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Review of wastewater monitoring applications for public health and novel aspects of environmental quality

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Full report

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1 Executive Summary

The rapid spread of severe acute respiratory syndrome coronavirus (SARS-CoVID-2) has devasted and overwhelmed public health systems across the world. The analysis of SARS-CoVID-2 in wastewater, via a technique known as wastewater-based epidemiology (WBE), has shown significant promise for monitoring disease spread. As a result, rapid and considerable infrastructure has been established to sample and analyse wastewater in the UK and internationally to track outbreaks. Whilst WBE is a relatively new field, the technique has expanded and developed over the past couple of decades to inform on varying aspects of public health. The aim of this project was to review the literature on what other areas WBE could be used to inform on public health.

1.1 Aims and objectives

1. Determine the existing and potential applications for WBE.
2. Outline where wastewater-monitoring is already being used, and for what purpose.
3. Highlight applications that are well-established, and which are potentially promising.
4. Identify the research gaps.
5. Determine the ethical considerations of WBE, what has been done already and what needs to be done.

1.2 Key findings

The review of the national and international literature on WBE found:

- WBE is a relatively new field and many of the studies to date have been proof of concept. Only very few applications of WBE exist that are ready to be implemented now 1) estimation of community wide illicit drug usage 2) estimation of lifestyle chemical usage, e.g. alcohol, nicotine and caffeine;
- Infectious disease tracking has historically been successful for monitoring potential polio cases within communities. WBE networks for SARS-CoVID-2 surveillance have been established regionally, nationally and internationally. Further research is needed to establish what virus loads indicate;
- Disease prevalence in a community for both non-communicable and communicable diseases have been estimated by pharmaceutical usage. Key to this is the analysis of both parent compounds and metabolites to determine consumption or direct disposal into a sewer;
- Recent studies have shown promise for WBE to monitor prevalence of allergies or asthma burden in a population linked with environmental factors;
- WBE has clear potential to estimate community-wide exposure to hazardous chemicals, including pesticides and plasticizers;
- The analysis of endogenous biomarkers (e.g. markers of inflammation or stress) in WBE would give valuable information on many aspects of public health and community lifestyles. However, very few endogenous biomarkers have been studied in WBE. Further work is needed in this area to identify suitable and representative biomarkers;
- Research gaps in WBE include a lack of understanding regarding stability, representative metabolites in wastewater and a lack of understanding of metabolism to undergo back-calculation of exposure;
- As WBE continues to advance, the ethical considerations must be established and kept up-to-date with developments.

1.3 Recommendations

WBE is a relatively new field. There are only a very few technology ready applications. These include estimation of community wide illicit drugs, lifestyle chemical usage (alcohol, nicotine and caffeine), infectious disease tracking and estimation of disease prevalence based on pharmaceutical usage (for diabetes, cardiovascular disease or mental health conditions). Required infrastructure includes specialised staff to undertake sampling and sample preparation as well as an investment in instrumentation. There is a clear potential to apply WBE to estimate community-wide exposure to hazardous chemicals (including pesticides and industrial chemicals) or the prevalence of non-communicable disease (including asthma). However, further essential research is required to fully appreciate WBE's potential to transform community-wide heath assessment. These include:

- Fundamental research on a new biomarker base to inform public health status;
- Novel approaches towards population equivalent estimation;
- Novel approaches towards sampling;
- Novel approaches towards analysis and sensing;
- Modelling and statistical analysis are required to fully appreciate spatiotemporal variability in large scale datasets.

2 Introduction

Wastewater-based epidemiology (WBE) has received increasing attention over the past year across the world. In the UK, local, regional and national wastewater monitoring programmes were established in 2020 to detect severe acute respiratory syndrome coronavirus (SARS-CoVID-2) patterns in human sewage to monitor outbreaks. This concerted effort between UK, Scottish and Welsh government, water companies, universities and research institutes has seen considerable investment into establishing the infrastructure, methodology and resources needed to sample, analyse, and interpret data from WBE. Whilst coronavirus has so far been the primary focus of these programmes, it is widely acknowledged that wastewater contains a diverse amount of chemical and biological information that can be used for wider public health purposes. The aim of this project was to review the literature on where else WBE could be utilised to inform public health.

2.1 What is wastewater-based epidemiology

WBE is a field that combines multiple disciplines, bringing together scientists and engineers. It is a technique where wastewater is analysed to give information on the communities within a wastewater catchment. Epidemiology is the study of the distribution and patterns of disease and health in defined populations, and WBE is using wastewater for this purpose. WBE is achieved through the analysis of indicators of health and disease, known as biomarkers, that have been excreted from individuals in a community into the sewer system.

Biomarkers are broadly defined as a characteristic that can be objectively measured and quantified as an indicator of biological response (World Health Organisation, 2001). These can be: (i) exogenous biomarkers (also known as external agents, stressors) such as pharmaceuticals consumed to treat diseases, air contaminants, food toxicants, or genetic material (e.g. DNA or RNA) from bacteria or viruses causing an infection and (ii) endogenous biomarkers (formed in humans) such as markers of inflammation or stress. They can be found in elevated or reduced levels in the body, for example in blood, tissues, faeces or urine.

2.2 The concept of wastewater-based epidemiology

WBE is conceptionally very simple. Influent wastewater (untreated, raw sewage) can be considered a pooled urine and faeces sample of the community that contributes (Figure 1). The total amounts of analysed biomarkers in wastewater can be linked back to the community via back-calculations to calculate the daily amounts or daily doses per 1000 people. Pharmaceuticals are popular biomarkers in WBE, as many pass through the body unchanged or excreted as metabolites. It is for this reason that the inclusion of metabolites of drugs in WBE can add a further dimension. The ratios between parent drugs and their corresponding metabolites in wastewater can be used to see if drugs have been consumed rather than directly disposed of (Petrie et al., 2016). This is particularly the case when the metabolism of a drug is well-understood.

There are several requirements for the quantification of biomarkers in WBE to be achieved. Firstly, that samples collected are 24-hour composite samples (Ort et al., 2010). This is where individual samples are taken at hourly

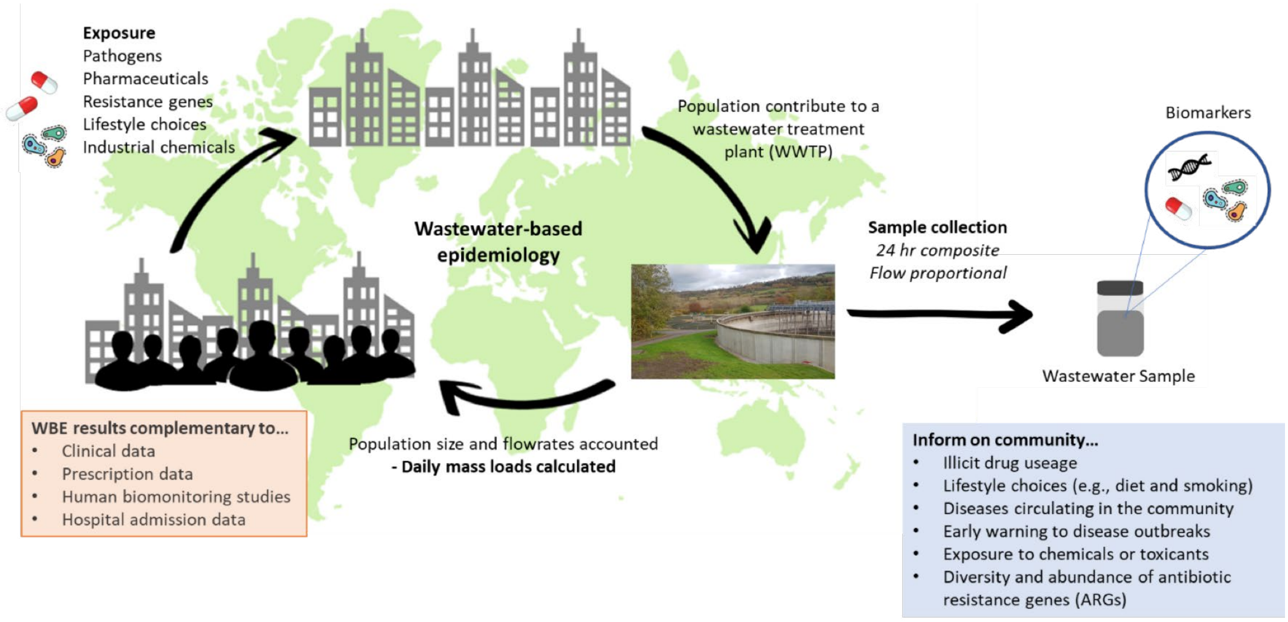

Figure 1. Graphical representation of the wastewater-based epidemiology (WBE) concept.

time intervals over a 24-hour period using autosamplers. These hourly samples are combined to represent community's wastewater over a calendar day. In contrast, grab samples are the process of taking a single sample from a time point and this can give valuable information about a specific snapshot in a moment of time. In the case of viruses, grab samples can be a cost-effective route of estimating disease prevalence in a community at a particular moment, potentially acting as an early warning system.

Secondly, is an understanding of the population size of the community. Population estimates are considered one of the largest uncertainties in WBE (Castiglioni et al., 2013). Wastewater treatment plants (WWTPs) treat a well-defined catchment area and have an understanding of general population size. However, fluctuations in catchment area including commuting and travel, result in challenges identifying number of individuals contributing to a WWTP. Accurate population estimates are vital for back calculations in WBE, for example intake of particular pharmaceuticals or exposure to certain toxins per 1000 people. Population sizes are also essential for normalising biomarker loads in wastewater to allow comparisons between different-sized communities. The uncertainties surrounding population estimates have led to an active and developing field of WBE (Been et al., 2014; Pandopulos et al., 2021; Thai et al., 2019; van Nuijs et al., 2011).

Many biomarkers have been proposed as potentials to estimate population size. Hydrochemical parameters, including biological and chemical oxygen demand and ammonia have been traditionally used (Been et al., 2014; van Nuijs et al., 2011). Potential candidates have been expanded to include certain pharmaceuticals (O'Brien et al., 2014; Rico et al., 2017), artificial sweeteners (O'Brien et al., 2014; Rico et al., 2017), creatinine (Brewer et al., 2012) and even DNA (Yang et al., 2015). However, limitations still exist for many of the proposed population biomarkers. These have included stability issues, plus amounts in wastewater can be influenced by industrial discharge and cultural behaviours in communities (Lin et al., 2019). This can lead to potentially misrepresentative estimates on population size.

