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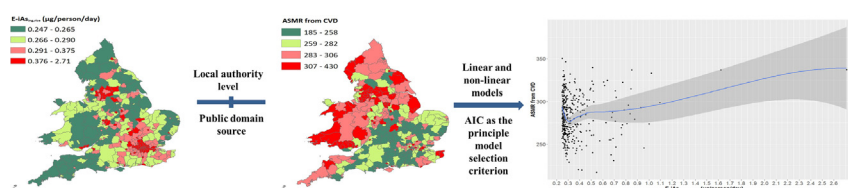
Association of low-level inorganic arsenic exposure from rice with age-standardized mortality risk of cardiovascular disease (CVD) in England and Wales

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HIGHLIGHTS

- Ecological study of health impacts associated with exposure to inorganic arsenic in rice
- Increased risk of cardiovascular mortality associated with increased inorganic arsenic exposure
- Non-linear models of the association were better than linear no-threshold models.
- More health-protective ways of selecting and cooking rice are indicated.
- Exposure to inorganic arsenic is a confounder for studies of other risk factors for cardiovascular disease.

GRAPHICAL ABSTRACT



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ABSTRACT

Adverse health outcomes, including death from cardiovascular disease (CVD), arising from chronic exposure to inorganic arsenic (iAs) are well documented. Consumption of rice is a major iAs exposure route for over 3 billion people, however, there is still a lack of epidemiological evidence demonstrating the association between iAs exposure from rice intake and CVD risks. We explored this potential association through an ecological study using data at local authority level across England and Wales. Local authority level daily per capita iAs exposure from rice ($E-iAs_{ing, rice}$) was estimated using ethnicity as a proxy for class of rice consumption. A series of linear and non-linear models were applied to estimate the association between $E-iAs_{ing, rice}$ and CVD age-standardized mortality rate (ASMR), using Akaike's Information Criterion as the principle model selection criterion. When adjusted for significant confounders, notably smoking prevalence, education level, employment rate, overweight percentage, PM_{2.5}, female percentage and medical and care establishments, the preferred non-linear model indicated that CVD risks increased with iAs exposure from rice at exposures above 0.3 $\mu\text{g}/\text{person}/\text{day}$. Also, the best-fitted linear model indicated that CVD ASMR in the highest quartile of iAs exposure (0.375–2.71 $\mu\text{g}/\text{person}/\text{day}$) was 1.06 (1.02, 1.11; p -trend <0.001) times higher than that in the lowest quartile (<0.265 $\mu\text{g}/\text{person}/\text{day}$). Notwithstanding the well-known limitations of ecological studies, this study further

Abbreviation: As, arsenic; iAs, inorganic arsenic; CVD, cardiovascular disease; $E-iAs_{ing, rice}$, daily per capita iAs exposure from ingestion of rice; ASMR, age-standardized mortality rates; ESP, European Standard Population; AIC, Akaike's Information Criterion; ONS, Office for National Statistics; ICD, International Classification of Diseases; MR, mortality rate; PHE, Public Health England; GVA, Gross Value Added per head; DEFRA, Department for Environment, Food & Rural Affairs; $E-As_{ing, water}$, daily per capita As exposure from drinking water; $E-As_{ing, soil}$, daily per capita As exposure from soil; C_{AIR} , annual mean As concentration in ambient air; GLM, generalized linear model; RERI, relative excess risk for interaction; PCA, principal component analysis; PM 2.5, particulate matter with an aerodynamic diameter ≤ 2.5 mm; eNOS, endothelial nitric oxide synthases.

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suggests exposure to iAs, including from rice intake, as a potentially important confounder for studies of the factors controlling CVD risks.

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1. Introduction

Originating from either geological sources or anthropogenic activities, arsenic (As) has been widely recognized as a human carcinogen since at least the 1950s (Currie, 1947; Hueper, 1967; Polya and Middleton, 2017), with its more toxic species, inorganic arsenic (iAs), being predominant or important in soil, water, air, rice and some other foods, including vegetables, and some fruit juices (Chen et al., 2011a; Diane et al., 2013; Currier et al., 2014; Molin et al., 2015; Yanez et al., 2015; Bae et al., 2017). Ubiquitously present in the environment (Tchounwou et al., 2004; Culioli et al., 2009; Bundschuh et al., 2012; Huda et al., 2014), individuals may be exposed via oral (ingestion), inhalation, dermal contact, and even parenteral routes (US Department of Health Human Services et al., 2007). Drinking water is a well-recognized source of iAs exposure for people living in certain geographic regions (Polya and Middleton, 2017; United Nations Children's Fund (UNICEF), 2018). Emerging data over the last 20 years, however, have suggested that iAs exposure is not only from contaminated drinking water but also, more commonly, from foodstuffs (Nriagu, 1994; Schoof et al., 1999; Meharg et al., 2007; Mondal and Polya, 2008; European Food Safety Authority, 2009, 2014; Mondal et al., 2010; Meharg and Zhao, 2012). Often containing considerably more As than other major staples due to a combination of its physiology and flooded paddy field geochemistry (Meharg and Rahman, 2003; Meharg et al., 2008), rice has particularly been regarded as an important source of iAs exposure (Food and Agriculture Organization of the United Nations, 2008). This is especially the case for some populations, such as in Bangladesh, South-East Asia, southern China and parts of South America, many of whom consume rice as their main staple (Meharg and Zhao, 2012). Even in areas, ranging from USA (Gossai et al., 2017), Spain (Signes-Pastor et al., 2017), to the UK (Meharg et al., 2007) and Australia (Islam et al., 2017b), where rice is not regarded as the daily staple for the majority of the population, its role in iAs exposure cannot be ignored, particularly for sub-populations who have relatively high rice consumption rates (Cleland et al., 2009; Awata et al., 2017; Mantha et al., 2017). There have also been particular concerns over iAs exposure in children from rice and rice products (Davis et al., 2014).

Recently, a considerable number of epidemiological, experimental toxicological, medicinal and in vitro mechanistic toxicological studies have shown that iAs exposure is associated with increased risk of detrimental health consequences in various organs or systems (Wadhwa et al., 2011; Bräuner et al., 2014; Steinmaus et al., 2014; Wang et al., 2014). Long-term iAs exposure is implicated in the etiology of some cancers, such as lung cancers (Wadhwa et al., 2011), bladder cancers (Steinmaus et al., 2014), liver cancers (Wang et al., 2014), skin cancers (Hsu et al., 2015) as well as kidney cancers (Ferrecio et al., 2013). Inorganic As exposure has also been reported to be associated with different neurological problems, including cognitive function (Nahar et al., 2014) and adverse neurobehavioral development (Carroll et al., 2017). Similarly, there is considerable evidence of its role in increased risk of problems of immune systems in new-borns (Laine et al., 2015), infant infections (Susko et al., 2017) and some health problems for pregnant women (Butts et al., 2015; Farzan et al., 2015b).

In addition, the association of iAs exposure with cardiovascular disease (CVD) risks has also been reported by several groups. For example, a prospective study conducted in Bangladesh with an average of 7 years follow-up indicated increased risks of mortality from ischemic heart disease and cerebrovascular disease for subjects exposed to higher concentrations of well water iAs (Chen et al., 2011b). There is also

substantial evidence of its impacts on the increased risk of hypertension (Hall et al., 2017; Hossain et al., 2017) and incident CVD even for low to moderate As levels (Moon et al., 2013; Moon et al., 2017b). Similar patterns were also observed for the risk of CVD markers (US Department of Health Human Services et al., 2007; Wu et al., 2012) and stroke (Rahman et al., 2014). More seriously, even exposure to drinking water As at concentrations below the WHO provisional guideline value (10 ppb), higher risks for different CVD types and CVD biomarkers could still be found (Xu et al., 2020). Among all these adverse health risks, CVD is regarded as the most serious non-cancer health outcome (Farzan et al., 2015a). Given the sizable global population exposed to iAs and the high level of CVD risks in the world, even small iAs-induced increase in the CVD risks could result in a large number of additional avoidable deaths (Chen et al., 2011b; Farzan et al., 2015a). Therefore, it is of great importance to quantify the dose-response effects of iAs exposure on CVD risks.

Unfortunately, although the association between iAs exposure from drinking water and CVD risks have already been well described (Chen et al., 2013; James et al., 2015), there is still a lack of epidemiological evidence demonstrating such risks from iAs exposure from rice intake despite the fact that rice intake is a, if not the, major iAs exposure pathway for over 3,000,000,000 people in the world (Meharg and Zhao, 2012). Therefore, it is necessary to further explore the effects of iAs exposure from rice intake on CVD risks.

In this study, we explored the potential associations between local authority level daily per capita iAs exposure from ingestion of rice ($E-iAs_{ing, rice}$) ($\mu\text{g}/\text{person}/\text{day}$) and CVD mortality, specifically in England and Wales. England and Wales was selected as the target for this study because (i) although CVD mortality rates have decreased from 1969 to 2015, CVD is still the second main cause of death (Timmis et al., 2017); (ii) rice has already been identified as an important iAs exposure route (Meharg et al., 2007); (iii) there is a wide range of rice consumption rates meaning that there is also a wide range of exposures to iAs from ingestion of rice (Mondal et al., 2019; MRC Elsie Widdowson Laboratory and NatCen Social Research, 2019); (iv) accurate data on CVD attributable mortality is readily available in the public domain (Office for National Statistics, 2016); (v) accurate data on major (potential) confounders, notably obesity, smoking, wealth, education level, air quality and drinking water quality is also readily available (IHS, 2014; National Health Service, 2015; Office for National Statistics, 2015b, 2015d, 2015e, 2015f, 2015g, 2015h, 2017; Public Health England, 2016).

