Spatial differences and temporal changes in illicit drug use in Europe quantified by wastewater analysis

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Running head
Wastewater data covering 24.74 million people

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Abstract

Aims Perform wastewater analyses to assess spatial differences and temporal changes of illicit drug use in a large population. **Design** Analyses of raw wastewater over a one-week period in 2012 and 2013. **Setting, Participants** Catchment areas of wastewater treatment plants (WWTPs) across Europe; 2012: 25 WWTPs in 11 countries (23 cities, total population 11.50 million); 2013: 47 WWTPs in 21 countries (42 cities, total population 24.74 million). **Measurements** Excretion products of five illicit drugs (cocaine, amphetamine, ecstasy, methamphetamine, cannabis) were quantified in wastewater samples using methods based on liquid chromatography coupled to mass spectrometry. **Findings** Spatial differences were assessed and confirmed to vary greatly across European metropolitan areas. In general, results were in agreement with traditional surveillance data, where available. While temporal changes were substantial in individual cities and years (*P* ranging from insignificant to $<10^{-3}$), overall means were relatively stable. The overall mean of methamphetamine was an exception (apparent decline in 2012), as it was influenced mainly by four cities. **Conclusions** Wastewater analyses can provide the most up-to-date evidence on illicit drug use in Europe. An increased number of countries and WWTPs serving rural areas should be considered in the future for a wider and better representation of the European population to obtain the most detailed information on illicit drug markets and trends, complementary to existing survey methods.

1/Introduction

Illicit drug use is a covert and hidden activity that presents methodological challenges for drug surveillance systems. Questionnaire-based survey methods have traditionally been an important component of the approaches employed to monitor drug use, but it is recognized that these methods are not sufficient to adequately and quickly monitor trends in drug use and require complementary data from other sources [1,2]. The analysis of the excretion products of illicit drugs in wastewater [wastewater analysis (WWA)] has been explored since 2008 as an additional approach for estimating illicit drug use within specified regions, i.e. the catchment areas of wastewater treatment plants (WWTP) [3,4]. While the approach cannot provide information on the behavior of single users and on their demographics, there are a number of ways in which WWA can complement other survey methods and provide additional information to better understand the illicit drug situation. Wastewater data can be obtained within short time-frames, are not prone to response biases, and can help in identifying the spectrum of illicit drugs being used by a population. This is potentially important given the emergence of new psychoactive substances [5]. Drug users are often unaware of the actual substance or mix of substances they are consuming, which makes self-report data unreliable. Wastewater analysis is therefore a potential approach to detect and estimate use of new psychoactive substances, however, it has to be noted that more information regarding their biotransformation pathways is necessary.

Wastewater analysis can provide information on daily, weekly, monthly and annual variations in illicit drug use. The weekly profile of cocaine and amphetamine-like stimulants use has already been assessed by collecting consecutive daily wastewater samples, which revealed higher use of these substances during weekends [6-12]. The monitoring of temporal trends in illicit drug consumption over a longer period of time (months) by WWA has been evaluated in three studies and the major conclusions were that there was typically an increase of illicit drug use during holiday periods [11,13,14]. Wastewater analysis was further applied to detect yearly trends in illicit drug consumption in Italy and Australia [15,16]. In conclusion, this approach can provide important and timely information on short- and long-term trends in illicit drug use.

Wastewater studies in different countries have also detected regional variations in illicit drug use [17-22]. The influence of urbanization on the use of illicit drugs was evaluated in Oregon (USA) and South Australia and Queensland (Australia), concluding that the use of illicit drugs was higher in urban regions compared to more rural areas [9,14,23]. Wastewater analysis has also been applied to detect transnational differences in illicit drug use. The consumption of five substances was evaluated by analyzing wastewater from 19 European cities for a one-week period in 2011 [24]. Wastewater analysis can thus complement survey methods for a better understanding of actual spatial differences and temporal changes in illicit drug use.

However, until now no international study has been performed covering multiple countries over multiple years with a common protocol and adequate quality control measures. Therefore, the aims of this study were to:

1) collect wastewater samples from multiple European locations in 2012 and 2013,
2) calculate population-normalized mass loads of benzoylecgonine [BE; as indicator for cocaine (COC) use], amphetamine (AMP), methamphetamine (METH), ecstasy [3,4-methylenedioxy-methamphetamine (MDMA)] and 11-nor-9-carboxy-delta9-tetrahydrocannabinol [THC-COOH; as indicator for tetrahydrocannabinol (THC) use],
3) perform analytical quality control through inter-laboratory tests.

2/Methods

2.1/Sewer system characterization

Relevant information for each WWTP catchment was systematically gathered by means of a standardized questionnaire. An extended version of the questionnaire developed for earlier studies [24,25] was used (Appendix S1). It comprises over 50 questions classified according to importance. The number of the most important questions per category is indicated in brackets (year 2012/year 2013): *General information* (1/1), *Catchment and population* (2/5), *Sewer system* (2/2), *WWTP influent* (1/1), *Sampling* (5/5), *Flow meter* (3/3), *Sample handling* (9/9), *Monitoring period* (5/5).

2.2/Sampling and analysis

A one-week period was targeted in 2012 (17-23 April) and 2013 (6-12 March). Daily 24-h composite raw wastewater samples were collected over seven consecutive days. Considering stability, metabolism and unambiguous indication of drugs actually having been consumed, the most suitable target residues were targeted: BE, AMP, METH, MDMA and THC-COOH [4]. It has to be noted that the consumption of COC and THC was monitored through the analysis of their main metabolite because of higher concentrations and higher stability in wastewater.

Samples were spiked with isotope-labelled internal standards, either filtered and immediately extracted on solid-phase extraction cartridges or frozen at -20°C until analysis. Each laboratory used fully validated analytical methods: target compounds present in the liquid phase of the wastewater were quantified in final extracts or with direct injection applying liquid chromatography coupled to tandem mass spectrometry or high-resolution mass spectrometry [25].

For quality assurance, each laboratory participated in yearly inter-laboratory tests [de Voogt et al., unpublished]. External quality control samples were evaluated (one standard in methanol and two fortified raw wastewater samples). A reliable estimation of the method limit of quantification (LOQ) was performed by evaluating the signal-to-noise ratio in these samples. In 2012, one of 14 laboratories did not meet the requirements for any compound in the inter-laboratory test and was excluded. In 2013, only METH results of one of 15 laboratories had to be excluded.

2.3/Calculations

Daily mass loads (g/day) of drug residues entering the WWTPs were calculated by multiplying measured concentrations (ng/L) in daily samples with the corresponding wastewater volumes (L/day). To compare cities of different sizes, mass loads are normalized by the population size of the catchment (mg/1000persons/day). The estimated consumption of COC (section 3.1) was back-calculated from the population-normalized mass loads of BE using a correction factor of 3.59 that takes the urinary excretion rate of COC into account for different dosages and routes of administration [25].