Finally the flow rates of influent wastewater are essential, as concentrations of a specific biomarker in wastewater can be instead calculated as normalised daily mass loads. Concentrations of biomarkers could appear more dilute due to higher volumes of water in the sewage systems (e.g. increased rainfall or increased community water usage). Higher flow rates could therefore skew biomarkers concentrations to read lower than they are. Accounting for both population size and flowrates allows the comparison of different sized communities to be achieved.

The ability to analyse diverse and numerous biomarkers from a single influent sample allows for many different aspects of public health to be studied. Furthermore, sampling wastewater periodically can allow long-term trends to be established for a community. The analysis of which could therefore reveal critical information for public health that is complimentary to current routes, for example assessing the effectiveness of public health interventions.

Part of WBEs growing popularity is due to its ability to overcome challenges that conventional routes to assessing public health have experienced. Examples of conventional routes include existing sources such as mortality and morbidity rates, prescription and hospital and admission data. Another is human biomonitoring studies (HBMs), where small representative samples from a population give samples (e.g., blood or urine) (Barr, 2008). Whilst all are valuable sources of public health information, there are several limitations. They can be biased, resource intensive and may involve lengthy ethical procedures (Bauer, 2008). Furthermore, these existing strategies are fragmented with different health issues considered distinct areas. There is often no easy mechanism for sharing of data between or being able to respond rapidly to upcoming health threats. WBE on the other hand can allow for real-time monitoring, with the ability to address the changing landscape of public health. Plus, as wastewater is from all the sewered community an overall reflection of health can be achieved.

2.3 Methodology for wastewater-based epidemiology

In WBE, biomarkers need to be extracted from wastewater before analysis. This poses several extraction and analytical challenges. Biomarkers are often in low concentration in wastewater plus the complex composition of wastewater, containing a diverse source of chemical and biological biomarkers, can pose problems for extraction and analysis (Chen et al., 2014; Daughton, 2012). Sample preparation usually includes a filtering and preconcentration step to ensure biomarker concentrations are in high enough levels to be quantified. This is usually achieved for chemical target biomarkers via methods including solid phase extraction and immunoassay approaches. The analytical technique of choice for WBE has been liquid chromatography-tandem mass spectrometry (Hernández et al., 2018). This technique has demonstrated the ability to create diverse multi-compound methods for analysis in water environments (Petrie et al., 2015; Proctor et al., 2019). For the extraction of biological based biomarkers, such as DNA and RNA, numerous commercial kits exist on the market allowing for the extraction of genetic material from samples. Analysis for these has been achieved through next generation DNA sequencing and quantitative PCR (q-PCR). These have allowed for non-targeted and targeted screening of a wide range of genetic targets, including viruses, bacteria and resistance genes (Diemert and Yan, 2019; Hellmér et al., 2014; Huijbers et al., 2020; Newton et al., 2015).

2.4 Biomarker selection

For biomarkers to be used in WBE there are several key criteria that need to be met (Chen et al., 2014; Daughton, 2012) 1) biomarker levels need to be high enough to quantify in wastewater; 2) biomarkers need to be characteristic to the exposure or disease/health status in question, for example they are released via human excretion and not formed in the sewer system; 3) Excretion from humans is well understood, this is essential for back calculations; 4) Stable in wastewater and in transport and storage.

2.5 Background of wastewater-based epidemiology

WBE has become a well-established field over the past two decades. The concept that the analysis of drug residues in wastewater could be linked back to a community was first theorised by Daughton (2001). This was achieved by Zuccato et al. (2005), who focused on cocaine in both wastewater and linked it back to the community. The first international network, SCORE (https://score-cost.eu/) was established in 2010. The approach was adopted by EMCDDA (https://www.emcdda.europa.eu/topics/pods/waste-water-analysis_en) to enable measurement of illicit drugs in Europe. This has led to a global standardised system with regular sampling campaigns taking place on annual basis (https://score-cost.eu/monitoring/interlab/) (https://score-cost.eu/monitoring/). Since then, many global networks of long-term wastewater monitoring have been established. These include: Australia Network, Underworld, The Spanish Network of Wastewater-Based Epidemiology.

Recently, WBE has seen a surge of attention for its ability to monitor genetic material from SARS-CoVID-2 as a means for tracking infections in a community (Daughton, 2020; Foladori et al., 2020; Kitajima et al., 2020; Polo et al., 2020). Popularity has grown largely due to the ability to give a whole community perspective from capturing input from asymptomatic carriers, and the potential to predict outbreaks. Several national and international collaborations have been established to further knowledge in using coronavirus in wastewater to monitor community spread.

Whilst popularity to WBE has increased, other benefits for widespread monitoring for wastewater have not always received as much attention as they could outside the academic community. Whilst the potential uses and benefits of WBE for public health have been widely acknowledged in the scientific literature (Choi et al., 2018b; Daughton, 2018; Kasprzyk-Hordern et al., 2014; Thomas and Reid, 2011; Vitale et al., 2021), there has sometimes been a gap between translating this research to implementing programmes nationally. The wide-spread implementation of the infrastructure to monitor SARS-CoVID-2 provides an opportunity to expand out on the analysis on wastewater samples collected to other recognised biomarkers. Not only could this provide key public health information by complementing current surveillance techniques, but also provide novel routes to assess public health interventions.

3 Current Research

The review presents the broad and diverse field of WBE and what has been achieved to date, Table 1 presents a small selection of biomarkers examples that have been used in WBE in each area of use. This is by no means an extensive list and only includes a very small example of biomarkers for each section.

Table 1. Biomarker examples that have been used in WBE

Biomarkers of…	Potential Biomarkers	Biomarker Examples	Treatment/indicator of	Reference of wastewater study
Infectious Disease	Antimicrobials and metabolites	Clarithromycin	Pneumonia, skin infections treatment	(Escolà Casas et al., 2021; Proctor et al., 2019; Senta et al., 2019)
		n-Desmethyl clarithromycin	Metabolite of clarithromycin	(Senta et al., 2019)
		Sulfamethoxole	Urinary tract infections, bronchitis	(Escolà Casas et al., 2021; Guerra et al., 2014; Kasprzyk-Hordern et al., 2009; Proctor et al., 2019)
		n-Acetyl sulfamethoxazole	Metabolite of sulfamethoxazole	(Escolà Casas et al., 2021)
		Oseltamivir phosphate	Influenza treatment	(Leknes et al., 2012; Takanami et al., 2012)
		Oseltamivir carboxylate	Metabolite of oseltamivir phosphate	(Leknes et al., 2012; Takanami et al., 2012)
		Acyclovir	Herpes simplex virus infections and shingles	(Funke et al., 2016; Prasse et al., 2010)
		Carboxy-acyclovi	Metabolite of acyclovir	(Funke et al., 2016)
		Ketoconazole	Skin infection fungal treatment	(Huang et al., 2010; Proctor et al., 2019)
		Miconazole	Skin infection fungal treatment	(Guerra et al., 2014; Kasprzyk-Hordern et al., 2009)
	Pathogenic DNA/RNA	Poliomyelitis (polio)	Infection that can affect the central nervous system (viral)	(Ndiaye et al., 2014)
		Severe acute respiratory syndrome (SARS-CoVID-2)	Respiratory infection (viral)	(W. Ahmed et al., 2020; Medema et al., 2020)
		Norovirus (GI/GII)	Gastroenteritis (viral)	(Hellmér et al., 2014)
		Influenza A	Respiratory infection (viral)	(Heijnen and Medema, 2011)
		Klebsiella pneumoniae	Pneumonia, UTI, bacteraemia and endophthalmitis (bacteria)	(Shannon et al., 2007)
		Enterococcus faecalis	UTIs, bacteraemia, septicaemia (bacteria)	(Shannon et al., 2007)
		Salmonella enterica	Fever, vomiting and abdominal pain (bacteria)	(Diemert and Yan, 2019; Yan et al., 2018)
		Candida spp.	Candidiasis (fungal)	(Assress et al., 2019)
		Cryptosporidium	Gastrointestinal illness (parasite)	(Wallis et al., 1996)
		Giardia lambli	Small intestine infections (parasite)	(Guy et al., 2003)
Antimicrobial resistance (AMR)	Antibiotic resistant genes	ermB	Erythromycin resistance	(Wang et al., 2015)
		sul1	Sulphonamide resistance	(Wang et al., 2015)
		mcr-1	Colistin resistance	(Hembach et al., 2017)
		qnr	Quinolone resistance	(Castrignanò et al., 2020)

Biomarkers of…	Potential Biomarkers	Biomarker Examples	Treatment/indicator of	Reference of wastewater study
Mental Health and well-being	Drugs and metabolites	Fluoxetine	SSRI antidepressant	(Boogaerts et al., 2019; Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021; Petrie et al., 2015; van Nuijs et al., 2015)
		Norfluoxetine	Metabolite of fluoxetine	(Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021; Petrie et al., 2016)
		Venlafaxine	SSRI antidepressant	(Boogaerts et al., 2019; Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021; Lai et al., 2011; Rice et al., 2020; van Nuijs et al., 2015)
		Desmethylvenlafaxine	Metabolite of venlafaxine	(Boogaerts et al., 2019; Kasprzyk-Hordern et al., 2021)
		Citalopram	SSRI antidepressant	(Boogaerts et al., 2019; Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021; Riva et al., 2020; van Nuijs et al., 2015)
		Norcitalopram	Metabolite of citalopram	(Boogaerts et al., 2019)
		n-Desmethylcitalopram	Metabolite of citalopram	(Kasprzyk-Hordern et al., 2021; Riva et al., 2020)
		Mirtazapine	Antidepressant	(Boogaerts et al., 2019)
Obesity and Cardiovascular disease	Drugs and metabolites	Atenolol	High blood pressure	(Escolà Casas et al., 2021; Lai et al., 2011; Petrie et al., 2015; Proctor et al., 2019; van Nuijs et al., 2015)
		Metformin	Diabetes drug	(Kasprzyk-Hordern et al., 2021; Proctor et al., 2019; van Nuijs et al., 2015; Xiao et al., 2019)
		Oxypurinol	Metabolite of allopurinol (gout treatment)	(F. Ahmed et al., 2020)
	DNA	Bacteroides spp. *Faecalibacterium* spp.	Faecal bacteria	(Newton et al., 2015)
Asthma/allergies	Drugs and metabolites	Salbutamol	Preventative inhalers for asthma	(Fattore et al., 2016)
		Cetirizine	Antihistamine, used to relieve mild allergy symptoms	(Harman et al., 2011; Proctor et al., 2019)
		Fexofenadine	Antihistamine, used to relieve mild allergy symptoms	(Choi et al., 2018a; Proctor et al., 2019)
	Endogenous biomarker	1,4-methylimidazole acetic acid	Indicator of histamine turnover	(Choi et al., 2018a)