The objectives of the study were to (i) determine the characteristics and spatial distributions of local authority level $E-iAs_{ing, rice}$ and CVD mortality risk; (ii) quantify the importance of $E-iAs_{ing, rice}$ and other confounders to the variability of CVD age-standardized mortality rates (ASMR); (iii) model the relationships between low level $E-iAs_{ing, rice}$ and CVD ASMR. We further discussed our exploratory findings, and in the light of these, made recommendations both for future work and for more protective ways to eat rice, reducing potential health risks arising from avoidable exposure to iAs.

2. Methods

In this study, we explored, for England and Wales for the year 2012, the potential linear and non-linear associations between iAs exposure from rice and CVD ASMR through an ecological study, utilizing a series of generalized linear models (GLMs). We leveraged local authority level iAs exposure and health information from public domain sources for England and Wales. Specifically, ASMR from CVD were calculated

via standardization using population in each age group as stated in European Standard Population 2013 (ESP 2013) (Glickman, 2013). Local authority level E-iAs_{ing, rice} was estimated using Office for National Statistics (ONS) reported ethnicity as a proxy for class of rice consumption. In addition, the influence of an appropriate range of local authority level socio-economic, demographic and lifestyle confounders were explored through minimizing objective model comparison criteria, notably Akaike's Information Criterion (AIC).

Because our present study only used publicly available local authority level data for the main analysis, ethical approval was not required in this regard. In addition, we also used data from National Diet and Nutrition Survey (2014/15–2016/17) for supplementary analysis. However, this is also publicly available and anonymized data, we, therefore, required no further ethical approval, noting that the authors of the National Diet and Nutrition Survey (2014/15–2016/17) had themselves obtained ethical approval for their study from the Cambridge South NRES Committee (Ref. No. 13/EE/0016).

2.1. Modelled local authority level E-iAs_{ing, rice}

Local authority level daily per capita iAs exposure from ingestion of rice ($\mu\text{g}/\text{person}/\text{day}$), E-iAs_{ing, rice}, was estimated using ONS reported ethnic group (including White: English/Welsh/Scottish/Northern Irish/British, Other White, Mixed/multiple ethnic groups: White and Black Caribbean, Mixed/multiple ethnic groups: White and Black African, Mixed/multiple ethnic groups: White and Asian, Mixed/multiple ethnic groups: Other Mixed, Asian/Asian British: Indian, Asian/Asian British: Pakistani, Asian/Asian British: Bangladeshi, Asian/Asian British: Chinese, Asian/Asian British: Other Asian, Black/African/Caribbean/Black British: African, Black/African/Caribbean/Black British: Caribbean, Black/African/Caribbean/Black British: Other Black and Other ethnic group) as a proxy for class of rice consumption using the following formula:

$$E-iAs_{ing, rice} = \sum_i EP_i \times RC_i \times (1 - W_{food}) \times C_{rice} \times (1 - LOSS_{cooking}) \times AV_{rice}$$

where EP_i is the population proportion of the subscripted ethnicity, i , in the local authority (2011); RC_i is the daily purchase of rice (uncooked) of the subscripted ethnicity, i , per person ($\text{kg}/\text{person}/\text{day}$); W_{food} is the estimated proportion of food that is wasted in England and Wales; C_{rice} is the iAs concentration in uncooked rice ($\mu\text{g}/\text{kg}$); $LOSS_{cooking}$ is the estimated proportion of iAs lost from rice upon cooking; AV_{rice} is the estimated bioavailability of iAs in cooked rice.

All parameters other than EP_i used in the calculation were assumed to be independent of local authority.

Data used in the calculation described above were extracted from the following sources: Local-authority level ethnicity distributions were obtained from the UK 2011 census from the ONS that includes the proportion of each ethnicity in different local authorities across England and Wales (Office for National Statistics, 2015c). Daily purchase of rice per person ($\text{kg}/\text{person}/\text{day}$) by different ethnicities was obtained from Expenditure and Food Survey (2002–2005) (DEFRA and ONS, 2007; Meharg et al., 2007) and the percentage of food purchased that is wasted in the UK was estimated as 25% (Quested et al., 2011). Mean rice iAs concentration was obtained from European Food Safety Authority (2014). Although dietary As exposure has often been calculated based on the total As or iAs concentration in different foodstuffs without considering As bioavailability (Li et al., 2011; Torres-Escribano et al., 2008), this tends to overestimate exposure, so we have followed Juhasz et al. (2006) in correcting for this, adopting the 40% iAs relative bioavailability value of Li et al. (2017) for cooked rice; a value of 5% for $LOSS_{cooking}$ was taken from Mwale et al. (2018) on the basis of cooking with rice-to-water ratios of 1:3 (the most common method used in Western countries (Sengupta et al., 2006)).

2.2. CVD mortality risk

CVD (International Classification of Diseases, Tenth Revision (ICD-10) I00-99 (World Health Organization, 2016)) mortality information in different age groups in 2012 was obtained from the ONS (Office for National Statistics, 2016). Due to data protection legislation, the health data for some local authorities has been randomized or set to zero where mortality rates were very low – as these events only accounted for about 0.1% of CVD in the dataset, we simply excluded them before statistical analysis. The age-structure in different local authorities was extracted from the 2011 UK Census with the main population size in each age-group being the usual resident population at the census day (27 March 2011) (Office for National Statistics, 2015a).

We calculated ASMR from crude local-authority level CVD mortality rates and age distributions with reference to the ESP 2013 (Glickman, 2013) by:

$$m_i = n_i/N_i \times 100000$$

$$ASMR = \left(\sum (P_i \times m_i) \right) / \left(\sum P_i \right)$$

where n_i is the death number due to CVD in the subscripted age group, i , in each local authority; N_i is the population in the subscripted age group, i , in each local authority; m_i is the observed crude mortality rate (MR) in the subscripted age group; and P_i is the population in the subscripted age group, i , of ESP 2013.

2.3. Potential confounders

In addition to the E-iAs_{ing, rice} and CVD mortality information, a range of local-authority level behavioral and socio-economic indicators were evaluated as potential confounders in our study. Firstly, smoking has been regarded as a leading cause of CVD morbidity and mortality in the world (Balakumar et al., 2016; Banks et al., 2019). Consequently, local authority level smoking prevalence was obtained and treated as a confounder (IHS, 2014). Also, as the relationships between type 2 diabetes and CVD risk have been widely described (Dambha-Miller et al., 2017; Zheng et al., 2017), diabetes prevalence in different local authorities was included as a confounder (National Health Service, 2012). Besides, with its unprecedented increasing prevalence over the last three decades (Basterra-Gortari et al., 2017), obesity has been regarded as an important causal factor for CVD (Mandviwala et al., 2016). To include such information in our modelling analysis, local authority level overweight percentage (body mass index greater than or equal to $25 \text{ kg}/\text{m}^2$) was extracted from the Public Health England (PHE) (Public Health England, 2016) and National Health Service WALES (National Health Service, 2015). In addition, a wide variety of socioeconomic indicators were regarded as either important predictors of CVD or As toxicity (Lang et al., 2011; Manriquegarcia et al., 2011; Notara et al., 2016; Darin-Mattsson et al., 2017). In this study, therefore, the confounding effects of socioeconomic indicators, such as local-authority education level, employment rate, gross disposable household income per head, economic activity rate as well as Gross Value Added per head (GVA), urban percentage and medical and care establishment per 1000 have been taken into account from different sources in ONS respectively (Office for National Statistics, 2015b, 2015d, 2015e, 2015f, 2015g, 2017). Furthermore, female percentage (Office for National Statistics, 2015h) and air quality PM_{2.5} data originated from Department for Environment, Food & Rural Affairs (DEFRA) (<https://uk-air.defra.gov.uk/data/pcm-data>) were also obtained and considered as potential confounders in our study.

Other exposure routes for As were also taken into account. Notably, it has been widely reported that drinking water, soil and air might be three important pathways for As exposure for some populations

(Tchounwou et al., 2004; Cleland et al., 2009; Meunier et al., 2010; Bundschuh et al., 2012; Rahman et al., 2018).

For the daily per capita As exposure from drinking water ($E-As_{ing,water}$) and daily per capita As exposure from soil ($E-As_{ing,soil}$):

$$E-As_{ing,j} = C_j \times RC_j \times AV_j$$

where $E-As_{ing,j}$: $E-As_{ing,water}$ or $E-As_{ing,soil}$; C_j : As concentration in soil (C_{soil}) ($\mu\text{g}/\text{mg}$) or water (C_{water}) ($\mu\text{g}/\text{L}$); RC_j : the daily intake of soil (RC_{soil}) (mg) or water (RC_{water}) (L) accordingly; AV_j : the median relative bioavailable fraction of As in soil (AV_{soil}) or in water (AV_{water}).