2.4/Uncertainty assessment

Mainly four components of uncertainty may affect the estimation of population-normalized drug loads: sampling (U_S), chemical analysis (U_C), flow rate measurement (U_F) and population estimation (U_P). Since the focus of this study is on mass loads in wastewater, uncertainties related to excretion rates and bio-degradation in sewers are not considered. When estimating the overall uncertainty U_T of a mean value over an n-day monitoring period, uncertainty components that are random and independent on every day will be reduced by sqrt(n). This applies to U_S, since each sample is collected physically independent of the day before. All other components cannot be reduced by sqrt(n): i) population is only estimated once, ii) chemical analysis is carried out for all samples in one batch, and iii) if a flow meter measures flows systematically wrong, it will be in the same direction every day. All components can be considered as independent. As long as U_S, U_C and $U_F \leq 30\%$ and $U_P \leq 10\%$ (RSD), an estimation of U_T is valid with an approximative formula [e.g. 26]. Since a conservative estimate of U_P in our study is 20%, a Monte Carlo simulation was used to avoid underestimating U_T systematically (see Appendix S2).

3/Results

Table 1 lists participating cities: in 2012, 25 WWTPs in 11 countries were included (23 cities, total population 11.50 million), in 2013, 47 WWTPs in 21 countries (42 cities, total population 24.74 million). For comparison, also 2011 data [24] was used (21 WWTPs in 11 countries; 19 cities, total population 14.12 million). Figures 1-5 summarize all results. Countries are ordered based on average loads over all years. The numbers in brackets indicate cities' overall ranks. While absolute variability within one-week periods (grey range) is obviously higher for high loads, relative variability is not substantially different throughout the entire load range and may vary from year to year even within a location. The color of lines between the means indicate whether the change from one week in one year to one week in another year is significant (Wilcox, α=0.05). Table 2 summarizes overall means, separately for cities that participated in all three years (cities in bold in Figures 1-5) and for all cities per year (excluding cities that exhibited explainable anomalies, i.e. cities in italics in Figures 1-5). Concentration values that were <LOQ were treated as follows: 1) if all values at a location for a certain compound were <LOQ, loads were set to zero; 2) if at least one value was >LOQ, values <LOQ were replaced with 0.5xLOQ. Dashed grey lines indicate a population-weighted overall mean for 2013 (all cities except cities in italics). When weekly patterns were evaluated in 2012, previous findings were confirmed, i.e. higher loads on weekends for BE, and MDMA and no substantial variation for AMP, METH and THC-COOH [24] (see Appendix S4).

3. 1/Benzoylecgonine

The highest weekly mean BE loads in the period 2011-2013 were observed in wastewater from Amsterdam, Antwerp, London and Zurich and were between 400-850 mg/1000persons/day (Figure 1). Loads were also relatively high (between 200-550 mg/1000persons/day) in Barcelona, Basel, Geneva, Utrecht and Eindhoven. The lowest values (<100 mg/1000persons/day) were observed in locations from Northern, Eastern and Southern Europe. These results suggest a clear geographical difference in cocaine consumption, with higher use in Western Europe. This is further demonstrated when BE loads in locations from Germany are evaluated. Loads in Dresden (eastern Germany) are negligible, similar to the amounts seen in the Czech Republic, while loads in Dortmund (western Germany) are comparable to the loads observed in the Belgian, Dutch and Swiss cities.

The overall population-weighted mean loads of BE for the 16 locations included in all three years were almost identical (Table 2). This suggests a stable use of COC in the investigated locations in the period 2011-2013. Location-specific results from 2011, 2012 and 2013 are generally in agreement (Figure 1), however, in some cases, variations occurred. An increase in BE loads from 2012 to 2013 was observed in the Belgian and Swiss locations, while a decrease was observed in two Dutch locations (Utrecht and Amsterdam).

Besides the high variation of mean BE loads observed across Europe, this study also highlights differences among locations within countries. Results from Belgium, Czech Republic, Germany, Serbia, Slovakia, Switzerland and Sweden suggest that the consumption of COC is lower in smaller towns compared to larger cities (Table 1, Figure 1). Qualitatively, this is in agreement with studies investigating more locations within a country [17-22], although some of these rely on grab samples or single days only. The difference between Dresden and Dortmund, two cities of similar size, is attributable to their geographic location within Germany as previously discussed.

The population-weighted mean COC consumption, calculated from BE loads (section 2.3), for locations included in all study years is similar between years and varies from 887 mg/1000persons/day in 2013 to 912 mg/1000persons/day in 2012. With 366 million people living in the urbanized regions of the European Union and a mean purity of 39% (SD: 12%) [27, 28], a rough extrapolation would imply that 832 kg of street purity COC per day is consumed by the urbanized population in the European Union in 2013.

3.2/Amphetamine and methamphetamine

Because AMP is a urinary metabolite of METH and since AMP in wastewater could subsequently result from the use of METH, loads of both substances in wastewater have to be evaluated in parallel. Moreover, the use of certain prescription drugs, such as selegiline, may also result in traces of AMP and METH in wastewater following its metabolism, however prescription rates indicate that any contribution would typically be <1% of the total AMP signal [24,29]. The most frequently amphetamine-like substance detected in the majority of the investigated locations was AMP. The highest AMP loads were found in Belgium and the Netherlands, followed by locations in Northern Europe and western Germany. The locations with the highest METH loads were found in the Czech Republic, Slovakia, eastern Germany and Northern Europe, while the observed METH loads in the rest of the studied locations was low to even negligible (Figure 2 and 3). The presented results suggest an apparent geographical difference in the use of the amphetamine-like stimulants. The consumption of AMP is more widespread in Western Europe, while the use of METH is clearly focused to Northern Europe, Slovakia and Czech Republic. The German results confirm the aforementioned trend in the use of amphetamine-like substances. In Dülmen and Dortmund (west), relatively high AMP and negligible METH use was observed, while for Dresden (east, proximity to Czech Republic) the opposite was found.

The weighted mean of METH loads for the cities that were included in all study years declined by 45% from 2011 to 2013 (Table 2), due to some location-specific changes. For AMP, the weighted mean of the cities included in the three years is similar (Table 2). In contrast to BE loads, the difference in AMP and METH loads between smaller towns and bigger cities within a country is less clear.

3.3/MDMA

The highest loads of MDMA were found in Western European locations, while locations in Northern, Eastern and Southern Europe presented substantially lower MDMA loads (Figure 4). This pattern is comparable to BE and AMP, as demonstrated by the locations within Germany, with low MDMA loads in Dresden and higher loads in Dortmund.