Biomarkers of…	Potential Biomarkers	Biomarker Examples	Treatment/indicator of	Reference of wastewater study
Lifestyle Factors	Illicit drugs	Cocaine	Stimulant	(González-Mariño et al., 2020; Kasprzyk-Hordern et al., 2021; Rice et al., 2020; van Nuijs et al., 2011; Zuccato et al., 2008, 2005)
		Benzoylecgonine	Metabolite of cocaine	(González-Mariño et al., 2020; Kasprzyk-Hordern et al., 2021; Rice et al., 2020; van Nuijs et al., 2011; Zuccato et al., 2008)
		Cocaethylene	Metabolite formed when cocaine and ethanol are consumed together	(Mastroianni et al., 2014)
		Amphetamine	Stimulant	(González-Mariño et al., 2020; Kasprzyk-Hordern et al., 2021; Rice et al., 2020; Zuccato et al., 2008)
	New Psychoactive substances (NPS)	Methcathinone Mephedrone	Stimulant, similar activity to amphetamine (synthetic cathinones)	(Castiglioni et al., 2021; González-Mariño et al., 2016) (Rice et al., 2020)
		Methoxetamine	Stimulant, similar activity to ketamine	(Rice et al., 2020)
		Para-methoxyamphetamine (PMA)	Psychoactive drug with similar effects to MDMA (phenethylamine)	(Castiglioni et al., 2021)
	Smoking	Nicotine	Predominantly found in tobacco	(Proctor et al., 2019; Rice et al., 2020)
		Cotinine	Metabolite of nicotine	(Castiglioni et al., 2015; Kasprzyk-Hordern et al., 2021; Proctor et al., 2019; Rice et al., 2020; Rodríguez-Álvarez et al., 2014)
		Hydroxy-cotinine	Metabolite of nicotine	(Castiglioni et al., 2015; Kasprzyk-Hordern et al., 2021; Rodríguez-Álvarez et al., 2014)
		Anatabine (ANATA)	Tobacco related toxicant/ carcinogens	(Tscharke et al., 2016)
		Anabasine (ANABA)	Tobacco related toxicant/ carcinogens	(Tscharke et al., 2016)
	Alcohol	Ethyl sulphate	Metabolite of alcohol consumption	(Baz-Lomba et al., 2016; Boogaerts et al., 2016; Mastroianni et al., 2014)
	Diet	Caffeine	Stimulant, found in coffee	(Kasprzyk-Hordern et al., 2021; Proctor et al., 2019; Rice et al., 2020)
		1,7-dimethylxanthine	Metabolite of caffeine	(Kasprzyk-Hordern et al., 2021; Proctor et al., 2019; Rice et al., 2020)
		Enterodiol and enterolactones	Fibre indicator	(Choi et al., 2020, 2019)
		Proline betaine	Citrus consumption indicator	(Choi et al., 2020, 2019)
		N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone3-carboxamide (4PY)	Vitamin B metabolite, formed via consumption of nicotinamide (a major B3 vitamer)	(Choi et al., 2020, 2019)
		4-pyridoxic acid	Dietary vitamin B6 intake biomarker	(Choi et al., 2020, 2019)
		Acesulfame, saccharin, and sucralose	Artificial sweeteners	(Choi et al., 2019)

Biomarkers of…	Potential Biomarkers	Biomarker Examples	Treatment/indicator of	Reference of wastewater study
Exposure	Plasticizers/ phthalates	Bisphenol A (BPA)	Plasticizer	(Lopardo et al., 2019, 2018; Wang et al., 2020)
		BPA sulphate	Metabolite of BPA	(Kasprzyk-Hordern et al., 2021; Lopardo et al., 2019; Wang et al., 2020)
		Monoethyl phthalate (MEP)	Metabolite of diethyl phthalate (DEP) exposure	(Du et al., 2018; González-Mariño et al., 2021, 2017; Tang et al., 2020)
		Monomethyl phthalate (MMP)	Metabolite of dimethyl phthalate (DMP) exposure	(Du et al., 2018; González-Mariño et al., 2021, 2017; Tang et al., 2020)
		Mono-i-butyl phthalate (MiBP)	Metabolite of di-iso-butyl phthalate (DiBP) exposure	(Du et al., 2018; González-Mariño et al., 2021, 2017; Tang et al., 2020)
	Pesticides	Atrazine desisopropyl (DIA)	Metabolite of triazine pesticide exposure	(Rousis et al., 2017b, 2016)
		Dimethyl thiophosphate (DMTP)	Metabolite of organophosphate pesticide exposure	(Rousis et al., 2017b, 2016)
		3-phenoxybenzoic acid (3-PBA)	Metabolite of pyrethroid pesticide exposure	(Kasprzyk-Hordern et al., 2021; Rousis et al., 2017b, 2017a, 2016)
	Flame retardants	Tris (2-butoxyethyl) phosphate (TBOEP)	Parent flame retardant	(O'Brien et al., 2015)
		Bis(2-butoxyethyl) phosphate (BBOEP)	Metabolite of TBOEP exposure	(Been et al., 2017)
		Bis(2-butoxyetyl) 3'-hydroxy-2-butoxyethyl phosphate (HO-TBOEP)	Metabolite of TBOEP exposure	(Been et al., 2017)
	Mycotoxins	Deoxynivalenol (DON) Fumonisins B1, B2 and B3	Toxicants commonly in grains (e.g., corn, wheat, oats)	(Gracia-Lor et al., 2020)
Endogenous Biomarkers	Oxidative stress	8-iso-PGF2α	Indicator of oxidative stress	(Bowers and Subedi, 2021; Ryu et al., 2016, 2015)
Population size	Hydrochemical markers	Chemical oxygen demand (COD) and Biological oxygen demand (BOD)	Population equivalent	(van Nuijs et al., 2011)
		Ammonia (NH_4^+)	Population equivalent	(Been et al., 2014)
	Endogenous biomarkers	Homovanillic acid (HVA) and vanillylmandelic acid (VMA)	Metabolites of dopamine, adrenaline and noradrenaline	(Pandopulos et al., 2021)

Abbreviations: UTI: urinary tract infection. SSRI: Selective serotonin reuptake inhibitor. spp.: species

3.1 Lifestyle choices

3.1.1 Illicit drugs

Scotland's rising illicit drug usage has been highlighted as a public health crisis. There was an estimated 55,800-58,900 people in Scotland with a drug usage problem in 2018 (NHS Scotland Information Services Division, 2019). Furthermore, an estimated 1,264 people died from drug related causes in 2019, a rise from 1,187 in 2018 (National Records of Scotland, 2020). This value was highlighted as higher than any other European country and over three times that of the UK as a whole. Estimating illicit drug prevalence in a community is widely acknowledged as being challenging, particularly as drug usage is associated with hidden and stigmatised behaviours. Traditional assessment of illicit drug usage in a community includes surveys, police seizures and hospital admissions (Kraus et al., 2003). Whilst these methods provide key public health information, they have several limitations. They can be time consuming and struggle to deliver up-to-date information in the changeable nature of illicit drug usage. Relying on these methods alone may result in the full picture of a community's drug usage problem being missed. These concerns have been highlighted by the UK Drug Policy Commission (UKDPC), it is recognised that drug usage is likely underreported and the full scope of a community's drug usage problem is underestimated (Reuter and Stevens, 2007).

The analysis of illicit drug residues in wastewater has demonstrated to be a dynamic and robust drug monitoring tool, with the ability to provide timely information on drug use patterns. The successes of WBE in this field have resulted in the EMCDDA establishing this technique as a novel and established drug use indicator (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2016). A broad number of illicit drugs and metabolites have been investigated in wastewater, including cocaine, heroin, methamphetamines and the respective metabolites across the world (Boleda et al., 2007; Castiglioni et al., 2006; Kasprzyk-Hordern et al., 2008; Zuccato et al., 2008). Studies have not only demonstrated drug use trends that have been consistent with other drug monitoring approaches but the ability to coordinate international studies through standardised approaches.

3.1.2 New psychoactive substances

WBE has continued to grow in this field, informing on the rising trend in usage of novel psychoactive substances (NPS). NPS, previously named 'legal highs' are drugs designed to mimic the effects of illegal substances such as cocaine or ecstasy (Stephenson and Richardson, 2014). It is estimated that NPS first appeared in the UK drug market in 2008/2009. The challenges associated with NPS, compared to more "traditional" illicit drugs, are the large number of new compounds and the rapidness that these can enter and leave the market (Peacock et al., 2019).

Several studies have analysed NPS in wastewater to link back with community (Bade et al., 2021, 2020; González-Mariño et al., 2016). One of the most extensive studies to date, published in 2021, reported wastewater results from 22 cities across 14 European countries over two years (Castiglioni et al., 2021). This study investigated 30 NPS, including synthetic cathinones and phenethylamines alongside the more "traditional" illicit drugs (e.g. cocaine, MDMA and methamphetamine). Results demonstrated that spatial and temporal trends of different NPS could be established and that WBE could inform on the rapid changes in drug usage in the community. It has been highlighted there are challenges to back-calculating NPS consumption in a community due to the limited information on human metabolism for NPS (Castiglioni et al., 2021). This is in contrast to many illicit drugs where metabolism is well known and reported. Further studies are therefore needed to identify the most suitable biomarkers for NPS consumption. However, initial work has clearly demonstrated WBE's ability to reflect trends of NPS usage over time and in different catchment areas. Thereby overcoming some of the challenges that traditional techniques experience in monitoring the dynamic and complex behaviours of drug usage.

3.1.3 Monitoring illicit drug and new psychoactive trends

The ability to monitor long-term trends in WBE for lifestyle factors can allow the effectiveness of policy interventions to be assessed. One UK-based study investigated in wastewater the trends of illicit and licit drug consumption between 2014-2018 in one city (Rice et al., 2020). Mephedrone was classified as a class B drug in 2010. Whilst mephedrone was quantified in wastewater the first two years of this study, after 2015 it was no longer detected. The lack of mephedrone detected could demonstrate a delayed shift upon illicit drug choice after implementing the new drug classification. Another policy intervention was the regulation of NPS in 2016. Results in wastewater here observed an increased amount of more "traditional" drugs of abuse including cocaine and ketamine. WBE can reflect the complexities of regulation with regards to illicit drugs, as restrictions of one class can lead to increased use of another, as potentially observed in this study. WBE provides valuable near-real time monitoring for illicit drug consumption that can aid in complementing and filling gaps for current routes of assessing usage. This can provide evidence to allow policy makers to make informed decisions.