To be specific, drinking water As concentration in different water-supply zones (Polya et al., 2018) and As concentration in soil (1 km \times 1 km grids) (DEFRA, 2012) in England and Wales were converted to local authority level weighted concentration respectively via the ArcGIS geoprocess tools 'Intersect'. Mean daily water and soil consumption level for the population were estimated as 2.003 L/day (Drinking Water Inspectorate, 2008) and 50 mg/day respectively with the relative bioavailable fraction of As considered to be 100% in water (Ruby et al., 1996) and 11% in soil (Cave et al., 2003).

Similarly, for annual mean As concentration in ambient air (C_{AIR}) in England and Wales, it was firstly provided by DEFRA in 1 km \times 1 km grids (DEFRA, 2012) and then transferred to local authority level weighted air As concentration.

2.4. Statistical analysis

Statistical analysis was conducted through R statistical software (version 3.4.3 (R Foundation for Statistical Computing)) and ArcGIS (version 10.4.1, ESRI, Redlands, CA).

Firstly, the local authorities were classified into quartiles based on their $E-iAs_{ing,rice}$ levels. Then CVD ASMR and all the estimated potential confounders were compared across these categories, treating the lowest quartile (Quartile 1) as the referent. After that, we quantified the individual and interactive contributions of $E-iAs_{ing,rice}$ and all the potential confounders to the variability of CVD ASMR through GLM (contributions (%) = $100 * (\text{null deviance} - \text{residual deviance}) / \text{null deviance}$). Among this, the importance of 2-way interactive effects was calculated based on the relative excess risk for interaction (RERI) according to Chen et al. (2011b), with a value over zero indicating the presence of synergy effects:

$$RERI = e^{(\beta_1 + \beta_2 + \beta_3)} - e^{\beta_1} - e^{\beta_2} + 1$$

where β_1 : the continuous coefficient of $E-iAs_{ing,rice}$; β_2 : the coefficient of the potential confounder; and β_3 : the interactive term coefficient.

The resultant p-values for interaction were obtained by adding a cross-product term between continuous iAs exposure and different confounders to the linear model.

We then analyzed the linear relationships between $E-iAs_{ing,rice}$ and CVD ASMR by GLMs adjusted by different confounders such as smoking prevalence, education level, diabetes prevalence, employment rate, household income, overweight percentage, $E-As_{ing,water}$, economic activity rate, GVA, PM2.5, urban percentage, female percentage, medical and care establishments, $E-As_{ing,soil}$ and C_{AIR} . For better modelling their relationships, we checked the existence of multicollinearity problems among all the potential confounders and conducted correlation analysis, principal component analysis (PCA) and stepwise regression using a forward addition technique to select confounders and to decipher final models. In this regression analysis, we treated the independent variable both categorically and continuously. For continuous analysis, we estimated ASMR in relation to a 1 $\mu\text{g}/\text{person}/\text{day}$ increase in $E-iAs_{ing,rice}$. For categorical analysis, ASMR for different exposure quartiles were estimated and compared between each of the higher 3 quartiles with the bottom one. The differences between exposure categories and the p-values for trend were estimated by Wald test.

Considering the assumption of the non-linear association of $E-iAs_{ing,rice}$, we also shaped the non-linear relationships through a series of GLMs by including higher order polynomial and interactive terms.

Given the sample size (348 local authorities in England and Wales), to take into account the number of variables included (Burnham and Anderson, 2002), AIC values were calculated and used to select the best and most parsimonious model.

Due to the importance of iAs exposure from drinking water and soil on the cardiovascular health (Jomova et al., 2011; Xu et al., 2020), modelling methods and model selection criteria mentioned above have also been used to quantify the relations between $E-As_{ing,water}$, $E-As_{ing,soil}$ and CVD ASMR respectively.

Population attributable fraction (PAF) for the selected best-fitted model was then calculated according to Rockhill et al. (1998):

$$PAF = \frac{\sum_{i=1}^n P_i \times RR_i - 1}{\sum_{i=1}^n P_i \times RR_i}$$

where P_i is the proportion of population at subscripted exposure level, i ; RR_i is the relative risk at subscripted exposure level, i ; n is the number of exposure levels.

In addition, frequency distributions of the residual values of all the linear and non-linear models have also been plotted to visualize their goodness-of-fit via R statistical software.

For subgroup analysis, local authorities in $E-iAs_{ing,rice}$ Quartile 4 were selected. To be specific, those local authorities were classified according to the ethnicity group accounting for the largest proportion, other than White British, of the population, viz. Black/African/Caribbean/Black British: African or Caribbean, Asian/Asian British: Chinese or other Asians, Asian/Asian British: Pakistani, Asian/Asian British: Indian and Asian/Asian British: Bangladeshi. To determine the potential role of other ethnicity related confounders, such as genetic and dietary factors, we analyzed the relationships between ethnicity and CVD ASMR by GLMs with ASMR for different ethnicity groups being estimated and compared with the referent group (Black/African/Caribbean/Black British: African/Caribbean). Similarly, for analyzing the modification effects of ethnicity on the association between $E-iAs_{ing,rice}$ and CVD ASMR, the association between CVD ASMR and $E-iAs_{ing,rice}$ for each of the five ethnicity has been calculated separately via GLM.

ArcGIS was used to map the spatial distribution of $E-iAs_{ing,rice}$ and CVD ASMR at local authority level in England and Wales. To be specific, geographic data for boundaries of local authorities across England and Wales were obtained from 'Local Authority Districts (December 2015) Full Clipped Boundaries in Great Britain' (Office for National Statistics, 2015). In addition, to visualize the goodness of our linear and non-linear models, ArcGIS has also been applied to map the spatial distributions of their residual values in England and Wales.

3. Results

3.1. $E-iAs_{ing,rice}$ in England and Wales

Mean rice consumption in England and Wales is calculated here to be 10.82 g/person/day, broadly comparable with the figure of 9.86 g/person/day derived from the Family Food Survey for UK households (DEFRA, 2018) (results not shown). This is calculated to give rise to mean local-authority level daily intake of iAs of 0.93 $\mu\text{g}/\text{person}/\text{day}$ (range 0.68 to 6.78 $\mu\text{g}/\text{person}/\text{day}$) or – assuming an average body weight of 70 kg (European Food Safety Authority, 2012) – 0.013 $\mu\text{g}/\text{kg-bw}/\text{day}$. This is broadly comparable to intake rates estimated by Meharg et al. (2007). The local authority level mean intake rates are considerably lower than the now withdrawn Provisional Tolerable Intake equivalent of 2.1 $\mu\text{g}/\text{kg-bw}/\text{day}$ (World Health Organization et al., 2011). We note, however, that the distribution of intakes in individuals would clearly be much greater. After correction for bioavailability, conservatively estimated to be around 40% (Li et al.,

2017), these mean local authority level exposures, $E-iAs_{ing, rice}$, are calculated to be $0.37 \mu\text{g}/\text{person}/\text{day}$ (range 0.25 to $2.71 \mu\text{g}/\text{person}/\text{day}$) (Fig. 1).

Significant associations were noted between $E-iAs_{ing, rice}$ and most of the potential confounders (Table 1 and Supplementary Fig. A.1). Specifically, local authorities with higher levels of $E-iAs_{ing, rice}$ tended to have higher percentage of urban population, higher $PM_{2.5}$, higher average education level, household income per person and GVA, whilst there were negative associations between $E-iAs_{ing, rice}$, and the percentage of females and those classified as overweight.

3.2. CVD ASMR in England and Wales

To a large extent crude CVD mortality rates showed differences in distribution by the age categorization of local authority populations with relatively higher diagnosis of CVD at older age groups (~40% after age 45 years (Office for National Statistics, 2016)) (results not shown). The mean local authority CVD ASMR in England and Wales was 284/100,000 and showed a strong spatial variation with notably higher CVD ASMR in the northern parts of England and Wales, reflecting a strong association with key spatially variable economic factors such as income and employment rate (Office for National Statistics, 2015e, 2015g) (Fig. 2). In addition, CVD ASMR in $E-iAs_{ing, rice}$ Quartile 3 is

significantly lower than for Quartile 1 ($p = 0.01$) and borderline lower in Quartile 2 ($p = 0.057$) (Table 1).

CVD ASMR was found to be significantly and positively associated with smoking prevalence, diabetes prevalence, overweight percentage, $E-As_{ing, soil}$, urban percentage and medical and care establishments, whilst higher average education level, employment rate, economic activity rate, $PM_{2.5}$, household income, GVA and $E-As_{ing, water}$ could be found in local authorities with lower CVD ASMR (Supplementary Fig. A.1).