The weighted mean of MDMA loads for the cities included in all three study years was stable (Table 2). No significant changes in per capita MDMA loads between years for the individual locations were observed, with some exceptions (Figure 4). The mass loads of MDMA from Eindhoven in 2012 and 2013 were much higher compared to 2011, and in Utrecht significantly higher loads for MDMA were observed in 2011 compared to 2012 and 2013. An explanation for these high loads in Utrecht (2011) and Eindhoven (2012) is most probably a release of unconsumed MDMA into the sewer system that was confirmed by specific enantiomeric profiling of the wastewater [30]. These outliers were not taken into account when assessing temporal changes. MDMA loads are generally higher in larger cities compared to smaller towns, as can be seen in different locations within Belgium, Finland, Germany, Serbia and Slovakia. A notable exception is St. Gallen in Switzerland that showed MDMA loads comparable to the larger city of Zurich.

3.4/THC-COOH

The determination of THC-COOH in wastewater poses some (pre-)analytical challenges, and as a result not all laboratories could report results for this THC metabolite. Furthermore, results from the performed inter-laboratory exercises revealed that participating laboratories that reported results for THC-COOH have satisfactorily comparable good analytical methods (Z-scores within the limits), but because of some unknown pre-analytical losses, underestimations of the absolute amounts are probably made [de Voogt et al., unpublished]. In the present study this is, however, not a real issue, because the focus lies on the relative comparison of THC-COOH loads.

In contrast to the other investigated substances, no clear geographical pattern could be observed for THC-COOH loads in the different European locations (Figure 5). The values for Amsterdam were (expectedly) the highest, since Amsterdam is known for its coffee shops and because the Netherlands produces large amounts of herbal cannabis with a relatively high content of THC [31]. Also notable are the high loads observed in the city of Novi Sad, Serbia.

The weighted mean of THC-COOH loads for cities that were included in all three years showed some subtle variation, pointing out a variable cannabis use (amount or potency) between 2011 and 2013 (Table 2). No clear difference in THC-COOH loads between smaller towns and larger cities could be observed from the gathered data.

4/Discussion

4.1/Comparison of wastewater results with surveillance data

Europe has an established multi-indicator system for drug surveillance that is based on standardized demand and supply information, as well as research and intelligence sources [36]. Prevalence estimates are derived from a mixture of survey results and indirect statistical methods that try to estimate the unobserved cases from registers of observed drug users, such as treatment attendees or arrestees [37]. These methods can provide information on the main classes of users, the frequency and mode of use of a drug as well as on the purity of the substances available on the market, while WWA can give objective and timely information on the total amount of a drug used in a specific area. These methods are highly complementary and, if used together, can substantially improve the quality of information on drug use patterns.

In terms of prevalence at the population level, the findings from WWA are broadly in agreement, in respect to relative drug use levels, with existing estimates, although they are not directly comparable. The wastewater data do however point out the need to consider the contribution of high and low prevalence areas in the estimates of total drug use within a population. Due to differences in demographics, the ranking of the city-based estimates reported in this study do not necessarily have to agree with national survey-based estimates. This points to the need to collect contextual information for a meaningful interpretation of wastewater data. Future monitoring campaigns should therefore i) include more cities with different demographics within a country and ii) evaluate monitoring design strategies to find an optimum among feasible logistics, sufficient quality control and representativeness for an entire year [38].

The spatiotemporal data on drug use data reported are largely, but not totally, in line with what is observed from surveys and other sources. The stable levels of COC suggested by the presented wastewater data differs from other demand and supply data, which report a decline in COC use [39]. With WWA, it is currently not possible to differentiate between smaller number of people using larger amounts or vice versa or even evaluating differences in consumption due to changes in purity. The analysis on METH and AMP accords with other data sources. The use of METH is long established in the Czech Republic, Slovakia and eastern Germany [40] and more recently supply side data point to an increase use of METH elsewhere; especially in Scandinavian countries where it has at times displaced AMP. The situation appears quite dynamic and largely supply side driven- the wastewater data reported here accords with, and complements, the existing analysis of this situation.

For both MDMA and cannabis use, the picture is less clear. High levels of MDMA and THC use might be expected in the Dutch cities sampled, but it is surprising that MDMA use stands out so prominently in respect to some of the other European cities. The most recent supply side data suggest that there is more MDMA available on the European market and it is interesting to note that there is no evidence of this from the wastewater data reported here. The findings for THC-COOH in Amsterdam are not too surprising as it is known for its large non-resident population using cannabis.

4.2/Uncertainty assessment

Details on estimating U_S can be found in [32,33]. Applying the same scenario as in [25] – i.e. 1% of users in the population with two relevant, substance-related toilet flushes – results in a maximum of 20% for a daily value of U_S. An objective assessment of U_C was derived from inter-laboratory tests and does not exceed 30% [de Voogt et al., unpublished]. Operational accuracy of flow meters (U_F) still proves to be a challenge and in this study was assumed conservatively to be 20% [34]. Despite advances in estimating U_P [35], it remains difficult to obtain a site-specific estimate and in our study we assume 20% (RSD) as an average [30, 35]. A conservative estimate of overall uncertainty for a seven-day average based on WWA is around 46% (RSD) for all substances and locations (see Appendix S2 for more details). A sensitivity analysis reveals that reducing all four uncertainty components U_i by about one quarter ($U_S \approx U_F \approx U_P \approx 15\%$, $U_C \approx 23\%$), has the same effect as trying to eliminate only one U_i (e.g. $U_C \approx 0\%$); in both cases the overall uncertainty would be around 33%.

In areas with leaky sewers the results from WWA may tend towards an underestimation of actual illicit drug loads. A certain fraction of the wastewater and illicit drugs discharged from households may not arrive at the WWTP. Information on the potential amount of exfiltration can be found in Table 1. Furthermore, in cases where population size is estimate from nutrient loads in the wastewater stream, the population could be overestimated if industrial contributions are not properly subtracted. This would lead to an underestimation of population-normalized drug loads. In contrast, WWA results may tend towards an overestimation of population-normalized drug loads, if only the residential population was used for normalization but a net increase on workdays is effective due to commuters. This and additional information is provided in Table 1 and Appendix S3 for further data interpretation.

5/Conclusions

Successfully increasing the number of participating cities to 42 in 2013 (2011: 19, 2012: 23) this is now the biggest application of WWA covering 24.7 million people. The wastewater from approximately 8 million people was analyzed for BE, AMP, METH and MDMA during a one-week period over three consecutive years (approximately 4 million for THC-COOH). As such, this study provides the most actual evidence for the quantification of spatial differences and temporal changes in the consumption of illicit drugs across European regions. Relatively stable loads for all investigated substances were observed, except for METH (apparent decline in 2012). In general, spatial differences were in agreement with surveillance data, where available. Wastewater analysis provides the possibility to collect, and report, measurements more quickly, cheaply and regularly than is the current norm for national surveys. Wastewater analysis provides a unique opportunity to obtain near-real-time data on illicit drug use and for future comparison with other surveillance data or particularly where such data is missing. Therefore, it should be considered for implementation on an annual, or even more frequent, basis. Systematically gathering information on catchment characteristics (sewer system and population) seems as indispensable as inter-laboratory tests for a meaningful comparison of wastewater data, which requires concerted efforts of numerous partners and disciplines.