It should be noted that WBE can aid in identifying correlations in both licit and illicit drugs, indicating polydrug usage. One recent study in China identified strong correlations indicting polydrug usage patterns between several pairs of illicit drugs, including heroin and cocaine, methcathione and ketamine (Liu et al., 2021). Another study observed correlations between antidepressants and opioids (methadone, codeine and tramadol), potentially reflecting polydrug use of patients prescribed opioids also prescribed antidepressants (Choi et al., 2019). Certain metabolites could also indicate co-consumption. Benzoylecgonine is the main metabolite for cocaine, but cocaethylene can be formed too when cocaine and ethanol (alcohol) are consumed together. Wastewater loads of cocaethylene has shown strong positive correlations to other metabolites of alcohol and cocaine in wastewater (Mastroianni et al., 2014). This relevance is highlighted as one of the causes of increased drug deaths in Scotland is attributed to the consumption of two or more drugs at the same time. The Scottish Government has reported that of the 1,264 deaths linked to illicit drugs in 2019, 94 % of these deaths were of people who took more than one substance (National Records of Scotland, 2020).

3.1.4 Alcohol consumption and smoking

WBE has been used to investigate other lifestyle choices, including for alcohol consumption and prevalence of smoking. It is recognised that smoking and alcohol consumption are amongst the most significant risk factors for disease burden in the UK (UK Government, 2019a). Increased disease risk includes cancers, heart and liver diseases. Both alcohol consumption and smoking rates are typically assessed by general population surveys and sale statistics. In the case of alcohol, stockpiling, international buying and consumption of illegal alcohol cannot be assessed by these routes.

WBE analysis for these two areas relies on the analysis of metabolites in wastewater. For alcohol consumption, the metabolite of ethanol, ethyl sulphate, has mostly been applied in WBE (Baz-Lomba et al., 2016; Boogaerts et al., 2016; Mastroianni et al., 2014). Back calculations of ethyl sulphate in wastewater can give values of L per 1000 people per day. Monitoring these levels over longer periods of time can demonstrate strong weekly trends, with clear differences between weekdays and weekends and variations in alcohol consumption can be observed in different cities.

Smoking on the other hand uses nicotine and its metabolites, cotinine and hydroxycotinine in WBE (Castiglioni et al., 2015; Rodríguez-Álvarez et al., 2014). Back-calculations here can calculate number of cigarettes per 1000 people per day. Recent research has also identified two further biomarkers linked to tobacco, anatabine and anabasine (Tscharke et al., 2016). These are urinary biomarkers that are excreted as a by-product of smoking and are specific to tobacco (unlike nicotine which can be found in nicotine patches and gum). WBE monitoring for both tobacco and alcohol consumption has successfully demonstrated its applicability in monitoring spatio-temporal trends in both local, national and international scales. The accurate monitoring of alcohol consumption and smoking in a community is essential if related health policies are to be evaluated.

3.1.5 Diet

Diet is another area of WBE that has been proposed in the last decade (Choi et al., 2018b; Daughton, 2018, 2012; Thomas and Reid, 2011). Diet is key for maintaining good health and well-being, a poor diet been associated with many health conditions and diseases. It is also linked to with sociodemographic patterns, with lower socioeconomic groups having poorer diets, for example lower fruit and vegetable intake (Maguire and Monsivais, 2015). Several biomarkers associated with diet in wastewater, including metabolites of fibre and fruits consumption and vitamins has been investigated in Australia (Choi et al., 2019). However a follow up study highlighted that whilst many urinary biomarkers associated with diet have been identified, many have been found to not be stable enough to be used in WBE and many experience significant degradation in the sewer system (Choi et al., 2020). Instead, several biomarkers were identified to be useful for qualitative/semi-quantitative work and back-calculations were in good agreement with literature values. These included enterodiol and enterolactone (indicators of fibre intake) and proline beta (indicator of citrus consumption) which could be used as a proxy for a healthy diet.

3.1.6 Monitoring behavioural changes and external stresses

WBE reveals unique insight and perspective of a community's lifestyle choices. Recent studies of WBE have been utilised to monitor how communities cope with certain environmental and social stresses. With one study investigating trends and correlations of both licit and illicit drugs in a defined period of economic stress and social strain (Thomaidis et al., 2016). Another study identified correlations between increased environmental temperature with increased usage of artificial sweeteners (e.g. acesulfame) in wastewater (Phung et al., 2017).

Furthermore, WBE not only gives insight upon behavioural patterns associated with drug consumption, but also with attitudes surrounding disposal of medications. Unused medications should be returned to pharmacies to be incinerated and disposed of. It is known however that people can incorrectly dispose of unused medications, ending up in landfill or put down sink or toilet to end up in wastewater treatment system (Tong et al., 2011). The ability to distinguish between consumption and direct disposal of the commonly prescribed antidepressant, fluoxetine has been investigated in wastewater (Petrie et al., 2016). This is done by understanding the chemical structures in the prescribed formulation of the parent drug and the ratios between parent and metabolite (norfluoxetine) excreted by an individual. It is expected the ratios between fluoxetine and norfluoxetine in wastewater will be at a constant level when the parent drug has been consumed. An irregularly high level of fluoxetine in wastewater one day where the norfluoxetine levels remains low, indicates a significant amount of the parent drug has been dumped rather than consumed. Back-calculation done in this study estimated the equivalent fluoxetine loads for around 900 tablets directly dumped into sewage system.

3.2 Communicable Diseases

Whilst monitoring for SARS-CoVID-2 in wastewater has attracted increasing attention during the past year. Using wastewater for disease surveillance is not a new concept and has been well discussed in the literature (Barras, 2018; O'Brien and Xagoraraki, 2019; Wigginton et al., 2015). Environmental surveillance of polio in wastewater for example has been established (Hovi et al., 2012; Roberts, 2013; World Health Organisation, 2003a). Others have retrospectively predicted outbreaks of hepatitis A and norovirus in wastewater (Hellmér et al., 2014) and influenza has also been detected in wastewater (Heijnen and Medema, 2011). Though notably less common, WBE has also been applied to monitor bacterial infections (Yan et al., 2018). For example, prevalence of enteric *Salmonella* in a population, causing sickness and diarrhoea, was monitored in Hawaii (Diemert and Yan, 2019). Researchers could observe elevated levels of a particular *Salmonella* strain in wastewater simultaneously with a clinically reported outbreak. Results also showed same strain re-emerged as a dominant species in wastewater a year later, potentially indicating a new outbreak of *Salmonella* in the community that was not detected by clinics.

Many of these mentioned studies have used genetic material from pathogens, e.g. DNA or RNA, to monitor spread in a community. However the benefit of including the analysis of other relevant biomarkers with genetic material of pathogen in question has been highlighted as more effective route to assessing disease spread at the community level (Daughton, 2020). Whilst the genetic material of a pathogen can be a very specific biomarker and have the potential to act as an early warning system, there are limitations as recognised by the literature (Daughton, 2020; Foladori et al., 2020; Kitajima et al., 2020; Polo et al., 2020). For example, with regards to coronavirus RNA, the amounts individuals excrete can be variable (Joynt and Wu, 2020). This can cause challenges with back-calculating RNA levels quantified in wastewater to the number of individuals potentially infected at the community level (Kitajima et al., 2020). This can be further complicated with the questionability on whether the genetic material present in wastewater has come from an active virus or from someone who has recently recovered from the virus (Daughton, 2020). This could result in overestimation of prevalence of the disease at the community level. Whilst these discussions have focused on coronavirus, they are applicable for other diseases monitored via WBE too. Other potential limitations that have been previously discussed prior to coronavirus are stability of the genetic material in wastewater, variability in sampling approaches and the low efficiency for virus concentration methods (Girones et al., 2010).

It is considered that analysing other biomarkers associated with diseases, including pharmaceuticals and endogenous biomarkers (e.g. inflammation) could help overcome some of these discussed limitations (Daughton, 2020). For example, pharmaceuticals used to treat specific diseases and corresponding metabolites can be a good reflection for disease presence in a community. Prevalence of hepatitis B has been done using the antiviral drug lamivudine (Hou et al., 2020). The limitations are recognised that prescribed drugs may not always be disease specific, in the case of lamivudine it is also prescribed for human immunodeficiency viruses (HIV) treatment, and it is impossible to distinguish whether treatment is from hepatitis B or HIV. This study also did not look at metabolites of lamivudine. Therefore, some of the levels of lamivudine observed could have resulted from direct disposal of lamivudine into the sewage system via toilet or sink rather than consumption. Endogenous biomarkers of disease and health are discussed later in this review.

3.3 Antimicrobial Resistance

Antimicrobial resistance (AMR) has been hailed as one of the greatest threats to public health risks threatening medicine in the 21st century (O'Neill, 2014). Antimicrobial resistance is defined by WHO as "microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective"(World Health Organisation, 2017). This process occurs naturally but is further accelerated by inappropriate use of medicines. The consequences of AMR are significant, and could result in easily treated infections being fatal (Bush et al., 2011). It has been estimated by 2050 there could be as many as 10 million deaths per year attributed to AMR (O'Neill, 2014). Poor surveillance has been highlighted as one of the critical problems regarding AMR. The Global Antimicrobial Resistance Surveillance

System (GLASS) in 2015 by WHO was established with the aims of sharing information on the global scale to strengthen data and aid decision making on national and international actions (World Health Organisation, 2015). Several limitations of current AMR surveillance were highlighted, including selection bias in samples and inconsistent global coverage. The result was a call to include AMR data from whole populations and not just from clinical studies alone.

Scotland's Antimicrobial Prescription Group (SAPG) (https://www.sapg.scot/) was established in 2008 with a primary aim to coordinate a national framework for antimicrobial stewardship. SAPG have developed surveillance systems and ensured standardised information on antimicrobial use and resistance that is accessible to NHS boards. In 2019, the Scottish One Health Antimicrobial Use and Antimicrobial Resistance report was published by Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) Scotland (Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), 2020). This report provides information on antibiotic use and resistance to antibiotics in Scotland during 2019. It supports the five-year United Kingdom National Action Plan and a 20-year vision for containing and controlling AMR (UK Government, 2019b). Currently, much surveillance is based on clinical data and prescription data. WBE provides an opportunity as a complimentary technique to achieve a whole population approach to tackling AMR.