3.3. Importance of different factors to CVD ASMR

To quantify the contributions of factors shown to influence CVD ASMR and to attempt to account for their importance, GLM was performed in our analysis. According to the results, smoking prevalence, education level, diabetes prevalence and employment rate were the most four important contributors for the variability of CVD ASMR, all of which accounted for over 20% of the observed variation. Meanwhile, the contributions of household income, overweight percentage and economic activity rate, though not the most standing out, might also be significant to the variability of CVD ASMR. However, GVA, $E-As_{ing, soil}$, $PM_{2.5}$, urban percentage, medical and care establishment and $E-As_{ing, water}$ were all significantly associated with CVD ASMR in the correlation analysis

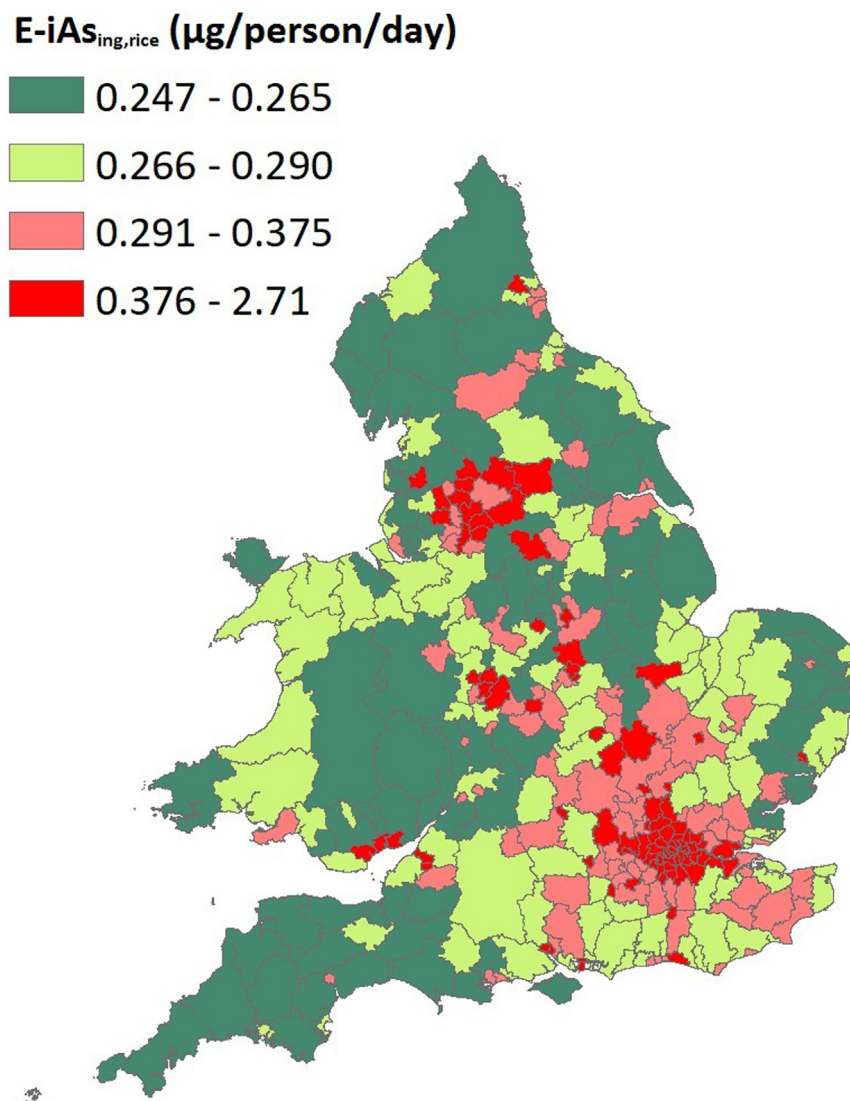


Fig. 1. Spatial distribution of the modelled local authority level daily per capita inorganic arsenic exposure from rice ($E-iAs_{ing, rice}$) in England and Wales using ethnicity as a proxy.

Table 1
General characteristics of local authorities based on modelled local authority level daily per capita inorganic arsenic (iAs) exposure from rice (E-iAs_{ing, rice}).

| Characteristic | Overall | Quartile of E-iAs _{ing, rice} , µg/person/day | | | | | | p-Value for trend | |
|-------------------------------------------------|-------------|--------------------------------------------------------|-----------------------------|----------------------|-----------------------------|----------------------|----------------------------|-------------------|----------------------|
| | | Quartile 1 (0.247–0.265) | Quartile 2 (0.265–0.290) | p-Value ^a | Quartile 3 (0.291–0.374) | p-Value ^a | Quartile 4 (0.375–2.71) | | p-Value ^a |
| CVD ASMR | 284 ± 37 | 290 ± 36 | 278 ± 38 | 0.057 | 277 ± 34 | 0.010 | 289 ± 40 | 0.957 | 0.119 |
| Smoking prevalence, % | 19.7 ± 3.9 | 19.6 ± 4.0 | 19.1 ± 4.3 | 0.282 | 19.8 ± 4.0 | 0.630 | 20.5 ± 3.2 | 0.105 | 0.309 |
| Level 4 qualifications and above, % | 26.9 ± 7.5 | 24.7 ± 5.1 | 25.3 ± 5.8 | 0.447 | 27.1 ± 7.0 | 0.035 | 30.6 ± 9.9 | <0.001 | <0.001 |
| Diabetes prevalence, % | 5.8 ± 0.9 | 6.1 ± 0.7 | 5.8 ± 0.8 | 0.020 | 5.5 ± 0.7 | <0.001 | 5.7 ± 1.1 | 0.005 | 0.786 |
| Employment rate, % | 72.3 ± 5.8 | 72.5 ± 5.4 | 73.1 ± 5.8 | 0.547 | 74.0 ± 5.4 | 0.077 | 69.5 ± 5.7 | <0.001 | <0.001 |
| Household income per person, thousand pounds | 18 ± 5 | 17 ± 2 | 17 ± 3 | 0.123 | 19 ± 4 | <0.001 | 20 ± 7 | 0.007 | <0.001 |
| Overweight prevalence, % | 50.2 ± 5.3 | 52.7 ± 4.2 | 51.8 ± 4.4 | 0.205 | 49.5 ± 4.2 | <0.001 | 46.8 ± 5.9 | <0.001 | <0.001 |
| Economic activity rate, % | 77.9 ± 4.5 | 77.7 ± 4.4 | 78.5 ± 4.5 | 0.166 | 79.3 ± 4.3 | 0.015 | 76.1 ± 4.4 | 0.017 | <0.001 |
| GVA, thousand pounds | 22 ± 13 | 18 ± 4 | 19 ± 5 | 0.111 | 23 ± 6 | <0.001 | 29 ± 24 | <0.001 | <0.001 |
| E-As _{ing, soil} , µg/person/day | 0.09 ± 0.04 | 0.10 ± 0.04 | 0.09 ± 0.04 | 0.076 | 0.09 ± 0.04 | 0.062 | 0.09 ± 0.02 | 0.406 | 0.391 |
| PM2.5, µg/m ³ | 10.7 ± 1.6 | 9.5 ± 1.3 | 10.1 ± 1.1 | 0.002 | 10.9 ± 0.9 | <0.001 | 12.3 ± 1.6 | <0.001 | <0.001 |
| Urban percentage, % | 75.7 ± 25.1 | 52.8 ± 24.7 | 69.7 ± 21.9 | <0.001 | 83.6 ± 18.3 | <0.001 | 96.6 ± 6.4 | <0.001 | <0.001 |
| Female, % | 50.9 ± 0.6 | 51.0 ± 0.5 | 51.0 ± 0.6 | 0.537 | 50.9 ± 0.7 | 0.043 | 50.6 ± 0.7 | <0.001 | <0.001 |
| Medical and care establishments per 1000 person | 0.46 ± 0.19 | 0.52 ± 0.18 | 0.52 ± 0.21 | 0.665 | 0.46 ± 0.20 | 0.004 | 0.35 ± 0.11 | <0.001 | <0.001 |
| E-As _{ing, water} , µg/person/day | 0.96 ± 0.99 | 0.73 ± 0.67 | 1.06 ± 1.35 | 0.034 | 0.95 ± 1.00 | 0.081 | 1.10 ± 0.79 | 0.002 | 0.001 |
| C _{AIR} , µg/m ³ | 0.52 ± 0.29 | 0.55 ± 0.43 | 0.47 ± 0.24 | 0.076 | 0.53 ± 0.26 | 0.231 | 0.51 ± 0.14 | 0.133 | 0.921 |

ASMR was expressed as a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the European Standard Population 2013.

GVA: gross value added per head.

E-As_{ing, soil}: daily per capita arsenic (As) exposure from soil.

E-As_{ing, water}: daily per capita As exposure from drinking water.

C_{AIR}: annual mean As concentration in ambient air.

^a Compared with Quartile 1 (0.247–0.265 µg/person/day).

(Supplementary Fig. A.1), but only explained a small percent. In addition, due to the low level E-iAs_{ing, rice} in England and Wales, this factor alone did not play an important role in CVD ASMR, contributing <1% (Table 2).

Aiming at accounting the importance of the interactive effects between E-iAs_{ing, rice} and all the potential confounders, we also calculated the relative excess risks and their contributions. According to Table 2, there were significantly synergetic effects between E-iAs_{ing, rice} and smoking prevalence, economic activity rate, overweight percentage, GVA, education level, urban percentage, medical and care establishment and household income per person as well as E-As_{ing, soil}, with their contributions ranging from 3% to 30%.

