (Boogaerts et al., 2024; Reinstadler et al., 2021). Differences in commuting and different movement patterns could lead to changes in population size and sociodemographic composition of catchment areas (Boogaerts et al., 2023). The Google Mobility data was the only form of standardized data on a population's mobility available in the majority of locations (Mathieu et al., 2020). This anonymized dataset contains information on peoples' movements throughout the pandemic, gathered from Google Location Services on mobile devices (e.g., use of Google Maps). Although the dataset was only available on a national scale, they show substantial population fluctuations across different types of places (e.g., parks, retail, workplace) during the different phases of the COVID-19 pandemic in the different countries (see Figure S49). This further highlights the need for dynamic population normalization to refine observed spatiotemporal trends.

In the current MLR models, conventional workweek/weekend days (Mon-Fri, and Sat-Sun) were used to compare workweek and weekend trends in the zPNML of the different stimulants. However, this classification does not always accurately reflect the actual excretion patterns of stimulants. The half-life and urinary excretion of these stimulants are highly variable and may extend over multiple days. To enable a consistent and transparent classification across sampling locations and compounds, the conventional workweek/weekend categorization was considered the most appropriate approach for the present analysis.

Additionally, non-overlapping WBE datasets and associated data gaps may further limit the spatial interpretation of the effect of the stringency index on illicit drug use. However, this retrospective study leveraged all available information from the 17 included countries. Furthermore, the measured PNML of amphetamine can be the result of both amphetamine and methamphetamine consumption due to metabolic overlap, in addition to metabolism of legally prescribed medication for attention deficit and hyperactivity disorder (ADHD) treatment. The contribution of amphetamine derived from methamphetamine and legal sources deviates in each country and confounds the sources of amphetamine measured in wastewater (Gao et al., 2022).

Conclusion

This large-scale multi-country investigation demonstrates that the effects of COVID-19 policy interventions on stimulant use were highly

heterogeneous and strongly context-dependent, reflecting complex interactions between local drug markets, behavioural adaptation, and structural restrictions. In most locations, stimulant consumption did not exhibit a consistent linear association with policy stringency, suggesting either rapid market resilience or behavioural adjustments that were not uniformly captured by aggregated policy indicators. Where associations were observed, they varied across substances and jurisdictions, underscoring the limitations of assuming uniform responses to broad containment measures.

Beyond its substantive findings, this study highlights the evolving role of wastewater-based epidemiology as a responsive, population-scale monitoring platform capable of capturing rapid changes in substance use during periods of societal disruption. The observed variability emphasizes that policy impacts on illicit drug markets are neither uniform nor predictable and must be evaluated within local structural and supply-demand contexts. Future integration of WBE with dynamic population normalization, mobility indicators, and advanced time-series modeling could further strengthen its utility as a real-time decision-support tool for public health and drug policy governance.

CRedit authorship contribution statement

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Declaration of competing interest

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

Acknowledgements

All water authorities are thanked for their technical support. T.B. (project number: 1225924N) and M.Q. (project number: G060920N) received funding of the Research Foundation – Flanders for conducting this investigation. M.P. and D.F.K. gratefully acknowledge the financial support provided by the National Addictions Authority of Cyprus (NAAC). A.E.D. and J.B.Q. thank Xunta de Galicia (ED431C-2025/21 and ED481B-2025/042). L.B. acknowledges grant RYC2020-028936-I funded by MCIN/AEI/ 10.13039/501100011033 and by “ESF Investing in your future”. He also wishes to thank the Ayuntamiento de Castelló and specifically the Municipal Technicians, Inés Beltrán Pitarch and Cristóbal Badenes Catalán. A.E.D., J.B.Q. & L.B. further acknowledge Instituto de Salud Carlos III-FEDER/ERDF funds (RD24/0003/0020). R. B. is the recipient of an Australian Research Council (ARC) Discovery Early Career Award (project number DE220100381). J.F.M. is the recipient of an ARC Laureate Fellowship (FL200100028). Data from Italy were financially supported by the Dipartimento per le Politiche Antidroga. This study was funded by the European Union Justice Programme – Drugs Policy Initiatives, EUSMe (contract number: 861602). T.T.L. also received funding from the municipality of Amsterdam and Utrecht and water authority De Dommel. B.K.H. and N.C. acknowledge the support of EPSRC Impact Acceleration Account (EP/R51164X/1, ENTRUST IAA), Wessex Water Innovative Pathways Control Project and GCRF EWS-C19 (EP/V028499/1). D.B. acknowledges support from NIH-NIDA (R15DA051792). N.R. has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie Grant Agreement No. 896141. Data from Australia were obtained thanks to funding from the Australian Criminal Intelligence Commission. C.G.M. acknowledges funding through “Agencia Nacional de Investigación y Desarrollo (ANID) FONDECYT Regular program #1251223, Centro Tecnológico de Innovación CTI 25002, and ANID/SCIA/DIFE/ATE250008. Data from New Zealand were obtained thanks to funding from New Zealand Police. V.S. and H.O. acknowledge funding by the ‘IKB-Forschungsförderung 2020 für Nachwuchswissenschaftlerinnen’ as well as the municipality of Innsbruck.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.drugpo.2026.105507](https://doi.org/10.1016/j.drugpo.2026.105507).

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