3.3.1 Patient compliance to pharmaceuticals

Prescription data in the UK is easily accessible, however just because a medication has been prescribed does not necessarily mean it was consumed. Patient compliance to medical treatments is known to vary. In the case of antibiotics, individuals often feel recovered before the end of a prescribed dose. The result this can be individuals do not complete the course of antibiotics, potentially leading to both stockpiling of leftover doses and self-prescribing at a later date. It has been previously highlighted that up to a third of patients do not comply to antibiotic treatment instructions and a quarter use doses leftover from previous treatment (Kardas et al., 2005). Leftover antibiotics are a key driver for AMR and non-compliance not only promotes resistance but has serious implications of costs of healthcare (Hughes et al., 2001). Estimating patient compliance is challenging, as it relies on self-reported questionnaires and counting leftover doses in clinics but results from these can be biased.

Whist numerous WBE studies exist for investigating licit and illicit drug consumption, only a handful of studies to date have compared spatial and temporal trends of pharmaceuticals and matched these to predicted concentrations (Baz-Lomba et al., 2016; Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021; Lai et al., 2011; Rice et al., 2020; Riva et al., 2020). This requires a knowledge of prescription data, formulations, excretion rates and can be utilised to investigate overall adherence of medications in a population. Whilst these studies have looked at a broad range of pharmaceuticals, a couple of these studies have included antibiotics (Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021). It is key that both parent compounds and metabolites are considered in wastewater analysis for two reasons 1) in the case for antimicrobials specifically both have implications for promoting resistance in bacteria in WWTPs; 2) in the case of pharmaceuticals more generally, the ratio between parent and metabolite is key for assessing if a pharmaceutical has been consumed (e.g. compliance can be investigated) or if it has directly been disposed of. An understanding of antibiotics in wastewater is important, as unlike other contaminants where cut off points can be identified, sub-lethal concentrations of antibiotics in wastewater can promote resistance (Jury et al., 2011).

3.3.2 Antimicrobial resistance surveillance

It has been proposed that the combined wastewater surveillance of antibiotics and metabolites with pathogens and antibiotic resistance genes (ARGs) could be a proxy for regional AMR and how changes can occur overtime (Kwak et al., 2015; Larsson et al., 2018). The presence of ARGs in wastewater will be complex, some genes may be excreted from the human community contributing and others will be from the diverse microbial communities found in wastewater. These microbial communities will be influenced from years of exposure to sub-lethal concentrations of multiple antibiotics and metabolites in wastewater. Furthermore, the varying consumption patterns in human populations will result in unique microbial communities in wastewater between different geographic locations. WBE also allows analysis of cofactors in wastewater. These include other micro-contaminants such as heavy metals and biocides (e.g., disinfectants), that can have a role in promoting or facilitating antimicrobial resistance in microorganisms (Baker-Austin et al., 2006; Tello et al., 2012).

There are numerous studies in the literature investigating AMR surveillance in wastewater (Castrignanò et al., 2020; Gao et al., 2012; Novo et al., 2013; Raven et al., 2019; Rodriguez-Mozaz et al., 2015). Recent studies have also demonstrated strong relationships existing between wastewater and clinical resistance prevalence, indicating wastewaters ability to potentially predict resistance in clinics (Huijbers et al., 2020; Pärnänen et al., 2019).

Due to the complexities of antibiotic pollution and impacts on resistance, robust surveillance methods are needed to assess resistance on a clinical level. Overall whilst total antibiotic usage has decreased by 7.6% since 2015 in

Scotland (ARHAI Scotland, 2020), it is recognised that there is more to be done if the UK's overall goal to reduce antibiotic usage in humans by 15% by 2024 is to be achieved (UK Government, 2019b). The ability of WBE to monitor long term trends will be key for AMR surveillance, as observing population-wide trends over several years will be required. Whilst the direct impact of interventions may be observed via reduced antimicrobial and metabolite levels in wastewater, to see the impacts interventions have on resistance in microbial communities in wastewater and environment may occur over many years. Having effective WBE in place to monitor antimicrobials, genes and cofactors will not only allow effective population-wide surveillance to be achieved but also allow interventions on the community scale to be monitored. Such data would be complimentary to current surveillance in Scotland where a national surveillance programme for monitoring AMR in clinically important pathogens was established in 2009 (based on the European Antimicrobial Resistance Surveillance System) (Nathwani et al., 2011).

3.4 Non-communicable diseases and well-being

3.4.1 Mental health

Mental health has been identified as one of the main causes of disease burden worldwide. The COVID-19 pandemic has exacerbated mental health issues in the UK. Evidence has indicated a worsening of mental health in the first national lockdown on the 23rd March 2020, with UK government identifying psychological distress, anxiety and depressive symptoms peaking in April 2020 (Public Health England, 2021). Isolation was identified as a significant contributor to rising rates of mental health services and access to medications. Antidepressant usage in a population is typically based on prescription data and general population surveys (Cadarette and Wong, 2015; Thacker and Berkelman, 1988). Whilst UK is fortunate to have easily accessible prescription data, the limitations with current routes include reporting bias for population surveys and as previously touched upon with antibiotics, whilst a drug has been prescribed does not necessarily mean it has been consumed. These limitations can potentially be attributed to fears of stigmatism surrounding issues with mental health.

Many studies have included antidepressants in multi-compound analytical methods in wastewater (Boogaerts et al., 2019; Choi et al., 2019; Petrie et al., 2015; Proctor et al., 2019; Thomaidis et al., 2016). One recent study focused entirely on antidepressants for WBE, developing an analytical method for 27 commonly prescribed antidepressants with several metabolites (Boogaerts et al., 2019). Back calculations for popular antidepressants including citalopram, venlafaxine and mirtazapine from wastewater sampled from four WWTPs in Belgium demonstrated the mass loads agreed with prescription data. Two UK-based studies investigated a broad selection of pharmaceuticals including antidepressants in WBE and linked back to prescription data (Kasprzyk-Hordern et al., 2021; Rice et al., 2020).

One of these UK-based studies monitored wastewater trends of both licit and illicit drugs in one city in the South-West of England between 2014-2018 (Rice et al., 2020). The ability to monitor long-term consumption trends by WBE were demonstrated here. For example, significantly increased levels of the antidepressant venlafaxine in wastewater reflected increases in prescriptions at the catchment level. Interestingly, wastewater loads of venlafaxine were in higher amounts then the concentrations predicted from prescription data. Rates of antidepressant prescription were rising in the decades prior to the study period and were expected to continue increasing (Mars et al., 2017). The UK has been experiencing a period of political economic austerity since 2010 including across the period of 2014–2018, and under similar circumstances in other European countries this has led to an increase in prescriptions of antidepressants and other drugs to treat mental health (Thomaidis et al., 2016). In line with expectations, venlafaxine prescription rates did increase significantly each year, although prescription rates of other antidepressants (amitriptyline and fluoxetine) did not change significantly from 2014 to 2018. Increasing demand for antidepressants coupled with the online availability of venlafaxine and its relatively lower cost, compared to NHS prescriptions, could explain the mismatch between prescription and wastewater data. Ultimately, the reason behind the discrepancy in wastewater and prescription data is unclear, but what is important is that the trends in both of them are the same, which helps to provide important context to the results.

A significant advantage of WBE over conventional routes is the ability to gain health information from the whole population. A limitation of monitoring pharmaceuticals alone in wastewater for estimating disease prevalence is that a portion of the population could be missed. For example, those who are experiencing mental health problems but have not sought out medical help or have chosen non-pharmaceutical therapies. Residues of antidepressants and metabolites in wastewater would imply an origin of an individual who has sought out help from a medical health professional and had antidepressants prescribed. However due to the stigmatism that still surrounds mental health problems today, it is highly likely a portion of the population who experience mental health problems will be missed.

The analysis of endogenous biomarkers that are elevated or decreased in urine when an individual is experiencing mental stress would be valuable for WBE (Daughton, 2012). It should be noted there are no routine diagnostics on urine analysis for mental health disorders. At a clinical level, several studies have investigated urinary metabolites that could be linked to mental health (Shimanoe et al., 2021; Zheng et al., 2016, 2013). However there has currently been no studies of endogenous biomarkers of mental health in wastewater, further research is needed to identify urinary biomarkers indicative of mental health that are suitable for WBE.

3.4.2 Obesity and cardiovascular diseases

The UK is experiencing growing problems of obesity with an estimated 63% of adults over a healthy weight and a half of these living with obesity (Public Health England, 2019). Scotland has been identified as having some of the highest obesity levels among the Organisation of Economic Co-operation and Development (OECD) countries (ScotPHO Public Health Information for Scotland, 2020). Obesity increases risks of developing certain diseases, including type 2 diabetes, high blood pressure and certain cancers (GOV.UK, 2017). Higher levels of obesity have been correlated to lower socio-economic status and links between lower self-esteem and mental wellbeing have been identified. Failure to address growing rates of obesity results in greater pressure on the NHS. It was estimated that the NHS spent £6.1 billion on overweight and obesity-related health in 2014-2015, with these UK-wide NHS costs projected to reach £9.7 billion by 2050 (GOV.UK, 2017).

Wastewater monitoring provides a multifaceted approach to assessing population-wide cardiovascular diseases and associated conditions. For example, analysis of antidiabetic drugs in wastewater have been good indicators of disease prevalence in the community. Metformin is a first-line medication for type 2 diabetes and helps lower blood sugar levels. One study used metformin as a biomarker in wastewater to assess trends of type 2 diabetes over a period of four years, with results showing increasing trends that matched prevalence results estimated from traditional surveys (Xiao et al., 2019). Linking into earlier discussions of how wastewater can provide information on a communities' diet, a large-scale study in Australia assessed the prevalence of gout in a population using WBE (F. Ahmed et al., 2020). Gout is a type of arthritis that can cause severe joint pain and has many risk factors including obesity and diet. Researchers analysed oxypurinol, a main urinary metabolite of the first-line gout treatment allopurinol, in the wastewater collected from 75 WWTPs. Many multi-residue analysis methods have been developed that include pharmaceuticals associated with cardiovascular diseases in wastewater exist in the literature (Choi et al., 2019; Escolà Casas et al., 2021; Petrie et al., 2015; Proctor et al., 2019).