3.4. Association between CVD ASMR and E-iAs_{ing, rice}

Univariate and multivariate generalized linear models were used in the linear regression analysis (Table 3). In the univariate model without any adjustment (Model 1), no monotonic increase was found between CVD ASMR and local authority level E-iAs_{ing, rice}. However, when corrected for some well-known confounders (multivariate models, see Model 2 to Model 5 in Table 3), the observed risk of CVD ASMR provided evidence of a significant and positive relationship with E-iAs_{ing, rice}. Specifically, when we adjusted all the potential confounders in Model 2, compared with the referent group (Quartile 1), CVD ASMR rose about 4% in Quartile 4 though not significantly (p-value = 0.087). But we did find a significant relationship between E-iAs_{ing, rice} and CVD ASMR when treating iAs exposure as a continuous variable in this model (p-value <0.05) with a 13% increase in CVD ASMR for a 1 µg/person/day increase in E-iAs_{ing, rice}. Model 3 was derived as the end-point of a 'stepwise' model modification based on AIC. However, its AIC value was not significantly lower than that of Model 4, the latter one (Model 4) which was adjusted by less confounders was, therefore, chosen as the best-fitted linear one. In the categorical analysis of Model 4, higher levels of ASMR (6% increase) could be observed for local authorities exposed with the highest level of E-iAs_{ing, rice}. Also, there was a significantly and positively steady increase in this model with a p-value for trend lower than 0.001, indicating that every increase of 1 µg/person/day E-iAs_{ing, rice} was related with an increase of 14% local-authority level CVD ASMR in England and Wales (Table 3). After we further adjusted E-As_{ing, water}, E-As_{ing, soil} and C_{AIR} on Model 4 (see

Model 5), a similar pattern was obtained. We found a 6% increase of ASMR for local authorities exposed with the highest level of iAs (Quartile 4), with a significantly and positively steady increase being found as well. However, based on the best and most parsimonious fit, as there is no significant improvement of AIC value for Model 5, Model 4 was still regarded as the best-fitted linear one, estimating that about 1.21% (CIs: -1.38–3.88%) CVD ASMR (population attributable fraction) is associated with exposure to iAs through rice for the entire population in England and Wales.

In the non-linear model, higher risks of CVD could be found for local authorities exposed with higher level iAs but, in contrast to the best-fitted linear model, CVD ASMR decreased before increasing from 0.3 µg/person/day and the increasing rate became more flat for higher exposure level (Fig. 3). Such a non-linear dose-response relationship is more consistent than a linear model with current understanding of the toxicology of As especially at low doses (Chavan et al., 2017; Moon et al., 2013; Moon et al., 2017a) and given that the AIC value of the non-linear model (AIC = 3286.9) was lower than the best-fitted linear one (AIC = 3287.4) (Model 4 in Table 3), albeit only marginally, we prefer the non-linear model as a more theoretically reasonable model. Application of this preferred non-linear model indicated that ~2.0% (CIs: 0.0–11.5%) of CVD ASMR (population attributable fraction) is associated with exposure to iAs from ingestion of rice for England and Wales residents.

In a brief sensitivity analysis, we explored the possibility that the association between E-iAs_{ing, rice} and CVD ASMR might be biased by two apparent outliers of E-iAs_{ing, rice} (see Fig. 3). However, excluding the data of Newham and Tower Hamlets where rice consumption levels were much higher than those in other local authorities nevertheless yielded results similar to those described above (Supplementary Table A.1). We conclude, therefore that the observed relationship between CVD ASMR and E-iAs_{ing, rice} do not arise because of these outliers.

The distributions of residual CVD ASMR of the best-fitted linear (Fig. 4(b)) and preferred non-linear model (Fig. 4(c)) are very similar, and both higher (red areas in Fig. 4) and lower (green areas in Fig. 4) residual values of different models indicate an overestimate or underestimate of CVD risks- accordingly there is still scope for model improvement especially for the consideration of confounding information.

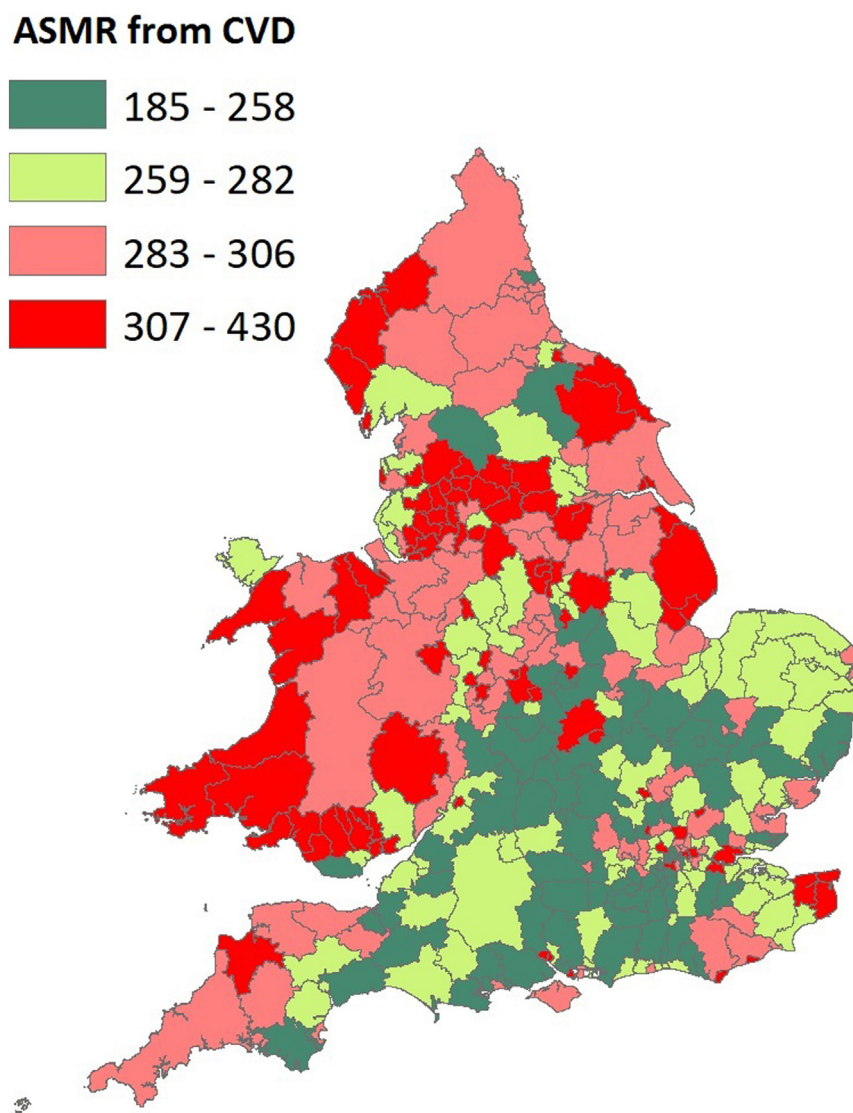


Fig. 2. Spatial distribution of the age-standardized mortality rate (ASMR) from cardiovascular disease (CVD) in England and Wales. ASMR was expressed as a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the European Standard Population 2013.

3.5. Association between CVD ASMR and $E-iAs_{ing,water}$, $E-iAs_{ing,soil}$

Table 4 has been used to illustrate the best-fitted (using AIC) linear model of the association between CVD ASMR and $E-iAs_{ing,water}$, and $E-iAs_{ing,soil}$ respectively. According to the results, there was no monotonic and only a slight association between CVD ASMR $E-iAs_{ing,water}$ and $E-iAs_{ing,soil}$. Specifically, CVD ASMR was negatively but not significantly associated with $E-iAs_{ing,water}$. For the continuous analysis, every increase of 1 $\mu\text{g}/\text{person}/\text{day}$ $E-iAs_{ing,water}$ was associated with a decrease of 0.1% CVD ASMR. Similarly, the higher three quartiles of $E-iAs_{ing,water}$ were associated with a slightly decreased CVD ASMR (1.00 (referent), 0.99 (95% CI: 0.96, 1.00), 0.96 (95% CI: 0.93, 0.99), and 0.97 (95% CI: 0.94, 1.00)) for the categorical analysis. In terms of the $E-iAs_{ing,soil}$, a slight but not significant increase could be observed for CVD ASMR with the increasing $E-iAs_{ing,soil}$ both categorically and continuously.

4. Discussion

In this local authority level ecological study conducted across England and Wales, we did not find a simple direct significant relationship between CVD ASMR and $E-iAs_{ing,rice}$. However, modelled high rice

consumption rates and hence high $E-iAs_{ing,rice}$ were found to be associated with trends in behavioral and socioeconomic characteristics known to be protective against CVD, viz. lower overweight percentage and smoking prevalence as well as higher economic and educational levels. When corrected for these significant known confounders, low level $E-iAs_{ing,rice}$ was found to be associated with a slight but significant elevation in the local authority CVD ASMR. In the best-fitted (using AIC) linear model (Model 4), CVD ASMR in the highest quartile of iAs exposure (0.375–2.71 $\mu\text{g}/\text{person}/\text{day}$) was found to be 1.06 (1.02, 1.11; p-trend <0.001) times higher than that in the lowest quartile (<0.265 $\mu\text{g}/\text{person}/\text{day}$). The non-linear model was regarded as the best model when compared with the linear ones. In the non-linear model, CVD ASMR decreased before increasing from 0.3 $\mu\text{g}/\text{person}/\text{day}$ followed by an increase. Though weak, such effects were somewhat similar to those expected from studies of CVD mortalities arising from low level iAs intake from drinking water in Spain (about 0.60% (CIs: 0.31–2.50%) CVD mortality was associated with exposure of water iAs) (Medrano et al., 2010). Similarly, the associations of $E-iAs_{ing,rice}$ was also consistent with those produced from a meta-analysis quantifying the effects on CVD mortality of drinking water As equal to or even lower than 10 ppb (Xu et al., 2020). Given the model uncertainties including those limiting