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Supporting information

Additional Supporting information may be found in the online version of this article at the publisher's website:

Appendix S1 Questionnaire 2012 and 2013.

Appendix S2 Uncertainty estimation.

Appendix S3 Answers from questionnaire and all analytical data 2012 and 2013 and P-values for changes of one week to another for all substances and locations (different spread sheets in separate Excel file).

Appendix S4 Weekly variation of drug loads 2012 (separate PDF file).

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Country	City WWTP	Population of the city under investigation ⓪	Estimated population in WWTP catchment 2011	① method (year)	2012	① method (year)	2013	① method (year)	Targeted 1-week monitoring period ✓ (n=7days) 2011 Mar 9-15	2012 Apr 17-23	2013 Mar 6-12	Loss of wastewater ②	Com-muters ③	Special events ④
BA	**Sarajevo** Butile	C: 291422, M: 515012 (W)					130000	b (2013)			✓	◐	▷	R (2013)
BE	**Antwerp D.** Deurne	498473 (E 2011)			213876	a (2011)	213876	a (2012)		✓	✓	○	▷	
	Antwerp Z. Zuid	498473 (E 2011)	117200	a (2010)	130218	a (2011)	130218	a (2012)	✓	✓	✓	○	▷	
	Brussels Noord	1136778 (E 2011)	1027300	b (2011)	953987	b (2012)	953987	b (2013)	✓	✓	✓	○	▷	
	Geraardsbergen Geraardsbergen	32629 (W)					29047	c (2011)			Mar 7-13	○	▷	
	Koksijde Wulpen	31207 (W)					78441	a (2012)			Mar 21-27	○	▶	
	Ninove Ninove	37295 (W)					36179	c (2013)			✓	○	▷	
CH	**Basel** ProRheno	C: 195743 (L 2013)			260000	c (2012)	260000	c (2012)		✓	✓	◐	▶	R (2012)
	Berne region bern	C: 137818 (L 2012)			206655	c (2012)	206700	c (2012)		Apr 21-27	✓	○	▶	R (2012)
	Geneva SIG	C: 194458 (L 2013)			410486	c (2012)	410500	c (2012)		Apr 22-28	✓	○	▶	R (2012)
	St. Gallen Au and Hofen (2 WWTPs)	C: 74070 (L 2013)			89000	c (2012)	89000	c (2012)		✓ (n=5)	✓	○	▶	R (2012)
	Zurich Werdhölzli	C: 394012 (L 2012)			410000	c (2012)	410000	c (2012)		✓	✓	○	▶	Y (2012)
CY	**Nicosia** Pano Deftera	234200 (E 2009)					28000	c (2012)			Mar 21-27	○	▶	Y (2013)
	Limassol Amathus	185100 (E2009)					272000	c (2010)			Mar 21-27	○	▶	Y (2013)
CZ	**Budweis** COV	93620 (E 2011)	112000	d (2010)	112000	d (2010)	110300	d (2013)	✓	✓	✓	◐	▶	Y (2011)
	Prague UCOV	1241664 (E 2011)			1300000	c (2011)	1300000	c (2011)		✓	✓	◐	▷	
DE	**Dortmund** Deusen	580956 (E 2012)					371788	c (2010)			Mar 13-19	○	▷	
	Dülmen Dülmen	46071 (W)					34495	c (2010)			✓	○	▷	
	Dresden Kaditz	529781 (E 2012)					593050	c (2012)			✓	○	▶	
DK	**Copenhagen** Lynetten	501285 (E 2003)					531000	c (2009)			Mar 6-13 (n=7)	○	▷	
ES	**Barcelona** Baix Llobregat	C: 1620943, M: 3202571 (E 2012)	1162000	c (2007)	1162000	c (2010)	1162000	c (2010)	Mar 16-22	✓	✓	○	▶	Y (2012/13) R
	Castellon Castellon de la Plana	C: 180204 (E 2012)	170600	a (2010)	204878	b (2012)	204878	b (2013)	✓	✓	Feb 20-26	○	▷	
	Santiago Silvouta	95671 (E 2012)	136500	d (2010)	136500	d (2010)	136500	d (2010)	✓ (n=6)	✓	✓	○	▶	
	Valencia Pinedo I+II° and QB°° (3 WWTPs)	C: 797028 (E 2012), M: 1353250 (L 2013)	1839000	a°°/b° (2011)			1357952	e°° (2011) / b° (2013)	✓		✓	○	▶	R (2011/13)
FI	**Helsinki** Viikinmäki	M: 1022139 (E 2009)	780000	a (2009)	780000	a (2009)	780000	a (2009)	✓	✓	✓	○	-	
	Turku Kakola	178630 (E 2012)	*275000	d (2011)	275000	d (2011)	275000	d (2011)	✓ (n=6)	✓	✓	○	-	R (2012)
FR	**Paris** Seine Centre[+]/Grésillon[++]	C: 2243718 (E 2010), M: 6507783 (E 2006)	[+]774600	b (2011)	[++]245500	f (2012)	[+]1004000	b (2013)	✓	Apr 21-27	✓	◐	▷	Y (2012)
GB	**London** Beckton	8174000 (L 2011)	3400000	a (2010)			3400000	e (2010)	✓ (n=6)		✓	-	-	
GR	**Athens** Psyttalia	M: 2989023 (E 2009)					3700000	c (2011)			✓	○	▷	
HR	**Zagreb** Central	C: 688163, M: 1107623 (W)	650000	c (2001)	650000	c (2001)	650000	c (2011)	✓	✓	✓	-	▶	
IT	**Milan** Nosedo	1295705 (E 2009)	1250000	c (2010)	1100000	b (2012)	1149477	b (2013)	✓	✓	✓	○	▷	
NL	**Amsterdam** West	779808 (E 2011)	694800	b (2011)	769000	c (2010)	769000	c (2010)	✓	Apr 17-25	✓	○	▷	Y (2012)
	Eindhoven Eindhoven	216036 (E 2011)	448700	b (2011)	450300	c (2005)	450300	c (2005)	✓	✓	✓	-	▷	Y (2011/12)
	Utrecht Utrecht	311367 (E 2011)	297000	b (2011)	300000	c (2010)	300000	c (2010)	✓ (n=5)	✓	✓	◐	-	Y (2011)
NO	**Oslo** VEAS	599230 (E 2011)	557000	c (2009)	557000	c (2009)	576000	c (2012)	✓	✓ (n=6)	✓	○	▷	
PT	**Lisbon** Alcantara	C: 537412, M: 1860256 (E 2012)					426964	c (2011)			✓ (n=6)	◐	▶	
RO	**Cluj Napoca** Cluj Napoca	304802 (E 2011)					350000	c (2011)			✓	-	-	
RS	**Belgrade** Sewer outlet Danube	C: 1232731, M: 1659440 (W)					284347	c (2008)			Mar 17-23 (n=6)	○	▷	
	Novi Sad Sewer outlet Danube	M: 341625 (W)					321282	d (2013)			Mar 14-19 (n=6)	-	-	R (2013)
SE	**Gothenburg** Ryaverket	513751 (E 2010)			664441	c (2011)	664441	c (2011)		✓	✓	○	▷	
	Stockholm Henriksdals (only 1 of 2 inlets)	C: 847073, M: 1550208 (E 2010)	315000	c (2009)					✓			-	-	
	Umeå Öns	115473 (E 2010)	115800	c (2010)	115800	c (2010)	115800	c (2010)	✓	✓	✓	○	▷	
SK	**Bratislava** Central and Petržalka (2	415589 (L 2012)					440000	c (2011)			✓	●	▶	Y (2013)
	Piestany Piestany	29660 (W)					30000	c (2011)			✓	●	▷	Y (2013)

