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Can wastewater-based epidemiology be used to evaluate the health impact of temperature? – An exploratory study in an Australian population

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ABSTRACT

Ambient temperature is known to have impact on population health but assessing its impact by the traditional cohort approach is resource intensive. Wastewater-based epidemiology (WBE) could be an alternative for the traditional approach. This study was to provide the first evaluation to see if WBE can be used to assess the impact of temperature exposure to a population in South East Queensland, Australia using selected pharmaceuticals and personal care products (PPCPs) as biomarkers. Daily loads of eight PPCPs in wastewater collected from a wastewater treatment plant were measured from February 2011 to June 2012. Corresponding daily weather data were obtained from the closest weather station. Missing data of PPCPs were handled using the multiple imputation (MI) method, then we used a one-way between-groups analysis of variance to examine the seasonal effect on daily variation of PPCPs by seasons. Finally, an MI estimate was performed to evaluate the continuous relationship between daily average temperature and each multiply-imputed PPCP using time-series regression analysis. The results indicated that an increase of 1 °C in average temperature associated with decrease at 1.3 g/d (95% CI: −2.2 to (−0.4), $p < 0.05$) for atenolol, increase at 36.5 g/d (95% CI: 25.2–47.8, $p < 0.01$) for acesulfame, and increase at 0.8 g/d (95% CI: 0.02–1.55, $p = 0.05$) for naproxen. No significant association was observed between temperature and the remaining PPCPs, comprising: caffeine, carbamazepine, codeine, hydrochlorothiazide, and salicylic acid. The findings suggested that consumption of sweetened drinks, risk of worsening cardiovascular conditions and pains are associated with variation in ambient temperature. WBE can thus be used as a complementary method to traditional cohort studies in epidemiological evaluation of the association between environmental factors and health outcomes provided that specific biomarkers of such health outcomes can be identified.

1. Introduction

Sampling and analysis of wastewater influent from wastewater treatment plants (WWTPs) has become a useful tool for measuring the consumption of chemicals in the population. Initially proposed in 2001 (Daughton, 2001), with the first study published in 2005 (Zuccato et al., 2005), the approach has been validated and successfully applied to monitor substances of abuse in large scale studies across the globe (e.g. Ort et al. (2014) for illicit drugs, Castiglioni et al. (2015) for tobacco, and Ryu et al. (2016) for alcohol consumption). Wastewater-based epidemiology (WBE), as it is commonly referred to, can also be used for other chemicals that are excreted to the sewer system after consumption and reach the WWTPs. In fact WBE has been applied to measure the concentrations of several pharmaceutical and personal care products (PPCPs) in order to estimate the population residing in the monitored catchment (Gao et al., 2016; Lai et al., 2015; O'Brien et al., 2014; Rico et al., 2017).

Until now, few WBE studies have interrogated the association of the levels of chemical consumption measured in a population with any health impacts or environmental health factors. To our knowledge, only one pilot study by Fattore et al. (2016) has reported the association between asthma and outdoor PM_{10} and $PM_{2.5}$ levels by using the levels of salbutamol in wastewater as an indicator of the occurrence of asthma. Such findings provided direct evidence of the effect of outdoor

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ambient air pollution on asthma which is usually difficult to obtain by other methods.

Ambient temperature is an important environmental risk factor. A recent study involving multiple countries has indicated that even mild temperature changes can increase the mortality risk to people (Gasparrini et al., 2015). The effect of ambient temperature on morbidity is also considered a significant public health issue with a large number of hospitalizations associated with exposure to extreme ambient temperatures such as heat waves and cold spells (Phung et al., 2016). Assessing the impact of ambient temperature on morbidity is difficult because the use of emergency department visits and hospitalizations, and medicine sales or prescriptions as markers for morbidity may underestimate the effect of mild temperature change since people can also use medications at home when they know the symptoms of these chronic diseases.

In this study, we utilised a unique WBE data set to investigate the association between the ambient temperature and the levels of eight PPCPs measured in wastewater from a South East Queensland catchment in Australia during a period of more than a year (Lai et al., 2015). The outcome was consequently used to select good candidate biomarkers for health impact of ambient temperature for future WBE studies.

2. Materials and methods

2.1. WBE data on the daily loads of PPCPs

The dataset of eight PPCPs (Table 1) in wastewater used in this study had been used previously to estimate the daily *de facto* population in the catchment of 230,000 (Census 2011 data) through Bayesian modelling (Lai et al., 2015). They are the only PPCPs that could be detected and measured in all daily samples at low cost (i.e. by direct injection LCMS as described below). The sample collection and chemical analysis were described in details in Lai et al. (2015). Briefly, daily composite wastewater samples were collected between February 2011 and June 2012 (with several days missing due to logistical or technical reasons) using a continuous flow-proportional sampling technique. The samples were refrigerated at 4 °C during collection, acidified on site to pH 2 using 2 M hydrochloric acid, and then frozen until analysis. Data on daily wastewater volumes were recorded and provided by the WWTP.