Table 2
Contribution of different factors separately and the importance of the interactive effects on the variability of the age-standardized mortality rate (ASMR) from cardiovascular disease (CVD).

| Factors | Contribution (%) | p-Value* | Interactive effects | | |
|-------------------------------------------------|------------------|----------|---------------------|------------------|---------|
| | | | RERI ^a | Contribution (%) | p-Value |
| E-iAs _{ing, rice} | 0.7 | 0.119 | | | |
| Smoking prevalence | 24.7 | <0.001 | 0.01 | 25.3 | <0.001 |
| Education level | 24.5 | <0.001 | 0.00 | 30.8 | <0.001 |
| Diabetes prevalence | 22.8 | <0.001 | -0.02 | 23.5 | <0.001 |
| Employment rate | 20.4 | <0.001 | -0.02 | 21.3 | <0.001 |
| Household income per person | 19.4 | <0.001 | 0.00 | 23.7 | <0.001 |
| Overweight percentage | 19.0 | <0.001 | 0.00 | 25.8 | <0.001 |
| Economic activity rate | 15.3 | <0.001 | 0.00 | 15.5 | <0.001 |
| GVA | 6.6 | <0.001 | 0.00 | 14.6 | <0.001 |
| E-As _{ing, soil} | 5.8 | <0.001 | 1.80 | 6.7 | <0.001 |
| PM 2.5 | 4.5 | <0.001 | -0.20 | 14.0 | <0.001 |
| Urban percentage | 2.5 | 0.003 | 0.01 | 4.9 | <0.001 |
| Female percentage | 2.3 | 0.004 | -0.19 | 2.8 | 0.021 |
| Medical and care establishment per 1000 persons | 1.8 | 0.011 | 0.03 | 3.5 | 0.006 |
| E-As _{ing, water} | 1.3 | 0.034 | -0.08 | 3.1 | 0.013 |
| C _{AIR} | 0.6 | 0.160 | -0.34 | 1.4 | 0.173 |

ASMR was expressed as a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the European Standard Population 2013.

E-iAs_{ing, rice}: local authority level daily per capita inorganic arsenic (iAs) exposure from rice.
GVA: gross value added per head.

E-As_{ing, soil}: daily per capita As exposure from soil.

E-As_{ing, water}: daily per capita As exposure from drinking water.

C_{AIR}: annual mean As concentration in ambient air.

The individual and interactive contributions of E-iAs_{ing, rice} and all the potential confounders to the variability of CVD ASMR were quantified through generalized linear model (GLM) (contributions (%) = 100 * (null deviance - residual deviance) / null deviance). Among this, the importance of 2-way interactive effects was calculated based on the relative excess risk for interaction (RERI) according to Chen et al. (2011b): $RERI = e^{(\beta_1 + \beta_2 + \beta_3)} - e^{\beta_1} - e^{\beta_2} + 1$, where β_1 is the continuous coefficient of E-iAs_{ing, rice}; β_2 is the coefficient of the potential confounder; and β_3 is the interactive term coefficient, with an estimation over zero indicating the presence of synergy effects. The accordingly p-values for interaction were obtained by adding a cross-product term between continuous iAs exposure and different confounders to the linear model.

^a Relative excess risk for interaction (RERI) with arsenic (As) exposure as a continuous variables.

* The accordingly p-values for the contribution of the single factor were obtained by F-test.

extrapolation to populations with contrasting diets, nutritional status and genetics indicators, however, further model exploration is required (cf. Chen et al., 2011b).

There is a suggestion in the data, supported by our non-linear and categorical analysis, however, that a non-zero consumption of iAs bearing rice (<0.3 µg/person/day) may actually be protective (Fig. 3). We speculate that, rather than indicating a protective role for iAs, which is not known to have a role as an essential trace element, this reflects the balance between the negative impacts of exposure to iAs from rice and the positive impacts arising from exposure to the fiber, protein and the wide range of micronutrients in rice (cf. Meng et al., 2005; Brotherton et al., 2014). However, we cannot conclude that 0.3 µg/person/day E-iAs_{ing, rice} is good for CVD prevention as the lower CVD ASMR observed in our model might not because of the non-zero iAs exposure (<0.3 µg/person/day) but rather due to ethnicity distribution itself. We assume that Black and Chinese with negative associations between E-iAs_{ing, rice} and CVD ASMR may drive the initial decreasing CVD risks. Similarly, the further increasing CVD ASMR for higher exposure level might be related to the susceptibilities of Indians or Bangladeshis to the negative effects of iAs on the CVD risks (Supplementary Table A.2).

Some limitations could be found in this study and this is especially the case for local authorities with the higher iAs exposures- the higher the exposure level, the larger the uncertainty of the estimated risks (Fig. 3).

The most substantial limitation to our study is that ethnicity has been used as a proxy for rice consumption. Given the differences of the spatial distribution of CVD ASMR and E-iAs_{ing, rice} (Figs. 1 & 2) as well as the non-significant associations with CVD ASMR observed for both E-As_{ing, water} and E-As_{ing, soil}, neither of which are calculated based on ethnicity distributions (Table 4), the associations observed in our study on the CVD risk might be mainly due not to E-iAs_{ing, rice} but rather, due to one or more ethnicity-related confounders, whether they be behavioral, dietary or genetic. Some ethnicity-related confounders are already well recognized including smoking percentage, education level, diabetes prevalence, obesity prevalence and household income (Chaturvedi et al., 1994; Cappuccio et al., 1997; Santos-Gallego and Badimón, 2012; Bostean et al., 2013) and have been accounted for in this study, notwithstanding this, other ethnicity-related confounders, notably diet and genetics, may well be indistinguishable in their impacts from those of rice consumption per se and iAs exposure. Thus, the so-called Japanese diet with adequate intake of total calories, fish and plant foods, but low consumption of refined carbohydrates and animal fat, has been identified as lowering the risk of coronary artery disease (Tada et al., 2011). Similarly, black rice which is an important food resource for high-rice consuming Asians, notably Korean, Japanese and southern Chinese, has been suggested to be protective against CVD (Kushwaha, 2016).

It is possible that the observed association between CVD risk and iAs exposure may reflect ethnicity-related gene polymorphisms involved in CVD vulnerability (Tsinovoi et al., 2018). In fact, several studies have already identified some ethnicity-related gene polymorphisms responsible for CVD risks. For example, genetic variants of three CVD-related clinically relevant endothelial nitric oxide synthases (eNOS) are distributed differently among different ethnicities, with both the C-781 and Asp298 variant being significantly more common in Caucasians than in African-Americans or Asians (Tanus-Santos et al., 2001). Miller et al. (2004) found that the Thr715Pro C allele was rare in Blacks and intermediate in South Asians compared to Whites in England, and which they concluded could partly explain the ethnic variations in coronary heart disease risk. Besides, distribution differences of genetic variants of CVD marker MMP polymorphisms and haplotypes exist between Blacks and Whites as the "C" allele for the C-1306T and "T" allele for the C-1562T polymorphism were more common in Blacks than in Whites (Lacchini et al., 2010). According to a study analyzing the role of genetics on the coronary risk in Asians, Malays were found to have the highest frequency of serum lipid profile-related epsilon4 compared with Chinese and Indian populations (Tan et al., 2003).

However, combined with the dose-response equation between drinking water iAs concentration and CVD risks produced by Xu et al. (2020), we assumed that the non-significant associations of E-As_{ing, water} and E-As_{ing, soil} in this study were not real ones but instead due to the fact that their effects were too small to be detected in such an ecological design (data not shown). Under such circumstances, though using ethnicity as a proxy, the possibility of a positive or even a significant positive association between E-As_{ing, rice} and CVD ASMR still cannot be excluded.

Uncertainties also exist in estimating dietary intake of iAs. These include: (i) imprecise estimation of iAs exposure from rice. On one hand, iAs concentration in rice is highly variable among different rice varieties imported to the UK (Meharg et al., 2007). Also, there may be some difference in the relative importance of different rice varieties in the diet of different ethnic groups or differences in rice consumption pattern across regions even within the same ethnicity; however, there is a lack of appropriate consumption data for these to be introduced as meaningful confounders into the present study. On the other hand, different ethnicities cook their rice quite differently, meaning that the 3-1 water-rice ratio does not hold true across ethnicities. According to

Table 3

Modelling analysis of categorical and continuous relations between modelled local authority level daily per capita inorganic arsenic (iAs) exposure from rice ($E-iAs_{ing, rice}$) ($\mu\text{g}/\text{person}/\text{day}$) and the age-standardized mortality rate (ASMR) from cardiovascular disease (CVD).