Table 1. Summary of participating cities and wastewater treatment plants (WWTP). More detailed information can be found in Supporting information (Appendix S3), which includes raw data and answers from the questionnaire.

⓪ Population of entire city/region C: City M: Metropolitan, greater region (E, W, L): Eurostat, Wikipedia and local bureau for population statistics (year) ① Method for population estimation in WWTP catchment (year of estimate); a, influent nutrient load over corresponding calendar year; b, influent nutrient load over actual sampling period; c, census d house connections / drinking water subscribers; e, values adopted from previous estimation; f, WWTP different from 2011/13 but wastewater from same catchment (central collection with subsequent distribution to different WWTPs). *Population estimate indicated in [24] was erroneous and population-normalized consumption estimates are corrected with updated value ② Loss of wastewater (exfiltration, questionnaire 2013). ♢**,** no loss expected; ♦, loss indicated (unknown amount or <20%)**;** ♦**,** loss >20% expected**;** -, information missing ③ Commuters (work days vs. weekend, questionnaire 2013). ▭, no substantial net population in-/decrease due to commuters; ➨ net increase of population on **work days; -** information missing ④ Special events during/adjacent to monitoring period. Y, please see Supporting information Appendix S3 for type of event (year provided in brackets); R, rain before/during monitoring period (higher flows but no substantial effect on drug loads expected).

Table 2. Population-weighted overall mean loads (units=mg/1000p/d). The loads in cities with all concentration values <LOQ were set to 0. Loads between cities range from (close to) 0 up to several 10-100 mg/1000 person/day implying large SD or 95%-CI for all substances' overall means. Significance of changes is assessed at cities' individual levels only (see Figures 1-5 and Supporting information Appendix S3).

	BE		MDMA		AMPH		METH		THC-COOH	
	a	b	a	b	a	b	a	b	a	b
2011 {14.12}	**249** [8.57]	311 [14.12]	**21** [7.82]	21 [13.38]	**29** [8.12]	30 [13.67]	**31** [7.51]	22 [13.07]	**71** [4.37]	69 [7.97]
2012 {11.50}	**254** [7.94]	229 [11.50]	**24** [7.19]	20 [10.75]	**29** [7.49]	32 [11.05]	**23** [6.89]	42 [11.50]	**60** [3.73	73 [9.07]
2013 {24.74}	**247** [8.77]	263 [24.74]	**25** [8.02]	18 [23.99]	**34** [8.32]	28 [24.20]	**17** [7.71]	33 [23.68]	**87** [4.53]	80 [15.55]

[a] Only cities participating in all 3 years are considered. These cities are labeled in **bold** in the corresponding figures. Cities with "explainable anomalies" for a particular substance are excluded from the calculation of overall means and labeled in *italic* (even if the anomaly occurred only in one year).

[b] All cities participating in the corresponding year are considered except the ones that were already excluded due to "explainable anomalies" in option a. Cities with "explainable anomalies" for a particular substance are excluded from the calculation of overall means and labeled in *italic* (even if the anomaly occurred only in one year).

{ } Total population in millions monitored (please note: not all substances were measured in all cities).

[ ] Population in millions contributing to the corresponding overall mean.