The concentrations of the PPCPs were measured in wastewater samples by direct injection liquid chromatography (Shimadzu, Nexera UHPLC system, Kyoto, Japan) coupled with tandem mass spectrometry (AB SCIEX QTRAP5500, Ontario, Canada) (LC-MS/MS). Separation of the targeted PPCPs was performed on a Kinetics C18 column (100 × 3 mm, 2.6 μm) using gradient mobile phases. Together with the calibration standards, concentrations of the PPCPs were measured using mass spectrometry with a multireaction monitoring (MRM) scheme. Two MRM transitions were used for identification and quantification of each analyte. Concentrations of the analytes were quantified using the isotope dilution method. Quality assurance and quality control (QA/QC) measures were performed for every batch of analysis. All results were within the acceptable range with detailed QA/QC information (Lai et al., 2015). The concentrations of PPCPs were then multiplied with the daily flow data to produce the daily loads which were subsequently used in the statistical analysis.

2.2. Temperature data retrieval and statistical analysis

Daily weather data were obtained from the closest airport weather station to the WWTP catchment for the corresponding time-span of PPCPs monitoring time (475 days). The data comprise of daily minimum, maximum, and average temperature (°C); relative humidity (%) and cumulative rainfall (mm). Three steps were involved in the data analysis. Firstly, the missing data of PPCPs was handled using the multiple imputation (MI) method which is a simulation-based approach for analysing incomplete data and is described elsewhere (Marchenko, 2010; Soley-Bori, 2013; Yang, 2017). Multiple imputation provides a useful strategy for dealing with data sets with missing values, in which each missing value with a set of plausible values is replaced by Rubin's (1987) multiple imputation procedure instead of filling a single value for each missing value, then these multiple imputed datasets involved analysis by using standard procedures for complete data and combining the results from these analyses. Regardless of which complete-date analysis is used, the process of combining results from different imputed data sets is essentially the same. In this study, we used the multiple imputation procedure in Stata statistical software (Stata Corporation, College Station, TX, USA) to impute missing data. Variables comprising the weather variables (average temperature, humidity, and cumulative rainfall), which were strongly correlated with incomplete PPCPs values were investigated using Pearson product-moment correlation coefficient, were fitted with the regression model where each PCPP was the dependent variable consisting of missing values, then 10 complete datasets for each PPCP were created using these selected multiple weather variables. A total run length of Monte Carlo simulations used with imputations was 10,000. The 10 imputed data sets were then used for regression analysis using the command “mi estimate: regress (vars)” created for mi package in Stata software 11.

We tested normality of PCPPs data by plotting probability density for visual check (Supplement 1) and used the Shapiro-Wilk and Kolmogorov-Smirnov tests. Secondly, we used a one-way between-groups analysis of variance to examine the seasonal effect on daily variation of PPCPs by seasons comprising: summer (December-February), autumn (March-May), winter (June-August), and spring (September-November). The statistical significance was set up at the level of $p \leq 0.05$. Finally, we performed MI estimate using standard linear regression (Equation 1) to evaluate the continuous relationship between daily average temperature and each multiply-imputed PPCP using time-series linear regression functions. This step determined how much the daily load of each PPCP changed in relation to a 1 °C increase in temperature. We used the Augmented Dickey-Fuller test (Mushtaq, 2011) to check stability of the data before running time-series regression analysis. We also conducted sensitivity analysis using different temperature (minimum and maximum) for the PPCPs which were

Table 1
Characteristics and Limit of Quantification (LOQ) of PPCPs measured in this study.

PPCP	Class	Prescription	Over-the-counter	Stability in sewer[a]	LOQ (ppb)
Acesulfame	Artificial sweetener	Food & soft drink content		√	5.0
Atenolol	Cardiovascular drug	√		√	0.1
Caffeine	Stimulant	Food & soft drink content		not stable	0.5
Carbamazepine	Anticonvulsant	√		√	0.05
Codeine	Analgesic drug	√	√	not stable	0.5
Hydrochlorthiazide	Diuretic and antihypertensive agent	√		√	1.0
Naproxen	Anti-inflammatory and analgesic antipyretic agent	√	√	√	1.0
Salicylic Acid	Skin drug and metabolite of aspirine	√	√	not stable	1.0

[a] O'Brien et al. (2017).