| Model | Quartile of $E-iAs_{ing, rice}$ ($\mu\text{g}/\text{person}/\text{day}$) | | | | | | ASMR per 1 $\mu\text{g}/\text{person}/\text{day}$ increase | p-Value for trend | AIC | Contributions (%) | |
|---------|----------------------------------------------------------------------------|--------------------------|----------------------|--------------------------|----------------------|-------------------------|------------------------------------------------------------|-------------------|--------|-------------------|----------------------|
| | Quartile 1 (0.247–0.265) | Quartile 2 (0.265–0.290) | p-Value ^a | Quartile 3 (0.291–0.374) | p-Value ^a | Quartile 4 (0.375–2.71) | | | | | p-Value ^a |
| Model 1 | 1.00 (Referent) | 0.96 (0.92, 1.00) | 0.046 | 0.96 (0.92, 0.99) | 0.021 | 1.00 (0.96, 1.04) | 0.983 | 1.05 (0.99, 1.12) | 0.119 | 3485.4 | 0.7 |
| Model 2 | 1.00 (Referent) | 0.97 (0.94, 1.00) | 0.057 | 0.99 (0.95, 1.02) | 0.455 | 1.04 (0.99, 1.09) | 0.087 | 1.13 (1.04, 1.21) | 0.003 | 3287.9 | 47.7 |
| Model 3 | 1.00 (Referent) | 0.97 (0.94, 1.00) | 0.036 | 0.98 (0.95, 1.02) | 0.327 | 1.04 (1.00, 1.09) | 0.076 | 1.14 (1.06, 1.22) | <0.001 | 3283.7 | 47.4 |
| Model 4 | 1.00 (Referent) | 0.98 (0.95, 1.01) | 0.132 | 1.00 (0.97, 1.03) | 0.997 | 1.06 (1.02, 1.11) | 0.001 | 1.14 (1.07, 1.21) | <0.001 | 3287.4 | 46.2 |
| Model 5 | 1.00 (Referent) | 0.98 (0.95, 1.01) | 0.123 | 1.00 (0.96, 1.03) | 0.794 | 1.06 (1.01, 1.10) | 0.008 | 1.13 (1.06, 1.21) | <0.001 | 3286.5 | 47.3 |

ASMR was expressed as a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the European Standard Population 2013.

Model 1: crude with ASMR only (univariate model).

Model 2: full model, adjusted by smoking prevalence, education level, diabetes prevalence, employment rate, household income per person, overweight percentage, economic activity rate, GVA, PM 2.5, urban percentage, female percentage and medical and care establishments per 1000 persons.

Model 3: constructed by 'stepwise' function in R language based on AIC values which was adjusted by smoking prevalence, education level, employment rate, overweight percentage, gross value added per head (GVA), PM2.5, urban percentage, female percentage and medical and care establishments per 1000 person.

Model 4: adjusted by variables widely adopted by previous studies, including smoking prevalence, education level, employment rate, overweight percentage, PM2.5, female percentage and medical and care establishments per 1000 person.

Model 5: further adjusted by daily per capita arsenic exposure from soil ($E-As_{ing, soil}$), daily per capita arsenic exposure from drinking water ($E-As_{ing, water}$) and annual mean arsenic concentration in ambient air (C_{AIR}) additionally on Model 4.

^a Compared with Quartile 1 (referent group) (0.247–0.265 $\mu\text{g}/\text{person}/\text{day}$).

the individual level National Diet and Nutrition Survey (2014/15–2016/17) conducted in the UK (details about this population-based cross-sectional study could be found in [MRC Elsie Widdowson Laboratory and NatCen Social Research \(2019\)](#)), differences of the daily iAs intake from rice & rice products could be observed between different ethnicities or across regions even for the same ethnic group (Supplementary Table A.3). However, when we used values of the daily iAs intake from rice & rice product of different ethnicities obtained from the National Diet and Nutrition Survey (2014/15–2016/17) ([MRC Elsie Widdowson Laboratory and NatCen Social Research, 2019](#)) to calculate local authority

level daily iAs intake, similar associations between iAs intake and CVD risks could still be found (Supplementary Table A.4); (ii) there may be substantial dietary intake of iAs from other sources. According to a probabilistic exposure modelling analysis in the USA and some surveys conducted in European countries, grain-based processed products (non-rice-based), vegetables, fruit, as well as milk and dairy products also contribute to dietary iAs exposure, with vegetables even accounting for >20% for the general US population ([Xue et al., 2010](#); [European Food Safety Authority, 2014](#); [MRC Elsie Widdowson Laboratory and NatCen Social Research, 2019](#)). Notwithstanding that As speciation in seafood is

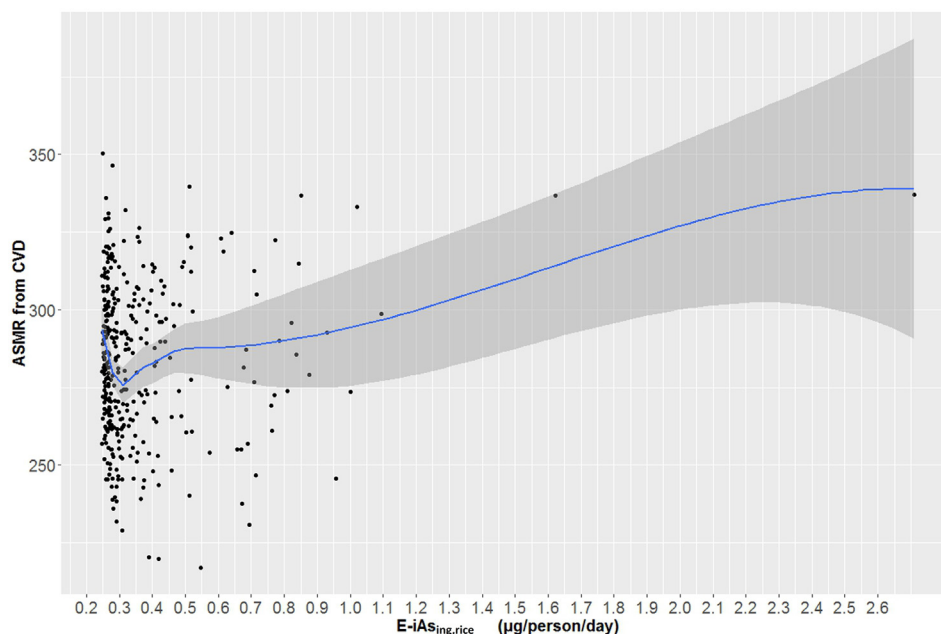


Fig. 3. Higher order polynomial model for association between the modelled local authority level daily per capita inorganic arsenic exposure from rice ($E-iAs_{ing, rice}$) and age standardized mortality rate per 100,000 persons (ASMR) from cardiovascular disease (CVD) in England and Wales in 2012. Non-linear model: $\log-ASMR \sim 0.162 * E-iAs_{ing, rice} - 0.039 * E-iAs_{ing, rice}^2 + 0.006 * \text{smoking prevalence} - 0.004 * \text{education level} - 0.004 * \text{employment rate} + 0.004 * \text{overweight percentage} - 0.018 * PM2.5 + 0.756 * \text{female percentage} - 0.008 * \text{female percentage}^2 + 0.098 * \text{medical and care establishments} - 12.4$, AIC = 3286.9.