It is not just pharmaceuticals and metabolites in wastewater that can give key population-wide information on cardiovascular diseases. The analysis of fragments of DNA from bacteria that reside in an individual's gut can also be used. It has been previously highlighted in the literature that several bacterial species that reside in the human gut microbiome (the community of microorganisms living together), are enough to differentiate between an obese individual and a lean one (Le Chatelier et al., 2013). Following on from this it was theorised that the human faecal microbiome could therefore potentially act as proxy to the human gut microbiome. One study analysed the bacterial communities in wastewater via gene sequencing from 71 cities in the US and found good predictors of estimated levels of obesity within the community (Newton et al., 2015). The analysis of biomarkers associated with obesity including pharmaceuticals and gut bacteria via WBE can act as an additional epidemiology tool to provide real time monitoring of community health. Disease prevalence and trends can be monitored long-term allowing the effectiveness of public health interventions to be assessed, providing up-to-date evidence for policy makers to make informed decisions.

As with antibiotics, patient compliance to medication is also another area of concern. On average, a course of antibiotics will typically last 5 days, in contrast many treatments associated with non-communicable diseases, including diabetes, tend to be long-term (Kardas et al., 2005; Muszbek et al., 2008). It was previously highlighted that nearly 9% of all cardiovascular diseases in Europe are attributed to poor adherence with medical treatments (Muszbek et al., 2008). It has further been estimated that in developed countries, compliance to long-term treatments does not succeed 50% (World Health Organisation, 2003b). As previously mentioned, only a handful of WBE studies to date have matched long-term trends and spatial differences with predicted concentrations calculated from prescription and excretion data (Baz-Lomba et al., 2016; Escolà Casas et al., 2021; Kasprzyk-Hordern et al., 2021; Lai et al., 2011; Rice et al., 2020; Riva et al., 2020). Whilst a relatively new area to WBE, these studies have shown potential with matching wastewater data to predicted values. Results could be invaluable for measuring community compliance for both long-term conditions, including diabetes and mental health problems and short-term treatments, such as antimicrobials.

3.4.3 Asthma and allergies

WBE has also been applied to monitor both asthma and allergies and have correlated levels with environmental factors. One example of this is estimating a populations burden to hay fever (allergic rhinitis) through wastewater. This can be achieved by monitoring medications used to treat hay fever. For example, cetirizine and fexofenadine are antihistamines and are common ingredients in over-the-counter hay fever medications. One study in Oslo demonstrated positive correlations between seasonal pollen and cetirizine levels in wastewater, with much higher loads observed in summer when compared to winter (Harman et al., 2011). Another study used WBE to investigate population hay fever burden with fexofenadine and 1,4-methylimidazole acetic acid (MIAA) (Choi et al., 2018a). MIAA is an endogenous urinary biomarker released by the body in response to histamine. Results demonstrated strong correlations between the two, indicating histamine burden is linked with fexofenadine intake.

A community's asthma burden associated with air pollution is another area of WBE that has shown promise in recent years. In the UK, air pollution has been identified as one of the largest risks to public health, with the annual mortality of human-made air pollution in the UK is roughly equivalent to between 28,000 and 36,000 deaths every year (Public Health England, 2020). It has been estimated that between 2017 and 2025, the total cost to the NHS and social care system of air pollutants will be £1.6 billion (Public Health England, 2020). Air pollution has been linked to many health conditions, including exacerbation of asthma, increases in respiratory and cardiovascular diseases, lung cancer and recent research affecting the brain causing dementia. Growing concerns of air pollution have led to clean air initiatives across the UK, including Scotland's Cleaner air for Scotland strategy for the next five years to improve air quality (Scottish Government, 2020a).

Whilst particulate matter is one way to directly monitor effects of interventions for air pollution, there is not always a clear link to assessing the public health impacts in real time. There are often delays in getting information of hospital admissions or prescriptions associated with air pollution and this may reflect only a small percentage of the population effected. WBE have demonstrated asthma burden in a population using the medication salbutamol as an indicator for asthma. Salbutamol is the active pharmaceutical in inhalers, acting as a bronchodilator which helps relax the muscles of the airways in the lungs. Salbutamol inhalers are known as reliver inhalers, as they give quick relief from breathing problems when required. As asthma is exacerbated by air pollution, salbutamol in wastewater is therefore a good indicator of when someone might have experienced symptoms and used one to relieve them. Inhaler usage is challenging to assess from prescription data alone as whilst inhalers have been prescribed, there is no information to when they have been used. This is added to the fact that NHS advice is to replace inhalers every six months, even if not empty. Salbutamol levels in wastewater can therefore reflect in near-real time a community to relieve symptoms via salbutamol inhalers. The relationship between salbutamol in wastewater and air pollution was investigated via a study in Milan (Fattore et al., 2016). Increased levels of airborne particulate matter with increased levels of salbutamol in wastewater were observed, indicating exacerbated asthma symptoms on days with higher levels of air pollution. WBE could therefore provide novel insight into estimation of allergy and asthma burden in a population much quicker than current public health monitoring tools. Further work has been identified as broadening the medications to analyse in wastewater to cover more hay fever and asthma medications.

3.5 Exposure of chemicals

An area of WBE that is currently under development is for monitoring community exposure to various chemicals. Currently human biomonitoring (HBM) studies are the main tool for assessing exposure for many classes of compounds, including pesticides and bisphenol A (BPA) (Barr, 2008; Dekant and Völkel, 2008). Limitations to HBM include stringent and lengthy ethical procedures, samples can be invasive (e.g., sampling blood) and excretion profiles of biomarkers can vary throughout the day (Bauer, 2008). The results from HBM will also only provide a snapshot of population exposure at a particular moment of time. In contrast, WBE can help overcome some of these limitations by being reflective of whole populations over a period of time. Whilst WBE would not replace HBMs, it can provide an efficient and cost-effective approach to complement them.

3.5.1 Pesticide exposure

Exposure to pesticides has been associated with neurological conditions including Parkinson's disease, cancer and sperm DNA damage (Allen and Levy, 2013; Saillenfait et al., 2015). Whilst it has been reported that overall pesticide usage has declined in Scotland since 2018, 98% of arable crops were still treated with a pesticide in 2018 (Scottish Government, 2019). There is currently a lack of pesticide exposure information for the general population in the UK, as many pesticide exposure studies have been focused on exposure farm workers might experience (Sleeuwenhoek et al., 2007). Whilst farmers may experience exposure from direct application of pesticide, the general population is exposed to pesticides through diet and through living close to agricultural areas where spraying occurs (Aprea, 2012). One study to date has investigated urinary biomarkers of pesticide exposure of residents in the UK, including East Lothian in Scotland (a major arable area) (Galea et al., 2015). Results demonstrated that were was no evidence of increased urinary biomarker excretion in residents following spray events. However, levels observed in urine were in agreement with other studies done internationally, indicating diet is a likely source of pesticide exposure. It was recognised however that pesticides have short half-lives in the body which presents a challenge for HBM data, as urine samples would need to be collected within a 24-hour period from a spray event ideally.

WBE could again be used to overcome this limitation. The first studies using WBE to investigate population exposure to pesticides was in 2016 and 2017 and have demonstrated regional differences and comparable results with HBMs (Rousis et al., 2017b, 2016). The most extensive study to date investigated population exposure to three classes of pesticides (triazines, organophosphates and pyrethroids) across eight cities across Europe (Rousis et al., 2017a). A selection of 15 urinary metabolites of pesticide exposure were evaluated in wastewater. Back-calculated intake of pesticides were compared with national statistics on insecticide sales for each country. The results indicated higher levels of a countries insecticide sales can lead to higher population exposure to pesticides. The back-calculated pesticide intake values were compared to results from HBM studies previously done, demonstrating comparable results and indicating WBE could be a cost-effective solution to population monitoring of pesticide exposure.

Another UK-based study assessed pesticide exposure via WBE for pyrethroid pesticides on five cities in the South-West (Kasprzyk-Hordern et al., 2021). This study demonstrated geographic differences between cities indicating different levels of pesticide exposure depending upon location. Whilst there is a push for reducing reliance of pesticide usage on crops, unprecedented population growth and climate change continues to put stress on food production. Due to the variance in exposure experienced in cities observed in WBE studies so far, the importance of assessing pesticide exposure across multiple locations is key to highlighting vulnerable populations. In the UK, studies utilising WBE to investigate pesticide exposure in communities has only been achieved in the South-west of England. Expanding out to multiple-cities could provide complementary data and build upon HBM work previously done in the UK. Long-term monitoring trends could expand on knowledge on population exposure through both diet and potential spraying effects.

3.5.2 Industrial chemicals exposure (bisphenol A, phthalates and flame retardants)

Exposure to industrial chemicals that individuals come across in everyday life is another area showing promise for WBE. Bisphenol A (BPA) is a common plasticizer which has been evidenced to have endocrine disrupting properties. Endocrine disrupting chemicals interfere with hormone regulation which can affect health and reproduction in both humans and animals (World Health Organisation, 2010). Diet has been highlighted as a major source of exposure, e.g. due to leaching from plastic packaging into food (Mustieles et al., 2020). Flame retardants are another class of chemicals used increasingly in consumer products yet have been associated with several human health problems including suspected carcinogens and concerns of neurodevelopment issues (Dishaw et al., 2011; van der Veen and de Boer, 2012). There is a lack of evidence on exposure to such chemicals and long-term effects of exposure are not fully understood. Growing evidence of the negative effects of BPA have led to replacements by other bisphenols, such as bisphenol S (Mustieles et al., 2020). However, these have also demonstrated to have endocrine disrupting properties. The growing areas of concern have catalysed Scotland's environmental charity, Fidra, to have designated projects for tackling both bisphenols and flame retardants in everyday products (https://www.fidra.org.uk/projects/). It is recognised there is an urgent need for cost-effective monitoring tools to timely assess human exposure for a range of chemicals. Not only can this inform upon current risks on exposure to chemicals in everyday use, but also assess exposure to potential chemical replacements.

There have been several studies of WBE for assessing community exposure of BPA (Kasprzyk-Hordern et al., 2021; Lopardo et al., 2019, 2018; Wang et al., 2020), phthalates (Du et al., 2018; González-Mariño et al., 2021, 2017; Tang et al., 2020) and for flame retardants (Been et al., 2017; O'Brien et al., 2015). One study investigated community exposure of certain flame retardants and plasticizers across five cities in Europe (Been et al., 2018). In the UK, several studies have been done investigative community exposure for BPA via WBE, similar to pesticides these studies have only been done in the South-west of the UK (Kasprzyk-Hordern et al., 2021; Lopardo et al., 2019, 2018). One study investigated BPA sulphate as a characteristic urinary metabolite of BPA exposure in wastewater of five major WWTPs. Results from this study demonstrated varying levels of BPA exposure between sites, with two of the five observing higher BPA sulphate loads corresponding to higher intakes of BPA. These were estimated to be well above the tolerable daily intake threshold set by the European Food Safety Authority (European Food Safety Authority (EFSA), 2015). As there are limited studies currently on chemical exposure to varying classes of compounds in the UK more evidence is needed for effective policy interventions. WBE could be applied as a cost-effective and timely tool to help identify vulnerable populations to chemical exposure.

