Title: **Potential and limitations of wastewater-based epidemiology in monitoring substance use**

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Statement of competing interest: Hayley Jones and Matthew Hickman have received funding from the European Commission as part of the 'WATCH' (Wastewater Analysis of Traces of illicit drug-related Chemicals for law enforcement and public Health) consortium.

Key words: Wastewater, prevalence, tobacco, alcohol

Concise statement:

Wastewater-based epidemiology (WBE) could be used to evaluate public health interventions aimed at reducing substance use and potentially could contribute to prevalence estimates when modelled in combination with other data sources. However, it is unlikely to replace other methods just yet due to difficulties in obtaining and analysing sufficient samples and the limited evidence base around excretion factors.

Commentary:

Lai *et al* (1) add to a growing body of evidence suggesting that the routine monitoring of population-level substance use through communal wastewater could be feasible. Their study of metabolites of alcohol and tobacco covers an impressive 45% of the Australian population and adds some support for the validity of wastewater-based measures by demonstrating broad consistency in geographical patterns over time and when compared with household survey data.

As with the vast majority of wastewater studies to date, Lai *et al* (1) based inferences on just seven days of sampling per year (in this case, over a two-year period). Further study is needed of longer data series (2-4) to determine whether this sampling scheme is sufficient given the multiple sources of uncertainty and variability. For example, how representative one week of sampling typically is of a year will depend on the population size, the amount of consumption of the substance of interest and its excretion profile, in addition to any changes in consumption throughout the year (2). Until the total level of uncertainty relating to the sampling scheme is better understood, we should be cautious in interpreting apparent changes based on small numbers of samples.

Although wastewater analysis has considerable potential for monitoring trends over time and making comparisons across locations, we are less optimistic about its use to estimate absolute consumption levels. This involves extrapolation of estimated metabolite loads based on the estimated proportion of the parent substance that is excreted as the metabolite. As noted by Lai *et al* (1), only an estimated 0.012% of all consumed alcohol is excreted as ethyl sulfate, the monitored metabolite. This means that the inflation factor required to estimate the volume of alcohol actually consumed is large, leading to considerable uncertainty in consumption estimates and high sensitivity to small changes in this estimated proportion.. This is particularly worrying as there are very few studies on metabolite excretion. For example, the figure of 0.012% for alcohol was based on a single study of 10 healthy, male volunteers (5). We note, however, the remarkable agreement between the authors' total estimate of the number of cigarettes smoked per capita in Australia and sales data (1), which helps to corroborate the excretion proportion.

Lai *et al* (1) used a regression model, with population size and day of the week as predictors, to extrapolate consumption estimates in the population studied to the whole of Australia. This approach could be extended to include other predictors, such as area-level deprivation indicators or indeed sales figures if easily available. There are clear similarities to the 'multiple indicator method' that is often used to extrapolate capture-recapture-based prevalence estimates to other geographical areas (6,7). It will be feasible to generate credible intervals around the resulting estimates by extending the Monte Carlo simulation approach to a fully Bayesian analysis, performing the wastewater based calculations and the regression analyses simultaneously (8). By modelling multiple indicators of consumption in a single model we can reduce reliance on any one data source (9).

The authors are right to highlight the utility of WBE for evaluating public health interventions that aim to reduce tobacco and alcohol (and potentially drug) consumption in the population. It is important, however, that statistical tests for change account for parameter uncertainty. WBE could be used to supplement and test the consistency of sales data and other routine health data – such as A&E attendances for alcohol and uptake of smoking-cessation clinics – and importantly to identify any geographical inequalities in consumption and in intervention effects. However, WBE data cannot tell us about changes in cessation or abstinence or in the pattern of use, for which population surveys are still required.

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