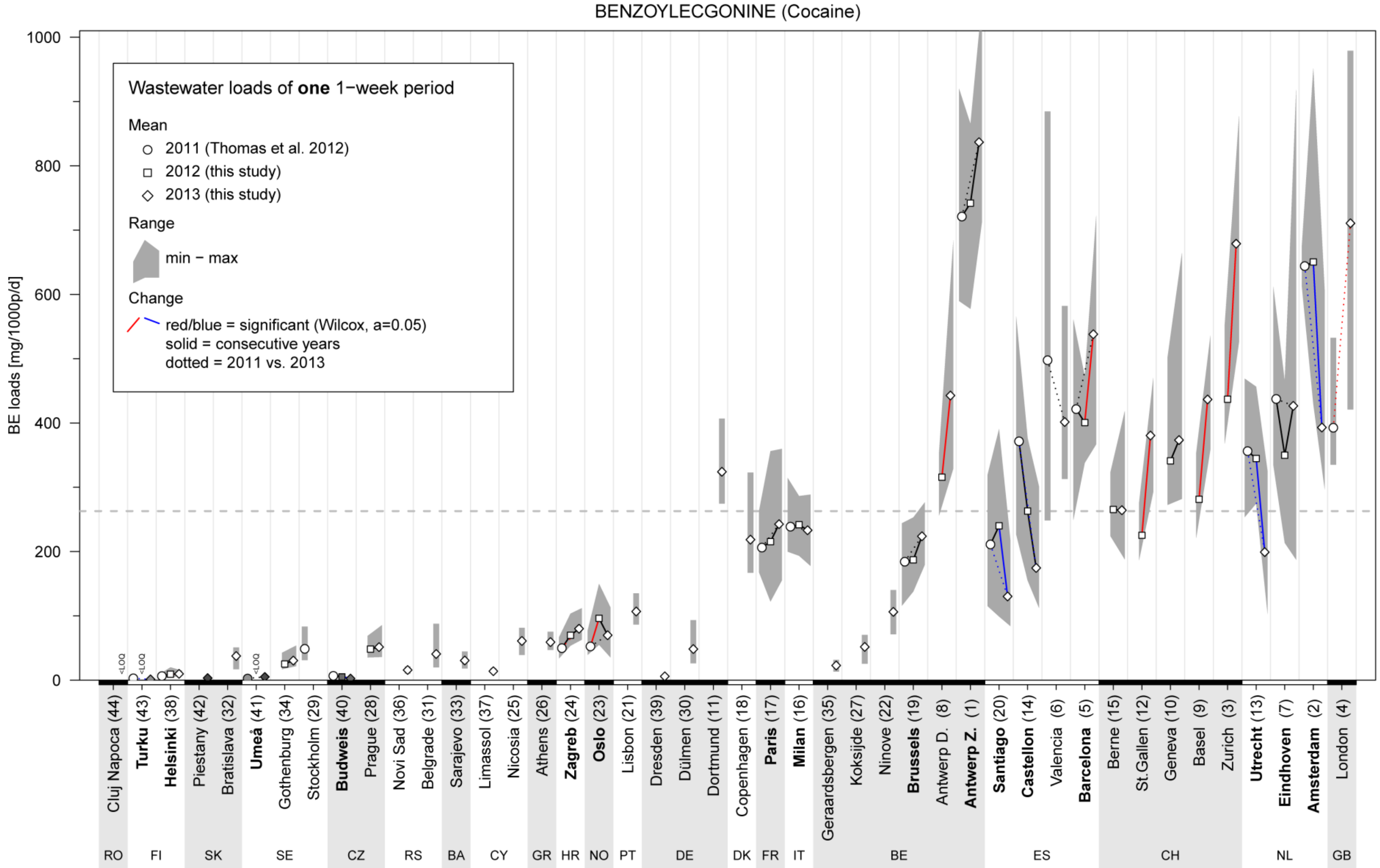

Figure 1. Population-normalized benzoylecgonine (BE) loads of one 1-week period per year. See Table 1 for more information. **<LOQ:** concentrations in all daily samples were below limit of quantification (LOQ). **Grey dashed line:** 2013 overall mean of all participating cities. **Dot color:** White: concentrations in all samples were above LOQ; Grey shading: one or more concentrations were below LOQ and set to 0.5*LOQ (the darker the grey, the more concentrations were below LOQ). **Numbers in brackets:** cities' rank (average over all available years). **Font:** Cities in bold participated in all three years and were used to calculate annual overall means (see Table 2). Cities in italic exhibited abnormal high values in at least one year (see text for more details). All p-values can be found in Supporting information Appendix S3.

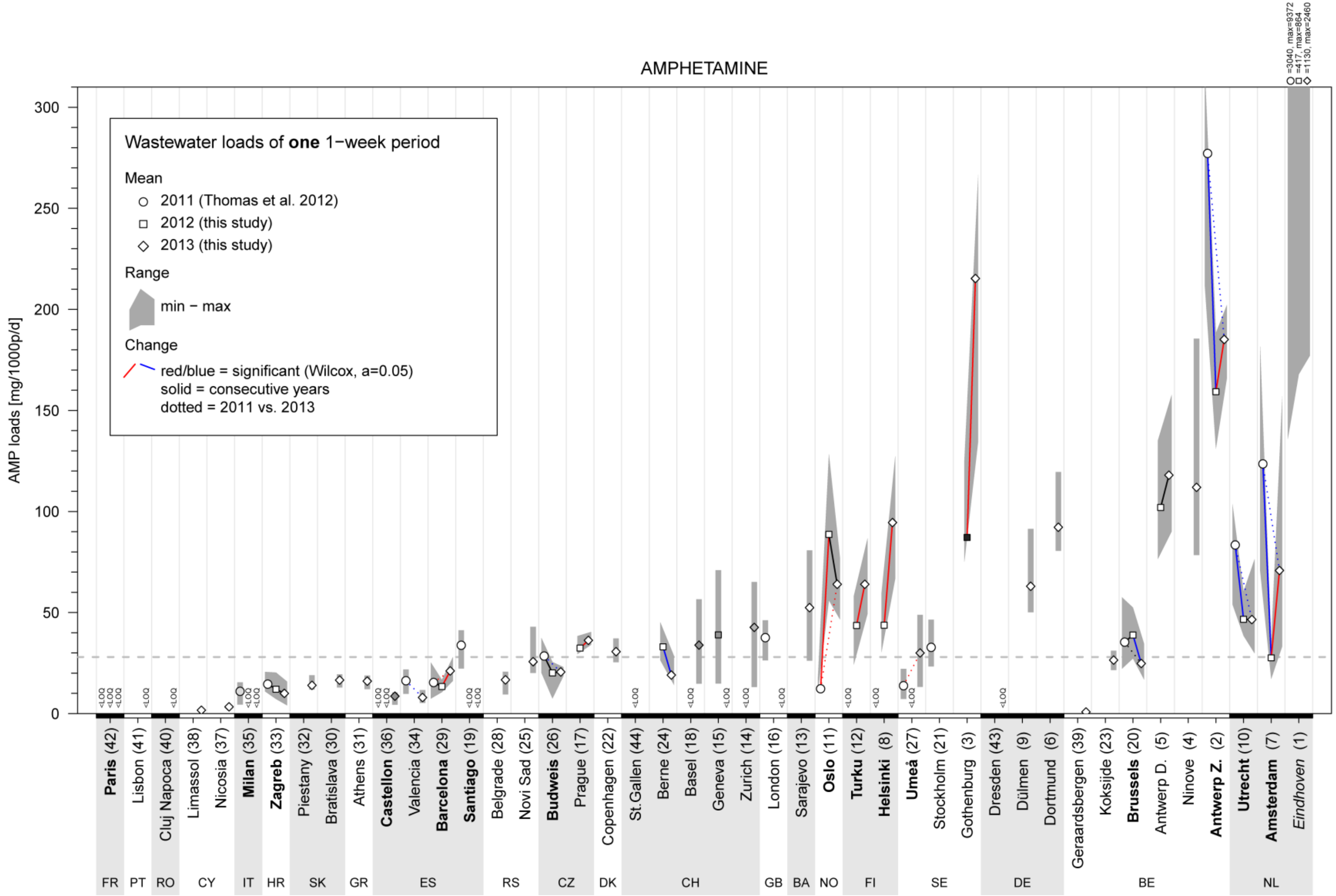

Figure 2. Population-normalized amphetamine (AMP) loads of one 1-week period per year. See Table 1 for more information. **<LOQ:** concentrations in all daily samples were below limit of quantification (LOQ). **Grey dashed line:** 2013 overall mean of all participating cities (except Eindhoven). **Dot color:** White: concentrations in all samples were above LOQ; Grey shading: one or more concentrations were below LOQ and set to 0.5*LOQ (the darker the grey, the more concentrations were below LOQ). **Numbers in brackets:** cities' rank (average over all available years). **Font:** Cities in bold participated in all three years and were used to calculate annual overall means (see Table 2). Cities in italic exhibited abnormal high values in at least one year (see text for more details). All p-values can be found in Supporting information Appendix S3.