3.5.3 Mycotoxin exposure

Exposure to mycotoxins in a community's diet is another area of promise for WBE. Mycotoxins are toxic compounds naturally produced via funguses that grow on food like cereals. Exposure to mycotoxins have shown harmful effects on both human and animal health, with links to cancers, birth defects and gastrointestinal disorders (Bhat et al., 1997; Fung and Clark, 2004; Hussein and Brasel, 2001). Due to the associated risks, maximum acceptable limits have been established for some mycotoxins in food (European Union, 2006). However, it is widely acknowledged gaps on the impacts of climate change and the prevalence of mycotoxins. Altered temperatures, increased rainfall could allow fungal species to be more prevalent or allow strains to evolve (Skelsey and Newton, 2015).

The main cereals grown in Scotland are barely (malting purposes) and oats (food and animal feed). It has been previously highlighted by that the main mycotoxin producing fungi of concern from a Scotland and a wider UK perspective are the *Fusarium* spp. (Food Standards Scotland, 2015). Infection of *Fusarium* spp. causes *Fusarium* head blight, producing the mycotoxins deoxynivalenol (DON) and zearalenone (ZON). Due to the robust nature and stability of mycotoxins they have been reported to pass into, fermented products including beer but not distilled products like whisky (Food Standards Scotland, 2015). This has caused concern for malting brewers regarding fungal contamination as this can impact quality and flavour of final product (Nielsen et al., 2014). Due to growing concerns of mycotoxin exposure, a number of urinary HBM studies have been investigated across the world (Tuanny Franco et al., 2019). In the UK, a handful of HBM studies have investigated mycotoxins in urine, these studies have focused on DON and urinary metabolites (Papageorgiou et al., 2018b, 2018a; Wells et al., 2017). Results from these studies reported certain groups in the UK, including young children and adolescents may be exceeding current limits of DON. Limitations with studies have been recognised as uncertainties with estimating mycotoxin dietary intake and the small number of communities been investigated. There is therefore a need for larger-scale and longer-term studies to address population exposure to a range of mycotoxins.

WBE has recently been applied to assess community exposure mycotoxins in four cities in Spain and Italy (Gracia-Lor et al., 2020). A selection of eleven urinary mycotoxins, including DON and fumonisins B1, B2 and B3 were investigated. It was reported that DON intake estimates that were back-calculated by WBE, were close to reported values in HBM studies. Whilst this new area of work for WBE, has study has demonstrated initial promise of using wastewater to assess as a community intake of mycotoxins, complimentary to current HBM approaches.

3.6 Endogenous biomarkers linked with disease or health status

As mentioned previously, endogenous biomarkers are produced by an individual's metabolism in response to either a disease or health status. For example, these could be biomarkers of inflammation or stress that are produced in the body in response to a disease. An earlier example of an endogenous biomarker applied in WBE was MIAA, a urinary biomarker released by the body in response to histamine. This was analysed alongside the hay fever medications in wastewater to estimate hay fever burden in a population (Choi et al., 2018a). The benefits of broadening WBE to include endogenous biomarkers has been well-discussed in the literature (Choi et al., 2018b; Daughton, 2020; Rice et al., 2020; Sims and Kasprzyk-Hordern, 2020). Daughton presented the Sewage Chemical-Information mining (SCIM) approach for this purpose (Daughton, 2018, 2012). Here the analysis of endogenous biomarkers in wastewater could reveal novel insight into general health or disease status in the community. Biomarkers analysed could be indicative of certain states, such as stress, inflammation or disease and the types of biomarkers could vary, including small molecules, proteins, sugars and lipids.

Oxidative stress has previously been highlighted as promising biomarkers for use in WBE, with isoprostanes highlighted as ideal candidates (Daughton, 2012). Oxidative stress is when there is an imbalance of free radicals and antioxidants in the body, the result of which can lead to cell and tissue damage. Whilst it's involved in natural processes such as aging, it is also linked to many diseases and lifestyle choices (e.g. smoking). Oxidative stress is a relatively new area for WBE, with a few studies discussing its potential use in WBE (Daughton, 2012; Ryu et al., 2015). One study has investigated the isoprostane oxidative stress biomarker, 8-iso-PGF2α, for its suitability as a marker of health (Ryu et al., 2016). Wastewater from 11 cities in Europe was analysed alongside metabolites of tobacco smoking (hydroxycotinine) and alcohol consumption (ethyl sulphate) to investigate potential correlations. Results reported strong correlations of 8-iso-PGF2α with tobacco consumption across studied cities. A follow up study investigated in-sewer stability of several isoprostanes and confirmed suitable stability for WBE (O'Brien et al., 2019). A more recent study in the US investigated several isoprostane isomers in wastewater to monitor community stress during the COVID-19 pandemic (Bowers and Subedi, 2021).

With regards to monitoring infectious disease spread at the community level via WBE, it has been highlighted that WBE should not be limited to monitoring the infectious genetic material alone. Instead WBE should be expanded out to targeting endogenous biomarkers that are significantly elevated in a diseased state (Daughton, 2020). The benefits of expanding out WBE to indirect, more generic markers of infection were highlighted as reduced costs for analysis and potentially such biomarkers could be better indicators of infection, possibly resulting in an improved early warning system. Furthermore, in the case of COVID-19 much uncertainty lies in variability of viral excretion (Joynt and Wu, 2020). Analysing indirect biomarkers of inflammation alongside genetic material could therefore help account for this. This information would be valuable as many diseases, both infectious and non-communicable, involve inflammatory damage and oxidative stress. There is still much work to be done in this field for expanding out WBE to include multiple endogenous markers to link back to public health. There is currently a lack of endogenous biomarkers reflecting chronic disease state (e.g. diabetes) and for well-being. However, with the growing field of metabolomics, it is expected more urinary endogenous biomarkers will continue to be identified.

4 Future Outlook

4.1 Environmental considerations

WBE uses analytical tools, infrastructure and knowledge base that were developed with environmental monitoring in mind. These include: liquid chromatography and mass spectrometry instrumentation that is widely used for quantitative analysis of regulated and emerging contaminants in water or composite samplers that are widely used at inlets and outlets of WWTPs to determine efficiency of wastewater treatment processes. There comes an opportunity for the development of an integrated local, regional or a national monitoring system focussed on whole river catchments to deliver critical information on both environmental and public health. Historically environmental health was evaluated independently of public health issues. This is counterproductive as environmental health is directly interlinked with public health, ie. environmental deterioration including pollution and loss of biodiversity has direct impact on public health.

As an example, a recent project undertaken in South-West of England designed an integrated sampling regime and developed analytical methods focussed on >100 chemicals in the River Avon Catchment in South West England (Kasprzyk-Hordern et al., 2021). A total of five WWTPs serving five towns and cities, covering an area of approximately 2,000 km^2 and the population of ~1.5 million (this constitutes >75% of the overall population in the catchment). Samples collected from wastewater influent and effluent allowed for verification of efficiency of treatment processes and identified problematic pollutants (also those of emerging nature or recommended for regulation, i.e. included on EU watchlists) that might require further attention. Samples from receiving river water allowed for the evaluation of environmental risks. Wastewater influent was used to inform public health status: pharmaceuticals from wide-ranging groups were used as proxies to inform prevalence of NCD (i.e. cardiovascular disease, diabetes, asthma) (paper in preparation) as well as antibiotic usage and prevalence of resistance genes. Spatiotemporal trends in chemical intake were observed as a result of occupational exposure (higher bisphenol A (BPA) intake during weekday), and lifestyle choices (higher cocaine and pyrethroid pesticides intake during weekend). WBE is not intended to estimate individual exposure to chemicals. It can however provide estimates at a community level, and as a result, it has the potential to be developed into an early warning system, a powerful tool for large scale screening studies identifying communities at risk and in need of high-resolution individual testing at a localised scale.

4.2 Ethical Considerations

WBE is currently subject to rapid developments. Is has been successfully applied in national and international SARS-CoV-2 surveillance. WBE is now acknowledged as one of epidemiology tools, hence, ethical considerations should also apply, especially when applying near-source tracking. Ethical guidelines exist only for WBE's first application, estimation of illicit drug usage via WBE, currently utilised to estimate drug use trends in the EU (EMCDDA, 2016).

There are key issues that need careful consideration especially in the context of near source tracking that is widely applied in SARS-CoV2 surveillance. For example, sampling from small communities could lead to stigmatisation of vulnerable groups. If data is made available to the public, this could lead to results being misused and misconstrued in the media. The ethical protocols first established for WBE regarding illicit drugs, established that sampling from population sizes >10,000 was large enough to ensure stigmatisation of smaller groups is avoided. This same protection might therefore not be extended for population sizes under this number. Sampling wastewater from small communities is possible but ethical procedures need to be put in place and it is essential that data is anonymised. To mitigate the risks of stigmatisation the following key points need to be established before sampling takes place i) clear aims and objectives of the sampling; ii) what biomarkers will be investigated and what possible implications these have; iii) population size of the community; iv) who will have access to this data and how will this data be used.

The concerns regarding the ethics and legalities surrounding WBE are valid, several discussions exist upon ethics on illicit drugs in WBE (Hall et al., 2012; Lancaster et al., 2019; Prichard et al., 2017, 2014) and more recently on SARS-CoV-2 (Gable et al., 2020). It is important that WBE should be treated and utilised as any other epidemiological tool and subjected to ethical review and scrutiny. In the context of the rapidly developing surveillance of SARS-CoV2 in wastewater, national and international ethical guidelines are urgently needed. Furthermore, these will need to be reviewed and updated, if wastewater samples collected are analysed for a broader set biomarkers. WBE as a tool to rapidly inform on public health can offer significant benefits and attraction, as observed by the recent surge of popularity in monitoring COVID-19 outbreaks. It is vital however that with these rapid developments occurring in WBE, that ethical considerations are not left behind.

4.3 Policy Relevance

WBE is relevant to a number of policy areas within Scottish Government, primarily health-related, but also with links to other fields. This section provides a brief (non-exhaustive) overview of where WBE and existing policies may interact.