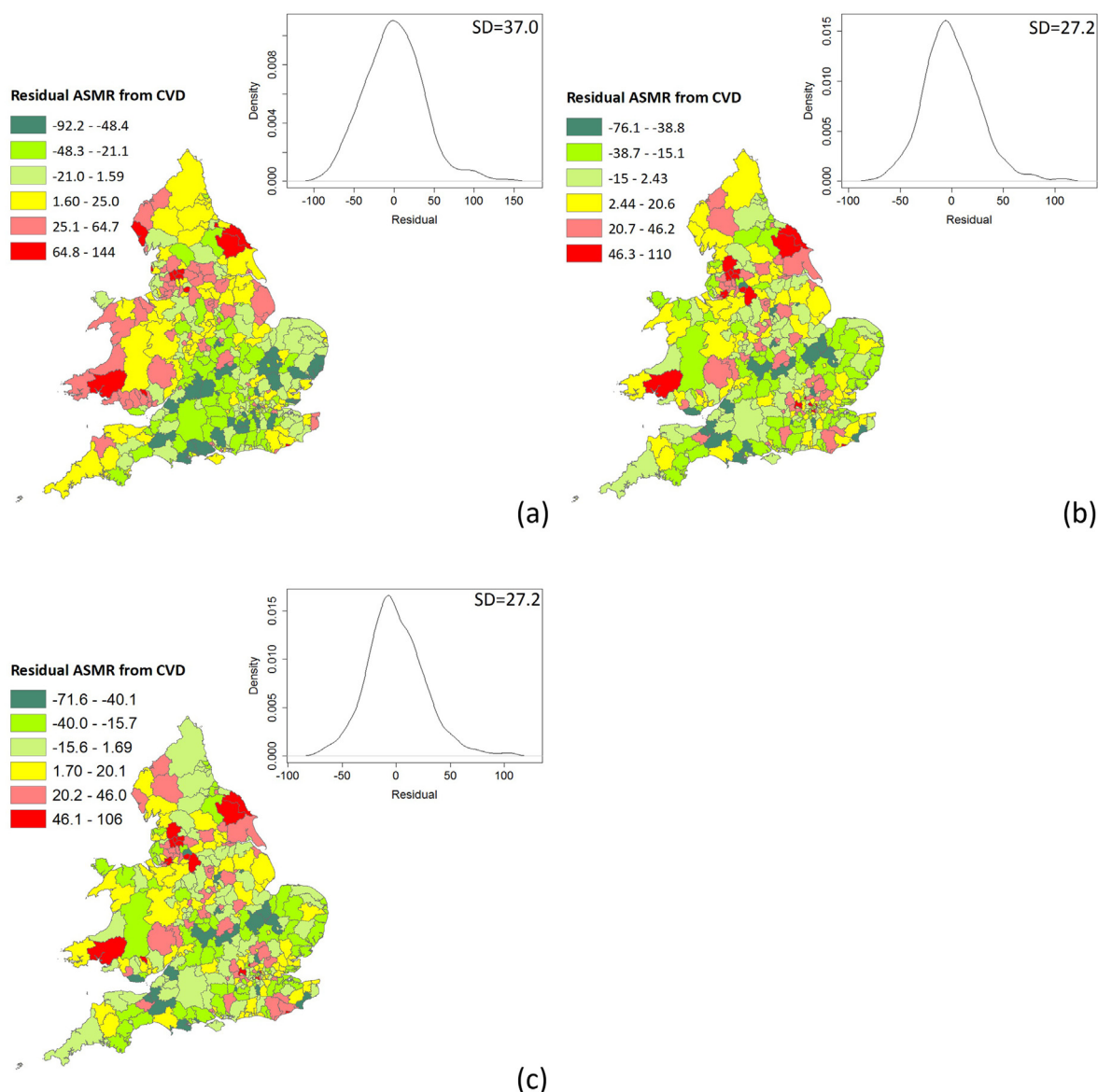


Fig. 4. Model 1(a), 4(b) and non-linear model(c) (see Table 3 & Fig. 3) Spatial distribution of residuals of Model 1, 4, and non-linear model of cardiovascular disease (CVD) age-standardized mortality rate per 100,000 person (ASMR) at a local authority level in England and Wales for 2012. Inset shows frequency and Standard Deviation (SD) of distribution of residuals. ASMR was expressed as a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the European Standard Population 2013. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

Table 4
Modelling analysis of categorical and continuous relations between modelled local authority level daily per capita As exposure from drinking water ($E-As_{ing,water}$), daily per capita As exposure from soil ($E-As_{ing,soil}$) ($\mu\text{g}/\text{person}/\text{day}$) and the age-standardized mortality rate (ASMR) from cardiovascular disease (CVD).

| Model | Quartile of As exposure ($\mu\text{g}/\text{person}/\text{day}$) | | | | | | | ASMR per 1 $\mu\text{g}/\text{person}/\text{day}$ increase | p-Value for trend | Contributions (%) |
|--------------------|--------------------------------------------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|------------------------------------------------------------|-------------------|-------------------|
| | Quartile 1 | Quartile 2 | p-Value ^a | Quartile 3 | p-Value ^a | Quartile 4 | p-Value ^a | | | |
| $E-As_{ing,water}$ | 1.00 (Referent) | 0.99 (0.96, 1.00) | 0.429 | 0.96 (0.93, 0.99) | 0.009 | 0.97 (0.94, 1.00) | 0.101 | 0.99 (0.98, 1.00) | 0.125 | 46.3 |
| $E-As_{ing,soil}$ | 1.00 (Referent) | 1.00 (0.99, 1.00) | 0.239 | 1.00 (0.98, 1.00) | 0.437 | 1.00 (0.99, 1.10) | 0.124 | 1.22 (0.93, 1.59) | 0.139 | 45.8 |

ASMR was expressed as a weighted average of the age-specific mortality rates per 100,000 persons, where the weights are the proportions of persons in the corresponding age groups of the European Standard Population 2013.

Best-fitted model for $E-As_{ing,water}$: adjusted by $E-iAs_{ing,rice}$, smoking prevalence, diabetes prevalence, female percentage, medical and care establishments, overweight percentage, PM2.5, GVA, $E-As_{ing,soil}$, urban percentage.

Best-fitted model for $E-As_{ing,soil}$: adjusted by $E-iAs_{ing,rice}$, smoking prevalence, diabetes prevalence, household income, female percentage, medical and care establishments, urban percentage, PM2.5, overweight percentage.

^a Compared with Quartile 1 (referent group). For $E-As_{ing,water}$: Quartile 1: 0.106–0.361 $\mu\text{g}/\text{person}/\text{day}$, Quartile 2: 0.362–0.621 $\mu\text{g}/\text{person}/\text{day}$, Quartile 3: 0.622–1.05 $\mu\text{g}/\text{person}/\text{day}$, Quartile 4: 1.11–8.96 $\mu\text{g}/\text{person}/\text{day}$; For $E-As_{ing,soil}$: Quartile 1: 0.042–0.069 $\mu\text{g}/\text{person}/\text{day}$, Quartile 2: 0.069–0.083 $\mu\text{g}/\text{person}/\text{day}$, Quartile 3: 0.083–0.100 $\mu\text{g}/\text{person}/\text{day}$, Quartile 4: 0.100–0.381 $\mu\text{g}/\text{person}/\text{day}$.

dominated by organoarsenic compounds, partial transformation to toxic arsenic metabolites and the occurrence of low concentrations of iAs might also act as potential confounders (Taylor et al., 2017). Despite issues of potential reverse causation (Steinmaus et al., 2010) and inaccurate hydration status correction methods (Middleton et al., 2016c), others (e.g. (Kurzius-Spencer et al., 2016; Middleton et al., 2016a; Middleton et al., 2016b)) have used exposure biomarkers (e.g. urinary As, hair As) as more reliable measures of overall iAs exposure, however such data were not available in this study. Notwithstanding this, such substantial other iAs exposures might only be expected to dampen the strength of association between CVD and iAs exposure from rice if the latter were a causal agent.

Ecological studies such as this are vulnerable to population level statistics not reflecting the actual distribution of individual level statistics (cf. ecological fallacy (Meliker et al., 2007)) and whilst there have been biologically plausible mechanistic processes previously proposed to support a causal link between iAs exposure and CVD (Sidhu et al., 2015), ecological studies do merely indicate an association rather than causality. Of course, the same applies to studies of the association of CVD with ethnicity and which have not considered iAs exposure as a confounder.

Several studies and our supplemental analysis have already indicated an association between CVD risks and ethnicity (Supplementary Table A.5). Reviewing >175 epidemiology studies and randomized controlled trials, several researchers summarized recent evidence on ethnic differences in CVD risks, such as coronary heart disease, stroke, hypertension, peripheral arterial disease and rheumatic heart disease as well as cerebrovascular disease (Gaines and Burke, 1995; Cleland and Sattar, 2005; Gasevic et al., 2015; Egan et al., 2017; Gazzola et al., 2017; Moon et al., 2017b; Muncan, 2018). For example, >50 cross-sectional studies and longitudinal investigations with North American evidence published from 2000 and onward have been generated by Gasevic et al. (2015), discussing the racial/ethnic disparities in hypertension among Aboriginal, African American, Chinese, European/white/Caucasian, Filipino, and Arab populations. However, these studies did not consider the dose-response effects of iAs exposure from rice. Notwithstanding the use here of ethnicity as a proxy for class of rice consumption, necessitated by a lack of data otherwise, this study does highlight the potential importance of E-iAs_{ing, rice} on cardiovascular health. So whilst, questions about the accuracy and validity of the associations found in our analysis are warranted to some extent, this study, which takes the iAs exposure from rice consumption into account, nevertheless, is a step forward compared to risk assessment without such considerations.

Taken together, a better relationships interpretation has been added to the currently limited epidemiologic evidence regarding such low-level iAs exposure from rice. Regression analysis in our study, whilst showing an overall significantly positive association between CVD ASMR and E-iAs_{ing, rice}, also suggests a negative association at low exposures up to 0.3 µg/person/day. Therefore, this study sheds light, at least in part, on the necessity of rice consumption management even in western countries, adding overall understanding of the consequences of low level iAs exposure from rice. It would be prudent for high rice consumers to consider ways in which to reduce their exposure to iAs via this route – given the otherwise nutritional benefits of rice consumption, eating rice in a more protective way might be indicated rather than not eating rice at all – for example by consuming polished rice instead of brown rice (European Food Safety Authority, 2014) or basmati rice instead of non-basmati rice (Islam et al., 2017a), cooking rice with a large excess of water (Mwale et al., 2018) or just limiting consumption of rice and rice products to four (children) or six times (adults) per week (National Food Agency of Sweden, 2015).

5. Conclusion

This study reveals that when corrected for confounders, the preferred best-fitted non-linear model shows that CVD risks in England and Wales decrease for iAs exposures up to 0.3 µg/person/day followed by an

increase at higher exposures. Also, a significantly and positively linear association exists between iAs exposure from rice intake and local authority level CVD ASMR in England and Wales. ASMR for the highest quartile of iAs exposure from rice (0.375–2.71 µg/person/day) was 1.06 (1.02, 1.11; $p < 0.001$) times higher than that in the lowest quartile (<0.265 µg/person/day). Though model uncertainties exist, especially arising from use of ethnicity as a proxy for rice consumption, the possibility of a positive or even a significant positive association between CVD ASMR and E-As_{ing, rice} still cannot be excluded. This study suggests that high rice consumers should eat rice in a more protective way. Lastly, the study also highlights that exposure to iAs should be considered as a potential confounder when exploring the key factors controlling incidence of and mortality arising from cardiovascular diseases.

CRedit authorship contribution statement

Lingqian Xu: Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing. **David A. Polya:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing - review & editing. **Qian Li:** Methodology, Software, Writing - review & editing. **Debapriya Mondal:** Supervision, Writing - review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

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