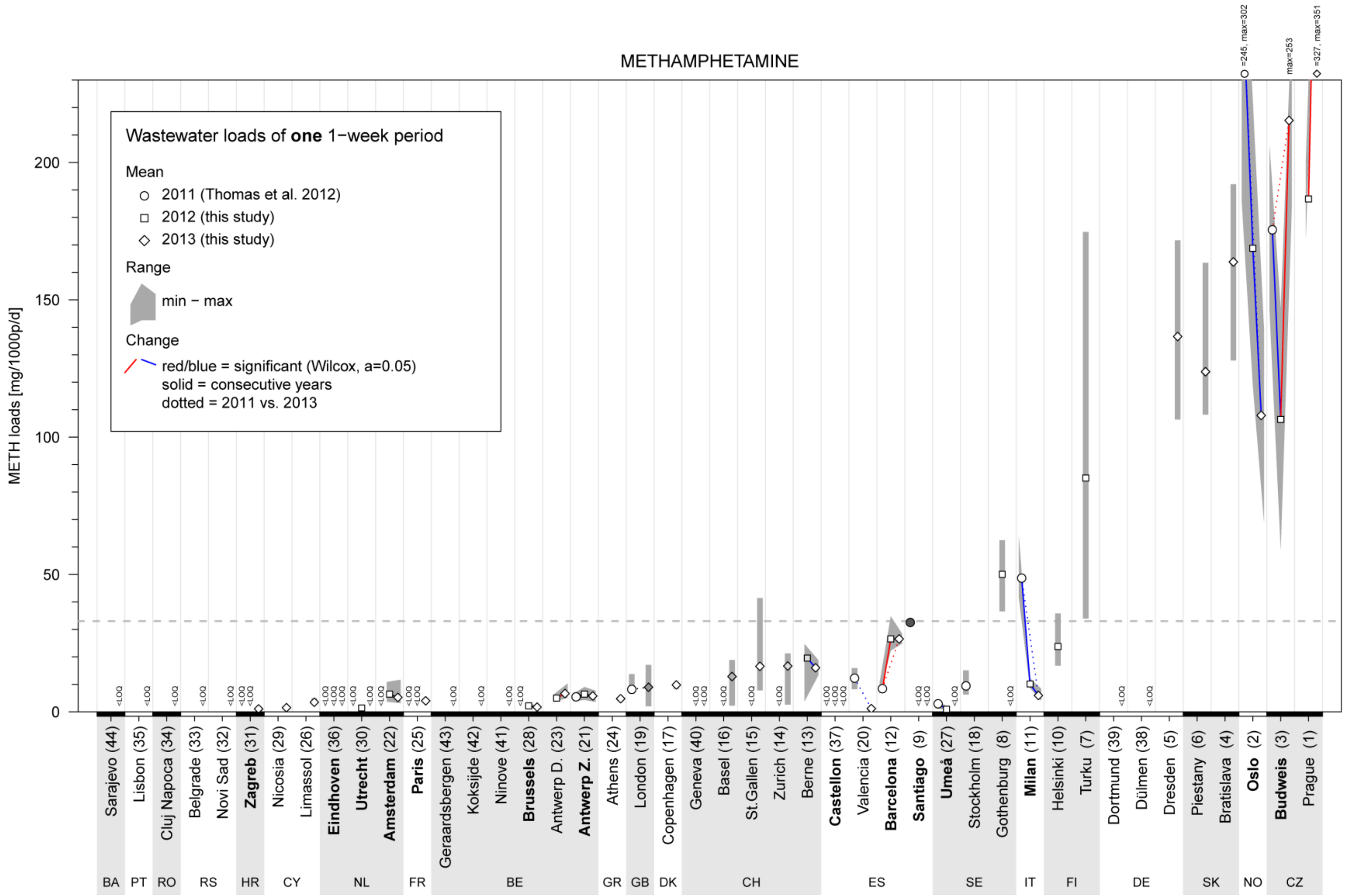

Figure 3. Population-normalized methamphetamine (METH) loads of one 1-week period per year. See Table 1 for more information. **<LOQ:** concentrations in all daily samples were below limit of quantification (LOQ). **Grey dashed line:** 2013 overall mean of all participating cities. **Dot color:** White: concentrations in all samples were above LOQ; Grey shading: one or more concentrations were below LOQ and set to 0.5*LOQ (the darker the grey, the more concentrations were below LOQ). **Numbers in brackets:** cities' rank (average over all available years). **Font:** Cities in bold participated in all three years and were used to calculate annual overall means (see Table 2). Cities in italic exhibited abnormal high values in at least one year (see text for more details). All p-values can be found in Supporting information Appendix S3.