Lifestyle choices including use of illicit drugs, alcohol and tobacco as well as diet and mental health all feature significantly in Scotland's Public Health Priorities strategy (Scottish Government, 2018a) implemented by the Population Health Directorate.

Data on illicit drug use currently focuses on information relating to drug offences and court proceedings, the use of drugs in prisons and prevalence studies and surveys (ScotPHO, 2021). By its nature, illicit drug use is likely to be underreported and difficult to monitor effectively. The ability to detect drug metabolites through WBE could provide enhanced surveillance at a population or even community level and thus provide additional data reinforcing the existing drug use policy framework.

A key policy document with respect to alcohol consumption is the "The Alcohol Framework 2018" (Scottish Government, 2018b). The potential for WBE to strengthen framework lies in the need for "establishment of a research and evidence network" (Alcohol Focus Scotland, 2017). Policy documents highlight the need to seek to improve sources of data, noting limitations of that currently gathered and the need for it to be rationalised against other data sources. WBE provides an opportunity to augment this existing monitoring of alcohol markers.

The Scottish Government is committed to reducing tobacco smoking and associated disease. The current relevant policy document in this respect is the five- year "Raising Scotland's Tobacco-free Generation: our tobacco control action plan 2018" (Scottish Government, 2018c), with an ambition for a tobacco-free Scotland by 2034 (Priority 4) (Scottish Government, 2018a).

The use of WBE to identify populations with elevated usage of illicit drugs, alcohol or tobacco may help to target priority geographical areas for intervention, feeding into Public Health Priority 4 – "A Scotland where we reduce the use of and harm from alcohol, tobacco and other drugs". The success of this priority depends upon understanding what drives consumption – thus WBE-based markers for these lifestyle choices could facilitate linkage with potential socioeconomic determinants of a given wastewater-producing population. Further, it feeds into Priority 2 "A Scotland where we flourish in our early years" and Priority 1 "A Scotland where we live in vibrant, health and safe places and communities" with on-going risk to children's health and wellbeing through substance abuse, indoor air quality and parental modelling of smoking behaviour.

WBE-based indicators for diet could help to underpin the Scottish Government's obesity strategy, published in 2018: "A Healthier Future: Scotland's Diet and Healthy Weight Delivery Plan" (ScotPHO, 2020). This specifically mentions a commitment to evidence-based policy (Scottish Government, 2018d) which could be further supported by WBE-monitoring of dietary markers for obesity or metabolites associated with specific food types, for example, enhancing the existing list of obesity indicators (Scottish Government, 2018e). It also highlights the need for both population-wide measures and targeted support to families most at risk. Similarly, the detection of metformin as a biomarker for Type 2 diabetes may feed into the strategy plan "A Healthier Future: type 2 Diabetes prevention, early detection and intervention framework" (Scottish Government, 2018f). WBE could potentially contribute to understanding both the national picture for such health issues and identifying at risk populations. Since dietary markers can highlight other lifestyle choices which may be influenced by wider issues (for example the relationship identified between increased prevalence of artificial sweeteners and environmental temperature (Phung et al., 2017) use of WBE may even link into environmental policy areas such as climate change targets (Scottish Government, 2020b). Other dietary markers may be relevant to the Heart Disease Improvement Plan – particularly as consideration is given to at risk (e.g. socially deprived) populations (Scottish Government, 2014a), the identification and surveillance of which may be supported by WBE.

Monitoring the prevalence of metabolites associated with antidepressants, anti-anxiety drugs and other prescription medications for mental health conditions, or indeed biomarkers directly associated with mental stress, is applicable to the Scottish Government's Mental Health Strategy (Scottish Government, 2017) in particular a key policy objective identified under the "What Research Matters for Mental Health Policy in Scotland" paper which is to "Achieve better outcomes which can be measured" (Mitchell and Kearney, 2015).

Scotland's Public Health Priority 1 includes making "improvements to the quality of the air we breathe" (Scottish Government, 2018a). Because air pollution is harmful to health, markers for asthma drug metabolites in wastewater not only support health policies but also have the potential to support strategies such as "Cleaner air for Scotland - 2" (Scottish Government, 2020a) accurately predicting the health benefits of further reducing air pollution is complex, therefore additional sources of data in this arena may be helpful.

Communicable diseases are a major policy area in which WBE could be pertinent to data collection. Health Protection Scotland (HPS) undertakes surveillance of a number of key bacterial and viral pathogens which cause communicable disease and are also shed in faeces. Examples include Norovirus, *Campylobacter*, *E. coli* O157, Toxoplasma and Hepatitis (Heath Protection Scotland, 2015). Outbreak identification and control is also undertaken by HPS and HPS integrates with animal and environmental health organisations to forms part of the "One-Health" approach to protecting Scotland from infection hazards. WBE offers the potential to apply either DNA-based or isolation/whole genome sequence-based approaches to assist outbreak investigation or as a means of population-level surveillance of specific organisms and/or strains, thus feeding directly into the Scottish Health Protection Network's "A Public Health Microbiology Strategy for Scotland" (Health Protection Scotland, 2018) and The Human Animal Infections and Risk Surveillance (HAIRS) (a multi-agency cross-government horizon scanning and risk assessment group of which Scottish Government and Health Protection Scotland are a part (Public Health England, 2015).

Scotland's Antimicrobial Prescription Group (SAPG, 2021) was established in 2008 with a primary aim to coordinate a national framework for antimicrobial stewardship. SAPG have developed surveillance systems and ensured standardised information on antimicrobial use and resistance that is accessible to NHS boards. In 2019, the Scottish One Health Antimicrobial Use and Antimicrobial Resistance report was published by Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) Scotland (Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), 2020). This report provided information on antibiotic use and resistance to antibiotics in Scotland during 2019. Alongside initiatives such as the One Health Breakthrough Partnership (a collaboration between NHS Highland, Scottish Water, SEPA, MedSmart, James Hutton Institute, University of the Highlands and Islands, Glasgow Caledonian University) which reports to Scottish Government (Scottish Parliament, 2020) - these provide join-up between public health, veterinary and environmental aspects of AMR. They support the five-year United Kingdom National Action Plan and a 20-year vision for containing and controlling AMR (UK Government, 2019b). Currently, much surveillance is based on clinical data and prescription data. WBE provides an opportunity as a complimentary technique to achieve a whole population approach to tackling AMR in a multifaceted way because it is possible to detect antimicrobial resistance genes, antibiotic residues and metabolites and co-selecting compounds such as heavy metals or personal care products. Further, if employed to better understand patient compliance with pharmaceutical prescriptions including antibiotics, through detection of parent compound-metabolite ratios in wastewater, WBE can further underpin the AMR strategies mentioned above.

WBE has potential to complement current practices in identifying and monitoring exposure to chemicals, for example accompanying the SASA Pesticide Survey data, relevant to the code of practice for using plant protection products in Scotland (Scottish Executive and Health and Safety Commission, 2007). In addition, understanding the prevalence of endocrine disrupting chemicals such as bisphenol A (common in food packaging), phthalates (household and personal care products) flame retardants (furnishings) could support related statutory instruments and policy groups. Examples include the Materials and Articles in Contact with Food (Scotland) Amendment Regulations (Scottish Statutory Instruments, 2019) and the Scottish Chemical Policy Network (UK Chemicals Stakeholder Forum, 2020), supporting understanding of dietary mycotoxin exposure may augment surveillance of food products undertaken by Food Standards Scotland (Munro and Gratz, 2018) and is pertinent to the Contaminants in Food (Scotland) Regulation (Scottish Statutory Instruments, 2013).

This review focusses primarily on the association of wastewater-based determinants as markers for population based health status. However, many wastewater-associated markers and chemicals directly or indirectly impact receiving waters and as such are relevant to a range of water-related environmental policies and plans including the Scotland River Basins Standards Directive (Scottish Government, 2014b), River Basin Management Plans (SEPA, 2021) and a raft of regulations under the water environment legislation (Scottish Government, 2018g).

5 Recommendations and conclusions

WBE is a relatively new field. There are only a very few technology ready applications. These include:

1. Estimation of community wide illicit drug usage (currently applied by EMCDDA in the EU and internationally (e.g. in Australia and in the US). Required infrastructure includes specialised staff to undertake sampling and sample preparation as

well as an investment in instrumentation (liquid chromatography coupled with mass spectrometry).

2. Estimation of lifestyle chemical usage: alcohol, nicotine and caffeine. Required infrastructure: as above.
3. Infectious disease tracking (e.g. polio, SARS-CoV-2). Required infrastructure includes specialised staff to undertake sampling and sample preparation as well as analysis with PCR and sequencing.
4. Estimation of disease prevalence based on pharmaceutical usage. Required infrastructure includes specialised staff to undertake sampling and sample preparation as well as an investment in instrumentation (liquid chromatography coupled with mass spectrometry).
5. There are research gaps though. These include lack of understanding of stability of pharmaceuticals and their metabolites in wastewater, lack of understanding of metabolism to undertake back-calculation of exposure.

There is a clear potential to apply WBE in:

1. Estimation of community-wide exposure to hazardous chemicals. Some initial work indicates that wastewater can provide information on community wide exposure to pesticides and industrial chemicals, which are linked with either occupational exposure or lifestyle choices.
2. Prevalence of non-communicable disease (NCD). Current WBE approaches allow for estimation of pharmaceutical usage to treat, e.g. diabetes, cardiovascular disease or mental health conditions.

However, further research is required to fully appreciate WBE's potential to transform community-wide heath assessment. These include:

1. Research on a new biomarker base to inform public health status (to expand WBE applications).
2. Novel approaches towards population equivalent estimation. These are required to undertake spatiotemporal quantitative analysis of community wide exposure or public health status (to provide more accurate WBE measurements).
3. Investment in new infrastructure might be required in terms of sampling and wastewater flow measurements to enable meaningful quantitative analysis of chemical markers (to provide more accurate WBE measurements).
4. Novel approaches towards sampling to allow for truly representative sample to be obtained. Current approaches utilise 24h composite samplers. These samplers are mainly deployed at wastewater treatment plants. New sampling approaches might be required when sampling near source (to provide more accurate WBE measurements).
5. Novel approaches towards analysis and sensing as wastewater analysis of biomarkers required highly selective and sensitive techniques (to provide more accurate WBE measurements and to expand WBE applications).
6. Modelling and statistical analysis required to fully appreciate spatiotemporal variability in large scale datasets (to provide more accurate WBE measurements).

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