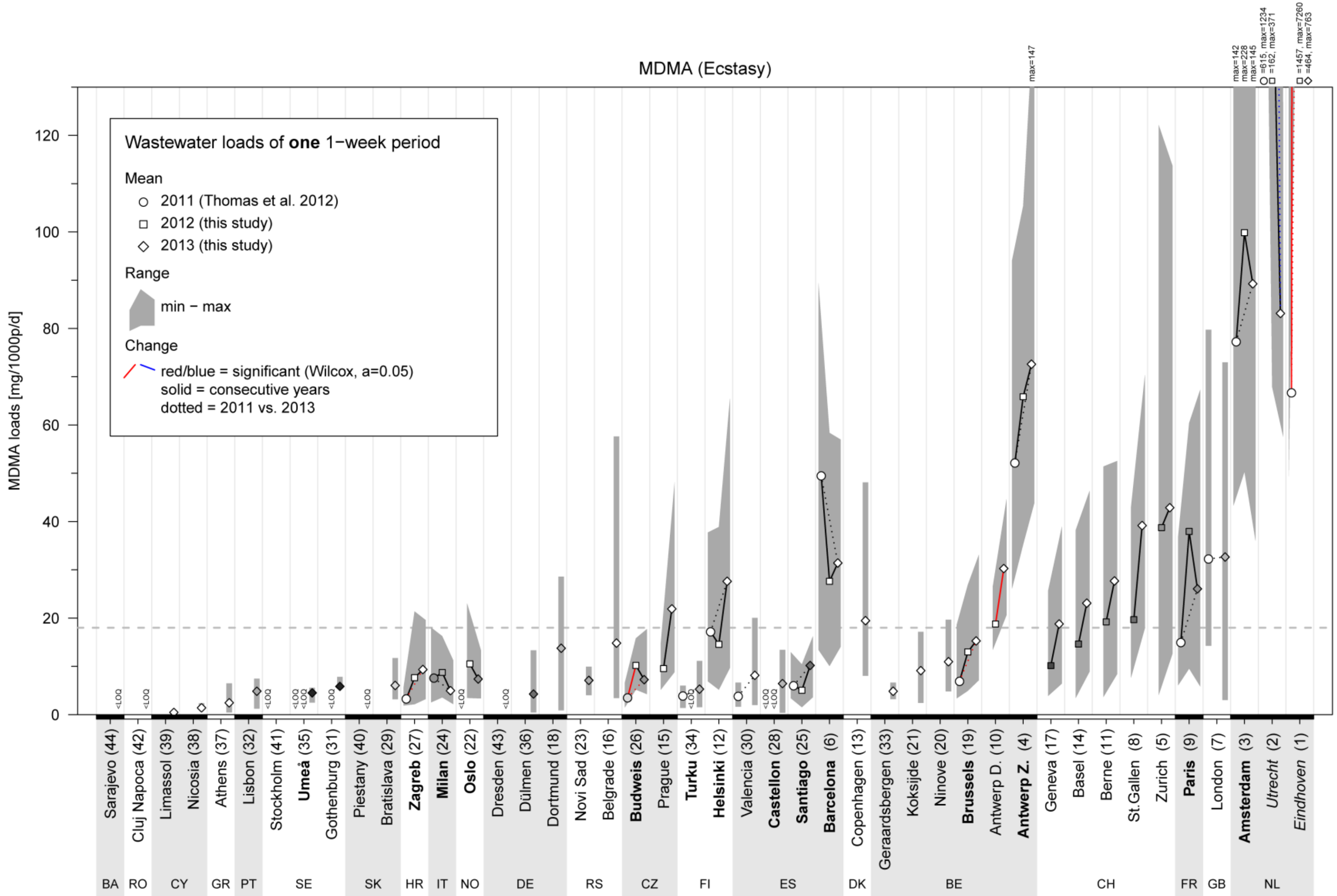

Figure 4. Population-normalized MDMA loads of one 1-week period per year. See Table 1 for more information. **<LOQ:** concentrations in all daily samples were below limit of quantification (LOQ). **Grey dashed line:** 2013 overall mean of all participating cities (except Utrecht and Eindhoven). **Dot color:** White: concentrations in all samples were above LOQ; Grey shading: one or more concentrations were below LOQ and set to 0.5*LOQ (the darker the grey, the more concentrations were below LOQ). **Numbers in brackets:** cities' rank (average over all available years). **Font:** Cities in bold participated in all three years and were used to calculate annual overall means (see Table 2). Cities in italic exhibited abnormal high values in at least one year (see text for more details). All p-values can be found in Supporting information Appendix S.

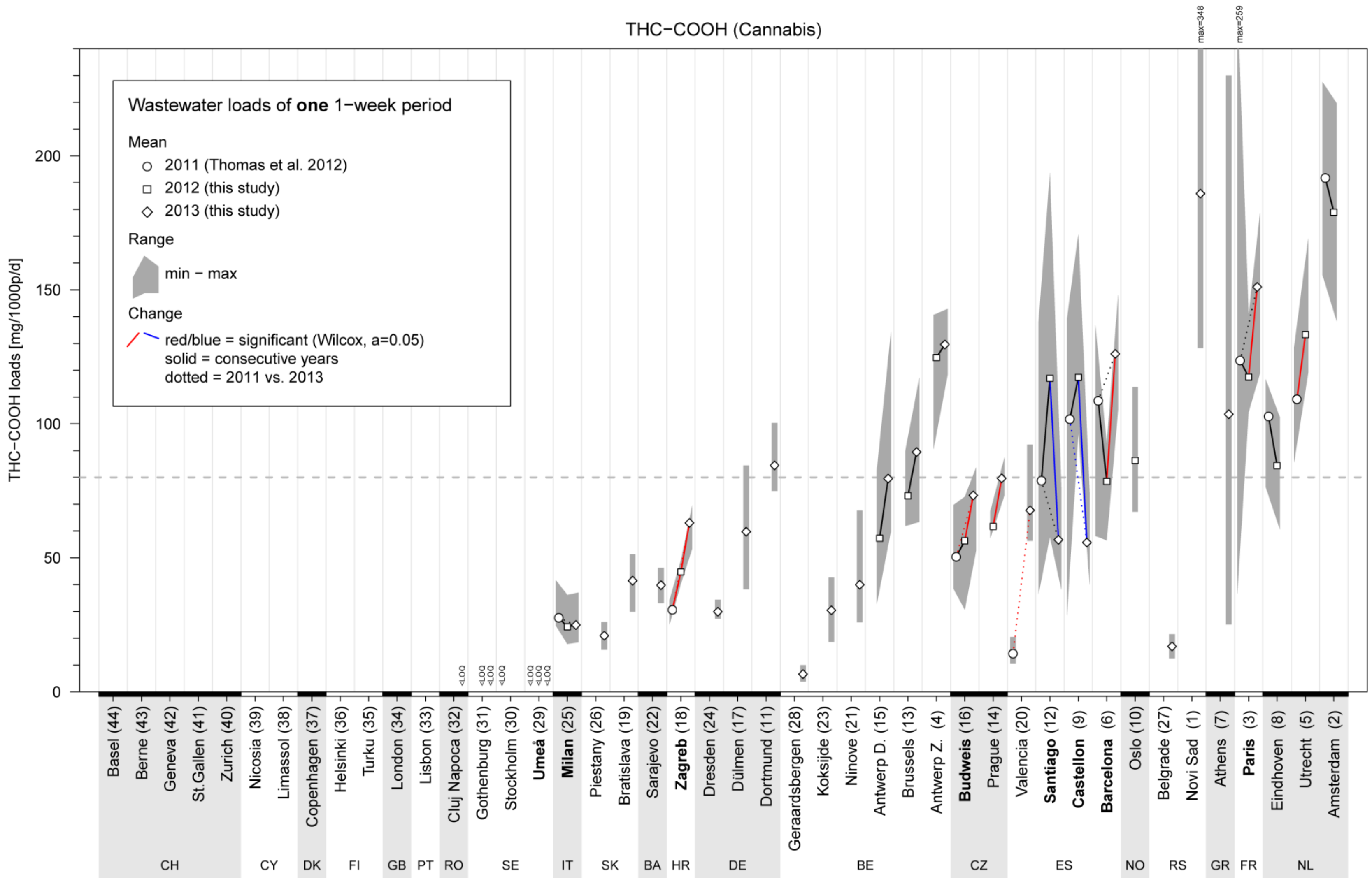

Figure 5. Population-normalized THC-COOH loads of one 1-week period per year. See Table 1 for more information. **<LOQ:** concentrations in all daily samples were below limit of quantification (LOQ). **Grey dashed line:** 2013 overall mean of all participating cities. **Dot color:** White: concentrations in all samples were above LOQ; Grey shading: one or more concentrations were below LOQ and set to 0.5*LOQ (the darker the grey, the more concentrations were below LOQ). **Numbers in brackets:** cities' rank (average over all available years). **Font:** Cities in bold participated in all three years and were used to calculate annual overall means (see Table 2). Cities in italic exhibited abnormal high values in at least one year (see text for more details). All p-values can be found in Supporting information Appendix S3.